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Serotonin and Disorders of Human Disinhibition: Alcohol Abuse and Dependence, Aggression and Impulsivity

by

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TABLES OF CONTENTS

TABLE OF CONTENTS i
ABSTRACT v
RÉSUMÉ vii
THESIS SPECIFICATIONS ix
ACKNOWLEDGEMENTS xii
STATEMENT OF ORIGINALITY xvi
LIST OF TABLES AND FIGURES xviii
LIST OF ABBREVIATIONS xix
OVERVIEW xxi
INTRODUCTION
Alcohol Abuse and Dependence: Scope of the Problem 1
The Neurochemistry of Alcoholism: Serotonin 1
Serotonin and Alcohol Intake, Abuse and Dependence: Clinical Evidence 4
Serotonin and Alcohol Intake, Abuse and Dependence: Findings of Animal Studies 16
Serotonin and Alcohol: Recent Developments 43
A Brief Review of the Genetics of Alcoholism 64
Behavioral Undercontrol and Impulsivity in Alcoholics and Individuals at High Risk for Alcoholism 69
Serotonin and Aggression, Impulsivity 73
The Acute Tryptophan Depletion Paradigm 84
Passive Avoidance Learning 92
The Present Work 95
STUDY ONE 96
Abstract 97

Introduction 99
Methods
Selection of Participants and Baseline Testing 101
Amino Acid Administration 102
Taylor Aggression Task 103
Go/No-Go Learning Task 104
Determination of Plasma Tryptophan Concentrations 106
Data Analysis 106
Ethics 107
Results
Demographic Data 108
Analysis of Serum Free and Total Tryptophan Levels 109
Modified Taylor Aggression Task 109
Go/No-Go Task 111
Changes in Mood 112
Variables Predicting Commission Errors 113
Comment 114
References 118
Tables & Figures 133
BRIDGE 140
STUDY TWO 144
Abstract 145
Introduction 146
Methods and Materials
Participants 149
Procedure and Instruments
Demographic Variables 149

Cognitive/Neuropsychological Variables.....151
Acute Tryptophan Depletion.....152
Amino Acid Administration.....153
Assessment of Disinhibition: The Go/No-Go Task.....154
Tryptophan Repletion.....156
Determination of Plasma Tryptophan Concentrations.....156
Data Analysis.....156
Ethical Approval.....157
Results.....158
Demographic Data.....158
Serum Free and Total Tryptophan Levels.....159
Go/No-Go Task.....160
Draw-a-Line Slowly Task.....161
Go/No-Go and Cognitive Variables: Interrelationships.....162
Mood Variables.....163
Discussion.....164
References.....172
Tables & Figures.....184
GENERAL DISCUSSION.....191
REFERENCES.....199
TABLE & FIGURE.....271
APPENDIX - STUDY THREE.....274
Abstract.....275
Introduction.....276
Methods
Participants.....278

Procedure.....279
Genotyping.....281
Data Analysis.....282
Results
Presence/Absence of Repeat 7 Polymorphism and Sensation Seeking, Extraversion, and IQ.....283
Presence/Absence of Repeat 7 Polymorphism and Go/no-go Performance.....284
Discussion.....285
References.....287
Table.....293

ABSTRACT

A wealth of data supports the hypothesis that the neurotransmitter serotonin regulates the intake of ethanol, and is involved in the development of alcoholism in humans. Reduced functioning of the serotonergic system hypothetically increases alcohol intake in both animals and humans. In this thesis, it was proposed that the effect of lowered serotonergic function on alcohol intake is mediated by an increase in disinhibition. The hypothesis that lowered serotonin increases disinhibition was tested in separate groups of individuals at high risk for the development of psychopathology: nonalcoholic young men with a strong family history of paternal alcoholism, and adolescent men with previous histories of physically aggressive behavior. Lowered serotonergic synthesis (and thus presumably function) was experimentally induced through a transient dietary reduction in the availability of the amino acid precursor of serotonin, tryptophan. Disinhibition was quantified using a go/no-go task previously shown to characterize psychopaths and children with attention deficit hyperactivity disorder as disinhibited. In the first study, acute tryptophan depletion had no effect on aggressive responding on a modified competitive reaction time aggression task, but increased disinhibition in young men at risk for alcoholism. This effect was independent of the tryptophan depletion-induced mood alterations. The effect tryptophan depletion on disinhibition was not replicated in the second study with previously aggressive adolescent men. A number of explanations for this were posited, including the presence of a ceiling effect. An association between disinhibition and executive functioning (cognitive abilities associated with proper functioning of the prefrontal cortex, such as working memory,

planning abilities) was demonstrated in the second study. In a third preliminary study, no association between disinhibition on the go/no-go task and allelic polymorphisms of the dopamine D4 receptor gene was noted. This runs contrary to recent population studies suggesting that a specific polymorphism of the dopamine D4 receptor gene is associated with novelty seeking (of which impulsivity is putatively a component). Overall, the results suggest that lowering serotonergic function increases disinhibition in young men at risk for alcoholism, a subgroup of individuals that may possess a susceptibility to the effects of acute tryptophan depletion. These individuals may demonstrate alterations in central serotonergic function that may be related to the increased risk for the future development of alcoholism noted in this group. The results also confirm the predicted association between poor executive functioning and disinhibition.

RÉSUMÉ

Plusieurs études supportent l'hypothèse selon laquelle la sérotonine, un neurotransmetteur, régularise la consommation d'alcool et est impliquée dans le développement de l'alcoolisme chez les humains. Une fonction de la sérotonine réduite contribuerait à cette augmentation chez les humains et les animaux. Cette thèse propose que l'effet de la réduction des fonctions de la sérotonine sur la consommation d'alcool est modulée par une réduction de l'inhibition. L'hypothèse selon laquelle la réduction de la sérotonine réduit l'inhibition fut vérifiée chez des groupes séparés d'individus à risque pour le développement de psychopathologie: de jeunes hommes non-alcooliques avec une densité familiale d'alcoolisme paternel élevée, et de jeunes hommes avec un historique d'agression physique. La méthode d'induction expérimentale d'une réduction de la synthèse de la sérotonine (présumément de sa fonction) fut appliquée par l'apport d'une diète transitoire de la disponibilité de l'acide aminé précurseur de la sérotonine, le tryptophane. La réduction de l'inhibition fut évaluée avec l'utilisation d'une tâche go/no-go validée chez des psychopathes et des enfants souffrant de trouble de l'attention et hyperactivité. Dans la première étude la réduction aigue du tryptophane n'a pas eu d'effet sur les réponses agressives lors d'une tâche compétitive de temps de réaction modifiée, mais a contribué à réduire l'inhibition chez de jeunes hommes à risque pour le développement de l'alcoolisme. Cet effet fut indépendant de changements d'humeurs induits par la réduction du tryptophane. Cet effet de la réduction du tryptophane ne fut pas reproduit dans la seconde étude chez les jeunes hommes ayant un historique d'agression physique. Plusieurs explications furent proposées afin d'expliquer ces

résultats, incluant la présence d'un effet de plafonnement. Une association entre la réduction de l'inhibition et le fonctionnement exécutif (les habiletés cognitives associées avec le fonctionnement normal du cortex frontal, telles la mémoire de travail et les habiletés de planification) fut démontrée dans la seconde étude. Dans une troisième étude préliminaire, aucune association entre la réduction de l'inhibition sur la tâche du go/no-go et un polymorphisme allélique du gène du récepteur D4 de la dopamine n'a été notée. Cela va à l'encontre d'études récentes de la population et qui suggèrent qu'un polymorphisme spécifique du récepteur D4 de la dopamine soit associé avec la recherche de la nouveauté (dont l'impulsivité serait une composante). Dans leur ensemble, les résultats suggèrent que la réduction de la fonction de la sérotonine réduit l'inhibition chez les jeunes hommes à risque pour l'alcoolisme, un sous groupe d'individus qui pourraient être sensibles aux effets de la réduction aigue du tryptophane. Ces individus pouraient démontrer des altérations des fonctions de la sérotonine centrale qui serait être reliée à l'augmentation du risque de développement de l'alcoolisme. Les résultats confirment également l'association prévue entre les pauvres fonctions exécutives et l'inhibition.

THESIS SPECIFICATIONS

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> If this option is chosen, **connecting texts that provide logical bridges between the different papers are mandatory**. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation". **The thesis must include:** A Table of Contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a comprehensive review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.
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> Additional material must be provided where appropriate (e.g., in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research report in the thesis.

In the case of manuscripts co-authored by the candidate and others, **the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent.** Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers. **Under no circumstances can a co-author of any component of such a thesis serve as an examiner for that thesis.**

Contributions

Dr. Robert O. Pihl was the primary research supervisor for this thesis, and co-author of the two reviews and three studies described herein. Dr. Chawki Benkelfat also co-authored the reviews and studies, and as well provided supervision and guidance, particularly during running of the research participants. Dr. Simon N. Young provided supervision during the course of the study, and was a co-author of the three studies contained within. Dr. Roberta M. Palmour, co-author of the three studies, assisted in the documentation of participants' family histories and in data interpretation. Dr. Richard E. Tremblay, co-author on the second and third studies, provided access to the longitudinal sample used in these studies. Dr. Jean R. Séguin, co-author on the second paper, provided access to the cognitive/ neuropsychological data of the longitudinal sample. Dr. José Mejia, a co-author on the third paper, was primarily responsible for the genetic analyses. Finally, the author and doctoral candidate, David LeMarquand, was involved in all aspects of the three studies presented

herein, including the genesis of the ideas, development of the research protocols, recruitment and running of the research participants, data analysis and interpretation, and primary authorship of the papers.

The two review papers that are a part of the introduction have been published:

LeMarquand, D., Pihl, R. O., & Benkelfat, C. (1994). Serotonin and alcohol intake, abuse and dependence: Clinical evidence. Biological Psychiatry, 36, 326-337.

LeMarquand, D., Pihl, R. O., & Benkelfat, C. (1994). Serotonin and alcohol intake, abuse and dependence: Findings of animal studies. Biological Psychiatry, 36, 395-421.

The first two studies ("Tryptophan Depletion-Induced Behavioral Disinhibition in Nonalcoholic Young Men with Multigenerational Family Histories of Paternal Alcoholism" and "Tryptophan Depletion, Executive Functions, and Disinhibition in Aggressive Adolescent Males") have been submitted for publication and are currently under review. The third study ("Associations Between Polymorphisms of the Dopamine D4 Receptor (D4DR) Exon III, Extraversion and Behavioral Impulsivity") is in preparation and will be submitted in the future.

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First and foremost, I would like to thank my supervisor, Dr. Robert O. Pihl. Without his acceptance of my application into the graduate program at McGill, none of this would have been possible. He proved over the years to be an excellent supervisor, trusting in my abilities, and providing me with the freedom to develop my own ideas and pursue my own interests while consistently being available for guidance and assistance. His brevity and clarity in expressing ideas were a source of guidance to me in those instances when I became lost in detail. Dr. Pihl's extensive research contacts and collaborations facilitated my development as a researcher. Additionally, he was a continual source of monetary support. The research contained herein was partly funded by a research grant awarded to Dr. Pihl by the Medical Research Council for the study of individuals at high risk for alcoholism.

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A number of individuals were integral to the completion of each

of the studies. Peggy Dean, Molly Fortin, Fabienne Gauthier and Claudine Morin performed the blood draws and assisted in the screening of some participants. A number of students assisted in the testing for first two studies: Tracy Hecht, Nadia Fazioli, Steve Reynolds, Ashley Monks, Bhavna Khanna, Dorothy Opatowski, Isabelle Tremblay, Jolène Gauthier, Richard Legros and Jennifer Weiner. Franceen Lenoff, Mark Gross, and David Kernaghan provided invaluable technical assistance. Judi Young and Liz Rusnak provided secretarial assistance. Rhonda Amsel provided much appreciated statistical assistance. Pierre Blier, MD, performed medical consultations and Dr. Karin Helmers provided additional guidance for the first study. Carole Blanchet contacted participants, and Muriel Rorive provided additional archival data for the second study. I thank Dr. José Mejia for his friendly collaboration on the third study. I would also like to thank Robert Roth for his friendship and initial collaboration on our first tryptophan depletion study. Mark Ellenbogen was a great help later in reorienting me to the developments in tryptophan depletion research.

My gratitude is owed to the research participants who gave of their time and consented to take part in these time consuming and challenging research protocols. This is particularly true of the young men and their families who are part of the Montréal Longitudinal-Experimental Study. Without people willing to participate, this type of research could not be accomplished.

To my parents, Harold and Ingrid LeMarquand, the deepest thanks from my heart. Their unwavering support and belief in my abilities were a constant source of strength for me. In particular, my father's constant questions concerning the progress of my thesis and my expected date of graduation were a source of motivation. My parents were also a financial well in times of strain. I thank brother

Ron and sister Leanne for the good times we shared during relaxing vacations back home. To my grandfather, August Hirn, who passed away during the my work in Montreal, I remember his soft, easy nature.

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STATEMENT OF ORIGINALITY

The research program described herein represents a logical extension of recent work on the neurochemistry of disinhibited behavior. The present work is original in that it incorporates dimensions that had not previously been investigated together, to this author's knowledge. The first study is in line with recent work by Drs. Virkkunen and Linnoila investigating the association between central serotonergic functioning and impulsive behavior. The principle behind this study was to employ a frequently used and recently validated technique of experimentally lowering central serotonergic synthesis, and thus presumably function, to study disinhibited behavior in the laboratory. The technique of reducing brain serotonergic synthesis through the dietary depletion of its amino acid precursor tryptophan in humans was pioneered principally by one of the co-authors of the investigations contained herein, Dr. Simon Young, along with Dr. Robert Pihl. The literature on the neurochemistry of impulsivity was also extended through the use of a behavioral measure of disinhibition, the go/no-go learning task, developed and extensively utilized by Dr. Joseph Newman at the University of Wisconsin - Madison. Previous studies on the relationship between serotonin and impulsivity have used self-report measures of impulsivity. The theoretical underpinnings of behavioral disinhibition and the go/no-go task were heavily influenced by the theorizing of Dr. Jeffrey Gray.

The consequences of reduced tryptophan availability on disinhibited behavior have not previously been investigated in the groups of individuals tested in these two studies: nonalcoholic young men with paternal family histories of alcoholism, and adolescent

males with previous histories of aggressive, disruptive behavior. The selection of the former group was primarily influenced by the large literature showing a relationship between serotonin and alcohol intake/alcoholism, and the long line of research carried out in the laboratory of Dr. Pihl using this population. Previous work in Dr. Pihl's lab involving men with paternal family histories of alcoholism includes studies by Dr. Peter Finn examining psychophysiological responses to aversive stimuli, and Dr. Jordan Peterson investigating alcohol-induced alterations in cognitive/neuropsychological functioning.

Selection of the latter sample (aggressive adolescent males) was made possible by Dr. Richard Tremblay. The effects of tryptophan depletion on disinhibited responding in this population have not previously been studied, nor has the relationship between disinhibition (as measured by the go/no-go learning task) and cognitive/neuropsychological functioning (rigorously assessed by Dr. Jean Séguin using a well-validated battery of tests). Finally, the third study represents original scholarship in that it tests the recently hypothesized association between novelty seeking (of which impulsivity is putatively a component) and a particular polymorphism of the dopamine D4 receptor gene using a behavioral measure of disinhibition (as opposed to questionnaire measures of novelty seeking and extraversion employed in earlier research).

LIST OF TABLES AND FIGURES

Introduction

Table 1 271

Figure 1 272

Study 1

Table 1 133

Table 2 135

Figure 1 136

Figure 2 138

Study 2

Table 1 184

Table 2 186

Figure 1 187

Figure 2 189

Study 3

Table 1 293

LIST OF ABBREVIATIONS

ADHD = attention-deficit hyperactivity disorder

ATD = acute tryptophan depletion

CEs = commission errors

CSF = cerebrospinal fluid

DA = dopamine

5,7-DHT = 5,7-dihydroxytryptamine

DRN = dorsal raphe nucleus

DZ = dizygotic

GABA = γ-aminobutyric acid

HAD = high alcohol drinking

5-HIAA = 5-hydroxyindoleacetic acid

HPA = hypothalamic/pituitary/adrenal

5-HT = 5-hydroxytryptamine

5-HTOL = 5-hydroxytryptophol

5-HTP = 5-hydroxytryptophan

HVA = homovanillic acid

ICV = intracerebroventricular

LAD = low alcohol drinking

LNAAs = large neutral amino acids

*m*CPP = *meta*-chlorophenylpiperazine

MHPG = 3-methoxy-4-hydroxy-phenylglycol

MPFH = multigenerational paternal family history of alcoholism

MRN = median raphe nucleus

MZ = monozygotic

NE = norepinephrine

NP = alcohol nonpreferring

OEs = omission errors

8-OH-DPAT = 8-hydroxy-2-(di-n-propylamino)tetralin

P = alcohol-preferring

PRL = prolactin

Pun = punishment

Rew = reward

SOMAs = sons of male alcoholics

SSRI = selective serotonin reuptake inhibitor

OVERVIEW

This dissertation is concerned with the role of the neurotransmitter serotonin in alcohol abuse/dependence and impulsivity. In the introduction, data attesting to the scope of alcohol abuse and dependence will be presented. This is followed by a discussion of the rationale for focusing on the role of the serotonin in alcoholism. Next, the relationship between serotonin and alcohol intake and alcoholism is thoroughly reviewed, ultimately hypothesizing that the link between serotonin and excessive alcohol intake may be partly mediated by behavioral disinhibition. A brief review of the genetics of alcoholism introduces the concept of a highly heritable, male-limited subtype of alcoholism, and the notion that a deficit in serotonin function may be one characteristic that is genetically transmitted, leading to a propensity toward behavioral disinhibition. Next, empirical investigations of impulsivity in alcohol dependent individuals and those at high risk for developing alcohol abuse/dependence, as well as the relationship between serotonin and disinhibited behavior, including impulsivity and aggression, are presented. The acute tryptophan depletion method of hypothetically lowering brain serotonergic functioning is explained, and studies using this technique are examined. Finally, a brief review of the measurement of behavioral impulsivity in humans is presented.

The introduction leads into the first of two experimental studies using the acute tryptophan depletion technique to investigate the role of serotonin in passive avoidance learning (disinhibition) in young men with a multigenerational family history of paternal alcoholism. This is followed by a bridge section discussing the role of executive functions in aggression and disinhibited behavior. The second study

similarly employs the acute tryptophan depletion technique to investigate disinhibition in male adolescents with past histories of aggressive, disruptive behavior. The thesis concludes with a general discussion. The appendix contains a third study investigating the association between polymorphisms of the dopamine D4 receptor gene and disinhibition.

INTRODUCTION

Alcohol Abuse and Dependence: Scope of the Problem

In a recent community study (Kessler et al., 1994), the lifetime prevalences of DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, third edition, revised) (American Psychiatric Association, 1987) alcohol abuse and dependence in the United States population were estimated at 9 and 14%, respectively; the prevalences of these two diagnoses in the previous 12 months were 2.5 and 7%, respectively. Thus in the U.S. alone, up to 40 million people are afflicted with these disorders at some time in their lives. In Canada, yearly alcohol-related costs have been estimated at five billions dollars (Eliany, 1989); in the U.S., annual estimates range from 100 to 150 billion dollars, resulting in over forty thousand deaths (Rice, 1993). Excessive alcohol consumption detrimentally affects numerous physiological systems, increasing the risk for a number of potentially life-threatening diseases (Dufour & FeCases, 1993). In short, alcohol dependence is a major public health problem.

The Neurochemistry of Alcoholism: Serotonin

Given the scope of the problem, much research has focused on identifying possible etiological factors contributing to the development of alcoholism[1]. Biochemical factors contributing to alcoholism have received extensive attention. A number of neurotransmitters have

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[1]The term "alcoholism" is intended to be synonymous with the DSM-IV (American Psychiatric Association, 1994) concept of alcohol dependence, describing a cluster of physiological (tolerance, withdrawal) and psychological (compulsive drug-taking) symptoms arising from chronic intake of high levels of alcohol. The two terms will be used interchangeably henceforth.

been implicated in the control of alcohol intake and the development and maintenance of alcohol dependence (Nevo & Hamon, 1995). The mesolimbic dopaminergic pathway from the ventral tegmental area to the nucleus accumbens has been implicated in the rewarding properties of drugs of abuse, including ethanol (Samson & Hodge, 1993). Endogenous opioid peptides may also play a role in the rewarding aspects of alcohol drinking (Herz, 1997). Gamma-aminobutyric acid (GABA) and glutamate may modulate dopaminergic functioning along brain reward pathways (Diana, Rossetti, & Gessa, 1993; Phillips & Shen, 1996), and may mediate some of the behavioral effects of alcohol (anxiolysis, sedation, hypnosis) (Luddens & Korpi, 1995; Sherif, Tawati, Ahmed, & Sharif, 1997). Norepinephrine (NE) and acetylcholine also appear to contribute to the neurobiology of alcohol use (Nevo & Hamon, 1995).

A large literature has investigated the role of the idoleamine serotonin (5-HT) in the neurobiology of alcohol drinking, abuse and dependence. Why serotonin? This neurotransmitter is known to have diffuse projections throughout the brain, raising the hypothesis that it may modulate the functioning of other neurotransmitter systems and affect behavior at a basic level. Most serotonergic neurons are contained in the nine cell groups of the midbrain raphe nuclei, but the activity of two of these, the dorsal and median raphe nuclei (DRN and MRN, respectively), constitute 80% of forebrain 5-HT (Azmitia, 1978). Both the DRN and MRN project widely to various subcortical and cortical regions, including the basal ganglia, amygdala, nucleus accumbens, cingulate cortex, septum, thalamus, hypothalamus, hippocampus, and the tempoparietal and frontal cerebral cortices (Azmitia, 1978; Azmitia & Gannon, 1986; O'Hearn & Molliver, 1984).

Contributing to the idea that serotonin may play a modulatory

role in the brain is the fact that serotonin has been implicated in the neurobiology of a number of psychopathological disorders. Serotonin has been related to anxiety (Graeff, Guimaraes, De Andrade, & Deakin, 1996), obsessions and compulsions (Dolberg, Iancu, Sasson, & Zohar, 1996), major depression (Meltzer, 1990), drug abuse and dependence (Buydens-Branchey, Branchey, Fergeson, Hudson, & McKernin, 1997b), bulimia (Brewerton, 1995), conduct disorder (Hughes, Petty, Sheikha, & Kramer, 1996), and antisocial personality disorder (Virkkunen, Rawlings, et al., 1994). This suggests that serotonin may be regulating basic mechanisms common across psychopathological conditions. Alcohol abuse and dependence tend to co-occur with, or are preceded by (in the case of conduct disorder and attention deficit hyperactivity disorder (Pihl, Peterson, & Finn, 1990)) many of these disorders (Kessler et al., 1997; Ross, Glaser, & Germanson, 1988).

As well, serotonin is known to be involved in the regulation of ingestive behavior, such as food intake (Blundell, 1984; Blundell, Lawton, & Halford, 1995). Serotonin neurons project into and through the hypothalamus (Azmitia, 1978; Mize & Horner, 1989; Parent, Descarries, & Beaudet, 1981), a brain region known to be involved in food intake and body weight regulation. As well, serotonergic neurons are found in the gut (Gershon & Dreyfus, 1977); changes in gastrointestinal functioning might be expected to influence ingestive behavior. That serotonin contributes to the modulation of ingestive behavior suggests that it may be involved in alcohol intake and alcoholism.

What follows is a comprehensive review of the relationship between serotonin and alcohol intake and alcoholism in animal and clinical studies.

REVIEW ARTICLE

Serotonin and Alcohol Intake, Abuse, and Dependence: Clinical Evidence

David LeMarquand, Robert O. Pihl, and Chawki Benkelfat

A large body of literature has emerged concerning the role of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) in the regulation of alcohol intake and the development of alcoholism. Despite the wealth of information, the functional significance of this neurotransmitter remains to be fully elucidated. This paper, part one of a two-part review, summarizes the available clinical research along two lines: the effects of alcohol on serotonergic functioning and the effects of pharmacological manipulation of serotonergic functioning on alcohol intake in normal (nonalcohol dependent) and alcohol-dependent individuals. It is concluded that considerable evidence exists to support the notion that some alcoholic individuals may have lowered central serotonin neurotransmission.

Key Words: 5-hydroxytryptamine, 5-HT, alcohol, alcoholism, alcohol dependence, humans

Introduction

Several neurotransmitters (norepinephrine, dopamine, serotonin, γ-aminobutyric acid [GABA]) have been implicated in the etiology of alcoholism (Tabakoff and Hoffman 1991). This review (parts one and two) focuses on serotonin (5-hydroxytryptamine, 5-HT), for three reasons.

First, abnormal behaviors associated with or perhaps due to a serotonergic dysfunction are often part of the comorbid clinical picture of alcohol abuse and dependence. Serotonin has been implicated in obsessions and compulsions (Insel et al 1990); anxiety (Charney et al 1990); depressed mood (Meltzer 1990); and the onset of bulimic binges (Jimerson et al 1990). These behaviors co-occur with a diagnosis of alcohol dependence with a high frequency (Ross et al 1988). Serotonin has also been implicated in the control of impulsive, aggressive, and suicidal behavior. For example, lower levels of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of 5-HT, have been reported in clinical studies of aggression (Insel et al 1990), suicide (Mann et al 1990; Roy et al 1990b), and impulsivity (Linnoila et al 1983). Aggressive impulsive, and suicidal behavior also tend to co-occur with alcohol use and dependence (Roy et al 1987).

Second, volitional intake of alcohol (ethanol) or alcohol preference has also been suggested to be directly affected by the status of serotonergic neurotransmission. In the serotonin hypothesis of alcoholism, a hypothesized biochemical abnormality is genetically transmitted which, when expressed, results in a brain deficit in 5-HT. Such a deficit is then thought to be partially responsible for turning on alcohol-seeking behavior and increasing the vulnerability to anxiety and mood disorders as well as impulsive/aggressive behaviors. The notion that neurochemical functioning is under genetic control has received empirical support. For example, Meltzer and Arora (1988) found that the intraclass

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correlation of the maximal velocity (V_{max}) of 5-HT uptake in blood platelets of monozygotic twins was significantly greater than that of dizygotic twins and pairs of unrelated volunteers. Alcoholism is at least partly under genetic control, as twin (Hrubec and Omenn 1981; Pickens et al 1991; Kendler et al 1992), family (reviewed in Cotton 1979) and adoption (Goodwin et al 1973, 1974; Cadoret et al 1980; Bohman et al 1981) studies have shown. Although these studies have been criticized on methodological grounds (Lester 1988; Searles 1988), other reviews (Murray et al 1983; Littrell 1988) have concluded that a significant heritable predisposition to alcoholism exists. Cloninger et al (1981; Cloninger 1987) have posited two distinct subtypes of alcoholism: type 1, purportedly a function of both environmental conditions and genetic background, and type 2, characterized as occurring in men only and high heritable (genetic expression regardless of environmental circumstances). Type-2 alcoholics have been described as violent and impulsive (Cloninger 1987), suggesting a link between alcohol intake and low serotonin.

Third, serotonergic neurons in the hypothalamus mediate food intake (Curzon 1990). Compounds that increase serotonergic neurotransmission (uptake inhibitors, releasers, direct agonists) have been shown to decrease food intake (Curzon 1990). As well, feeding reportedly releases hypothalamic 5-HT, implicating 5-HT in the termination of feeding behavior. Thus, it is possible that the same serotonergic system that controls food and water intake may also regulate alcohol consumption.

The following review paper (parts one and two) attempts to elucidate the role of serotonin in alcohol intake and alcoholism. In part one, clinical evidence associating serotonergic neurotransmission and alcohol intake will be investigated from two standpoints: the effects of manipulations of serotonergic neurotransmission on alcohol intake in normal (nonalcohol dependent) and alcohol dependent individuals, and the effects of alcohol intake on serotonergic neurotransmission. Given the brief review above, it is expected that abstinent alcoholics will evidence diminished serotonergic functioning. Furthermore, acute and chronic ethanol should facilitate 5-HT functioning. Finally, interventions that increase serotonergic functioning should decrease ethanol intake, and vice versa. In part two, animal studies on the role of 5-HT in alcohol intake will be reviewed.

Ethanol and Serotonergic Functioning in Healthy Individuals

In general, investigations of serotonergic functioning following acute ethanol challenge in healthy individuals have not supported the notion that ethanol increases 5-HT functioning. An acute ethanol dose in healthy individuals lowers blood tryptophan (TRP), CSF TRP, blood 5-HT and increases platelet 5-HT uptake, peripheral events suggesting decreased central 5-HT levels and neurotransmission (see Table 1).

Despite the fact that the majority of urinary 5-HIAA arises from 5-HT metabolized in the periphery (Aizenstein and Korf 1979), studies have used urinary 5-HIAA as an index of central 5-HT functioning. Acute ethanol decreases urinary 5-HIAA excretion in healthy individuals, a decrease fully accounted for by a shift in 5-HT metabolism from the oxidative to the reductive pathway, and thus by an increase in 5-hydroxytryptophol (5-HTOL) and its conjugates (Davis et al 1967). This process likely occurs exclusively in the periphery, not in the central nervous system (CNS) (Ecclesson et al 1969), as no shift in 5-HT metabolism from 5-HIAA to 5-HTOL could be demonstrated in the rat caudate nucleus after acute ethanol (Tyce et al 1968).

In three separate postmortem studies, the presence of ethanol in the blood at autopsy was related to decreased binding of the 5-HT_{1A} agonist [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in several cortical regions at the frontal-parietal level (Dillon et al 1991), and increased [^{3}H]imipramine binding in the hippocampus (Gross-Isseroff and Biegon 1988). Alcohol had no effect on [^{3}H]ketanserin binding to 5-HT_2 receptors (Gross-Isseroff et al 1990). Thus, acute ethanol may facilitate serotonin reuptake in the hippocampus and decrease 5-HT_{1A} receptor functioning in the cortex. Sample sizes in these studies were small, however.

Dietary TRP augmentation/depletion failed to decrease/increase alcohol consumption, respectively, in male social drinkers, although sample sizes in this study were small (Pihl et al 1987). TRP augmentation and depletion also did not influence ethanol intoxication as measured by self-report, memory, and motor task performance (Zacchia et al 1987). Finally, in a recent study, the 5-HT_3 antagonist ondansetron attenuated some of alcohol's pleasurable subjective effects and reduced the desire to drink in healthy males (Johnson et al 1993).

Studies on Ethanol Dependent Individuals

The status of serotonergic functioning in alcoholics has been the subject of numerous studies employing a wide variety of methodologies (see Table 2). These studies are plagued with methodological difficulties, including small sample sizes, diagnostic variability, and the confounding effects of chronic alcohol abuse on serotonergic functioning. Nevertheless, the cumulative evidence drawn from these investigations points to at least some involvement of the serotonergic system in alcoholism; however, its specific role remains unclear.

5-HT UPTAKE INHIBITORS, RELEASERS. The efficacy of 5-HT uptake inhibitors in reducing alcohol intake in some alcoholic patients provides indirect support for the notion

Table 1. Summary of Studies Investigating Responses of the Serotonergic System to Acute Ethanol Challenges in Healthy Individuals

Hypothesis	Total no. of studies	Supporting	Refuting	Equivocal/ no change
↑ Plasma TRP following acute ETOH admin.	3		2[1–3]	1[3]
↑ CSF TRP following acute ETOH admin.	1		1[4]	1[4]
↑ Whole blood 5-HT following acute ETOH admin.	1		1[5]	
↓ In vivo, in vitro platelet 5-HT uptake following acute ETOH admin.	2	1[5]	1[6]	1[6]
↑ 5-HT receptor binding following acute ETOH admin.	2		1 (5-HT_{1A})[7]	1 (5-HT_2)[8]
↓ Imipramine binding following acute ETOH admin.	1		1 HIP[9]	
↑ Urinary 5-HIAA levels following acute ETOH admin.	8		7[10–16]	1[17]
TRP (precursor) admin.: ↑ 5-HT functioning; ↓ ETOH consumption	1			1[18]
TRP (precursor) depletion: ↓ 5-HT functioning; ↑ ETOH consumption	1			1[19]

Notes: ↑ = increase; ↓ = decrease; ETOH = ethanol; TRP = tryptophan; 5-HTP = 5-hydroxytryptophan; admin. = administration; CSF = cerebrospinal fluid; 5-HT = 5-hydroxytryptamine; 5-HIAA = 5-hydroxyindoleacetic acid.

that serotonergic functioning might be deficient in a subgroup of these individuals. Zimeldine, citalopram, viqualine, and fluoxetine have been shown to decrease alcohol consumption in male moderate "social" drinkers (Amit et al 1985), low dependence problem drinkers (7 drinks/day average) (Naranjo et al 1984, 1987, 1989, 1990, 1992b), and men with a DSM-III diagnosis of alcohol dependence (Gorelick and Paredes 1992) (see Table 2). These drugs increased the number of abstinent days (zimeldine, citalopram, viqualine) and decreased the number of drinks on drinking days (viqualine, fluoxetine) as well as the desire to drink and alcohol's reinforcing effects (citalopram, fluoxetine). Additionally, in uncontrolled trials, the 5-HT releaser fenfluramine has been effective in treating chronic alcoholics (Krasner et al 1976; Spencer 1972). The beneficial effects of 5-HT uptake inhibitors do not appear to be due to antidepressant or anxiolytic effects, expectancy effects, aversive side effects or aversive interactions with ethanol (Naranjo and Kadlec 1991). Although these studies have found statistically significant decreases in alcohol intake, the clinical significance of these drugs has been questioned. Many studies have involved mild to moderately dependent alcoholics (Naranjo et al 1992b), with decreases in alcoholic intake in the order of 10 to 20% (Gorelick 1986), and treatment periods typically only two weeks long (Naranjo et al 1992b), although some have ranged up to 12 weeks (Naranjo and Bremner 1993).

5-HT AGONISTS, ANTAGONISTS: RECEPTOR FUNCTIONING. Selective 5-HT receptor agonists and antagonists offer the potential to identify specific 5-HT receptor mechanisms that may be controlling alcohol craving and intake. Early reports suggest the 5-HT_{1A} agonist buspirone reduces self-report alcohol craving and drinking behavior in alcohol abusers (Bruno 1989; Tollefson et al 1991; Kranzler and Meyer 1989). Conversely, the nonspecific 5-HT_{1C} agonist *m*-chlorophenylpiperazine (*m*-CPP; Middlemiss and Hutson 1990) reportedly elicits alcohol craving and feeling akin to alcohol intoxication in abstinent alcoholics (specifically type 2/early onset alcoholics) (Benkelfat et al 1991; D.T. George et al 1993 unpublished data). The latter finding relates well to that of Signs and Schechter (1988), who found that the 5-HT agonist TFMPP (a compound structurally similar to *m*-CPP) produced an ethanol interoceptive cue in rodents. This suggests that agonists that reduce alcohol consumption in laboratory animals (e.g., MK-212, quipazine, etc), perhaps in particular those that activate 5-HT_{1C} receptors, may produce an ethanol interoceptive cue through serotonergic activation that abolishes the need for ethanol ingestion. In a recent preliminary replication, *m*CPP

Table 2. Summary of Studies Investigating Serotonergic Functioning in Alcohol-Dependent Individuals. The Left Column Presents Various Tenets of the Hypothesis that Alcoholics Have a Premorbid Deficit in 5-HT Functioning

Hypothesis	Total no. of studies	Supporting	Refuting	Equivocal/ no change
5-HT uptake inhibitor/releaser admin.: ↑ 5-HT functioning: ↓ ETOH consumption	9	8		1
5-HT agonist admin.: ↑ 5-HT functioning: ↓ ETOH consumption	1			1
5-HTP admin.: ↑ 5-HT functioning: ↓ ETOH consumption	1			1
5-HT antagonist admin.: ↓ 5-HT functioning: ↑ ETOH consumption	2		1	1
Decreased plasma TRP (5-HT precursor) levels	5	5		
Increased tryptophan oxygenase (pyrrolase) activity	2	2		
Decreased CSF TRP levels	2		1	1
Decreased CSF 5-HIAA levels	18	7		11
Decreased urinary 5-HIAA levels	6	2	1	3
Decreased brain 5-HT/5-HIAA levels postmortem	4	2	1	1
Increased platelet 5-HT uptake: decreased synaptic availability	8	5	5	
Increased platelet [^{3}H]-imipramine, [^{3}H]-paroxetine binding: ↑ 5-HT release and functioning	4	1	1	2

produced transient alcohol-like effects in some abstinent alcoholics (Krystal et al 1992). In the only study that has looked directly at the effects of a 5-HT agonist on alcohol consumption, buspirone had no effect on alcohol craving, time to first drink, time to 5 consecutive drinking days, time to first intoxication, and number of standard drinks per drinking day in nonabstainers in a sample of anxious alcoholics (Malcolm et al 1992).

Recently the 5-HT_3 antagonist ondansetron (Tyers 1990) was reported to reduce daily ethanol consumption by 30% in male alcohol abusers (Tonesmo et al 1991). This preliminary clinical trial of a 5-HT_3 antagonist corroborates data obtained in laboratory animals showing reductions in ethanol intake following 5-HT_3 antagonist administration. That a 5-HT antagonist clinically reduces drinking compulsions/ethanol consumption runs counter to the notion that decreased serotonergic functioning increases alcohol intake. The efficacy of 5-HT_3 antagonists may be due to their ability to block ethanol-induced increases in dopamine release in certain brain regions (Carboni et al 1989; Yoshimoto et al 1992; see Discussion, part two), possibly antagonizing the rewarding effects of alcohol-induced activation of the mesolimbic dopaminergic system.

Simonsson and Alling (1988) have demonstrated impaired 5-HT_2 receptor functioning in the platelets of recently detoxified alcoholics, as assessed by a reduction in the 5-HT-stimulated production of inositol monophosphate, an effect also found in the rat cortex immediately following chronic ethanol administration, with no change in 5-HT_2 receptor number (Pandey et al 1991, 1992b). This effect did not persist 3 weeks into abstinence in a sample of platelets from predominantly type-2 alcoholics (Simonsson et al 1992). Extended withdrawal from chronic ethanol caused a decrease in 5-HT_2 receptor number in the rat cortex along with decreased production of 5-HT-stimulated inositol monophosphate (Pandey et al 1992a,b). Acute ethanol potentiates both the basal and 5-HT-stimulated production of phosphatidic acid through 5-HT_2 receptors in the platelets of nonalcoholic subjects (Simonsson et al 1989a), and the 5-HT-stimulated production of inositol phosphate in as-

troglial cells of the rat cerebral cortex (Simonsson et al 1989b). These studies suggest that although acute ethanol may potentiate 5-HT_2 receptor functioning, chronic ethanol impairs it, perhaps promoting further alcohol intake. Pharmacologic blockade of the 5-HT_2 receptor with the 5-HT_2 antagonist ritanserin has been shown to decrease the desire, craving, and compulsion to drink in heavy drinkers and alcoholics (Monti and Alterwain 1991a,b; Naranjo et al 1993), with no associated reductions in alcohol intake (Naranjo et al 1993). These findings suggest that the 5-HT_2 receptor may be involved in the rewarding effects of alcohol.

PLASMA TRP. Measurement of peripheral indices of 5-HT function in alcoholic subjects have yielded somewhat controversial results, with only some agreement for a "5-HT deficit" hypothesis in alcoholism. The more convincing evidence supporting such a hypothesis is the finding of decreased serum TRP levels after TRP challenge (Hjorth et al 1981), decreased basal plasma TRP levels (Siegal et al 1964; Branchey et al 1981), and more importantly a decreased ratio of plasma TRP to the other large neutral amino acids (LNAAs) (Branchey et al 1981; Buydens-Branchey et al 1989), in samples of alcoholics. A lower ratio of TRP to the other LNAAs has also been found in aggressive, assaultive alcoholics compared to alcoholic and nonalcoholic controls (Branchey et al 1984). The TRP:LNAA ratio was lowest 1 day after cessation of alcohol intake and increased over the ensuing 2 to 3 weeks (Buydens-Branchey et al 1989). When the alcoholic sample was divided into early- versus late-onset (before or after 20 years of age), the low TRP ratio was correlated with depressive and aggressive tendencies in the early-onset group only. The investigators hypothesized that early-onset alcoholics (i.e., type 2; Cloninger et al 1981) evidence alcohol-seeking and antisocial behavior early in life, possibly the result of a preexisting serotonergic defect. Their subsequent high alcohol intake leads to biochemical changes, one being a reduced availability of TRP for conversion to 5-HT in the brain, possibly contributing, in susceptible individuals, to further aggression and depressive episodes (Buydens-Branchey et al 1989).

Decreased plasma TRP availability may be due to an increase in tryptophan oxygenase (tryptophan pyrrolase) activity in abstinent alcoholics, as evidenced by increased production of urinary kynurenine after TRP challenge (Buydens-Branchey et al 1988; Friedman et al 1988), although these studies suffer from small sample sizes and lack of nonalcoholic controls groups. Diehl et al (1986) also noted lower levels of TRP as well as many other amino acids in men and women who were alcoholics after 2 weeks of sobriety, possibly indicating a reduction in TRP availability, however a group comparison of the ratio of TRP to concentrations of the other LNAAs was not carried out.

CEREBROSPINAL FLUID INDICES OF 5-HT FUNCTIONING. A common method of assessing central serotonergic functioning in alcoholics involves the measurement of cerebrospinal fluid 5-HIAA. Problems exist in the interpretation of these data, however. Low levels of CSF 5-HIAA could be interpreted as lower rates of degradation and thus increased 5-HT synaptic availability. Alternatively, low CSF 5-HIAA could indicate decreased brain 5-HT content. Furthermore, CSF 5-HIAA may be more indicative of 5-HT metabolism in the spinal cord than the brain. Spinal neurons have been shown to contribute significantly to 5-HIAA levels in lumbar CSF (Bulat and Zivkovic 1971; Post et al 1973; Garelis and Sourkes 1973). A more serious caveat is the notion that CSF 5-HIAA levels may not be indicative of monoaminergic neuronal activity (Commissiong 1985). Despite these concerns, CSF 5-HIAA has been proposed as a valid indicator of general changes in 5-HT metabolism in the CNS (Weir et al 1973; Garelis et al 1974; Aizenstein and Korf 1979; Banki and Molnár 1981). Furthermore, a decrease in CSF 5-HIAA has been assumed to indicate decreased central serotonergic functioning. Although not a direct test of this hypothesis, it has been shown that CSF 5-HIAA levels positively correlate with 5-HIAA levels in the cerebral cortex of humans at autopsy (Stanley et al 1985).

Seven studies have found lower CSF 5-HIAA levels in alcoholics compared to controls, suggesting subnormal serotonergic activity in alcoholics during abstinence from alcohol. CSF 5-HIAA measurements have been made after periods of abstinence ranging from two weeks (Banki 1981) to three months (Borg et al 1985), in an effort to separate the effects of ethanol withdrawal on the 5-HT system from a preexistent deficit in serotonergic functioning. Among these findings, Ballenger et al (1979) noted no differences in CSF 5-HIAA between alcoholics and personality-disordered individuals when measured postintoxication, but lower 5-HIAA in the former group after 4 weeks' abstinence, suggesting that chronic alcohol normalizes diminished 5-HT functioning during abstinence. Supporting this line of reasoning is a study by Zarcone et al (1975), who found that low CSF 5-HIAA levels in a small sample of abstinent alcoholics increased significantly after 1 week of alcohol drinking followed by 12 days of withdrawal. Lower CSF 5-HIAA has been noted in abstinent female alcoholics (Banki 1981), suggesting that a 5-HT deficit may not be limited to the putatively highly heritable male-limited type-2 alcoholism.

How probable is it that the lower levels of CSF 5-HIAA found in these samples of abstinent alcoholics represent a premorbid dysfunction of the serotonergic system? The

possibility exists that these findings are a direct consequence of long-term alcohol use or biochemical changes resulting from such. Several studies (Beck et al 1980a,b, 1982) have found higher levels of 5-hydroxytryptophol in alcoholics versus controls after alcohol intoxication. This heightened 5-HTOL continued well into abstinence, possibly indicating an alcohol-induced shift in 5-HT metabolism from the oxidative (5-HIAA) to the reductive (5-HTOL) pathway in the brain. This mechanism could account for the lower levels of CSF 5-HIAA noted in alcoholics, even after long periods of abstinence.

Experimentally, studies with rodents have documented increased levels of 5-HIAA after chronic ethanol administration (see part two of this review), however, these measurements are primarily determined shortly after cessation of alcohol intake, not following a period of prolonged abstinence. Furthermore, concentrations of 5-HIAA are predominantly determined directly from the brain in experimental studies, whereas CSF samples are taken in humans, for obvious reasons. Tabakoff et al (1975) have found that acute ethanol inhibits 5-HIAA transport from the brain by the choroid plexus, a mechanism that could account for the increase in brain 5-HIAA in rodents. This process may also be responsible for the lower levels of CSF 5-HIAA found in alcoholics, particularly if it persists into abstinence. It is not clear how chronic alcohol ingestion and subsequent abstinence affects 5-HIAA transport from the brain in humans.

As one might expect, a number of studies have found no differences in CSF 5-HIAA between alcoholics and controls. These null findings are not accounted for by failures to do CSF determinations during abstinence (Lidberg et al 1985), however, several studies lacked adequate nonpsychiatric control groups (Ashcroft et al 1966; Beck et al 1980a; Banki et al 1983). Roy et al (1990a) posited that low numbers of type-2 alcoholics in their sample may have led to their null findings, however, even after dividing their a larger alcoholic sample into early- (type 2) and late- (type 1) onset, there remained no differences between groups (Roy et al 1991). Banki and Molnar (1981) failed to find lower CSF 5-HIAA between alcoholics and controls when the CSF was extracted from the cisternal region, the region containing most of the 5-HIAA originating from the raphe nuclei.

Enough evidence exists to question the conditions under which lowered CSF 5-HIAA is observed. A distinct subset of alcoholism may exist in which lowered CSF 5-HIAA is a feature, however, the other defining characteristics of this putative subgroup remain unspecified.

URINARY INDICES OF 5-HT FUNCTIONING. Urinary 5-HT is generally considered to be a poor measure of central serotonergic functioning. Approximately 8% of urinary 5-HIAA in the rat originates in the CNS (Aizenstein and Korf 1979). Nevertheless, this measure has been used to study the 5-HT/alcoholism relationship. Two studies have found evidence of lower urinary 5-HIAA in alcoholics relative to controls (Olson et al 1960; Thomson and McMillen 1987), as well as after TRP challenge (Olson et al 1960). As urinary 5-HT likely reflects 5-HT metabolism in the periphery rather than the CNS, decreased urinary 5-HIAA in alcoholics may be further evidence of a reduction in TRP availability in the periphery, thus reduced TRP availability for brain uptake. Alternatively, decreased urinary 5-HIAA may represent a shift in 5-HT catabolism to the reductive (5-HTOL) pathway (Beck et al 1980b).

ACUTE ETHANOL CHALLENGE IN ALCOHOLICS. An acute ethanol challenge in abstinent alcoholics reduces CSF 5-HIAA (Ornberg et al 1976; Zarcone et al 1980), and does not affect plasma TRP levels (Siegal et al 1964). The findings of the former two studies may be a direct result of an alcohol-induced inhibition of 5-HIAA transport from the brain (Tabakoff et al 1975), or a shift in 5-HT catabolism to increased 5-HTOL. CSF 5-HIAA may not be a valid indicator of central 5-HT levels after acute ethanol.

POSTMORTEM STUDIES. Cochran et al (1976) found no differences in 5-HT levels in 33 brain areas between alcoholic suicide victims, depressed suicide victims and healthy controls, a surprising result in given that low 5-HT has also been associated with suicidal behavior (Mann et al 1990). On the other hand, Carlsson et al (1980) found reduced hippocampal, caudate, and hypothalamic 5-HT and 5-HIAA in alcoholics after controlling for age at death and the length of the interval between death and autopsy. Interestingly, a decrease in the number of hippocampal binding sites (i.e., lower B_{max}) for [^{3}H]-paroxetine which labels 5-HT uptake binding sites) in alcoholics compared to controls has also been found (Chen et al 1991). No differences in hippocampal binding affinity (K_d) or either parameter in the frontal cortex was found. Neuronal loss or adaptations of the central 5-HT system to chronic alcohol abuse were suggested to account for these results, rather than a premorbid deficit in 5-HT functioning.

BLOOD PLATELETS/WHOLE BLOOD 5-HT STUDIES. The blood platelet has been suggested as a model for the central nervous system neuron due to similarities in uptake, storage and release of 5-HT in both tissues (Roman 1983; Sneddon 1973). Several studies have found significantly lower platelet 5-HT content (Rolf et al 1978; Bailly et al 1990), lower whole blood 5-HT content (Banki 1978; Simonsson et al 1992), or decreased 5-HT storage (Baccino et al 1987b) in abstinent alcoholics compared to normal controls. Lower platelet or whole blood 5-HT content may be due to lowered 5-HT synthesis by enterochromaffin cells of the gastrointestinal tract, decreased platelet uptake, or increased platelet

release (Sneddon 1973). Moreover, if lower platelet 5-HT content suggests lower neuronal 5-HT levels in the CNS, this could either imply increased CNS serotonergic functioning through increased 5-HT release and utilization, or decreased CNS serotonergic functioning through decreased 5-HT synthesis.

Studies investigating 5-HT platelet uptake have shown an increased affinity (lower K_m) of 5-HT for its carrier (Baccino et al 1987b; Boismare et al 1987; Neiman et al 1987; Lhuintre et al 1988), or an increase in the maximal velocity (higher V_{max}) of platelet 5-HT transport (Daoust et al 1991; Ernouf et al 1993) in alcoholics relative to controls when measured in alcoholics not withdrawn from alcohol (Lhuintre et al 1988), at abstinence (e.g., Baccino et al 1987b), or after one to 11 years' abstinence (Boismare et al 1987). These platelet studies suggest a decreased availability of 5-HT in the synapse. Some platelet studies, however, suggest the opposite. A decreased rate of platelet serotonin absorption in alcoholics relative to controls (Bokii et al 1984), decreased affinity (Ernouf et al 1993), and decreased platelet 5-HT uptake (lower V_{max}) in nonabstinent and abstinent alcoholics versus nonalcoholic controls (Baccino et al 1987b; Boismare et al 1987; Lhuintre et al 1988; Kent et al 1985) have been reported.

Platelet imipramine binding is highly correlated with serotonin uptake (Rotman 1983). Studies using [^{3}H]-imipramine and [^{3}H]-paroxetine as ligands to investigate platelet 5-HT uptake parameters have produced no clear support for the notion of reduced uptake or decreased number of binding sites in alcoholics.

Studies with Individuals at High Risk for Alcoholism

Recently, the serotonergic functioning of nonalcoholic individuals putatively at high genetic risk for alcoholism by virtue of a family history of alcoholism in their first and, in some studies, second degree relatives, has been studied. If a genetically transmitted deficit in 5-HT neurotransmission does contribute to the development of alcoholism, this population is particularly beneficial for study in that experimental results are not confounded by the effects of long-term alcohol use. In support of the notion that central serotonin functioning is reduced in family history positive (FH+) individuals, depressed (Rosenthal et al 1980) and impulsive Linnoila et al 1989) individuals with first-degree alcoholic relatives were found to have lower CSF 5-HIAA levels than depressed and impulsive individuals (respectively) without a family history of alcoholism. More recently, FH+ men (i.e., men with alcoholic fathers) (Rausch et al 1991) and adult (>14 years of age) and child (<14 years) offspring of alcoholic parents (Ernouf et al 1993) had higher platelet 5-HT uptake (higher V_{max}) compared to their respective family history negative control groups, suggesting an increased capacity to remove 5-HT from the synaptic cleft and decreased availability for neurotransmission.

Two studies do not support the notion that FH+ individuals have decrements in central serotonergic functioning. Nonalcoholic males with at least three alcoholics among their first-degree blood relatives had a lower mean maximum number (B_{max}) of platelet binding sites for [^{3}H]-imipramine compared to controls, implying reduced central serotonergic uptake (Suranyi-Cadotte et al 1989). Additionally, when administered the nonselective 5-HT_{1C} agonist *m*-CPP, only one of 11 nonalcoholic male adult children of alcoholics (ACOAs) reported pleasurable feelings and none reported alcohol craving (Schmitz et al 1990), contrary to the findings of Benkelfat et al (1991). Taken together, limited support exists for the notion that FH+ individuals evidence diminished serotonergic functioning, however further research with this population is warranted.

Discussion

Perhaps the strongest evidence for a deficit in 5-HT neurotransmission in alcohol-dependent individuals can be found in those studies demonstrating low CSF 5-HIAA and low plasma TRP availability in this population. Also suggestive are studies demonstrating decreases in ethanol intake in alcoholics following 5-HT uptake inhibitor administration. 5-HT_3 antagonists may hold the most promise for the treatment of alcohol dependency. They have been shown to decrease self-reported desire for alcohol in normal subjects and ethanol intake in alcohol abusers. Furthermore, a mechanism of action involving antagonism of ethanol-induced dopamine release in the mesolimbic dopaminergic reward system has been proposed.

Despite their significance, studies with alcohol dependent individuals characterize serotonergic functioning in a neurochemical system affected (and possibly altered) by chronic ethanol intake. Although the use of nonalcoholic individuals with extensive family histories of alcoholism (FH+) appears to be a step in the right direction, the informative value of biological measurements collected in clinical studies remains limited, and often controversial. To more fully investigate neurochemical interactions and neuroanatomical pathways involved in serotonin's control of alcohol intake, one must turn to experimental/animal studies. This will be the focus of part two, a review of the animal literature on serotonergic mechanisms of alcohol intake, along with an integrative summary of both the animal and clinical literature in light of contemporary theories of the role of 5-HT in behavior in general.

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4. Beck et al (1983)	23. Naranjo et al (1990)	42. Ramsing et al (1987a)	61. Payne et al (1974)
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16. Helander et al (1992a)	35. Diehl et al (1986)	54. Linnoila et al (1991)	73. Kent et al (1985)
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REVIEW ARTICLE

Serotonin and Alcohol Intake, Abuse, and Dependence: Findings of Animal Studies

David LeMarquand, Robert O. Pihl, and Chawki Benkelfat

Despite a relatively large body of literature on the role of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) in the regulation of alcohol intake, the functional significance of serotonergic neurotransmission and its relationship to alcohol intake, abuse, and dependence remains to be fully elucidated. In part two of this review, the experimental (animal) data is summarized along two lines: the effects of serotonergic manipulations on the intake of alcohol, and the effects of acute and chronic alcohol intake, as well as the withdrawal of chronic alcohol, on the serotonergic system. It is concluded that serotonin mediates ethanol intake as a part of its larger role in behavior modulation, such that increases in serotonergic functioning decrease ethanol intake, and decreased serotonergic functioning increases ethanol intake. Ethanol produces transient increases in serotonergic functioning that activate the mesolimbic dopaminergic reward system. The results are discussed in light of recent theories describing the regulatory role of serotonin in general behavior.

Key Words: 5-Hydroxytryptamine, 5-HT, alcohol, ethanol, alcoholism, alcohol dependence

Introduction

In part one of this review, we concluded that evidence exists suggesting that some alcohol-dependent individuals may have lowered central serotonin (5-hydroxytryptamine; 5-HT) neurotransmission. A number of difficulties with the clinical paradigm, however, necessitated a thorough review of the animal literature on the relationship between serotonergic neurotransmission and alcohol intake. In addition to allowing for the direct manipulation of brain 5-HT functioning under experimental conditions, studies using animals help to document possible neurochemical interactions and neuroanatomical pathways involved in the regulation of alcohol intake.

The following review proceeds from two standpoints: examining the effects of manipulations of serotonergic neurotransmission on alcohol intake, then the effects of alcohol intake on serotonergic neurotransmission. It is expected that pharmacological interventions facilitating 5-HT neurotransmission will decrease ethanol intake, and vice versa. Furthermore, acute and chronic ethanol should facilitate 5-HT functioning. The article concludes with a discussion of the role of 5-HT in governing alcohol intake in light of current theories regarding the role of 5-HT in the regulation of behavior in general.

Effects of Altered Serotonergic Neurotransmission on Ethanol Intake

Pharmacological Manipulation of the 5-HT System and Alcohol Consummatory Behavior

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Table 1. Studies Investigating the Effects of Interventions Decreasing Serotonergic Functioning on Ethanol Intake

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal/ no change
*p*CPA or *p*CA treatments: ↓ brain 5-HT: ↑ ETOH consumption	20	3[1–3]	14[4–17]	6[8,11,18,18–20]
Neurotoxins 5,6-DHT and 5,7-DHT; electrolytic lesions of 5-HT pathways: ↓ brain 5-HT: ↑ ETOH consumption	7	6[21–26]	2[26,27]	2[22,23]
5-HT antagonists block serotonergic post-synaptic receptors: ↓ brain 5-HT functioning: ↑ ETOH consumption	20	2[28,29]	14[17,30–42]	5[43–46]
5-HT uptake enhancer tianeptine ↑ 5-HT uptake: ↓ 5-HT availability: ↑ ETOH consumption	1		1[47]	

Notes: ↑ = increase; ↓ = decrease; ETOH = ethanol; 5-HT = 5-hydroxytryptamine; *p*CPA = *p*chlorophenylalanine; *p*CA = *p*chloroamphetamine; 5,6-DHT = 5,6-dihydroxytryptamine; 5,7-DHT = 5,7-dihydroxytryptamine.

INTERVENTIONS DECREASING SEROTONERGIC FUNCTION. Given the proposed role of serotonin in governing ethanol intake, one would expect pharmacological manipulations that decrease serotonergic functioning to increase ethanol intake. The most consistent evidence supporting this supposition comes from studies using 5,6-dihydroxytryptamine (DHT) and 5,7-DHT, neurotoxins that selectively eliminate brain 5-HT neurons and consistently increase ethanol intake (see Table 1). A large number of studies have employed *p*-chlorophenylalanine (*p*CPA), a compound that depletes brain 5-HT by inhibiting tryptophan hydroxylase, the enzyme that converts tryptophan (TRP) to 5-hydroxytryptophan (5-HTP) and thus 5-HT. This compound, as well as *p*-chloroamphetamine (*p*CA; also a central 5-HT depletor) most often decrease ethanol intake. Three temporally related mechanisms appear to be overriding *p*CPA's central effect of 5-HT depletion, accounting for these results: a short-term accumulation of highly toxic acetaldehyde on alcohol ingestion; a rebound increase in the synaptic activity of 5-HT; and a conditioned taste aversion due to the association of *p*CPA's noxious side effects with the ingestion of alcohol (Myers and Melchior 1977).

The development of 5-HT agonists and antagonists with high affinities for specific 5-HT receptor subtypes is an advancement over intervention manipulating gross synaptic 5-HT levels. With these compounds, selective 5-HT receptor subtypes can be activated or blocked, respectively. Contrary to expectation, a proliferation of reports demonstrate that 5-HT postsynaptic antagonists reduce ethanol consumption (for example, 5-HT_3 antagonists zacopride, ondansetron (GR38032F), and ICS 205-930; 5-HT_2 antagonist ritanserin; and the mixed 5-HT_1 agonist/5-HT_2 antagonist FG 5893). This effect appears to be relatively specific for ethanol intake, as water and food intake are generally unaffected. Other antagonists (5-HT_{1C2} metergoline and methysergide, 5-HT_3 granisetron) have no effect or increase (nonspecific cinanserin, 5-HT_3 MDL 72222) ethanol intake. As well, discriminative responding for ethanol in pigeons and rats is significantly reduced after injections of the 5-HT_3 antagonists MDL 72222 or ICS 205-930, but not the 5-HT_3 antagonist zacopride or the 5-HT_2 antagonist ketanserin (Grant et al 1990; Grant and Barrett 1991; Grant 1992). These data suggest that the 5-HT_3 receptor subtype in particular may mediate the rewarding qualities of ethanol ingestion. The putative role of the 5-HT_3 receptor subtype in mediating reward and ethanol intake will be discussed below.

INTERVENTIONS INCREASING SEROTONERGIC FUNCTION. As shown in Table 2, evidence indicates that increasing serotonergic neurotransmission through various means decreases ethanol consumption. Serotonin, 5-HT precursors (TRP and 5-HTP), the L-5-HTP derivative triptosine (possibly a 5-HTP releaser), and 5-HT releasers (fenfluramine), and uptake inhibitors (zimeldine, norzimeldine, alaproclate, fluoxetine, fluvoxamine, indalpine, viqualine, citalopram, and sertraline) consistently decrease ethanol consumption in rats, as well as in monkeys and chickens. Studies employing 5-HT precursor (TRP/5-HTP) and releaser/uptake inhibitor (fenfluramine/fluoxetine) combinations generally show that precursor pretreatment enhances

Table 2. A Summary of Studies Examining Ethanol Intake Subsequent to the Administration of Compounds that Increase Serotonergic Functioning

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal/ no change
Direct brain injection of 5-HT: ↑ 5-HT functioning: ↓ ETOH consumption	1	1[48]		
Peripheral 5-HT admin.: ↑ 5-HT functioning: ↓ ETOH consumption	1			1[48]
TRP admin.: ↑ 5-HT functioning: ↓ ETOH consumption	5	2[49,50]	2[51,52]	2[52,53]
5-HTP admin.: ↑ 5-HT functioning: ↓ ETOH consumption	8	8[4,11,12,35,48, 54–56]		
Tryptosine admin.: ↑ 5-HT functioning: ↓ ETOH consumption	1	1[57]		
5-HT uptake inhibitor or releaser admin.: ↑ 5-HT functioning: ↓ ETOH consumption	25	25[2,10,40,41,47, 48,50,51,58,59–72]		
5-HT receptor agonist admin.: ↑ 5-HT functioning: ↓ ETOH consumption	11	11[10,40,48,49,61, 71,74–79]		

Notes: admin. = administration; TRP = tryptophan; 5-HTP = 5-hydroxytryptophan; 5-HIAA = 5-hydroxyindoleacetic acid.

the effects of the releaser or uptake inhibitor on ethanol intake (Fisher et al 1991; Gorelick 1989; Lu et al 1992, 1993). The attenuating effect of 5-HTP on ethanol intake is blocked by pretreatment with the 5-HTP decarboxylase inhibitor RO 4–4602 (a compound that inhibits the conversion of 5-HTP to 5-HT) (Geller et al 1981).

The failure of dietary TRP supplements to decrease ethanol intake in some studies may be due to mode of administration (Zabik 1989), as peripherally administered TRP may be primarily metabolized by hepatic tryptophan pyrrolase and thus decrease TRP availability for brain uptake and conversion to 5-HT (Myers and Melchior 1977). Tryptophan pyrrolase (or tryptophan oxygenase) is the enzyme responsible for TRP degradation along the hepatic kynurenine-nicotinic acid pathway, quantitatively the most important pathway for TRP catabolism in the body. Furthermore, only the electrically evoked release of 5-HT is enhanced by pretreatment with systemically administered TRP; basal 5-HT release is unaffected (Sharp et al 1992). Thus dietary TRP may increase brain 5-HT levels but not 5-HT release and function; serotonergic neuronal activity must also be increased to facilitate increased 5-HT release.

The mechanism of action and specificity of effect of 5-HT uptake inhibitors have been the subject of some speculation. Metergoline (5-HT_{1C2} antagonist) (Rockman et al 1982; Amit et al 1984), cinanserin (nonspecific antagonist) (Gill and Amit 1989), or methiothepin (presynaptic antagonist) (Amit et al 1984) pretreatments do not prevent zimeldine-induced decreases in ethanol consumption. Metergoline pretreatment, however, does partially attenuate the effects of norzimeldine on ethanol intake, and ritanserin (5-HT_2 antagonist) and metergoline do reverse the dexfenfluramine-induced suppression of ethanol intake (Higgins et al 1992). Furthermore, pretreatment with *p*CPA does not block the attenuation of ethanol intake brought about by zimeldine or norzimeldine, but, on the contrary, temporally extends the effects of the 5-HT uptake inhibitors in Sprague-Dawley rats (Amit et al 1984; Gill et al 1985). As well, 5,7-DHT-induced lesions of the nucleus accumbens potentiate the attenuating effects of sertraline on ethanol intake in rats (Myers and Quarfordt 1991). These findings have led some to suggest that 5-HT uptake inhibitors may decrease ethanol intake through non-5-HTergic mechanisms (Amit et al 1991). Some of fluoxetine's effects on alcohol consumption have been attributed to increased activity of the renin-angiotensin system, which is known to decrease ethanol intake (Grupp et al 1988). Furthermore, some researchers have suggested that reductions in ethanol intake by 5-HT uptake inhibitors may be secondary to the attenuation of feeding (Gill and Amit 1989; Gill et al 1988b), as 5-HT uptake inhibitors reduce the intake of water, food, and other nutritive substances (e.g., saccharin) (Fisher et al

1991; Amit et al 1991), as well as the administration of other drugs, such as morphine (Rockman et al 1980) and amphetamine (Yu et al 1986). Some evidence, however, suggests that reductions in food/water and ethanol intake after fenfluramine and fluoxetine are independent (Lu et al 1993).

Studies with 5-HT agonists, including quipazine (nonspecific 5-HT agonist) (Fuller et al 1976), MK-212 (5-HT_{1C2} agonist), and 8-hydroxy-2-(di-N-propylamine)tetralin (8-OH-DPAT), gepirone, ipsapirone and buspirone (all 5-HT_{1A} agonists) (Hamon et al 1990), show consistent reductions in ethanol intake in rats and monkeys. There is also evidence that the putative 5-HT_{1B} agonist 1-[3-(trifluoromethyl)-phenyl]-piperazine (TFMPP) (Middlemiss and Hutson 1990) substitutes for certain doses of ethanol in drug discrimination paradigms, suggesting that this agonist and ethanol act via a common receptor site to produce the ethanol interoceptive cue (Signs and Schechter 1988; Grant and Colombo 1992). (Depletion of 5-HT with *p*CPA also blocks the ethanol-interoceptive cue (Schechter 1978). Assessing the net effect of an agonist on 5-HT neurotransmission is difficult, however. Serotonin agonists, particularly 5-HT_{1A} agonists, effect both presynaptic (somato-dendritic autoreceptors), and postsynaptic receptors (Hamon et al 1990). Moreover, serotonin agonists generally lack specificity, acting at more than one 5-HT receptor subtype as well as at receptors of other neurotransmitter systems. The development of agonists with greater specificity is clearly indicated, as is further research into the functional consequences of specific receptor activation on the 5-HT system. With these caveats in mind, the most parsimonious explanation accounting for the results reviewed above is that 5-HT precursors, agonists and uptake inhibitors decrease ethanol intake by increasing serotonergic neurotransmission.

Serotonergic Functioning in Selectively Bred Alcohol-Prone Rodent Strains

Various rodent species have been selectively bred to be high or low alcohol preferring (Yoshimoto et al 1985; Li et al 1988). These include P (alcohol-preferring) and NP (alcohol-nonpreferring) rats, HAD (high-alcohol-drinking) and LAD (low-alcohol-drinking) rats, UChB (high-alcohol consumer) and UChA (low-alcohol consumer) rats, AA (Alko, alcohol) and ANA (Alko, nonalcohol) rats, N/Nih high and low alcohol-preferring rats, and high and low alcohol-preferring mice. The P line of alcohol-preferring rats will orally self-administer alcohol in a free-choice station with water or some other equally palatable fluid available ad libitum, achieving pharmacologically meaningful blood alcohol concentrations (Li et al 1988). These animals are particularly valuable for studying the role of 5-HT in ethanol preference in that they putatively possess a genetic propensity to consume high levels of ethanol and can be tested before ever having been exposed to ethanol (i.e., alcohol-naive).

The majority of studies support the notion that alcohol preferring animals have consistently lower 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels in various brain regions relative to their nonpreferring counterparts, as measured before ethanol exposure (Murphy et al 1982; Gongwer et al 1989) or after two-day (Yoshimoto et al 1985; Yoshimoto and Komura 1987) or three- to four-week (Murphy et al 1986, 1987a) washout periods (see Table 3).

Lower 5-HT and metabolite levels in P rats may be attributed to lower 5-HT fiber densities detected in various brain regions of P (versus NP) rats. Moreover, the binding density (B_{max}) and affinity (K_d) of [^{3}H]-serotonin to 5-HT_1 receptors and (specifically) [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors, are higher in a number of brain regions of P rats (Wong et al 1988, 1990). This may be due to an increase in the genetic expression, or alternatively an up-regulation (supersensitivity), of 5-HT_{1A} receptors as a compensatory mechanism for lower presynaptic 5-HT concentrations or lower 5-HT fiber densities in various brain regions of P rats. Alternatively, lower 5-HT_{1A}, 5-HT_{1B} and 5-HT_2 densities found in a number of brain regions of P rats may be due to decreased 5-HT fiber densities.

In contrast to the findings in P rats, alcohol-naive AA rats consistently evidence higher 5-HT/5-HIAA levels compared to ANA rats. Korpi et al (1988) has suggested that ANA rats may have fewer 5-HT neurons and higher 5-HT turnover resulting in the lower brain 5-HT content (thus higher 5-HT in AA rats), although if this were true one might expect a change in 5-HT receptor binding (B_{max} or K_d). This has not been found for either 5-HT_1, 5-HT_2, or 5-HT_3 receptors (Korpi et al 1992) (in this study an increase in [^{3}H]5-HT binding to 5-HT_1 receptors was noted in ANA rats but attributed to behavioural manipulations, not to line differences). It is possible that two different subgroups of alcohol-preferring rats (P, HAD, and N/Nih versus AA) with differing neurochemical characteristics have been produced through genetic selection (Korpi et al 1988). Alternatively, McBride et al (1989a) stress the need to demonstrate that all alcohol-preferring inbred rodent strains have strong alcohol consummatory drives and that alcohol is positively reinforcing in the central nervous system (CNS) of these animals, as has been demonstrated in P rats.

Rodent strains that spontaneously exhibit an ethanol preference (as opposed to being selectively bred for that characteristic; for example, Fawn Hooded [F-H] rats and C57 mice) also evidence deficient 5-HT functioning. Alcohol-naive C57 mice have lower brain TRP, 5-HT, and 5-HIAA levels compared to nonpreferring CBA mice, differences attributed to a decrease in TRP availability secondary to higher levels and activity of liver tryptophan pyrrolase activity associated with a higher circulating corticosterone concentration (Badawy et al 1989). Higher

Table 3. Summary of Studies on Serotonergic Functioning in Selectively Bred Alcohol-Prone Rodent Strains

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal or no change	Animal strain(s)
Baseline brain 5-HT/5-HIAA levels ↓ in ETOH-pref. vs. nonpref. animals	16	6 (CEREC. SN. HIP. aSTR. THAL. HYP. NA)			P; HAD; N/NIH pref.; ETOH-pref. inbred mice
			7 WB; HYP	5	AA
					HAD
					ETOH-pref. C57BL vs. nonpref. DBA mice
Fewer 5-HT fibers in ETOH-pref. vs. nonpref. rats	2	2 vHYP. dHIP. vHIP. pCINGC. mNA. aFC. STR; MRN		1 IFC. INA. aNA	P
Baseline brain precursor levels (TRP or 5-HTP) ↓ in ETOH-pref. vs. nonpref. animals	3	1			ETOH-pref. C57 vs. nonpref. CBA mice
				2; HYP	AA
Rate of 5-HT synthesis (brain 5-HTP accumulation after blockade of amino acid decarboxylase) ↓ in ETOH-pref. vs. nonpref. animals	2			2	AA
5-HTP admin.: ↑ 5-HT functioning; ↓ ETOH consumption	2	2			UChB. P
Direct 5-HT injection in NA: ↑ 5-HT functioning; ↓ ETOH consumption	1	1			P
5-HT uptake inhibitors/releasers: ↑ 5-HT functioning; ↓ ETOH consumption	11	11			P. HAD. UChB. F-H ETOH-pref. rats
Baseline 5-HT$_1$ receptor binding ↑ in ETOH-pref. vs. nonpref. animals	6	3 FC. HIP. mNA. mPFC. vHIP	3 DRN (5-HT$_{1A}$). CAU-PUT. mNA (5-HT$_{1B}$)	3 INA. SN. AC	P
				P. MB. HIP. FC. HYP	AA
			STR. BS (5-HT$_{1A}$)	FC. HIP. HYP (5-HT$_{1A}$)	F-H ETOH-pref. rats

(Continued on the following page)

Table 3. *(Continued from previous page)*

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal or no change	Animal strain(s)
Baseline 5-HT$_1$ receptor binding ↑ in ETOH-pref. vs. nonpref. animals	4		1 CEREC (IV layer), CLAU, NA, OT, CAU-PUT[116]	3[112]	P
				P, MB, HIP, FC, HYP[88]	AA
		1 FC, STR[113]		HIP, HYP, BS[113]	F-H
Baseline 5-HT$_1$ receptor binding ↑ in ETOH-pref. vs. nonpref. animals	2			1[117]	P
				1 AMYG, NA, HIP, FC[72]	AA
5-HT agonist admin.: ↑ 5-HT functioning; ↓ ETOH consumption	6	6[108,109,110–120]		1[118]	P, HAD, ETOH-pref. inbred & outbred Wistar rats
5-HT antagonist admin.: ↓ 5-HT functioning; ↑ ETOH consumption	3		1[121]	2[84,100]	P Sardinian ETOH-pref. rats
*p*CPA; 5,6- or 5,7-DHT; electrolytic lesions of 5-HT pathways; ↓ 5-HT functioning; ↑ ETOH consumption	5		5[84,120,122–124]		AA, high ETOH-pref. rats, UChB

Notes: pref. = preferring; a = anterior; d = dorsal; l = lateral; AMYG = amygdala; AC = amygdaloid complex; BS = brain stem; CAU = caudate nucleus; CEREC = cerebral cortex; CINGC = cingulate cortex; CLAU = claustrum; FC = frontal cortex; HIP = hippocampus; HYP = hypothalamus; MB = midbrain; nonpref. = nonpreferring; m = medial; p = posterior; v = ventral; NA = nucleus accumbens; OT = olfactory tubercules; P = pons; PFC = prefrontal cortex; PUT = putamen; MRN = median raphe nucleus; SN = septal nuclei; STR = striatum; THAL = thalamus; WB = whole brain.

cerebrospinal fluid (CSF) TRP (but no differences in CSF 5-HIAA) have been noted in spontaneously ethanol-preferring vervet monkeys compared to nonpreferring monkeys (Ervin et al 1990) after one month's abstinence from alcohol following three months' ethanol exposure, possibly an inherent difference in the ethanol preferring monkeys or a consequence of prior ethanol exposure. Other studies with rodents (see below) and alcoholics (e.g., Beck et al 1983) have demonstrated increases in brain and CSF TRP levels subsequent to chronic ethanol intake.

As with unselected rat lines, interventions increasing 5-HT functioning (e.g., the 5-HT uptake inhibitors fluoxetine, fluvoxamine, zimeldine, and citalopram; the releasers fenfluramine and dexfenfluramine) all diminish ethanol intake in a variety of alcohol-preferring rat strains. Fluoxetine also attenuates the palatability-induced ethanol intake of NP rats, while not affecting the intake of a sugar solution in control groups (Gatto et al 1990). Consistent with earlier data, the 5-HT antagonists methysergide (5-HT$_{1C2}$ antagonist; Peroutka et al 1990) and LY 53857 (5-HT$_2$ antagonist) failed to attenuate fluvoxamine-induced reductions in ethanol intake in P rats (Murphy et al 1985). Serotonin receptor agonists, including 8-OH-DPAT, buspirone, ipsapirone, and NDO-008 (5-HT$_{1A}$ agonists), TFMPP (5-HT$_{1B}$ agonist), and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (5-HT$_2$ agonist) also consistently decrease alcohol consumption in alcohol-preferring rodent strains. Local application of 8-OH-DPAT into the dorsal raphe nucleus (but not the nucleus accumbens) reduces ethanol preference (Schreiber et al 1993). 8-OH-DPAT reportedly interferes

BIOL PSYCHIATRY 1994;36:395–421

with motor function (Murphy et al 1987b, 1988b; McBride et al 1989b), which could explain its effectiveness in reducing ethanol intake. Ipsapirone-induced decreases in ethanol preference can be blocked by the nonselective 5-HT_{1A} antagonist spiperone, or attenuated by *p*CPA pretreatment (Schreiber et al 1993). The putative 5-HT_{1A} antagonist spiroxatrine (Nelson and Taylor 1986) had no effect on ethanol intake in P rats, but augmented decreases in ethanol intake resulting from separate doses of fluoxetine and 8-OH-DPAT, suggesting that spiroxatrine may possess partial post-synaptic 5-HT_{1A} agonist properties or modulate 5-HT_{1A} receptor sites to enhance the actions of 5-HT agonists (McBride et al 1989b).

A floor effect (the inability of an intervention to diminish 5-HT functioning due to already low 5-HT levels) may explain a number of disparate findings with alcohol-preferring rats. Administration of the antagonists methysergide (5-$HT_{1C/2}$) or LY 53857 (5-HT_2) (Murphy et al 1985; Weiss et al 1990), lesions of the midbrain raphe nuclei or 5,6-DHT injections (Kiianmaa 1976; Zhukov et al 1985), 5,7-DHT injections (Kiianmaa and Attila 1979), or oral *p*CPA (Kiianmaa 1976; Contreras et al 1990) fail to alter ethanol consumption in alcohol-preferring rats, even when the same treatments in nonpreferring rats lead to greater ethanol intake (Zhukov et al 1985). Consistent with other studies using 5-HT_3 antagonists reviewed above, MDL 72222 dose-dependently decreased voluntary ethanol consumption in Sardinian ethanol preferring rats, with no changes in total fluid intake (Fadda et al 1991), although it did not antagonize the discriminative effects of ethanol in HAD and LAD rats (Krimmer 1992).

Section Summary

Despite the wide variety of methodologies, species and strains of animals, and pharmacological manipulations employed, a sizable number of studies have provided support for the notion that facilitation of serotonergic neurotransmission leads to decreases in ethanol intake. The corollary of this hypothesis, that decreased serotonergic neurotransmission facilitates ethanol intake, has received much more equivocal support. Two lines of research need further elucidation. First, the mechanisms through which compounds that decrease ethanol consumption exert their effect, particularly the 5-HT uptake inhibitors, need to be elucidated. It is likely that interactions with other neurotransmitter systems are involved. Second, the net effect of specific 5-HT agonists and antagonists on 5-HT neurotransmission needs to be clarified.

Effect of Ethanol on CNS Serotonergic Neurotransmission: Experimental Studies

If a genetically transmitted deficit in central serotonergic functioning exists in some individuals that leads to increased alcohol intake, then perhaps, as Tabakoff and Hoffman (1991) suggest, the consumption of ethanol facilitates serotonergic neurotransmission and ethanol is being used by alcoholics to self-medicate serotonergic hypoactivity. It is therefore important to understand the effects of acute and chronic ethanol administration, as well as the withdrawal of chronic ethanol, on the serotonin neurotransmitter system.

Acute Ethanol

As portrayed in Tables 4 and 5, studies measuring the steady-state brain levels of 5-HT and 5-HIAA as well as the release and uptake of 5-HT suggest that acute ethanol facilitates serotonergic functioning. Decreases in brain 5-HT after acute ethanol may also suggest increased 5-HT neurotransmission, as typically these studies find concomitant increases in 5-HIAA, suggesting increased 5-HT turnover. Increases in brain 5-HIAA after acute ethanol may be due, however, to an ethanol-induced inhibition of 5-HIAA clearance from the brain, rather than an increase in serotonergic neuronal activity (Tabakoff et al 1975a,b; Nutt and Glue 1986). For example, Tyce et al (1970) noted a slower rate of decline in brain 5-HIAA concentration in ethanol-treated rats after the monoamine oxidase inhibitor (MAOI) pargyline compared to controls. Evidence contrary to this notion includes the observation that greater 5-HIAA elevations with smaller doses of ethanol at lower blood alcohol levels, even though it might be expected that higher ethanol doses would produce greater inhibition of the active transport of 5-HIAA out of the brain, and thus higher brain 5-HIAA levels (Holman and Snape 1985). In addition, 5-HIAA has also been shown to be increased in certain brain regions although not in others. If an inhibition of clearance were responsible for increased brain 5-HIAA, one would expect global increases in 5-HIAA in almost all brain regions (Khanib et al 1988).

Despite increases in 5-HT levels, one must be cautious in concluding that acute ethanol facilitates 5-HT functioning, as two studies on the firing rates of raphe neurons after acute ethanol had equivocal results. As well, the majority of studies investigating 5-HT metabolism suggest that acute ethanol does not facilitate 5-HT turnover. Similarly, acute ethanol consistently increases tryptophan pyrrolase activity, suggesting reduced levels of circulating plasma TRP available for brain uptake. As TRP competes for brain uptake with a number of other large neutral amino acids (LNAAs; e.g., tyrosine, phenylalanine, leucine, and others), brain TRP uptake is dependent not only on the concentration of plasma TRP but also on the plasma concentrations of the other LNAAs competing for the same transport mechanism across the blood–brain barrier. Because a number of studies have demonstrated increases in brain TRP and 5-HTP following acute ethanol, this suggests either that the ratio of TRP to other LNAAs is in-

Table 4. Summary of Changes in 5-HT and Metabolite Levels after Acute Ethanol in Specific Brain Regions of Rodents

5-Hydroxytryptamine (5-HT)			
Brain area	Increase	Decrease	No change
Whole brain			
Brain stem	MB/BS MB	BS P-MED MB DRN RF VTA	BS LC
Cerebellum		CEREBC	CEREB
Diencephalon	HYP aHYP/POA	HYP HYP aHYP/POA	HYP THAL
Limbic system		AMYG HIP LF	d,vAMYG HIP SN LSN
Corpus striatum	STR NA	STR CAU NA	STR pSTR NA
Cerebral cortex	FB TEL FC	CERE mPFC	CEREC CEREH OB OT FC PFC

5-Hydroxyindoleacetic acid (5-HIAA)			
Brain area	Increase	Decrease	No change
Whole brain			
Brain stem	P-MED MB RF BS		VTA lower BS
Cerebellum	CEREBC		CEREB
Diencephalon	HYP		HYP THAL
Limbic system	vAMYG		AMYG HIP SN LSN LF
Corpus striatum	STR CAU NA	STR NA	STR NA
Cerebral cortex	CEREC	CEREC	CEREC OB OT FC mPFC

Brain stem = medulla (MED), pons, midbrain, dorsal raphe nuclei (DRN), reticular formation (RF), ventral tegmental area (VTA), locus coeruleus (LC).
Cerebellum = cerebellar cortex (CEREBC), cerebellum (CEREB).
Diencephalon = thalamus, hypothalamus, preoptic area (POA).
Limbic system = hippocampus, septal nuclei, lateral septal nucleus (LSN), amygdala (amygdaloid complex), limbic forebrain (LF).
Corpus striatum = striatum (caudate, putamen), nucleus accumbens.
Cerebral cortex = cerebrum (CERE), cerebral cortex, cerebral hemispheres (CEREH), forebrain (FB), telencephalon (TEL), olfactory bulbs (OB), olfactory tubules, frontal cortex, prefrontal cortex.

creased (i.e., ethanol decreases the plasma concentrations of other LNAAs more than that of TRP), or that ethanol facilitates the actual brain uptake of TRP.

Evidence indicates that acute ethanol may decrease the uptake or increase the release of 5-HT in rat brain tissue and blood platelets. Studies investigating the effects of acute ethanol on the binding of serotonergic ligands to receptor subtypes suggest that very high ethanol doses inhibit receptor binding. It is questionable whether acute ethanol affects 5-HT receptor binding at lower, pharmacologically relevant doses, given that even at high doses, the effects of ethanol on receptor binding were small (Bockholtz et al 1989).

Some evidence suggests that acute ethanol may have a biphasic effect on brain 5-HT. Badawy and Evans (1976) report that acute ethanol initially increased the concentrations of free serum TRP, brain TRP, brain 5-HT, and brain 5-HIAA in Wistar rats above control levels because of increased TRP availability. Seven to 8 hr after ethanol administration, the concentrations of these compounds decreased below control values due to increasing tryptophan pyrrolase

1994:36:395–421

Table 5. Summary of Studies Investigating Serotonergic Functioning in Animal Species after Acute Doses of Ethanol

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal/ no change
Brain 5-HT levels ↑ after acute ETOH	45	15	15	21
Brain 5-HIAA levels ↑ after acute ETOH	24	14	5	13
ETOH facilitates firing of neurons in the DRN and MRN	2	1	1	
Brain 5-HT metabolism ↑ after acute ETOH: studies using MAOIs and radiolabelled 5-HT	14	2	5	7
↓ liver tryptophan pyrrolase activity after acute ETOH	11		11	
Plasma TRP levels ↑ after acute ETOH	4	1	2	1
Brain TRP levels ↑ after acute ETOH	7	3	1	3
Brain TRP uptake ↑ after acute ETOH	2			2
Brain tryptophan hydroxylase activity ↑ after acute ETOH	3		2	2
Brain 5-HTP levels ↑ after acute ETOH	8	4	1	3
Brain and platelet 5-HT uptake ↓ after acute ETOH	4	4	1	
Brain and platelet 5-HT release ↑ after acute ETOH	3	2		1
Brain 5-HT receptor binding ↑ after acute ETOH	3		2	1
5-HT$_3$ receptor-mediated ion current ↑ after acute ETOH	2	2		

Notes: MAOIs = monoamine oxidase inhibitors.

levels. Mørland et al (1985) found additional evidence for an alcohol-induced biphasic alteration in the serotonergic system, as plasma TRP levels were increased 15 min after acute ethanol administration, followed by increased tryptophan oxygenase (pyrrolase) activity 5 hr later. Many of the disparate results of studies reviewed above may be accounted for by including changes in the serotonergic system over time following acute ethanol.

It is clear that serotonergic neurotransmission is a complex process, and that ethanol can affect this system at any number of points. At this time the picture is not clear enough to draw firm conclusions concerning the effects of ethanol on 5-HT neurotransmission; however, the overall evidence suggests that acute ethanol facilitates serotonergic functioning.

Chronic Ethanol

There is strong evidence that chronic ethanol administration (anywhere from 3 days to 25 months) increases brain serotonergic functioning (see Tables 6 and 7). Chronic ethanol increases 5-HT and 5-HIAA in whole brain samples and in specific brain regions, as well as enhances precursor availability (decreased tryptophan pyrrolase, increased plasma and brain TRP, increased tryptophan hydroxylase activity and increased 5-HTP).

On the other hand, some studies have found that chronic ethanol decreases 5-HT metabolism and increases 5-HT uptake. Branchey et al (1981) have reported lower plasma TRP levels and more importantly a decreased ratio of TRP to the other amino acids competing for brain entry in "alcoholic" baboons and rats chronically treated with ethanol, and lower levels of brain TRP and 5-HT in the chronic ethanol consuming rats. The reason for the marked discrepancy between these studies and others showing increased TRP after chronic ethanol is not known; however, in Branchey et al's (1981) and others' (Ledig et al 1982) studies, total caloric intake between control and experimental groups was equated, a factor some experiments overlook. Peripheral and central 5-HT precursor levels will be in-

Table 6. Summary of Changes in 5-HT and Metabolite Levels after Chronic Ethanol in Specific Brain Regions of Rodents

5-Hydroxytryptamine (5-HT)			
Brain area	Increase	Decrease	No change
Whole brain	[illegible]	[illegible]	[illegible]
Brain stem	RHOM[220] MES[220]	BS[illegible] P-MED[168] MES[168] RF[132] VTA[131] DRN[131] LC[131]	BS[illegible] MB[147]
Cerebellum	CEREB[220]		
Diencephalon	DIEN[220]	DIEN[168] lHYP[132] PN[134]	DIEN[221] LvmHYP[131]
Limbic system		SN[131] d,vAMYG[131]	LS[221] HIP[illegible]
Corpus striatum	STR[221,222]	STR[131] CAU[132]	STR[221,229]
Cerebral cortex		CEREH[225] TEL[168]	CEREC[168,220] CEREH[168,221] FB[147]

5-Hydroxyindoleacetic acid (5-HIAA)			
Brain area	Increase	Decrease	No change
Whole brain	[illegible]	[illegible]	[illegible]
Brain stem	MES[220] RHOM[220] DRN[131] LC[131]		BS[221,222] P-MED[168] MES[168] RF[132] VTA[131]
Cerebellum			CEREB[220]
Diencephalon		PN[131]	DIEN[168,220,222] lHYP[131,132] vmHYP[131]
Limbic system	HIP[223]		LS[221] HIP[illegible] SN[131] d,vAMYG[131]
Corpus striatum	STR[131,168,222] CAU[132] NA[132]		STR[221–226]
Cerebral cortex	CEREC[168,220] CEREH[221]		CEREH[220] TEL[168]

Brain stem = rhombencephalon (RHOM), mesencephalon (MES).
Diencephalon (DIEN) = paraventricular nucleus (PN).
Limbic system (LS).

fluenced by between-group variations in total caloric intake, as TRP competes for brain uptake across the blood–brain barrier with other LNAAs. Paradoxically, other studies that have equated groups on total caloric intake (Pohorecky et al 1974, 1978) have found results opposite to those of Branchey et al (1981) (i.e., higher TRP after acute ethanol).

No clear effect of chronic ethanol exposure on 5-HT receptors has been noted, however chronic ethanol decreased the number of 5-HT_{1A} binding sites in the hippocampus, with no changes in the binding characteristics of 5-HT_{1A} or 5-HT_2 receptors in the frontal cortex, or striatal and hypothalamic 5-HT_{1B} receptors (Ulrichsen 1991). This was interpreted as a down-regulation in inhibitory postsynaptic hippocampal 5-HT_{1A} receptors, leading to a hyperactivity that counteracted the depressant effects of ethanol and led to ethanol tolerance (Ulrichsen 1991). This seemingly indicates a facilitation of hippocampal serotonergic neurotransmission. Alternatively, the down-regulation of 5-HT_{1A} receptors may have been a direct result of ethanol-induced increases in synaptic 5-HT, however. Wu et al (1986) noted a significant reduction in the K^+ evoked release of hippocampal [^{14}C]5-HT after chronic ethanol, evidence against this hypothesis.

A number of studies found increased 5-HT uptake after chronic ethanol, suggesting a decreased availability of 5-HT in the synapse. Prominent strain effects were noted between Sprague-Dawley and Fawn Hooded rats. In Sprague-Dawley rats, chronic ethanol increased increased hippocampal 5-HT uptake. In Fawn Hooded rats, chronic ethanol decreased a high basal uptake of 5-HT prior to ethanol intake, suggesting that ethanol increases low basal serotonergic functioning in this ethanol-preferring rat strain (Daoust et al 1991).

Withdrawal from Chronic Ethanol

Indicators of central serotonergic functioning measured following the withdrawal of chronically administered ethanol

Table 7. Summary of Studies Investigating Serotonergic Functioning in Animal Species after Chronic Ethanol Administration

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal or no change
Brain 5-HT levels ↑ after chronic ETOH	38	13	9	21
Brain 5-HIAA levels ↑ after chronic ETOH	24	15	4	11
Brain 5-HT metabolism ↑ after chronic ETOH (including studies using MAOIs)	6	1	3	2
↓ liver tryptophan pyrrolase activity after chronic ETOH	14	11	2	1
Plasma, brain and CSF TRP levels ↑ after chronic ETOH	14	11	3	1
Brain tryptophan hydroxylase activity ↑ after chronic ETOH	3	3		
Brain 5-HTP levels ↑ after chronic ETOH	2	2	1	
Brain and platelet 5-HT uptake ↓ after chronic ETOH	4	1	3	2
Brain and platelet 5-HT release ↑ after chronic ETOH	2		1	1
Brain 5-HT receptor binding ↑ after chronic ETOH	2		1	2

Notes: CSF = cerebrospinal fluid.

have generally suggested a decrease in serotonergic functioning due to the loss of the facilitating effects of ethanol on this neurotransmitter system (see Tables 8 and 9). Serotonin functional indicators have generally been measured 12 hr and beyond after the final dose of ethanol, following the disappearance of signs of intoxication (e.g., loss of equilibrium) and at the onset of signs of withdrawal (e.g., tremors, seizures).

Many studies have found no differences in 5-HT/5-HIAA levels in the whole brain and specific brain regions or 5-HT accumulation after pargyline after withdrawal of chronic ethanol. When taking the time course of changes into account, however, the withdrawal from chronic ethanol initially reduces brain 5-HT and 5-HIAA levels, which subsequently return to control values as the withdrawal period continues (Kahn and Scudder 1976; Badawy et al 1980b; Badawy and Evans 1983; Blagova et al 1982). This effect has been interpreted as a rebound decrease from increased 5-HT/5-HIAA levels during chronic ethanol. This interpretation fits well with the notion that decreased functioning of the serotonergic system on withdrawal from chronic ethanol ingestion may be at least partly responsible for the initiation of further ethanol intake. Other evidence fits this interpretation. Tryptophan pyrrolase rebounds from decreased levels during chronic ethanol intake to increases after ethanol withdrawal (Badawy and Evans 1973, 1983), suggesting a decreased availability of TRP for brain uptake and conversion to 5-HT. Congruent with this, a number of studies have found depressed serum and brain TRP levels (see Table 8). Furthermore, the accumulation of radioactive 5-HT and 5-HIAA after [^{14}C]TRP injection is reduced during ethanol withdrawal (Tabakoff et al 1977).

Alternatively, it is also possible that the increases in whole brain 5-HT following the withdrawal of chronic ethanol (Table 9) indicate increased turnover and functioning of the serotonergic system. These increases subsequently decline to control levels as the withdrawal period continues (Griffiths et al 1974; Littleton et al 1974). It has also been suggested that the increases in brain 5-HIAA seen after withdrawal of ethanol represent a carryover effect of ethanol's inhibition of the clearance of 5-HIAA from the CSF (Tabakoff and Boggan 1974).

Some studies suggest a selective sensitivity of the hippocampus to ethanol in some rodent strains. Chronic ethanol decreased hippocampal 5-HT release and increased uptake; during withdrawal from chronic ethanol 5-HT binding was decreased in the hippocampus. Both sets of data may be indicative of decreased hippocampal serotonergic functioning. Decreased hippocampal [^{3}H]5-HT binding (Muller et al 1980), specifically the number of hippocampal 5-HT$_{1A}$ binding sites (Ulrichsen 1991) after chronic ethanol withdrawal, has been found. One might expect a compensatory

Table 8. Summary of Studies Investigating Serotonergic Functioning in Animal Species after the Withdrawal of Chronic Ethanol Administration

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal/ no change
Brain 5-HT levels ↓ after ETOH withdrawal	19	7	3	11
Brain 5-HIAA levels ↓ after ETOH withdrawal	10	4	4	5
Brain 5-HT metabolism ↓ after ETOH withdrawal using MAOIs and radiolabelled 5-HT	2	1		2
↑ liver tryptophan pyrrolase activity after ETOH withdrawal	2	2		
Precursor levels (plasma & brain TRP, brain tryptophan hydroxylase activity & 5-HTP) ↓ after ETOH withdrawal	6	4	1	2
Brain 5-HT receptor binding ↑ after chronic ETOH withdrawal	4	1 STR. BS	2 HIP. HIP (5-HT_{1A})	3 FC ($5\text{-HT}_{1A,2}$) STR. HYP (5-HT_{1B}). CAU. HIP. COR (5-HT_{1}). ($5\text{-HT}_{1A,2}$)
Brain 5-HT release ↓ after ETOH withdrawal	1			1 HIP. HYP

Notes: COR = cortex.

up-regulation of 5-HT postsynaptic receptors following the withdrawal of chronic ethanol. Assuming ethanol increases 5-HT levels and facilitates 5-HTergic neurotransmission early in a chronic ethanol administration paradigm, a down-regulation (i.e., decrease in number) of 5-HT receptors would occur in response to increased availability of 5-HT. As ethanol administration progressed (and tolerance developed), alcohol-induced increase in 5-HT levels would gradually attenuate, and receptor numbers would up-regulate slightly and stabilize. Following withdrawal and a decline in synaptic serotonin, a compensatory up-regulation in 5-HT receptors should occur. Some support for this line of reasoning comes from a study noting increased striatal and brain stem [^{3}H]5-HT binding after the withdrawal of chronic ethanol administration (Muller et al 1980).

Selectively Bred Alcohol-Prone Rodent Strains

Studies investigating various parameters of serotonergic functioning in selectively bred alcohol-preferring and nonpreferring rodent strains after acute and chronic ethanol (summarized in Table 10) also support the notion that ethanol potentiates serotonergic functioning. Acute and chronic ethanol administration increases brain 5-HT/5-HIAA levels (and 5-HTP accumulation) in a number of brain regions and in a variety of alcohol-preferring (and nonpreferring) rodent strains. For example, a 20% increase in 5-HIAA in the nucleus accumbens, frontal cortex, and anterior striatum of P rats after acute ethanol (Murphy et al 1983) suggests increased activity of dorsal raphe neurons projecting to these brain areas (McBride et al 1990). Chronic ethanol also raises CSF TRP and 5-HIAA levels in spontaneous alcohol-preferring monkeys compared to controls not exposed to ethanol (Ervin et al 1990). Finally, chronic ethanol ingestion can desensitize the response of the serotonergic system to an ethanol challenge (McBride et al 1990), as an acute dose of ethanol administered to alcohol-tolerant P rats (on daily ethanol for 4 to 5 weeks) and nontolerant P rats led to a significantly decreased elevation of 5-HIAA in the nucleus accumbens of the tolerant P rats (Murphy et al 1988a).

Section Summary

The studies reviewed in this section suggest that acute and chronic ethanol produce transient increases in 5-HT levels and functioning. The facilitation of serotonergic functioning likely becomes less and less with successive doses of ethanol as the serotonergic system adapts to chronic ethanol administration. After withdrawal of chronic ethanol, a decrease in 5-HT/5-HIAA levels and concomitant decrease in serotonergic functioning occurs, producing the biochemical

Table 9. Summary of Changes in 5-HT and Metabolite Levels after the Withdrawal of Chronic Ethanol in Specific Brain Regions of Rodents

5-Hydroxytryptamine (5-HT)			
Brain area	Increase	Decrease	No change
Whole brain			
Brain stem			BS P-MED MES
Cerebellum			
Diencephalon		HYP	DIEN THAL
Limbic system		HIP	HIP
Corpus striatum		STR	STR
Cerebral cortex		FB	CERE CEREC FB TEL OB FC

5-Hydroxyindoleacetic acid (5-HIAA)			
Brain area	Increase	Decrease	No change
Whole brain			
Brain stem	P-MED MES		BS
Cerebellum			
Diencephalon	DIEN THAL		HYP
Limbic system			HIP
Corpus striatum		STR	
Cerebral cortex	CEREC CERE TEL		CEREC FB OB FC

conditions for a resumption of ethanol intake. Wide variation exists in the results of these studies due to between-study differences in dependent measures, doses of ethanol, routes of ethanol administration, assessment times, species and strains of animals, and brain regions employed. Reliable differences in serotonergic functioning after ethanol have been demonstrated across brain regions (Kempf et al 1985), rodent strains (Kempf et al 1990), and times of assessment (Badawy and Evans 1976).

A recent review by Tabakoff and Hoffman (1991) has reached conclusions similar to those above, namely that acute ethanol facilitates serotonergic functioning. Earlier reviews, however, concluded that chronic ethanol decreased 5-HT turnover (Tabakoff and Hoffman 1983; Hoffman and Tabakoff 1985). Clearly evidence exists for both hypotheses. Electrophysiological studies on the effects of acute and chronic ethanol on the firing rates of serotonergic neurons projecting to different brain regions may assist in clarifying whether increases in 5-HT levels and turnover lead to increases in neurotransmission, and in which specific brain regions.

Discussion

In this review (parts one and two), it was proposed that chronic alcohol intake may be mediated by a functional deficit in serotonergic neurotransmission. The evidence reviewed, though far from conclusive, suggests that decreased 5-HT functioning through synthesis inhibition, postsynaptic antagonism or neurotoxic lesioning leads to increased alcohol intake. A stronger relationship has been demonstrated between increased 5-HT functioning, through uptake inhibition or receptor agonism, and reductions in ethanol intake.

By what mechanism(s) do alterations in 5-HT transmission affect ethanol intake? In experimental animals, decreased 5-HT functioning increases dopamine (DA)-induced locomotor activity, increases exploratory behavior and the propensity to intersperse alternate behaviours with exploratory behaviour, releases punishment-induced behavioural suppression, increases responding for reward and nonreward, increases food intake and sexual behavior, and facilitates aggression (for comprehensive reviews, see Spoont 1992; Soubrié 1986). Increased serotonergic functioning leads to the converse of these behaviors in many instances. Soubrié (1986), in his review of the mechanisms of benzodiazepine-induced anxiolysis, argues that the behavioural manifestations of low 5-HT functioning, although

Table 10. Summary of Studies Investigating Serotonergic Functioning in Selectively Bred Alcohol-Preferring Rodent Strains after Acute and Chronic Ethanol Administration

Hypothesis	Total No. of studies	Supporting	Refuting	Equivocal/ no change	Animal strain(s)
Brain 5-HT levels ↑ after acute ETOH	2	1 NA[97]			HAD and LAD
				1[247]	P
Brain 5-HT levels ↑ after chronic ETOH	3	2 HYP. MB. COR[88,97]			AA
				1[247]	P
Brain 5-HIAA levels ↑ after acute ETOH	4	3 NA. FC. aSTR[88,247,248]			P: AA and ANA
				1[93]	HAD and LAD
Brain and CSF 5-HIAA levels ↑ after chronic ETOH	4			3[88,97,247]	AA: P
		1[250]			ETOH-prefer. vervet monkeys
Brain 5-HTP levels ↑ after acute ETOH	1	1[88]			AA and ANA

similar to those following benzodiazepine administration, do not reflect anxiolysis. Instead, animals with low 5-HT transmission are primarily impelled to make active motor responses. Secondarily, the probable consequences of active responding are less important in controlling behavior. Decreased 5-HT functioning lowers the threshold for passivity or constraint tolerance. Soubrié likens lowered 5-HT neurotransmission to increased impulsiveness and "acting out" behavior.

From an information processing perspective, 5-HT stabilizes signal propagation in neural systems, inhibiting impingement of the neural system by exogenous signal sources unless they are of sufficient intensity or psychological relevance to the organism (Spoont 1992). Once the signal gains access to the system, 5-HT constrains its intensity to prevent an overshoot in the system. Consequently, decreased serotonergic functioning (1) increases the sensitivity of a neural system to perturbation by exogenous stimuli such that its ability to maintain self-organization is compromised; and (2) increases the propensity for overshoot of other dynamic elements within the system. The overshoot outlined in (2) is manifested behaviorally by (a) an increase in the likelihood that a given behavior will occur and an increase in the magnitude of responding (due to an impairment of 5-HT's negative feedback modulation) (b) a slower recovery time of a behavior initiated in the absence of 5-HT's constraining action (i.e., the behavior persists longer), and (c) a decrease in sensitivity to cues that would attenuate the behavior.

In this context, increases in ethanol ingestion subsequent to decreased serotonergic transmission may be a consequence of an increased propensity towards active responding. Moreover, in accordance with Spoont's analysis, decreased 5-HT functioning may allow for perturbation of the neural system by an exogenous stimulus such as the presence of ethanol (and the expectation of reward associated with its presence). Once the signal has gained access to the system, diminished 5-HT functioning allows for an overshoot in signal intensity and in the ensuring behavioral response (increasing the magnitude and persistence of ethanol ingestion and decreasing the sensitivity of the organism to cues that could attenuate alcohol ingestion: for example, internal cues of satiety, cues for punishment associated with excessive alcohol consumption). Conversely, increasing serotonergic functioning inhibits the impingement of the external stimulus (ethanol) on the neural system, and increases sensitivity of the animal to cues that attenuate ethanol ingestion.

Contrary to Soubrié, who assigns a secondary role to 5-HT in anxiety, Gray ascribes the ascending forebrain serotonergic pathways originating in the dorsal and median raphe nuclei in the transmission of signals of punishment (primarily), and signals of reward used in the detection of nonreward (secondarily), that activate the "behavioral inhibition system" (BIS) (Depue and Spoont 1986; Gray 1982a,b). The BIS compares actual with expected stimuli, remaining in checking mode until a mismatch between actual and expected is detected or the stimulus is expected to

be aversive. At this point the BIS is activated, inhibiting ongoing behavior, increasing arousal, and increasing attention of the organism to the environment to facilitate assessment of the stimulus event. Stimuli associated with punishment and frustrative nonreward, as well as novel stimuli, activate the BIS. The affective correlates of increased BIS activity are fear (elicited by cues for punishment), frustration (elicited by cues for nonreward), and anxiety (elicited by novelty) (Depue and Spoont 1986). Neuroanatomically, the septohippocampal system and its interconnections comprise the BIS, with the hippocampus functioning as stimulus comparator (Gray 1982a). A second "behavioral facilitation system" (BFS) (Depue and Spoont 1986) works in concert with the BIS, mobilizing the organism into active engagement with the environment. The BFS, neuroanatomically located in the mesolimbic dopaminergic system, directs unconditioned behaviour (e.g., eating, drinking, sexual responding, and spontaneous exploratory locomotion), as well as conditioned behavior (behavior in the presence of cues for reward and nonpunishment) (Depue and Spoont 1986; Gray 1982a).

Persistently low 5-HT functioning may shift the BIS/BFS balance toward the BFS, such that the organism exhibits an increased responsiveness to signals of reward and nonpunishment and a decreased responsiveness to signals of punishment, nonreward and (possibly) novelty, leading to persistent behavioral activation (Depue and Spoont 1986). Decreased serotonergic functioning impairs the flow of information within the BIS and leads to behavioral impulsivity through activation of a hypersensitive BFS. Increased serotonergic functioning facilitates BIS information processing, leading to behavioral constraint in the appropriate stimulus contexts.

Antianxiety drugs (anxiolytics: namely benzodiazepines, barbiturates, and alcohol)) interfere with the proper functioning of the septohippocampal system such that the BIS no longer inhibits behavior under conditions of threat (cues for punishment and nonreward) and novelty (Gray 1982a). Specifically, alcohol may disrupt the transmission of cues for punishment and nonreward transmitted by serotonergic neurons, relieve the fear and anxiety elicited by these stimulus contexts, and release BIS-induced behavioral suppression. This analysis implies that alcohol impairs 5-HT neurotransmission, consistent with previous reviews of preclinical studies concluding that serotonergic hyperfunctioning is associated with anxiety, and that decreasing serotonergic functioning relieves anxiety states (Schreiber and De Vry 1993; Iversen 1984; Gardner 1986). This notion is difficult to reconcile with the second major conclusion of this paper, that acute and chronic ethanol administration increase serotonergic neurotransmission. Perhaps, as Soubrié (1986) argues, a reduction in 5-HT transmission is neither necessary nor sufficient to produce the anxiolytic effects of antianxiety drugs, such as benzodiazepines and alcohol. In this way, ethanol's effects on the 5-HT system are independent of its effects on anxiety. The mechanisms that lead to behavioral disinhibition after alcohol and after reductions in 5-HT neurotransmission may involve distinct neuronal substrates and neuropsychological processes (Soubrié 1986). This position is clearly at variance with that of Gray (1982a).

Alternatively, ethanol may have a biphasic effect on serotonergic functioning, initially increasing then decreasing serotonergic neurotransmission. The consequences of ethanol-induced increases in 5-HT functioning appear to involve activation of the mesolimbic dopaminergic reward system (Wise and Bozarth 1987). Serotonin and 5-HT$_3$ receptor agonists stimulate the release of striatal dopamine, an effect that can be blocked by 5-HT$_3$ antagonists (Blandina et al 1988). Furthermore, 5-HT$_3$ antagonists block ethanol-induced increases in dopamine release in the nucleus accumbens (Carboni et al 1989; Yoshimoto et al 1992b). 5-HT$_3$ antagonists may function to extinguish ethanol consumption in animals (Oakley et al 1988; Tomkins and Sellers 1992; Hodge et al 1992; Fadda et al 1991) and alcoholics (Toneatto et al 1991) by inhibiting the alcohol-induced firing of mesolimbic dopaminergic neurons and blocking the rewarding effects of activation of this pathway. Taken together, these findings suggest that with an individual acute dose, alcohol may first facilitate serotonergic neurotransmission, stimulating the dopaminergic reward pathway, then decrease serotonergic neurotransmission, interfering with BIS functioning and leading to behavioural disinhibition. Evidence for such a biphasic effect of alcohol on 5-HT functioning has been noted previously (Badawy and Evans 1976; Mœland et al 1985). The involvement of other neurotransmitters (γ-aminobutyric acid [GABA], glutamate) in alcohol's anxiolytic effects would modify this story somewhat. In particular, acute alcohol facilitates rat brain GABA neurotransmission (Nestoros 1980), and antianxiety drugs increase GABAergic inhibition of neurons in the raphe (Gallager 1978). Furthermore, ethanol decreases N-methyl-D-aspartate (NMDA) related CA^{2+} flux, reducing excitatory neurotransmission (Lovinger et al 1989, 1990). Thus possible interactions of 5-HT with GABA and glutamate systems need to be considered when attempting to explain the anxiolytic effects of alcohol.

Clinically, low serotonergic functioning has been implicated in a number of psychiatric symptoms commonly subsumed under the rubric of impaired impulse control, including aggressivity and self-injurious behavior (including suicide) (Insel et al 1990; Mann et al 1990; Roy et al 1990). Serotonin likely mediates the propensity to inhibit active responses, such that decreased serotonergic functioning leads to impulsive responding (i.e., the tendency toward active responding in the face of cues that normally suppress

such behavior, such as cues for punishment and nonreward). Alcohol-dependent individuals often manifest behavior characteristic of impaired impulse control (e.g., aggression, suicide) (Linnoila et al 1989; Roy and Linnoila 1989; Roy et al 1987, 1990). Thus chronic alcohol consumption appears to be one of a spectrum of behavior end-points mediated by low central 5-HT neurotransmission. From this perspective, serotonin does not control alcohol intake per se, but rather the tendency to respond in a particular fashion given the presence/absence of certain environmental stimuli.

The difficulty in interpreting the clinical work examining the relationship between 5-HT and alcohol dependence lies in separating the effects of chronic alcohol intake on the serotonergic system from a putative premorbid serotonergic dysfunction. A promising avenue for future research involves the study of individuals at high risk for the development of alcoholism by virtue of a family history of the disorder. The utility of this population for studying the neurochemical basis of alcoholism is predicated on the assumption that a genetic abnormality exists in these family history positive (FH+) individuals that subsequently leads to maladaptive alcohol intake in the presence of certain environmental influences (most notably, the availability of alcohol). As noted in part one of this review, clinical data suggest the existence of a significant genetic component in alcohol dependence.

A large literature has accumulated on the behavioral, psychophysiological, and cognitive characteristics of FH+ individuals. Subsequent to a review of the literature on nonalcoholic sons of male alcoholics (SOMAs) (Pihl et al 1990a), Peterson and Pihl (1990; Pihl et al 1990b) hypothesized that SOMAs may have an inherent cognitive dysfunction and/or deficiency in serotonergic functioning leading to physiological hyperreactivity to novel/threatening environmental stimuli and syndromes of impaired behavioral regulation (hyperactivity, conduct disorder, antisocial personality). In these individuals, alcohol is negatively reinforcing, dampening the autonomic hyperreactivity (Levenson et al 1987; Finn and Pihl 1987, 1988; Finn et al 1990) and alleviating the negative affective state (i.e., anxiety) that occurs on exposure to threat/novelty. SOMAs may also be more susceptible to the rewarding qualities of ethanol ingestion, as they evidence greater baseline increases in heart rate under alcohol compared to controls (Finn and Pihl 1987, 1988; Finn et al 1990), a putative indicator of the rewarding characteristics of a drug (Wise and Bozarth 1987; Fowles 1983). In this model, 5-HT may mediate physiological reactivity and/or general behavioral responsivity to environmental stimuli. SOMAs have been characterized as behaviorally disinhibited and/or impulsive (Schulsinger et al 1986; Knop et al 1985; Pihl et al 1990a; see Pihl et al [1990a] for a review). As reduced serotonergic functioning has been associated with increased impulsivity and aggressivity (Brown et al 1979a,b, 1982; Insel et al 1990), diminished serotonergic functioning may underlie the behavioral disinhibition noted in SOMAs.

Future research should focus on the serotonergic functioning of FH+ individuals, investigating plasma TRP, tryptophan pyrrolase, CSF 5-HIAA and platelet 5-HT binding parameters. Serotonin precursor and agonist/antagonist challenges will provide further information on serotonergic functioning in these individuals, especially when various stimulus contingencies are manipulated (e.g., cues for punishment, nonreward) subsequent to neurochemical alteration. Assessment of 5-HT challenges in humans should be approached from many different levels of analysis, including the behavioral, phenomenological, hormonal, biochemical, and psychophysiological. Molecular genetics studies may pinpoint the locus of the genetic abnormality in the serotonergic system in alcoholism. The gene for tryptophan oxygenase (pyrrolase) in humans has recently been localized, with possible implications for serotonergic functioning in alcoholism (Comings et al 1991; Comings and Comings 1990). Genetic abnormalities in tryptophan pyrrolase activity, TRP uptake across the blood–brain barrier, and tryptophan hydrogenase activity are good starting points in the search for candidate genes in molecular genetics studies. For example, an abnormality in the gene coding for tryptophan hydroxylase has recently been reported in alcoholic impulsive offenders, and has been associated with low CSF 5-HIAA and suicidal attempts in these individuals (Virkkunen and Linnoila 1993). A mutation in the gene coding for monoamine oxidase A (MAOA) activity has also been associated with impulsive aggression (Brunner et al 1993).

To summarize, the data reviewed here strongly indicate that the serotonergic system mediates ethanol intake as part a more general role in the control of behavioral activation/inhibition. Acute and chronic ethanol intake facilitate serotonergic functioning, however, a biphasic effect of ethanol is suggested, with initial increases in 5-HT neurotransmission activating reward pathways, and subsequent decrements in 5-HT neurotransmission affecting BIS functioning

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Serotonin and Alcohol: Recent Developments

Since the previous two reviews were written and published several years ago, it is necessary to update this information to illustrate the present state of knowledge concerning serotonin/alcohol interrelationships. The following section will review the field according to the hypotheses put forward in the previous two reviews.

Preclinical Experimental Studies

Decreasing Serotonergic Levels (and Function): Increased Ethanol Intake

In the second review (LeMarquand, Pihl, & Benkelfat, 1994b), the most consistent evidence supporting the notion that decreased serotonergic synthesis and function leads to increased ethanol intake was found in studies using 5-HT neurotoxins to lesion the serotonergic system. Two additional studies demonstrate that neurotoxic lesioning with 5,7-dihydroxytryptamine (5,7-DHT) increased ethanol preference (Jankowska, Bidzinski, & Kostowski, 1994; Wang, Shum, Lin, & Wang, 1996). Two studies, however, found no changes in ethanol intake following 5,7-DHT lesions; in the DRN and MRN in Sprague-Dawley rats (Adell & Myers, 1995), or in low alcohol drinking (LAD) rats (Adell & Myers, 1996), a rat strain selectively-bred to consume low levels of alcohol (possibly due to higher levels of cerebral 5-HT). Additionally, 5,7-DHT lesions did not affect ethanol-induced conditioned taste or place aversions in rats, suggesting that central serotonergic pathways are not primarily involved in the aversive effects of high ethanol doses (Bienkowski, Iwinska, Piasecki, & Kostowski, 1997). Adell and Myers

(1996) suggested that 5-HT may play a role in the maintenance of the basal intake of alcohol, but not necessarily in the consumption of this fluid after 5,7-DHT lesioning.

Administration of 5-HT_{1A} agonists has generally been shown to decrease ethanol consumption (LeMarquand et al., 1994b). 5-HT_{1A} agonists act on both presynaptic somatodendritic autoreceptors as well as post-synaptic receptors. Activation of presynaptic autoreceptors might be expected to decrease serotonergic functioning (via inhibition of presynaptic 5-HT release) and consequently increase ethanol consumption. Tomkins et al. recently confirmed that smaller, systemic doses of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) (Tomkins, Higgins, & Sellers, 1994), or local low dose injections directly into the MRN or DRN (Tomkins, Sellers, & Fletcher, 1994), enhanced ethanol (but not food or water) intake in rats. The selective 5-HT_{1A} antagonist (+)-WAY100135 blocked this effect in the latter study. Tomkins et al. proposed that the activation of somatodendritic 5-HT_{1A} autoreceptors reduced serotonergic functioning and increased alcohol intake. Higher doses activate postsynaptic 5-HT_{1A} receptors, leading to the serotonin syndrome characterized by behaviors incompatible with ethanol intake. That 8-OH-DPAT increased ethanol preference over that of water or food suggests that ethanol had a particular incentive value (unrelated to caloric need), perhaps because 8-OH-DPAT enhances the salience of certain stimuli by reducing the inhibitory control of 5-HT over the mesolimbic and nigrostriatal dopaminergic pathways (Fletcher & Davies, 1990; Montgomery, Rose, & Herberg, 1991).

Interestingly, mice engineered to lack the 5-HT_{1B} receptor subtype (which are predominantly presynaptic auto- and heteroreceptors, perhaps functioning to inhibit neurotransmitter

release) displayed increased alcohol consumption, possibly reflecting developmental compensations in serotonergic or other neurotransmitter systems (Crabbe et al., 1996). 5-HT_{1B} knockout mice also showed reduced sensitivity to the rewarding effects of ethanol in an ethanol-induced conditioned place preference paradigm (Risinger, Bormann, & Oakes, 1996), suggesting that ethanol consumption may be increased in an attempt to activate subsensitive reward pathways.

Increasing Serotonergic Levels (and Function): Decreased Ethanol Intake

The predominant finding that 5-HT_{1A} agonists decrease ethanol consumption has been confirmed in more recent studies (Hedlund & Wahlstrom, 1996; Kostowski & Dyr, 1992; Mosner, Kuhlman, Roehm, & Vogel, 1997; Svensson et al., 1989; Wilde & Vogel, 1994; Wilson, Neill, & Costall, 1996). Higher doses of the 5-HT_{1A} agonists 8-OH-DPAT, ipsapirone, and buspirone antagonized ethanol-induced locomotor activity in mice without reducing locomotor activity per se (Blomqvist, Söderpalm, & Engel, 1994). Reductions in ethanol intake following 5-HT_{1A} agonist administration may be mediated through postsynaptic 5-HT_{1A} receptor activation, leading to increased 5-HT neurotransmission and inhibition of dopaminergic neurotransmission in the mesolimbocortical system (Blomqvist et al., 1994). Alternatively (or additionally), higher doses of 5-HT_{1A} agonists may reduce the palatability of ethanol (Svensson, Fahlke, Hård, & Engel, 1993), leading to decreased intake. Partial support for this mechanism comes from a study in which systemic ipsapirone increased the duration of aversive groomings following intraoral infusion of ethanol. In this study, alcohol consumption remained unaffected, suggesting a dissociation

between the palatability of ethanol (the negative, aversive effects) and the ingestion of ethanol (the positive, hedonic aspects) (Fahlke, Thomasson, Hård, Engel, & Hansen, 1994).

The picture becomes even more intricate when one accounts for the following findings: in rats induced to display a high preference for ethanol via intracerebroventricular (ICV) injections of 5,7-DHT (the 5-HT neurotoxin), the 5-HT_{1A} agonist 8-OH-DPAT did not reduce ethanol intake, while tropisetron (ICS 205-930; 5-HT_3 antagonist) did. This suggests that the effect of 8-OH-DPAT depends on the neuroanatomical integrity of the 5-HT system, and that the mechanism of action of 8-OH-DPAT is on presynaptic receptors, whereas that of tropisetron is on postsynaptic receptors (Jankowska et al., 1994). In rats lesioned with ICV injections of 6-hydroxydopamine, a dopamine (DA) neurotoxin, 8-OH-DPAT reduced ethanol consumption while the effect of tropisetron was reduced, suggesting that brain DA neurons are involved in the tropisetron-induced inhibition of ethanol intake, but not in the antipreference effect of 8-OH-DPAT (Jankowska, Bidzinski, & Kostowski, 1995).

It was hypothesized earlier (LeMarquand et al., 1994b) that 5-HT *antagonist* administration would reduce 5-HT function by blocking the 5-HT binding to post-synaptic receptors and consequently increase alcohol intake. It now appears that the predominant effect of 5-HT antagonists is the opposite, a *decrease* in ethanol intake. The 5-HT_2 antagonist ritanserin reduces ethanol intake (Lin & Hubbard, 1994; Panocka, Ciccocioppo, Polidori, & Massi, 1993; see also Claudi et al., 1997), an effect that may be mediated specifically by the nucleus accumbens (and not the ventral tegmental area or the medial prefrontal cortex) (Panocka, Ciccocioppo, Polidori et al., 1993). Ritanserin may cause DA release through the activation of 5-HT_2

(Panocka, Ciccocioppo, Polidori et al., 1993) or even 5-HT_3 (Panocka et al., 1996) receptors in the nucleus accumbens, activating reward pathways and consequently decreasing ethanol intake.

Some (McMillen, Walter, Williams, & Myers, 1994; Myers, 1994) have suggested that 5-HT_2 antagonism alone is not sufficient to reduce alcohol intake, as the 5-HT_2 antagonist amperozide reduced ethanol consumption, whereas the 5-HT_2 antagonist trazodone did not. Amperozide's additional actions (as a 5-HT reuptake inhibitor, and a compound that increases the extracellular concentration of DA in nucleus accumbens) were suggested as necessary to reduce ethanol consumption.

Concerning the effects of 5-HT_3 antagonists on alcohol intake, there has been increasing interest in serotonergic/dopaminergic interactions. In the previous review (LeMarquand et al., 1994b), the data suggested that 5-HT_3 antagonists may decrease alcohol intake by inhibiting the alcohol-induced firing of mesolimbic dopaminergic neurons, thus blocking the rewarding aspects of ethanol. Further research appears to support this hypothesis. Separate bilateral microinjections of the 5-HT_3 antagonists ondansetron and tropisetron in the amygdala (Dyr & Kostowski, 1995) and bilateral injections of tropisetron in the nucleus accumbens septi (Jankowska & Kostowski, 1995) reduce ethanol intake in rats. 5-HT_3 antagonists also reduce the ethanol-induced increased extracellular levels of DA in various brain regions (nucleus accumbens, ventral tegmental area) (Campbell, Kohl, & McBride, 1996; Wozniak, Pert, Mele, & Linnoila, 1991; Yoshimoto, McBride, Lumeng, & Li, 1992). In contrast, the 5-HT_3 *agonist* 1-(m-chlorophenyl)-biguanide (CPBG) *enhances* extracellular ventral tegmental area DA, an effect abolished by the 5-HT_3 antagonist ICS 205-

930 (Campbell et al., 1996). CPBG (ICV and into the nucleus accumbens) had no effect on ethanol intake in rats; whereas a second 5-HT_3 agonist, 2-Me-5-HT, reduced ethanol intake (Dyr & Kostowski, 1997). The co-administration of ethanol and CPBG enhances nucleus accumbens DA, an effect blocked by ICS 205-930 (Campbell & McBride, 1995). As well, the 5-HT_3 antagonist MDL 72222 reduced alcohol-induced hyperlocomotion, similar to the effect described above following 5-HT_{1A} agonist administration (Rajachandran, Spear, & Patia Spear, 1993). These data suggest that 5-HT_3 antagonists reduce the rewarding effects of alcohol-induced brain DA release. There are conflicting reports, however (Iusco et al., 1997); the 5-HT_3 antagonists ondansetron or ICS 205-930 did not modify ethanol-induced increases in locomotor activity (Lê, Tomkins, Higgins, Quan, & Sellers, 1997). Other studies have shown that 5-HT_3 antagonists do not mediate the stimulus properties (Stefanski, Bienkowski, & Kostowski, 1996) or the aversive effects (Bienkowski, Kuca, Piasecki, & Kostowski, 1997) of ethanol.

Reductions in ethanol intake following ondansetron are sustained following chronic treatment (Tomkins, Lê, & Sellers, 1995), however one study found that both single injections and b.i.d. administration over blocks of five days of the 5-HT_3 antagonists ondansetron, granisetron, and SC-51296 failed to alter the ethanol self-administration in rats (Beardsley, Lopez, Gullikson, & Flynn, 1994). The failure to find an expected effect of 5-HT_3 antagonists on ethanol consumption may be due to the fact that the animals in this study had to lever press according to an operant schedule for ethanol access (vs. free choice paradigm) (Beardsley et al., 1994), (although an effect of the 5-HT antagonist ICS 205-930 on ethanol-reinforced behavior has been found in a previous study (Hodge, Samson, Lewis, & Erickson, 1993)).

The inhibition of ethanol intake by 5-HT antagonists may be dose dependent. In general, higher doses have led to decreased (or unchanged) ethanol consumption (Rockman, Amit, Brown, Bourque, & Ögren, 1982; Weiss, Mitchiner, Bloom, & Koob, 1990). Lu, Wagner and Fisher (1994), however, found *increased* ethanol and water intake in male rats in two of three experiments after low doses of methysergide. Methysergide also separately reversed fenfluramine- and fluoxetine-induced decreases in ethanol consumption (Lu et al., 1994). This effect may be explained by 5-HT_3 antagonism of post-synaptic receptors leading to decreased 5-HT functioning. Note that this dose effect mirrors that found by Tomkins, Higgins et al. (1994) concerning 5-HT_{1A} receptors.

In addition to serotonergic/dopaminergic interactions, serotonergic/opioidergic interactions in the regulation of ethanol intake have also been explored. High doses of tropisetron attenuated morphine-induced increases in ethanol intake (Hodge, Niehus, & Samson, 1995), and small doses of ondansetron and naltrexone, ineffective when administered alone, suppressed alcohol intake when co-administered to mice and rats (Lê & Sellers, 1994).

A number of studies reviewed earlier (LeMarquand et al., 1994b) demonstrated that 5-HT precursor administration decreases ethanol intake. Zabik, Sprague, and Binkerd (1994) confirmed that initial decreases in ethanol intake after 5-hydroxytryptophan (5-HTP) were due to the central effects of 5-HT, as xylamidine, a peripheral 5-HT receptor antagonist, did not attenuate the 5-HTP-induced decreases in ethanol intake, whereas methysergide, a centrally-acting 5-HT antagonist (with some peripheral actions) did. Xylamidine attenuated the persistent refusal to drink ethanol following 5-HTP treatment, suggesting the development of a peripheral conditioned taste aversion

(Zabik et al., 1994). Direct injection of 5-HT into the paraventricular nucleus of the hypothalamus (involved in regulating ingestive behavior) did not reduce basal ethanol intake in rats, but did attenuate an NE-induced increase in ethanol intake (Hodge, Slawecki, & Aiken, 1996).

The importance of peripheral factors mediating ethanol intake was underscored in a study that found reductions in ethanol intake via systemic injections of the metabolites of serotonin (5-HIAA and 5-hydroxytryptophol, or 5-HTOL) in male rats (Messiha, 1978). Furthermore, 5-HTOL increased liver alcohol dehydrogenase, suggesting greater availability of hepatic alcohol dehydrogenase for the metabolism of ethanol.

Selective serotonin reuptake inhibitors (SSRIs) were found to reduce alcohol intake consistently in a large number of studies (Gulley, McNamara, Barbera, Ritz, & George, 1995; LeMarquand et al., 1994b). Recent work suggests a mechanism for SSRI-induced decreases in ethanol intake in rats: fluoxetine and paroxetine (administered separately) substituted for the discriminative stimulus effects of ethanol (Maurel, Schreiber, & De Vry, 1997). Ethanol excites putative DA neurons in the ventral tegmental area; both 5-HT (Brodie, Trifunovic, & Shefner, 1995), and the SSRI clomipramine (Trifunovic & Brodie, 1996), can potentiate this ethanol-induced excitation, suggesting that SSRIs may reduce alcohol intake by activating DA reward pathways. The selective 5-HT_{2A} antagonist MDL 100,907 blocked the substitution of fluoxetine, whereas the selective 5-HT_{1A} receptor antagonist WAY-100635 had no effect, suggesting that the stimulus similarities may be mediated by 5-HT_{2A} receptor stimulation (Maurel et al., 1997). Not unexpectedly, co-administration of the 5-HT releaser/reuptake inhibitor fenfluramine and the DA agonist

amphetamine reduces alcohol consumption in alcohol-dependent and alcohol-nondependent rats (Yu, Fisher, Sekowski, & Wagner, 1997).

Serotonergic Functioning in Selectively Bred Alcohol-Prone Rodent Strains

In the earlier review (LeMarquand et al., 1994b), it was noted that studies on the alcohol-preferring AA and nonpreferring ANA rat lines in general found few differences in indicators of serotonergic functioning, while studies on the P and NP rat lines found robust differences. Recent studies confirm this state of affairs, while not providing an adequate explanation. Kiianmaa, Nurmi, Nykänen, and Sinclair (1995) found no group differences in concentrations of brain 5-HIAA in AA versus ANA rats, and no ethanol-induced changes in 5-HIAA levels in the nucleus accumbens. No differences in the density of 5-HT_{2A} receptors in various brain regions of AA rats compared to ANA rats have been found as well (Ciccocioppo, Ge, Barnes, & Cooper, 1997). In contrast, high alcohol-drinking adult male rats from the F_2 generation of PxNP intercrosses had lower concentrations of nucleus accumbens 5-HT and 5-HIAA (as well as DA), with no differences in 5-HT or 5-HIAA in the frontal cortex, anterior striatum, or hippocampus (McBride, Bodart, Lumeng, & Li, 1995). Recent reports demonstrate significantly lower densities of 5-HT_{1B}, 5-HT_2, and 5-HT_{2A} receptors, higher and lower densities of 5-HT_{1A} receptors, higher densities of 5-HT_{2C} receptors, no differences in 5-HT_3 receptors, fewer 5-HT-immunostained neurons and lower 5-HT fiber density in a number of brain regions of alcohol-naive alcohol-preferring P rats compared to nonpreferring (NP) rats (Ciccocioppo et al., 1997; McBride, Chernet, Rabold, Lumeng, & Li, 1993; McBride et al., 1997; McBride, Guan,

Chernet, Lumeng, & Li, 1994; Pandey, Lumeng, & Li, 1996; Zhou, Bledsoe, Lumeng, & Li, 1994; Zhou, Pu, Murphy, Lumeng, & Li, 1994). Taken together, the results suggest a loss or lack of development of 5-HT neurons/fibers and/or lower levels of 5-HT in certain brain regions of P rats, leading to fewer 5-HT_2 receptors or decreased formation of 5-HT_2 sites, an up-regulation of 5-HT_{1A} postsynaptic receptors and fewer 5-HT_{1A} autoreceptors. Changes in indicators of serotonergic functioning have similarly been noted in other alcohol preferring rodent lines (Ciccocioppo, Panocka, Stefanini, Gessa, & Massi, 1995; Deckel, Vavrousek-Jakuba, & Shoemaker, 1995).

As 5-HT receptor antagonists reduce ethanol consumption in unselected rat strains, they also do so in alcohol-preferring rat lines. The 5-HT_2 antagonist amperozide (Lankford, Björk, & Myers, 1996; McMillen & Williams, 1995; Myers & Lankford, 1996; Myers, Lankford, & Björk, 1993), and 5-HT_4 antagonist GR113808 (Panocka, Ciccocioppo, Polidori, Pompei, & Massi, 1995) reduced ethanol consumption in alcohol-preferring rats, as did the combination of amperozide and the opiate receptor antagonist naltrexone (Lankford & Myers, 1996). In contrast, there have been two studies which did not find an effect of the 5-HT_{1A} agonist ipsapirone (McMillen & Williams, 1995) or the 5-$HT_{2A/2C}$ antagonist ritanserin (Panocka, Ciccocioppo, Pompei, & Massi, 1993) on alcohol intake in alcohol-preferring rat lines. A lower, subchronic risperidone (5-HT_2/D_2 antagonist) dose which produces 5-HT_2 antagonism but low D_2 antagonism did not reduce ethanol preference in sP rats, but a higher risperidone dose (which produces D_2 antagonism) did (Panocka, Ciccocioppo, Pompei, et al., 1993), suggesting that involvement of the DA system is necessary for a reduction of ethanol intake by 5-HT_2 antagonists.

A number of novel drugs with affinities for both 5-HT_{1A} and 5-HT_2 receptors attenuate ethanol drinking in high alcohol-drinking rats, such as FG5974 and FG5865, mixed 5-HT_{1A} agonist/5-HT_{2A} antagonists (Lankford et al., 1996; Long, Kalmus, Björk, & Myers, 1996). FG5893, a drug with similar affinities as FG5974, suppresses drinking in cyanamide-treated rats but had no effect on alcohol intake in P rats, possibly due to differences in the pharmacokinetics of the two drugs (Lankford et al., 1996). FG5938, also with affinities for 5-HT_{1A} and 5-HT_{2A} receptors, decreased ethanol intake and paradoxically increased food intake in P rats (Piercy, Björk, & Myers, 1996).

An amino acid mixture devoid of tryptophan (the amino acid precursor of 5-HT) did not alter volitional alcohol intake in moderate to high alcohol drinking/preferring vervet monkeys, relative to the control amino acid mixture (Palmour, Ervin, & Young, in press), consistent with the studies on healthy male humans (Pihl, Young, Ervin, & Plotnick, 1987). On the other hand, an amino acid mixture devoid of phenylalanine and tyrosine (the amino acid precursors of the catecholamines DA and NE) decreased ethanol intake relative to the control mixture (Palmour et al., in press). Finally, as might be expected, SSRIs also reduced ethanol intake in alcohol-preferring rats (Kampov-Polevoy & Rezvani, 1997; Rezvani & Grady, 1994).

In summary, studies with rat lines bred to be alcohol-preferring or high alcohol drinking animals continue to reinforce the notion that lowered serotonergic functioning is causally implicated in alcohol drinking. Particularly compelling are the many studies showing defects in the serotonergic system in alcohol-naive P alcohol-preferring rats.

Effects of Ethanol on Central Serotonergic Neurotransmission

In the second review (LeMarquand et al., 1994b), it was concluded that acute doses of ethanol transiently increase serotonin levels and the function of serotonergic neurons in animals. With chronic administration, the increase in serotonergic functioning appears to attenuate. Studies continue to show that ethanol administration increases serotonergic levels (Alari, Sjöquist, & Lewander, 1987; Jarman, Pattichis, Peatfield, Glover, & Sandler, 1991; Portas, Devoto, & Gessa, 1994; Yan, Reith, Jobe, & Dailey, 1996) or receptor function (Barann, Ruppert, Gothert, & Bonisch, 1995). However, there have been an equal number of studies that have found no effect (Beck, Eriksson, Kiianmaa, & Lundman, 1986; Gil-Martin, Colado, Fernandez-Lopez, Fernandez-Briera, & Calvo, 1996) or decreased levels (Gil-Martin et al., 1996; Wang, Wei, & Sun, 1993) of 5-HT and it metabolites in various brain regions following acute or chronic ethanol administration. As well, no effect (Lau & Frye, 1996) or decreased (Pistis, Muntoni, Gessa, & Diana, 1997; Sanna, Dildy-Mayfield, & Harris, 1995) functioning of the various aspects of the 5-HT system following acute or chronic ethanol have been noted. Achieving a comprehensive understanding of the effects of ethanol on 5-HT levels is difficult due to between-study variation in the parameters studied, ethanol doses, brain regions, rat strains, etc., variables that clearly have an impact (Selim & Bradberry, 1996). A comprehensive understanding of the effect of alcohol on serotonergic functioning may only be obtained by accounting for these complexities.

Pandey and associates (Pandey, Davis, & Pandey, 1995; Pandey & Pandey, 1996) have extensively investigated the effect of ethanol on 5-HT receptor numbers and functioning. In general, acute ethanol had

no effect on the maximum number of binding sites (B_{max}) or the affinity (dissociation constant, K_d) of 5-HT_{1A} or 5-HT_{1B} receptors in various brain regions (Pandey, Piano, & Pandey, 1996; Rilke, May, Oehler, & Wolffgramm, 1995). Chronic ethanol appears to increase the density of 5-HT_{1B} and 5-HT_{1C} receptors in some brain regions, with no changes in 5-HT_{1A} or 5-HT_2 receptor parameters (Pandey et al., 1993; Pandey, Piano, et al., 1996; Pandey, Piano, Schwertz, Davis, & Pandey, 1992), suggesting an upregulation of some 5-HT receptor subtypes following chronic ethanol, possibly due to decreased 5-HT release. This interpretation is supported by the fact that 5-HT-stimulated [3H]inositol 1-phosphate formation is increased following chronic ethanol as well (Pandey et al., 1993).

The hypothesis that chronic ethanol may up-regulate some 5-HT receptor subtypes is supported by a study investigating the 5-HT_3 receptor and DA interactions (Yoshimoto et al., 1996). In chronic alcohol-treated rats, perfusion of ethanol into the nucleus accumbens increased the extracellular levels of DA, compared to controls. Perfusion of the SSRI sertraline into the nucleus accumbens enhanced the extracellular levels of 5-HT in both chronic alcohol-treated rats and controls, but incremented ethanol-induced DA release in chronic alcohol-treated rats alone. Similarly, perfusion of the 5-HT_3 receptor agonist 2-methyl-5-HT (2-Me-5-HT) also enhanced extracellular DA, with a greater magnitude of DA in chronic alcohol-treated rats. Ethanol-induced 5-HT release was inhibited in alcohol-treated rats. The authors concluded that chronic alcohol intake increases the sensitivity of 5-HT_3 receptors, 5-HT_3 receptors regulate DA release in the nucleus accumbens, and that dopaminergic neuronal systems associated with the 5-HT_3 ionophore in the nucleus accumbens are upregulated after chronic alcohol (Yoshimoto et al., 1996).

Concerning the withdrawal of chronic ethanol, it was concluded in the second review paper (LeMarquand et al., 1994b) that serotonergic functioning may be decreased due to the loss of the facilitating effects of ethanol. This has received some support in recent studies. Rats that experienced key jingling-induced seizures following chronic ethanol withdrawal had lower levels of striatal 5-HT compared to those rats who did not seize (Mirovsky, Wagner, Sekowski, Goldberg, & Fisher, 1995). Joint administration of amphetamine (DA agonist) and fenfluramine (5-HT releaser and uptake inhibitor) prevented seizures during ethanol withdrawal, and reduced intake of ethanol during and immediately following ethanol withdrawal (Mirovsky, Yu, et al., 1995). An increased density of 5-HT_{1B} receptors, a decreased the density of 5-HT_2 receptors (Pandey, et al., 1992; Pandey, Piano, et al., 1996), decreased 5-HT-stimulated [3H]-IP1 formation (Pandey, et al., 1992), decreased 5-HT neuron firing rates (Pistis, et al., 1997), and decreased brain tryptophan and 5-HT synthesis and turnover (possibly due to increased tryptophan pyrrolase activity) (Bano et al., 1996; Oretti et al., 1996) have all been noted following the withdrawal of chronic ethanol. These studies suggest that serotonergic functioning may be lower following during ethanol withdrawal, possibly motivating the resumption of drinking. This hypothesis has received some direct support: chronic ethanol self-administration increased both DA and 5-HT release in the nucleus accumbens of non-alcohol dependent rats; withdrawal suppressed the release of both neurotransmitters; and reinstatement of ethanol self-administration reinstated DA release at prewithdrawal levels, with 5-HT levels recovering somewhat later (Weiss et al., 1996).

Clinical Studies

The concentration of 5-HIAA in the CSF is widely considered to be a relatively direct measure of brain 5-HT levels in humans. In the previous review (LeMarquand, Pihl, & Benkelfat, 1994a), a number of studies found lower levels of CSF 5-HIAA in alcoholics relative to controls. Recently, it was demonstrated that early-onset alcoholics (excessive alcohol consumption before age 25) have low CSF 5-HIAA levels (with no differences in CSF the DA metabolite homovanillic acid [HVA], the NE metabolite 3-methoxy-4-hydroxy-phenylglycol [MHPG] or tryptophan levels) compared to late-onset alcoholics, further supporting the notion that a particular subgroup of alcoholics may be characterized by reduced central serotonergic turnover (Fils-Aime et al., 1996; see also Higley, Suomi, & Linnoila, 1996a for this relationship in primates). CSF levels of metabolites and precursors were not different between alcoholics with alcoholic fathers or alcoholic mothers compared to the rest of the sample, but those alcoholics with both alcoholic fathers and mothers had lower CSF 5-HIAA, HVA, and tryptophan. In one additional smaller study, Kaakkola, Tuomainen, Mannisto, and Palo (1993) found no differences in the CSF 5-HIAA in eight alcoholic men with ataxia relative to individuals with late onset cerebellar ataxia and controls.

In one study investigating precursor levels, serum free tryptophan was *higher* in abstinent alcoholics compared to controls, regardless of age of onset of alcoholism, family history of alcoholism or sociopathic traits, suggesting a greater tryptophan availability for brain uptake (Farren & Dinan, 1996). A large number of studies suggest the opposite, however (LeMarquand et al., 1994a).

Lowered CSF 5-HIAA in alcoholics may be a consequence of neuronal loss due to alcohol use or other factors. Postmortem, alcoholics with various neurological disorders (Wernicke's encephalography, Korsakoff's psychosis) had significant serotonergic neuronal loss in the midbrain, pons and medullary regions (in the order of 80-90%) (Halliday, Ellis, Heard, Caine, & Harper, 1993), as well as in the median raphe (Baker, Halliday, Kril, & Harper, 1996b). Conversely, there was no evidence of neuronal loss in the dorsal (Baker, Halliday, Kril, & Harper, 1996a) or median (Baker et al., 1996b) raphe nuclei of chronic alcoholics without Wernicke-Korsakoff syndrome or cirrhosis compared to controls. These findings suggest that alcohol alone is not sufficient to cause neuronal loss in the raphe nuclei, and that thiamine deficiency may partly contribute to serotonergic neuronal loss. These results underscore the need to consider the impact of Wernicke-Korsakoff syndrome in studies of serotonergic functioning in alcoholics.

An increasingly popular paradigm for investigating 5-HT receptor functioning involves administering a serotonin agonist and measuring its effects on neuroendocrine hormones (Yatham & Steiner, 1993). Serotonin stimulates the release of hypothalamic/pituitary/adrenal (HPA) axis hormones (cortisol, adrenocorticotropic hormone and growth hormone) and prolactin (PRL) (Tuomisto & Männistö, 1985). At least four serotonergic receptor subtypes, 5-HT_{1A}, 5-HT_{2A} (previously the 5-HT_2), 5-HT_{2C} (previously the 5-HT_{1C}), and 5-HT_3 are involved in stimulating the secretion of these hormones (Jørgensen, Knigge, & Warberg, 1992; Lee, Nash, Barnes, & Meltzer, 1991; Lesch et al., 1990; Levy & Van de Kar, 1992). In general, the majority of studies have demonstrated blunted hormonal responses (primarily PRL) to various 5-HT agents, including MK-212 (a

5-HT_{2A}/5-HT_{2C} agonist) (Lee & Meltzer, 1991), *m*CPP (Buydens-Branchey, Branchey, Fergeson, Hudson, & McKernin, 1997a), sumatriptan (a 5-HT_{1D} agonist) (Coiro & Vescovi, 1995; Vescovi & Coiro, 1997), fenfluramine (Balldin, Berggen, Engel, & Eriksson, 1994), and L-5-HTP (Lee & Meltzer, 1991), in alcoholics compared to controls. Predictably, there have been a number of negative results (Lee & Meltzer, 1991; Balldin, Berggen, Engel, & Eriksson, 1994; Handelsman et al., 1996), including no differences between type 1 and type 2 alcoholics and controls on hormonal responses following a single-blind, non-placebo controlled challenge with clomipramine, a relatively selective 5-HT reuptake inhibitor (George et al., 1995). Overall, these studies suggest subsensitive functioning of hypothalamic 5-HT_{2A}/5-HT_{2C} (and possibly 5-HT_{1A}) receptor subtypes in alcohol dependent individuals, possibly a neurophysiologic consequence of chronic alcohol use.

Interestingly, Lee and Meltzer (1991) noted that three of the fourteen alcoholics in their study reported an "alcohol-like" effect after MK-212, similar to the "high" feeling following *m*CPP (but not placebo) administration reported in alcoholics (Buydens-Branchey et al., 1997a), particularly type 2 alcoholics (Benkelfat et al., 1991; George et al., 1997). This effect has been replicated and extended: *m*CPP (a mixed 5-$HT_{2C/D}$ and 5-HT_{2A} agonist) but not yohimbine (an α_2-adrenergic receptor antagonist) or placebo was rated as more similar to the effects of ethanol, cocaine and marijuana in alcohol dependent men (Krystal, Webb, Cooney, Kranzler, & Charney, 1994). This effect appears to be related to either an increase (Krystal et al., 1994) or decrease (Buydens-Branchey et al., 1997a) in craving for alcohol in alcoholics following *m*CPP. No change in craving is reported following yohimbine or placebo (Krystal et al., 1994). Stimulation of 5-HT_{2A}/5-

HT_{2C} receptors may produce the discriminative properties of drugs of abuse in humans and be involved in craving for alcohol.

Another novel method of assessing serotonergic functioning has been put forward by Hegerl et al. (1993). They suggest that the response pattern of primary auditory cortices to auditory stimuli of differing intensities depends on the level of central 5-HT neurotransmission, such that a pronounced amplitude increase with increasing auditory stimulus intensity indicates low 5-HT neurotransmission, and vice versa. Alcoholics (abstinent for one week) with strong antisocial tendencies showed a stronger intensity dependence of their evoked responses from primary auditory cortices compared to alcoholics with fewer antisocial tendencies, which was not related to age of onset of alcoholism or family history (Hegerl, Lipperheide, Juckel, Schmidt, & Rommelspacher, 1995). This suggests that the former group may be characterized by serotonergic hypofunction (and provides support for the notion of low 5-HT functioning in type 2, antisocial alcoholics specifically). A nonalcoholic control group was not included in this study (Hegerl et al., 1995). This intensity dependence is reduced when alcoholics are tested in an intoxicated state, and is reduced in healthy individuals after ethanol challenge (Hegerl, Juckel, Schmidt, & Rommelspacher, 1996), consistent with the idea that alcohol has 5-HT agonist effects.

Clinical treatment studies using SSRIs continue to demonstrate modest therapeutic gains in alcoholic individuals (Balldin, Berggren, Engel, Eriksson, Hård, et al., 1994; Balldin, Berggren, Bokström, et al., 1994; Cornelius et al., 1993; Gerra et al., 1992; Naranjo, Bremner, & Lanctôt, 1995; Naranjo, Poulos, Bremner, & Lanctôt, 1994). Fluoxetine reduced the number of drinks consumed in alcoholics with a parental history of alcoholism (Gerra et al., 1992), congruent with the notion of a

serotonergic abberation in familial alcoholism. Serotonin agonists and antagonists are also effective in treating alcoholics. The 5-HT_{1A} agonist buspirone (Kranzler et al., 1994) in anxious alcoholics, the 5-HT_2 antagonist ritanserin (Naranjo et al., 1995), and the 5-HT_3 antagonist ondansetron (Sellers et al., 1994) all had modest positive effects on alcohol-related outcome variables, with ritanserin showing somewhat less efficacy. Ondansetron-induced reductions of alcohol intake in alcoholics may be mediated through an enhancement of the discriminant effects of alcohol, as ondansetron augmented selected stimulant, sedative and subjective effects of alcohol in social drinkers (Swift, Davidson, Whelihan, & Kuznetsov, 1996).

A number of studies show no effect of SSRIs on alcohol-related outcomes in alcoholics, however (Kabel & Petty, 1996; Kranzler et al., 1995; Kranzler, Del Boca, Korner, & Brown, 1993). For example, type B alcoholics (roughly analogous to type 2 alcoholics) treated with cognitive-behavioral therapy and fluoxetine, did poorer on drinking-related outcomes at posttreatment (but not at follow-up) than those treated with cognitive-behavioral therapy and placebo (Kranzler, Burleson, Brown, & Babor, 1996). As outlined above, animal studies have suggested that SSRIs may substitute for the discriminative stimulus effects of ethanol (Maurel et al., 1997). In a small study, however, the SSRI zimelidine had no effects on ethanol-induced body sway and subjective effects in healthy men (Scott, Fagan, & TipLady, 1982).

In the previous review (LeMarquand et al., 1994a), alterations in platelet 5-HT levels in alcoholics had been found, however the significance of these findings was unclear. Recent studies shed little light on this subject. Platelet 5-HT levels during withdrawal from alcohol and after two weeks' abstinence were significantly lower in

alcohol abusing and dependent individuals versus controls. These results were interpreted as reflecting the biphasic effect of alcohol on 5-HT levels (chronic alcohol lowering 5-HT levels) (Bailly et al., 1993). Additionally, serotonin uptake in human peripheral blood lymphocytes was found to be higher in abstinent alcoholics compared to controls (Faraj, Olkowski, & Jackson, 1997), consistent with the notion of decreased synaptic availability (LeMarquand et al., 1994a). Finally, platelet 5-HT_2 receptor functioning was unaltered in abstinent alcoholics relative to controls (Reist et al., 1995), consistent with previous work (LeMarquand et al., 1994a).

Summary

Clearly, low serotonin is implicated in alcohol intake and dependence. A number of mechanisms have been proposed to explain this relationship. Alcohol facilitates 5-HT_3 receptor-mediated increases in DA in the nucleus accumbens, a neuroanatomical pathway putatively involved in the rewarding aspects of psychoactive drugs (Wise & Bozarth, 1987), suggesting that the 5-HT system may indirectly participate in the rewarding properties of ethanol. A more general mechanism has been hypothesized involving an alteration in signals for satiety following manipulation of serotonergic functioning. Additionally, a general effect of low central serotonergic functioning on locomotor activity has been proposed.

Soubrié (1986), following an extensive literature review, concluded that low 5-HT functioning disinhibits behavior typically suppressed by threat of punishment or nonreward. Similarly, Gray (1982) reviewed the experimental literature, demonstrating that serotonergic antagonists reverse punishment-induced response

suppression, an effect most likely mediated at hippocampal serotonergic terminals. Conversely, serotonergic agonists produce behavioral suppression. Gray thus implicated the ascending serotonergic pathways originating in the raphe nuclei in the production of behavioral inhibition in an animal exposed to aversive stimuli (Gray, 1982). The reduction in response suppression seen in animals with impaired forebrain serotonergic function is not due to a loss of sensitivity to the primary aversive reinforcer (pain sensitivity can even be increased), but appears to be due to a general increase in motor disinhibition, as evidenced by increases in motor activity (under certain conditions, such as exposure to a novel environment [bright lights and noise]), hyperactivity to mild tactile stimuli, aggressive responding following foot-shock, and increased open-field ambulation. Interference with forebrain serotonergic systems has a less consistent effect on behavioral inhibition induced by non-reward; Gray implicated the dorsal noradrenergic bundle in the transmission of signals of reward used in the detection of non-reward (Gray, 1982).

This leads us to the general hypothesis tested in this thesis: that the effects of low serotonin on alcohol intake may be mediated by an increase in disinhibited behavior in certain susceptible individuals. In this model, a genetic predisposition in individuals at risk for alcohol dependence may be expressed through low serotonergic functioning, contributing to that individual's propensity to respond, under certain stimulus conditions, in a disinhibited, impulsive fashion, and ultimately predisposing the individual to increased alcohol intake and alcoholism.

One group that is at an increased risk for developing alcoholism is nonalcoholic young men with a family history of alcoholism, for two

primary reasons. First, alcoholism is more prevalent in men than in women. The lifetime prevalence of alcohol abuse in males is 12.5%; in females 6.4%. For alcohol dependence, the respective prevalences are 20.1% and 8.2%, respectively. Twelve-month prevalences for alcohol abuse are 3.4% and 1.6% for males and females, respectively; for alcohol dependence 10.7% and 3.7% (Kessler et al., 1994). Thus, the prevalence of alcohol dependence is anywhere from 2 to 3 times higher in men than in women.

Second, genetic evidence suggests that a highly heritable subtype of alcoholism may be limited to males. Studies concerning the genetics of alcoholism are reviewed briefly below.

A Brief Review of the Genetics of Alcoholism

Ample evidence suggests that alcoholism is partly genetically determined. Twin studies compare monozygotic (MZ) and dizygotic (DZ) twin pairs with the expectation that former will be more concordant for a behavior or disorder than the latter, as MZ twins share 100% of their genes while DZ twins share, on average, 50%. Some studies report the heritability (h^2) of a characteristic, defined as the proportion or percentage of variance attributable to genetic factors. Twin studies demonstrate that, by and large, MZ twins are more concordant for alcohol abuse or dependence than DZ twins (Hrubec & Omenn, 1981; Kaij, 1960; Koskenvuo, Langinvainio, Kaprio, Lönnqvist, & Tienari, 1984; Romanov, Kaprio, Rose, & Koskenvuo, 1991), with moderate to high heritability estimates (0.30 to 0.60) (Hrubec & Omenn, 1981; Koskenvuo et al., 1984; Pickens et al., 1991; Prescott et al., 1994; Romanov et al., 1991). Gender differences in heritability have been suggested, with significant genetic contributions for male alcoholism

but negligible genetic effects in females (Caldwell & Gottesman, 1991; McGue, Pickens, & Svikis, 1992; Pickens et al., 1991), however other studies have demonstrated a substantial genetic contribution towards female alcoholism (Kendler, Heath, Neale, Kessler, & Eaves, 1992; Kendler, Neale, Heath, Kessler, & Eaves, 1994). The method of proband ascertainment may contribute to the observed differences, as female abusers diagnosed clinically and in treatment (the former studies) may not be typical of women with drinking problems in the general population (the latter studies). Males with early onset of alcohol problems (first symptom by age 20) have a higher heritability (73%) than those with later onset (30%) (McGue et al., 1992). Some studies have not found differences in concordance rates between MZ and DZ twins pairs (Allgulander, Nowak, & Rice, 1991; Gurling, Clifford, & Murray, 1981; Gurling, Oppenheim, & Murray, 1984) or significant heritability estimates (Allgulander et al., 1991; Grove et al., 1990), however small and unrepresentative samples limit the validity and generalizability of some of these results (Prescott et al., 1994). Family studies, comparing the prevalence of alcoholism in families of alcoholics to those of nonalcoholics, have shown that alcoholics are anywhere from two to six times more likely to have family members who are alcoholic (reviewed in Cotton, 1979).

Adoption studies compare the rates of alcoholism in adopted-out adult offspring whose biological parents are alcoholic to those whose biological parents are not alcoholic. The earliest adoption study of alcoholism found no evidence for a genetic component for alcoholism (Roe, 1944), however studies since that time have established that a significant heritable component exists in male (Bohman, 1978; Cadoret, Cain, & Grove, 1980; Cadoret & Gath, 1978; Cadoret, O'Gorman,Troughton, & Heywood, 1985; Cadoret, Troughton,

& O'Gorman, 1987; Goodwin et al., 1974; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973; Schuckit, Goodwin, & Winokur, 1972), and perhaps female (Bohman, Sigvardsson, & Cloninger, 1981) alcoholism (although see Goodwin, Schulsinger, Knop, Mednick, & Guze, 1977). Cloninger, using Bohman's (1978) data, delineated two distinct subtypes of alcoholism (Cloninger, 1987b; Cloninger, Bohman, & Sigvardsson, 1981). Type 1, loss of control, or milieu-limited alcoholism is characterized by adult onset (>20 years old), with rapid progression from mild abuse to severe alcohol dependence, little or no criminality, and in many cases, biologic parents with similar patterns of abuse. Type 1 alcoholism is expressed only when there is a combination of a characteristic genetic and characteristic environmental background. Type 1 alcoholics are described as having passive-dependent or "anxious" personalities: they are high in harm avoidance, high in reward dependence, and low in novelty seeking. They are described as emotionally dependent, rigid, perfectionistic, inactive, quiet, patient and introverted, with guilt and fear over becoming dependent on alcohol (Cloninger, 1987b). Onset purportedly develops after heavy drinking is reinforced by social determinants, such as drinking at lunch or after work through the encouragement of friends.

In contrast, spontaneous alcohol-seeking behavior or the inability to abstain, known as male-limited type 2 alcoholism, is characterized by a early onset (<20 years of age) of moderate alcohol abuse regardless of external circumstances and frequent criminality. The liability for type 2 alcoholism is 90% heritable in men but seldom seen in women. The biologic fathers of these individuals often have had an early onset of severe alcohol abuse, extensive treatment for their alcohol abuse, and serious criminality beginning in adolescence or early adulthood. Type 2 alcoholics are described as antisocial: high

in novelty seeking, low in harm avoidance, and low in reward dependence. They are described as impulsive, aggressive, impatient, confident, talkative, and active (Cloninger, 1987b).

A recent replication of the "Stockholm Adoption Study" (Cloninger et al., 1981; Bohman et al., 1981) verified the distinction between these two forms of alcoholism in males (Sigvardsson, Bohman, & Cloninger, 1996). Specifically, the lifetime risk of severe alcoholism was elevated four-fold in adopted men with both type 1 genetic and environmental backgrounds. Neither a genetic or environmental background alone led to this type of alcoholism. In contrast, the lifetime risk for type 2 alcoholism was increased six-fold in male adoptees with a type 2 genetic background regardless of their environmental background (Sigvardsson et al., 1996). Cadoret et al. (1995) independently identified three pathways leading to alcohol abuse/dependence in male adoptees roughly analogous to the type 1/type 2 distinction. The first pathway was a direct effect of alcohol problems in the biologic parent increasing the risk for alcohol abuse/dependence in the adoptee, the second a direct environmental effect of alcohol problems in the adoptive relatives leading to alcohol abuse/dependency in the adoptee. The final pathway began with antisocial personality disorder in the biologic parent, leading to antisocial personality disorder in the adoptee, which then led to alcohol abuse/dependency in the adoptee. Type 1 alcoholism was likened to a combination of the first and second pathways, and type 2 alcoholism to the third.

Although the studies investigating a genetic contribution to the etiology of alcoholism have been criticized on a number of methodological grounds (Lester, 1988; Littrell, 1988; Murray, Clifford, &

Gurling, 1983; Searles, 1988) , it is widely agreed that a significant heritable component of alcoholism exists (Littrell, 1988; Murray et al., 1983). As Higley et al. (1993) suggest, a genetic predisposition, expressed through monoamine concentrations, may determine an individual's behavior in a circumscribed fashion to the stimuli to which he/she is exposed. As such, stable neurochemical differences may predispose an individual to be more sensitive to alcohol's rewarding properties, less sensitive to its detrimental effects, and/or more behaviorally disinhibited in general. Such a genetic predisposition, expressed in part through neurochemical functioning, may ultimately lead an individual to consume alcohol in great quantities, given certain environmental conditions (most notably, the availability of alcohol).

The hypothesis put forward in the present thesis is that a deficit in serotonergic levels and function is genetically transmitted, leading to increased disinhibition and alcoholism in susceptible individuals (i.e., young men with a family history of alcoholism). There is some evidence that serotonergic levels (and presumably function) may be genetically determined. Genetic factors significantly contribute toward determining cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) levels, the primary metabolite of serotonin, in rhesus monkeys (Higley et al., 1993). In humans, although not statistically significant, the correlation for CSF 5-HIAA concentrations in MZ twins was nearly twice that of DZ twins (Oxenstierna et al., 1986). As well, there is evidence that impulsivity is, at least to a certain extent, genetically determined. A self-report factor labelled "impulsive irritability" has been shown to be partly genetically determined (Coccaro, Bergeman, & McClearn, 1993). Moreover, some studies have shown that the personality dimension of aggressivity, in which impulsivity may be a component, is partly heritable (Ghodsian-Carpey & Baker, 1987;

O'Connor, Foch, Sherry, & Plomin, 1980; Tellegen et al., 1988). Others have not, however (Plomin, Foch, & Rowe, 1981; Vandenberg, 1967).

Given the model outlined above, one might expect alcohol dependent individuals (or a subset of), as well as their offspring, to demonstrate behavioral disinhibition. Moreover, indices of central 5-HT functioning should be inversely related to aggressive and impulsive behavior. The following sections will address these issues.

Behavioral Undercontrol and Impulsivity in Alcoholics and Individuals at High Risk for Alcoholism

At this point, it is important to review the various definitions of impulsivity that have been put forward in the literature. Helmers, Young, and Pihl (1995) have summarized various definitions of impulsivity, including acting without thinking (Barratt & Patton, 1983), the inability to plan ahead (Barratt & Patton, 1983; Buss & Plomin, 1975; Eysenck & Eysenck, 1977), the tendency to respond quickly to stimuli rather than inhibiting responses (Barratt & Patton, 1983; Buss & Plomin, 1975; Prior & Sanson, 1986), the lack of capacity to delay gratification (a preference for smaller immediate reinforcers as opposed to larger delayed reinforcers) (Logue, 1995), or a failure to withhold responses that lead to punishment or loss of expected reward (Gray, 1982). Clinically, impulsivity may be described as the repetition of deviant behavior characterized by a lack of reflectivity and delay (Glueck & Glueck, 1968; Oas, 1983). These definitions encapsulate a number of concepts: a lack of forethought (difficulty planning ahead, envisioning the consequences of one's actions), a difficulty learning from the consequences of one's actions, and a quickened behavioral tempo.

As discussed earlier, type 2 alcoholics have been characterized via self-report questionnaires as low in impulse control (Sher & Trull, 1994; Virkkunen, Kallio, et al., 1994), and higher in novelty seeking (Howard, Kivlahan, & Walker, 1997). Very few studies have investigated behavioral impulsivity in alcoholics. One study measured behavioral restraint using a task in which individuals must turn a knob as slowly as possible without stopping. Alcoholics were found to do this faster than pathological gamblers and controls (Carlton & Manowitz, 1992), suggesting a deficit in behavioral inhibition. A cluster analysis revealed that a subset (half) of the gamblers performed similarly to the alcoholics, while half were "hyperrestrained", performing more slowly than the controls. Both clinical groups were found to have a greater history of symptoms of Attention Deficit Disorder than controls.

As alcohol detrimentally affects multiple physiological systems, research into the etiological processes involved in alcohol dependence using alcoholics risks confusing cause and consequence (Pihl et al., 1990). Studies have focused on unaffected young men with paternal family histories of alcoholism (e.g., sons of male alcoholics, or SOMAs), due to the higher prevalence of alcohol dependence in men, and evidence suggesting the existence of a highly heritable male-limited subtype of alcoholism, as reviewed above. Individuals with a multigenerational paternal family history of alcoholism (MPFH) are at an even greater risk for the development of alcoholism compared to those with alcoholic fathers alone. A recent population study indicated that family histories characterized by an alcoholic father, paternal grandfather and at least one other paternal male relative increased the odds of alcohol dependence in a proband by 167% (Dawson, Harford, & Grant, 1992).

The assessment of aggressivity and impulsivity, or "behavioral undercontrol" (Sher, 1991), in SOMAs has been limited primarily to self- and other-reports. SOMAs score higher than controls on a number of scales indicative of undercontrolled traits: the MacAndrew scale and the Psychopathic Deviate scale of the Minnesota Multiphasic Personality Inventory, the Socialization scale of the California Personality Inventory, and the Novelty Seeking dimension of the Tridimensional Personality Questionnaire (Mann, Chassin, & Sher, 1987; Saunders & Schuckit, 1981; Sher, Walitzer, Wood, & Brent, 1991). Note that a large number of studies have failed to find differences between SOMAs and controls on the Tridimensional Personality Questionnaire (Hesselbrock & Hesselbrock, 1992; Howard, Cowley, Roy-Byrne, & Hopfenbeck, 1996; Moss, Yao, & Maddock, 1989; Peterson, Weiner, Pihl, Finn, & Earleywine, 1991; Schuckit, Irwin, & Mahler, 1990; Zaninelli, Porjesz, & Begleiter, 1992), including the subscale hypothesized to be related to serotonergic neurotransmission, that of Harm Avoidance (Cloninger, 1987b). Studies finding no difference between SOMAs and controls on the MacAndrew scale (Alterman, Bridges, & Tarter, 1986; Alterman, Searles, & Hall, 1989) have been criticized for low sample sizes (Sher, 1991). As noted by Sher (1991), the effect sizes are moderate in this literature, with substantial overlap between the groups, possibly at least partly explained by the reliance on SOMAs in college as research participants. Presumably a significant proportion of those behaviorally undercontrolled SOMAs at risk for later alcoholism do not advance into college (Pihl et al., 1990).

Prospective studies draw similar observations: SOMAs, rated by teachers and/or interviewers, are more impulsive/restless than controls (Aronson & Gilbert, 1963; Knop, Teasdale, Schulsinger, & Goodwin, 1985; Schulsinger, Knop, Goodwin, Teasdale, & Mikkelsen,

1986). Although negative findings exist (Berkowitz & Perkins, 1988; Tarter, Hegedus, Goldstein, Shelly, & Alterman, 1984), Sher (1991) concludes that "traits subsumed under the behavioral undercontrol rubric [aggression, sensation seeking, impulsivity, socialization] appear to correlate with each other, with alcohol use/abuse, and with family history of alcoholism" (p. 76).

Some studies have utilized behavioral measures of aspects of impulsivity. One study measuring a concept related to behavioral undercontrol, response perseveration, found that MPFH young men played more cards in a task in which the probability of winning decreased with more cards played (Giancola, Peterson, & Pihl, 1993). This suggests a difficulty in discerning the implicit rules of the task, an insensitivity to punishment, and/or a disinhibited style of responding driven by the possibility of reward in these individuals. Young adult children of alcoholics were also found to be more disinhibited and less persistent after consuming alcohol than children of nonalcoholics (Baer, Novick, & Hummel-Schluger, 1995).

There is only preliminary evidence that an impulsive behavioral style may be associated with excessive alcohol intake. Impulsivity, as measured by the delay-of-reward paradigm, was positively related to the magnitude of alcohol self-administration in rats (Poulos, Lê, & Parker, 1995). In humans, depressed, impulsive adolescents have been found to drink more heavily than depressed, nonimpulsive adolescents or nondepressed adolescents (Hussong & Chassin, 1994). Additionally, using structural equation modelling, it has been demonstrated that early aggressive behavior (possibly related to an impulsive behavioral style) leads to increases in alcohol use and alcohol-related aggression in adolescent males (White, Brick, & Hansell, 1993).

If deficient serotonergic functioning is associated with disinhibited behavior in general, then behaviors characterized by disinhibition, such as aggression, should be associated with low central 5-HT. Similarly, experimental manipulations that lower central serotonergic functioning should produce a tendency toward disinhibited behavior and aggression.

It is important to define the concept of aggression. Bushman and Cooper (1990) view aggression as "behavior directed toward the goal of injuring another living being, who is motivated to avoid such treatment". Others have attempted to classify aggressive acts according to their characteristics, e.g., physical/verbal, active/passive, and/or direct/indirect (Buss, 1961). Valzelli (1981) distinguished between instrumental aggression (aggression as a means to reward), and hostile aggression (aggression with the goal of minimizing aversive conditions). Pihl, Peterson and Lau (1993), focusing on the consequences of aggressive behavior (i.e., the production of an aversive state), note that aggressive acts intend to punish (produce physical and/or psychological pain) or to threaten. They include this distinction in a 2 X 2 X 2 definition of aggression, the other characteristics being instrumental versus defensive (an unconditioned response consequent to punishment), and prosocial versus antisocial (Pihl et al., 1993). These definitions underscore the heterogeneity of aggressive behavior, and suggest that not all types of aggressive behavior may be related to serotonergic functioning. Given the current line of reasoning, one would expect impulsive aggression to be most strongly correlated to central nervous system serotonergic functioning.

Animal Studies

Comprehensive reviews of the animal literature clearly demonstrate that aggressive behavior in rodents can be elicited by manipulating 5-HT experimentally (see Olivier et al., 1990; Pucilowski & Kostowski, 1980). Most recently, mice strains genetically altered and bred for specific neurochemical characteristics have been used to explore the 5-HT/aggression link. Mice bred to be lacking the 5-HT_{1B} receptor (the rodent homolog of the human 5-$HT_{1D\beta}$ receptor) were more aggressive when provoked by an intruder compared to control mice, suggesting a role for the 5-HT_{1B} receptor in aggressivity and perhaps impulsivity (Saudou et al., 1994). Knock-out mice deficient in the calmodulin-dependent kinase II gene evidence decreased dorsal raphe 5-HT cell firing, decreased fear and increased aggressivity (Chen, Rainnie, Greene, & Tonegawa, 1995). Transgenic mice overexpressing the human growth factor TGFα are characterized by a decreased brain 5-HIAA/5-HT ratio, increased aggressivity, and "behavioral despair" (Hilakivi-Clarke et al., 1995). Mice engineered to be deficient in monoamine oxidase A functioning (the enzyme responsible for the breakdown of 5-HT, NE and DA) evidenced dramatically increased brain 5-HT, DA and NE concentrations, decreased brain 5-HIAA and the DA metabolite dihydroxyphenylacetic acid, and enhanced aggressive behavior in males (Cases et al., 1995). This finding may, at face value, conflict with the notion that lowered brain 5-HT function causes increased aggression, however increased brain 5-HT may lead to down-regulation of postsynaptic 5-HT receptors, so it is difficult to assess the overall effect of lowered monoamine oxidase A on serotonergic functioning.

Primate studies have added to the evidence that low 5-HT is associated with aggression and impulsivity, and increased 5-HT function with prosocial behavior. Cerebrospinal fluid 5-HIAA is negatively associated with spontaneous aggression (Doudet et al., 1995; Higley et al., 1992; Higley, Suomi, & Linnoila, 1996b; Mehlman et al., 1994), risk-taking (Mehlman et al., 1994), and excessive mortality (Higley, Mehlman, et al., 1996), and positively correlated with prosocial behavior, age of emigration (Mehlman et al., 1995) and social dominance rank (Higley, Suomi, & Linnoila, 1996b) in male as well as female (Higley, King, et al., 1996) rhesus monkeys. Raleigh, McGuire, Brammer, and Yuwiler (1984) have reported elevated whole blood serotonin in dominant male adult vervet monkeys that fell subsequent to a reduction in their position in the social hierarchy. A mixture of amino acids devoid of tryptophan, the amino acid precursor of 5-HT, increased aggressive behavior during competition for food in male vervet monkeys (Chamberlain, Ervin, Pihl, & Young, 1987).

In addition to the animal work on serotonin and disinhibition summarized by Soubrié (1986), a number of recent studies deserve specific attention. Poulos, Parker, and Lê (in press) found that dexfenfluramine, a 5-HT releaser, decreased impulsivity (i.e., reduced the choice of the immediate small reward in a delay of reward paradigm) in rats. In addition, low doses of 8-OH-DPAT, a 5-HT_{1A} agonist, increased impulsivity while higher doses decreased it (Poulos et al., in press), a finding similar to that of Tomkins, Higgins, et al. (1994) concerning alcohol consumption. This finding suggests that low doses of 8-OH-DPAT acted on presynaptic 5-HT_{1A} autoreceptors, resulting in decreased 5-HT function and increased impulsivity, while higher doses acted on postsynaptic 5-HT_{1A} receptors, resulting in the converse.

Human Studies

Low CSF 5-HIAA has been repeatedly associated with aggression and impulsivity in a number of clinical groups. Impulsive violent offenders (Linnoila et al., 1983; Virkkunen & Linnoila, 1993; Virkkunen, Rawlings, et al., 1994) and fire-setters (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), personality-disordered individuals with a history of aggressive/impulsive behavior (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Brown et al., 1982), aggressive/impulsive individuals with borderline personality disorder without major affective disorder (Brown et al., 1982), incarcerated personality disordered individuals with XYY (Bioulac, Benezech, Renaud, Roche, & Noël, 1978; Bioulac, Benezech, Renaud, Noël, & Roche, 1980), homicidal offenders who had killed a sexual partner (Lidberg, Tuck, Åsberg, Scalia-Tomba, & Bertilsson, 1985) or their own child (Lidberg, Åsberg, & Sunquist-Stensman, 1984), and depressed individuals (Rydin, Schalling, & Åsberg, 1982), as well as alcoholic males (Limson et al., 1991) and normal volunteers (Roy, Adinoff, & Linnoila, 1988) who self-report high aggression have been shown to have low CSF 5-HIAA levels. There were no differences, however, in CSF 5-HIAA between violent and matched nonviolent patients with schizophrenia (Kunz et al., 1995).

Additional studies with the sample of violent offenders and impulsive fire-setters (Virkkunen et al., 1987) demonstrate that a low blood glucose nadir following oral glucose challenge and low CSF-5-HIAA predicted recidivism (Virkkunen, De Jong, Bartko, Goodwin, & Linnoila, 1989), that those who had a history of serious suicide attempts had lower CSF 5-HIAA and MHPG levels (Virkkunen, De Jong, Bartko,

& Linnoila, 1989), and that those with fathers who were alcoholic had lower CSF 5-HIAA levels and were more often impulsive than those without alcoholic fathers (Linnoila, De Jong, & Virkkunen, 1989; Virkkunen, Eggert, Rawlings, & Linnoila, 1996). Personality scales indicate that low CSF 5-HIAA is associated with self-report irritability and impaired impulse control in alcoholic violent offenders (Virkkunen, Kallio, et al., 1994), and with extroverted aggression (but low introverted aggression) in normal volunteers (Moller et al., 1996). Additionally, the L allele of the tryptophan hydroxylase gene has been associated with low CSF-5-HIAA in impulsive alcoholic violent offenders but not in nonimpulsive alcoholic violent offenders or controls, and also with a history of suicidal behavior in the alcoholic violent offenders, irrespective of impulsivity, suggesting a possible reduced capacity to hydroxylate tryptophan to 5-HTP (Nielsen et al., 1994). Recently this finding has been challenged, as Abbar et al. (1995) found no association between the tryptophan hydroxylase gene and suicidal behavior, and notes that, in actuality, there was no difference in the tryptophan hydroxylase allelic frequencies between the alcoholic violent offenders who had attempted suicide and the controls in the Nielsen et al. (1994) study (but see also Nielsen et al., 1996).

Cerebrospinal fluid 5-HIAA has also been negatively correlated with aggression in children and adolescents with disruptive behavior disorders (characterized by hyperactive, impulsive and aggressive behaviors), and was lower in these young people than in a comparison sample of pediatric patients with obsessive-compulsive disorder (Kruesi et al., 1990). CSF 5-HIAA significantly predicted severity of physical aggression at two-year follow-up (Kruesi et al., 1992).

As a whole, methodological problems exist in the studies investigating the CSF 5-HIAA/aggression/impulsivity relationship.

For example, impulsivity, derived from police records and/or self-reported life histories, has been operationalized as a criminal act committed without provocation or premeditation and without the possibility of economic gain, with the victim(s) unknown to the offender (Virkkunen, De Jong, Bartko, Goodwin, et al., 1989). This definition fails to demonstrate impulsivity as a stable personality characteristic, and suffers from the possibility of falsification on the part of an individual to avoid more severe punishment (Tuinier, Verhoeven, & van Praag, 1995). Nevertheless, one review concluded that eight of the 22 published studies judged to be methodologically rigorous demonstrate the hypothesized relationship, particularly for relatively young, white, personality-disordered males with histories of criminal acts (Tuinier et al., 1995). The specificity of this relationship has been questioned as well; a recent meta-analysis suggests that low CSF 5-HIAA may not be specific to impulsive aggression and violence, but instead a characteristic of psychiatric illness in general (Balaban, Alper, & Kasamon, 1996).

Aggressive behavior expressed towards the self (suicide) has similarly been associated with low CSF 5-HIAA, regardless of diagnosis (Åsberg, Träskman, & Thorén, 1976; Brown et al., 1982; Brown et al., 1979; Träskman-Bendz, Åsberg, & Schalling, 1986; van Praag, 1983). This relationship holds true particularly for violent suicide (Åsberg et al., 1976; Mann & Malone, 1997). Annual variability in plasma L-tryptophan and the ratio of L-tryptophan to amino acids competing for brain uptake has been negatively associated with violent suicides in Belgium (Maes et al., 1995). These data suggest again that it may be aggression (whether outwardly or inwardly directed) characterized by its violent severity and impulsive quality that is related to low 5-HT functioning.

Recently, a mutation in gene coding resulting in deficient monoamine oxidase A activity has been associated with aggression and impulsive behavior in a large kindred with several males characterized with borderline mental retardation and abnormal behavior (arson, attempted rape, exhibitionism) (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993). This finding compares well with that reported earlier in mice, and suggests that the low CSF 5-HIAA found in impulsive aggressive individuals may be a consequence of low monoamine oxidase A activity. Lower monoamine oxidase A activity suggests lower 5-HT catabolism and increased 5-HT levels, although a down-regulation in post-synaptic 5-HT receptor functioning may result in overall reduced serotonergic functioning.

Indeed, the neuroendocrine evidence demonstrates on the whole that aggression/impulsivity is associated with blunted hormonal responses to 5-HT agonists relative to controls, suggesting lower receptor numbers or impaired functioning. Some studies have looked at impulsive and/or aggressive groups and compared their neuroendocrine responses to controls. Blunted prolactin and/or cortisol responses to various 5-HT agonist (fenfluramine, *m*CPP) challenges have been noted in individuals with past histories of suicide attempts, impulse control disorders (bulimia, substance dependence, pathological gambling), and personality disorders (borderline, narcissistic) (López-Ibor, Lana, & Saiz, 1991), murders with antisocial personality disorder (O'Keane et al., 1992), borderline personality disorder patients with histories of impulsive and aggressive behavior (Siever et al., 1987), patients with histories of self-mutilation or suicide (New et al., 1997), and men with antisocial personality disorder (Moss, Yao, & Panzak, 1990). The prolactin response in the latter study was inversely correlated with assaultive

aggression (measured by the Buss-Durkee Hostility Inventory) but not impulsivity (as measured by behavioral self-report or measurement of cognitive tempo). Interestingly, patients with *compulsive* personality had higher impulsive aggression scores than noncompulsive patients, and had blunted prolactin responses to fenfluramine compared to noncompulsive patients and nonpatient controls (Stein et al., 1996).

Other studies have correlated the neuroendocrine response to 5-HT agonists with self-report aggressivity. Prolactin responses to fenfluramine challenge have been inversely related to: past histories of suicide attempts in patients with major affective disorder and/or personality disorders, and with impulsive aggression in patients with personality disorders only (Coccaro et al., 1989); an increased risk of impulsive personality traits (and marginally to familial alcoholism) in the first-degree relatives of these patients (Coccaro, Silverman, Klar, Horvath, & Siever, 1994); Buss-Durkee Hostility Inventory "direct assault" in eight personality-disordered individuals (Coccaro, Kavoussi, & Hauger, 1995); a laboratory measure of aggression (Coccaro, Berman, Kavoussi, & Hauger, 1996); and self-report life histories of aggression in personality-disordered individuals (Coccaro, Kavoussi, Cooper, & Hauger, 1997). In the latter study, aggression was *positively* related to CSF 5-HIAA (Coccaro, Kavoussi, Cooper, et al., 1997). Neuroendocrine responses to other 5-HT agents have similarly been correlated to aggression and impulsivity (Cleare & Bond, 1997; Coccaro, Gabriel, & Siever, 1990; Handelsman et al., 1996; Netter, Hennig, & Roed, 1996). There have been a number of studies showing no relationship between neuroendocrine measures following serotonergic challenge and impulsivity or aggressivity (Coccaro, 1992; Wetzler, Kahn, Asnis, Korn, & van Praag, 1991), and some that demonstrate positive associations between these variables (Fishbein, Lozovsky, &

Jaffe, 1989; Moeller et al., 1994; Reist, Helmeste, Albers, Chhay, & Tang, 1996).

The relationship between neuroendocrine functioning following 5-HT agonist challenge and aggression has, in general, not been noted in children and adolescents. A d,l-fenfluramine challenge in preadolescent and adolescent males with disruptive behavior disorders found no differences in prolactin or cortisol release relative to controls (Stoff et al., 1992), and neuroendocrine response was unrelated to aggression levels in those patients with disruptive behavior. PRL responses to fenfluramine challenge in younger aggressive attention deficit hyperactivity disorder (ADHD) boys were greater compared to nonaggressive ADHD boys (Halperin et al., 1994); in an older cohort, PRL response was slightly higher in the nonaggressive boys, suggesting that normal boys may show a developmental increase in serotonergic functioning not found in aggressive boys (Halperin, Newcorn, Schwartz, et al., 1997). A more recent study with part of this sample and additional participants found blunted prolactin responses to fenfluramine in aggressive boys with a parental history of aggressive behavior, suggesting that familial transmission of aggressive behavior may be mediated by low central 5-HT functioning (Halperin, Newcorn, Kopstein, et al., 1997). Prolactin response to fenfluramine was related positively to self-report aggressivity and adverse-rearing environmental conditions in younger brothers of convicted delinquents, again suggesting that a developmental change in the serotonin-aggression relationship may occur (Pine et al., 1997).

Platelet receptor binding studies assess the density (B_{max}) and affinity (K_d) of platelet receptors using various 5-HT ligands. Significantly lower ketanserin binding to platelet 5-HT_2 receptors has

been found in adolescent violent delinquents compared to controls (Blumensohn et al., 1995). Similarly, the density of platelet 5-HT_{2A} receptors was lower in boys with parents with histories of incarceration or substance abuse compared to family history negative boys (Pine et al., 1996). These findings may reflect decreased central 5-HT_2 postsynaptic receptor function.

Platelet 5-HT uptake studies are consistent in their finding of a negative association between 5-HT uptake and aggression/impulsivity (although studies finding no (Castrogiovanni, Capone, Maremmani, & Marazziti, 1994; Maguire et al., 1997) or the opposite (Sarne et al., 1995) relationship exists). Conduct-disordered children have a reduced number of platelet ^{3}H-imipramine maximal binding sites (i.e., low B_{max}) versus healthy controls; B_{max} was inversely correlated with aggressive and externalizing factors on a parent assessment for the entire sample (Stoff, Pollack, Vitiello, Behar, & Bridger, 1987). Platelet 5-HT uptake and aggressive behavior were negatively associated in both schizophrenic and conduct-disordered adolescents (Modai et al., 1989). The B_{max} of platelet tritiated paroxetine binding was inversely correlated with total self-report aggression and the tendency to respond to provocation with physical assaultiveness in personality-disordered individuals relative to controls (Coccaro, Kavoussi, Sheline, Lish, & Csernansky, 1996). The B_{max} for platelet ^{3}H-imipramine binding was lower in highly aggressive mentally-retarded adults and suicide attempters compared to controls (Marazziti et al., 1993; Marazziti et al., 1996). Also, male outpatients with "episodic aggression" had a lower mean 5-HT uptake compared to male nonaggressive controls; 5-HT uptake was negatively correlated with impulsivity measures (Brown et al., 1989). Coccaro, Kavoussi, et al. (1996) have posited that reduced 5-HT uptake might lead to increase synaptic availability, reduced

sensitivity of terminal 5-HT autoreceptors, a greater release of 5-HT per neuronal impulse, and a subsensitivity of post-synaptic 5-HT receptors, with the net effect being reduced 5-HT neurotransmission.

Studies of blood serotonin have generally noted a positive correlation with aggression, whether it be in depressed inpatients (Mann, McBride, Anderson, & Mieczkowski, 1992), hyperactive (Cook, Stein, Ellison, Unis, & Leventhal, 1995) or conduct-disordered (Unis et al., in press) youth, violent male juvenile offenders (Pliszka, Rogeness, Renner, Sherman, & Broussard, 1988), children or adolescents with behavior disorders (Hughes et al., 1996), or individuals with episodic aggression (Brown et al., 1989). Blood serotonin levels were related to violence in an epidemiological study as well (Moffitt et al., in press). There have been studies that have found the reverse, however: lower blood 5-HT levels related to aggression (Greenberg & Coleman, 1976; Hanna, Yuwiler, & Coates, 1994). That high, rather than low, blood serotonin levels relate to aggression may be explained by increased platelet serotonergic transport (Cook et al., 1993, 1995). No association between plasma 5-HIAA and self-report measures of anger and hostility was found in seven violent criminals (Davis et al., 1993).

Low tryptophan levels and availability in adolescents with impulsive behavior have been found in a small study (Candito, Askenazy, Myquel, Chambon, & Darcourt, 1993), however other studies have found increased tryptophan and competing large neutral amino acids in violent offenders compared to nonviolent offenders and nonoffenders (Eriksson & Lidberg, 1997) and a positive relationship between tryptophan levels and self-report extroverted aggression (Moller et al., 1996). The impact of these results on tryptophan uptake into the brain is difficult to assess, because it is the ratio of tryptophan to the other large neutral amino acids that determines brain uptake.

Clinical treatment studies suggest the utility of serotonergic agonists in reducing aggression. Citalopram, a selective 5-HT reuptake inhibitor, and oral tryptophan, were effective in reducing aggressive incidents in hospitalized schizophrenics (Vartiainen et al., 1995; Morand, Young, & Ervin, 1983). There have been relatively few studies investigating the possible anti-aggressive effects of serotonergic compounds; more research is warranted in this area.

As is evident from the review above, the majority of studies linking aggressivity to serotonergic functioning are correlational in nature. In a recent experimental study, both aggressive and nonaggressive responding on a point subtraction aggression paradigm was reduced following the 5-$HT_{1A/1B}$ agonist eltoprazine in healthy males, an effect attributed to the sedative effects of the compound (Cherek, Spiga, & Creson, 1995). Despite the lack of studies demonstrating a causal link, it is clear that an inverse correlation exists between serotonergic functioning and aggression. Moreover, a number of studies suggest that aggression characterized by an impulsive quality is particularly associated with impaired 5-HT functioning. In the following section, the technique of acute dietary tryptophan depletion will be described, a procedure that hypothetically allows one to investigate the behavioral consequences of reduced serotonergic function. Additional experimental studies investigating the effects of acute tryptophan depletion on aggressive behavior will be reviewed.

The Acute Tryptophan Depletion Paradigm

The acute tryptophan depletion (ATD) paradigm is an experimental procedure which theoretically allows one to observe the

behavioral and psychological consequences of decreased central nervous system serotonin functioning. Aside from the administration of selective 5-HT receptor antagonists, there are no other effective means of reducing central 5-HT functioning in humans. Thus the ATD paradigm provides a valuable tool for investigating the behavioral effects of diminished serotonergic neuronal functioning.

Depletion of plasma tryptophan (i.e., tryptophan circulating in the blood stream) in humans is achieved through the oral administration of a mixture of amino acids devoid of tryptophan (Young, Smith, Pihl, & Ervin, 1985). Brain 5-HT metabolism can be significantly influenced by changes in the availability of its precursor tryptophan in plasma (Fernstrom & Wurtman, 1971). The enzyme tryptophan hydroxylase represents the rate-limiting step in the conversion of tryptophan to 5-HT (see Figure 1). Tryptophan hydroxylase converts tryptophan into 5-HTP, which is then converted to 5-HT via aromatic amino acid decarboxylase. Tryptophan hydroxylase is estimated to be only half-saturated with tryptophan (Friedman, Kappelman, & Kaufman, 1972; Young & Gauthier, 1981), therefore changes in tryptophan concentration can lead to changes in the rate of 5-HT synthesis, and changes in 5-HT levels. In rats, an amino acid diet devoid of tryptophan significantly reduces brain tryptophan, 5-HT and 5-HIAA levels (Biggio, Fadda, Fanni, Tagliamonte, & Gessa, 1974; Gessa, Biggio, Fadda, Corsini, & Tagliamonte, 1974; Moja, Cipolla, Castoldi, & Tofanetti, 1989). In vervet monkeys, an amino acid load devoid of tryptophan lowers plasma tryptophan by 50-60%, CSF tryptophan by 61% and 5-HIAA by 34%, with no changes in CSF HVA or MHPG, the respective metabolites of dopamine and norepinephrine (Young, Ervin, Pihl, & Finn, 1989). Since vervet monkeys and humans share 92% of their genes (King,

Yarbrough, Anderson, Gordon, & Gould, 1988), and CSF measurements of biogenic amine metabolite levels in these primates and humans are comparable (Young & Ervin, 1984), the effects of ATD in vervet monkeys provides circumstantial evidence of what likely occurs in humans. Recent ATD studies have achieved plasma tryptophan depletions of 80-90%, suggesting a larger reduction in 5-HT synthesis may occur in humans. A positron emission tomography/magnetic resonance imaging study using the radio-labelled tryptophan analogue ^{11}C-α-methyltryptophan found a 9.5-fold decrease in healthy males and a 40-fold decrease in females in the rate of *in vivo* brain 5-HT synthesis following ATD (Nishizawa et al., 1997). It should be noted that ATD may also alter the brain levels of other potentially psychoactive metabolites of tryptophan, such as tryptamine (Young & Gauthier, 1981), melatonin (Zimmerman et al., 1993), quinolinic acid, kynurenic acid, 5-HTOL (Young & Anderson, 1982), or perhaps brain protein synthesis itself.

Two mechanisms produce a subsequent decline in brain tryptophan following ATD. A mixture of amino acids devoid of tryptophan promotes the synthesis of new protein (Gessa et al., 1974). The tryptophan that is incorporated into the protein is drawn from pools in the blood and tissues, thus decreasing plasma and brain tryptophan levels. Protein synthesis is a crucial step in the depletion of plasma tryptophan levels; ingestion of an amino acid load devoid of tryptophan along with cycloheximide, a protein synthesis inhibitor, blocks the lowering of plasma tryptophan in rats (Moja et al., 1991).

A second mechanism plays a smaller role in the decline in brain (but not plasma) tryptophan. All large neutral amino acids (LNAAs; tyrosine, phenylalanine, leucine, isoleucine, valine, and tryptophan) compete for the same carrier system for transport across the blood brain

barrier (Oldendorf & Szabo, 1976). Brain tryptophan levels therefore depend not only on plasma tryptophan levels but also on the levels of the other LNAAs. As the levels of circulating plasma tryptophan decrease following the administration of an amino acid mixture devoid of tryptophan (due to protein synthesis), less tryptophan is available to compete for brain uptake relative to the other LNAAs (Pardridge, 1979). In investigating the relative importance of the second mechanism in affecting brain 5-HT, Gessa et al. (1974) found that a mixture of six amino acids which share a common transport system with tryptophan did not change plasma tryptophan, decreased brain tryptophan by 19%, decreased brain 5-HIAA by 22%, and did not affect brain 5-HT. In contrast, a mixture of nine of ten essential amino acids (tryptophan is the tenth), including five of the six that compete for the same transport system, decreased plasma tryptophan by 67%, brain tryptophan 57%, brain 5-HT 26%, and brain 5-HIAA 44%. (Note: essential amino acids, i.e., those that cannot be synthesized at a rate adequate to meet metabolic requirements and thus must be obtained from the diet, include arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine). Thus competition at the blood brain barrier plays a lesser role in regulating brain tryptophan than does protein synthesis.

Questions remain as to whether the effects of ATD on central 5-HT levels translate into changes in serotonergic release and postsynaptic functioning. In rats, reduced 5-HT synthesis leads to reduced presynaptic release, under certain conditions. The *in vivo* hippocampal release of 5-HT following electrical stimulation of the DRN or d-fenfluramine administration was attenuated following administration of an amino acid load (Gartside, Cowen, & Sharp, 1992). As well, a tryptophan-free amino acid load in rats decreased both basal

and *d*-fenfluramine-induced 5-HT release in the dorsal hippocampus (Stancampiano et al., 1997). In the cat, the release of 5-HT is dependent on nerve activity (Hery et al., 1979), and the rate of firing of 5-HT neurons is positively associated with behavioral arousal levels (Trulson & Jacobs, 1979). Thus, changes in tryptophan availability and brain 5-HT levels may be most likely to alter 5-HT release and postsynaptic function when 5-HT neurons are firing at a high rate (Young, 1986; Young, Pihl, & Ervin, 1988). A state of behavioral arousal may facilitate a differential in 5-HT release and post-synaptic function between ATD and balanced amino acid manipulations, producing robust behavioral effects of ATD in humans.

Further support (albeit circumstantial) for the notion that ATD affects 5-HT neurotransmission lies in the behavioral findings of ATD studies. The ATD paradigm has been used to investigate the oft-noted relationship between 5-HT and mood (lower central 5-HT functioning associated with lowered mood). ATD lowers mood in healthy volunteers in some studies (Cleare & Bond, 1995; Smith, Pihl, Young, & Ervin, 1987a; Weltzin, Fernstrom, McConaha, & Kaye, 1994; Young et al., 1985), but not in others (Abbott et al., 1992; Benkelfat, Ellenbogen, Dean, Palmour, & Young, 1994; Danjou et al., 1990; Oldman, Walsh, Salkovskis, Laver, & Cowen, 1994), an effect that may be dependent on baseline mood (Young, 1992): lowered mood after ATD is found in those individuals with high normal baseline depression and/or anxiety scores, as opposed to being euthymic at baseline. ATD led to a significant aggravation of premenstrual symptoms, particularly irritability, in women diagnosed with late luteal phase dysphoric disorder (Menkes, Coates, & Fawcett, 1994). In psychiatric populations, ATD induced a partial relapse to symptoms of clinical depression in remitted depressives on antidepressant medication (especially SSRIs)

(Delgado et al., 1990; see also Barr, Heninger, Goodman, Charney, & Price, 1997), and in depressive individuals with seasonal affective disorder in remission following light therapy (Lam et al., 1996; Neumeister, Praschak-Rieder, Hebelmann, Rao, et al., 1997). In a recent positron emission tomography study, remitted depressed patients on SSRIs who experienced an ATD-induced depressive relapse (versus those who did not) had decreased brain metabolism in the dorsolateral prefrontal cortex, thalamus, and orbitofrontal cortex, suggesting that these brain regions may mediate the symptoms of patients with major depression (Bremner et al., 1997). ATD also increased symptoms of depression in obsessive-compulsive disorder patients with a lifetime history of depression (Barr et al., 1994).

ATD had no effect on mood in unmedicated obsessive-compulsive disorder patients (Smeraldi et al., 1996), unmedicated depressed seasonal affective disorder patients (Neumeister, Praschak-Rieder, Hebelmann, Vitouch, et al., 1997), or in patients with major depression remitted with electroconvulsive therapy (Cassidy, Murry, Weiner, & Carroll, 1997). ATD had little effect in remitted bipolar patients on long-term lithium (Benkelfat et al., 1995) and variable, inconsistent effects in unmedicated depressed patients (Delgado et al., 1994). In remitted, medication-free former patients with major depression, ATD induced transient relapses in two studies (Moreno, Gelenberg, Potter, & Delgado, 1995; Smith, Fairburn, & Cowen, 1997), or had no effect (Leyton et al., 1997). This effect may be dependent on a history of suicide attempts and suicidal ideation, as those participants with these features evidenced greater mood lowering responses (Leyton, Young, & Benkelfat, 1997). A significantly greater proportion of young men at risk for depression by virtue of a strong family history of major affective disorder showed a mood lowering effect following

ATD compared to controls with no family history (Benkelfat et al., 1994). ATD also lowered mood in normal women when compared to the balanced amino acid condition (congruent with the finding that females are at higher risk for depression than males), however when tryptophan depleted at least one month later, a poor temporal stability of the ATD response was noted (Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996).

Other clinical groups have been studied. ATD increased ratings of anxiety, body image distortion, overreactivity, indecision, fatigue and depression in bulimic women compared to a balanced drink, with only increases in fatigue differentiating the ATD response of the clinical group to that of healthy females (Weltzin et al., 1994). A subsequent report found that bulimic women increased their caloric intake and reported greater irritability following ATD relative to healthy controls (Weltzin, Fernstrom, Fernstrom, Neuberger, & Kaye, 1995). ATD had no effect on anxiety in panic patients (Goddard et al., 1994), or on obsessive-compulsive symptoms in obsessive-compulsive disorder patients treated with SSRIs (Barr et al., 1994) or unmedicated (Smeraldi et al., 1996). ATD did increase respiratory ventilation in panic disorder patients compared to controls (Kent et al., 1996). In cocaine dependent individuals, ATD reduced the desire for cocaine following cue exposure (Satel, Krystal, Delgado, Kosten, & Charney, 1995), and reduced the subjective "high" induced by a test dose of intranasal cocaine (Aronson et al., 1995).

In normal volunteers, ATD abolished morphine-induced analgesia in the cold-pressor test, implicating serotonin as a mediator of the antinociceptive effect of morphine (Abbott et al., 1992). Cognitively, ATD reduced performance on tests of visual discrimination and paired associates, with no effect on executive

functions (subsumed by the frontal lobes), suggesting a role for 5-HT in learning and memory (Park et al., 1994).

Increased aggressive responding in healthy males following ATD has been found in studies characterized by an element of provocation (Cleare & Bond, 1995; Moeller et al., 1996; Pihl et al., 1995). Studies lacking provocation (Salomon, Mazure, Delgado, Mendia, & Charney, 1994; Smith, Pihl, Young, & Ervin, 1987b) have not demonstrated an effect of ATD on aggressivity. This may relate once again to the notion that behavioral arousal (in this case produced via provocation) is a necessary precondition to achieve differences in central 5-HT function following ATD and thus observable behavior changes (Young et al., 1988). In a recent study investigating the combined effects of ATD and alcohol on aggression, alcohol and tryptophan manipulations did not interact, producing independent, additive increments in aggressive responding (Pihl et al., 1995).

Related to the notion of susceptibility to ATD-induced mood changes discussed above, Finn, Young, Pihl, and Ervin (in press) found that normal males high in hostile or antisocial traits demonstrated greater associations between ATD-induced changes in plasma tryptophan and changes in hostility compared to those low in hostile or antisocial traits, respectively. Thus, individuals possessing traits related to low 5-HT activity (high antisociality or hostility) may be more susceptible to ATD-induced psychological changes (Finn et al., in press), just as those with high normal baseline depression scores may be more susceptible to the mood-lowering effect of ATD. Additionally, Cleare and Bond (1995) selected young men either high or low on the Buss-Durkee Hostility Inventory, and found increased subjective and behavioral aggressivity after ATD in the high trait aggressive group only.

In summary, ATD is a safe, effective method of investigating the behavioral effects of lowered central serotonergic synthesis (and presumably function) in humans. It is one of the only methods to induce transient alterations in central serotonergic synthesis and function in humans. This procedure has been used productively in a number of patient populations to test hypotheses relating to the role of serotonin in various psychopathologies.

Passive Avoidance Learning

The large majority of studies investigating the relationship between serotonergic functioning and impulsivity in humans have assessed impulsivity either by administering self-report questionnaires (Coccaro, Kavoussi, Sheline, Berman, & Csernansky, 1997) or by assessing the impulsive nature of crimes committed by the individual (Virkkunen, Rawlings, et al., 1994). Few studies have attempted to correlate indices of serotonergic functioning in humans with behavioral measures of impulsivity.

One method of investigating *behavioral* disinhibition in humans is through passive avoidance learning tasks. Passive avoidance is defined as the ability to withhold a response that would have led to punishment or loss of potential reward. Newman (1987) has extensively explored passive avoidance learning and disinhibition in humans using a go/no-go discrimination task. In this task, participants learn by trial and error to respond (press a button) to active stimuli (two-digit numbers flashed on a computer screen) for monetary reward and withhold response to passive stimuli to avoid punishment (loss of money). Two types of errors are possible: omission errors (OEs), failing to respond to active stimuli; and commission errors (CEs), or

passive avoidance errors, failing to inhibit responding to passive stimuli. This contingency is summarized in Table 1 as reward-punishment (Rew-Pun). Three other feedback contingencies have been employed with this task. In the reward-only (Rew) condition, participants are rewarded for responding to active stimuli and withholding responses to passive stimuli; in the punishment-only condition (Pun), participants are punished for not responding to active stimuli and responding to passive stimuli (Table 1). Iaboni, Douglas and Baker (1995) added a final condition, punishment-reward (Pun-Rew), in which participants are punished for not responding to active stimuli and rewarded for not responding to passive stimuli.

Extraverted college students, incarcerated psychopaths and low-anxious psychopathic juvenile delinquents commit more CEs than controls, with similar OEs (Newman & Kosson, 1986; Newman & Schmitt, in press; Newman, Widom, & Nathan, 1985; Patterson, Kosson, & Newman, 1987). Furthermore, extraverts respond faster after punishment than following reward, whereas introverts respond slower (Nichols & Newman, 1986; Patterson et al., 1987). Neurotic extraverts (as defined by Eysenck & Eysenck, 1975) also spend less time reflecting following punishment in a modified go/no-go task that allows subjects to terminate feedback themselves. In these studies, the amount of time a participant pauses after punishment significantly predicts passive avoidance learning (Patterson et al., 1987). Extraverts also tend to respond to reward more quickly overall, when only reward is given (Nichols & Newman, 1986). Newman and colleagues conclude that, in disinhibited individuals, reward availability appears to engender a dominant response set that is resistant to modulation. Consequently, disinhibited individuals do not pause to process feedback following punishment. This failure to pause does not allow

for the formation of extensive stimulus-response associations, and would be expected to impair recognition of the punishment stimulus context on subsequent occasions (Newman & Wallace, 1993). In contrast to Newman's findings, Iaboni et al. (1995) found that ADHD children made more CEs compared to controls on all conditions of the go/no-go task, indicating more generalized inhibitory and reward seeking problems in this clinical group.

Impulsivity in humans has been assessed primarily by self-report questionnaires. Despite the ability of commission errors on the go/no-go to discriminate between impulsive and non-impulsive individuals in clinical and nonclinical samples, behavioral impulsivity (measured by the go/no-go) did not correlate with self-report impulsivity (as assessed by a variety of paper-and-pencil instruments) in normal males (Helmers et al., 1995). It may be that impulsive behavior found in clinical populations is qualitatively different from that found in normal individuals, and not on a continuum.

The go/no-go passive avoidance task represents an attempt to operationally define and measure behavioral impulsivity under controlled conditions. Given that commission errors were higher in clinical and nonclinical samples that one would expect, a priori, to be more impulsive, commission errors on the go/no-go represent a valid measure of disinhibition. The measurement of behavioral, as opposed to self-report, impulsivity would represent a step forward in the literature investigating the relationship between impulsivity and serotonergic functioning in humans.

The Present Work

The present studies investigate the effects of ATD on impulsivity in two samples of individuals who may be susceptible to the effects of perturbations of the serotonergic system by virtue of being either 1) unaffected offspring with multigenerational paternal family histories of alcohol dependence, a disorder known to be related to serotonergic hypofunction, or 2) positive for a personal history of overt aggression, behavior also associated with decreased serotonergic functioning. The first study proposes to test one link in the hypothesized pathway leading from a serotonergic dysfunction to alcohol dependence: that experimentally lowering brain 5-HT function through ATD will lead to increased behavioral disinhibition in young men at risk for the development of alcohol dependence by virtue of a multigenerational paternal family history of alcoholism. The second study will test whether the effect of ATD on behavioral disinhibition is replicable in a second sample of adolescent men hypothetically susceptible to serotonergic perturbation by virtue of a past history of aggressive, disruptive behavior.

Tryptophan Depletion-Induced Behavioral Disinhibition in Nonalcoholic Young Men with Multigenerational Family Histories of Paternal Alcoholism

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ABSTRACT

Background: The neurotransmitter serotonin has been linked experimentally and clinically to impulsive behavior, as well as disorders characterized by disinhibition (e.g., alcoholism, aggression). The present study tested the hypothesis that young men at high risk for alcoholism would demonstrate greater behavioral disinhibition following dietary depletion of tryptophan, the amino acid precursor of serotonin.

Methods: A double-blind placebo-controlled between-subjects design was used. Plasma tryptophan was manipulated through the administration of a tryptophan-deficient amino acid mixture. Participants were nonalcoholic young men with a multigenerational paternal family history of alcoholism or with no family history of alcoholism in two previous generations. All were tested five hours following amino acid ingestion on a modified Taylor task quantifying aggression, and a go/no-go task measuring disinhibition.

Results: Plasma tryptophan was reduced in both groups five hours following administration of the tryptophan-deficient amino acid mixture. Tryptophan depletion had no effect on aggression. In contrast, tryptophan-depleted individuals with a family history of alcoholism made more commission errors (responses to stimuli associated with punishment or loss of reward) compared to tryptophan-depleted individuals with no family history of alcoholism, and those receiving the balanced (control) amino acid mixture in either group.

Conclusions: The data support the theory that low serotonin may be implicated in the increased disinhibition observed in individuals with a genetic vulnerability to alcohol abuse/dependence. The possibility

that disinhibition is an additive risk factor for the development of alcohol or drug abuse remains to be tested.

INTRODUCTION

Reduced central nervous system serotonin (5-hydroxytryptamine, 5-HT) may be involved in the etiology of alcohol abuse/dependence[1], suicide[2], bulimia[3], antisocial personality[4] and conduct disorder[5], and aggression[6-8]. One possible common role of serotonin in these disorders is behavioral inhibition[9]. Animal studies demonstrate that increasing central serotonin function inhibits responses to a number of stimuli[10]; clinically, low serotonin is associated with impulsive aggressive behavior[11-16] .

One focus of this study is alcoholism. Some alcoholics, particularly early- onset, have low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in their cerebrospinal fluid (CSF)[17-19]. Low CSF 5-HIAA is also associated with a positive paternal family history of alcoholism in impulsive violent offenders and fire-setters[20,21]. To avoid possible effects of alcohol on serotonin metabolism, nonalcoholic young men with family histories of alcoholism have been studied[22]. Men of this type are more susceptible to alcoholism given that alcohol dependence is two to three times more prevalent in males than females[23], and that twin[24-28], family[29], and adoption[30-33] studies suggest a heritable component to alcoholism. Males with a multigenerational paternal family history (MPFH) of alcoholism are at greater risk for alcoholism than those with alcoholic fathers alone[34]. A relatively rare, but highly heritable male-limited subtype of alcoholism, Cloninger's type 2, is characterized by an early onset of moderate alcohol abuse, regardless of external environment, and frequent criminality. Fathers of type 2 alcoholics also have an early onset of severe alcohol abuse, and exhibit serious criminality[35,36].

Sons of male alcoholics are also at higher risk for impulsive behavior and conduct disorder[37-39]. Additionally, MPFH young men perseverate on a card-playing task[40], suggesting a difficulty in discerning the implicit rules of the task, an insensitivity to cues for punishment, and/or a heightened sensitivity to cues for reward, possibly contributing to the etiology of their impulsivity.

One method for studying serotonin function in humans is the acute tryptophan depletion (ATD) technique. Participants ingest an amino acid (AA) mixture containing all the essential AAs except tryptophan (T- mixture) or a control mixture containing tryptophan (balanced, or B, mixture). Recent data suggest that ATD lowers brain serotonin synthesis by approximately 90%[41]. Changes in serotonin synthesis are hypothetically most likely to alter serotonin release and postsynaptic function when serotonin neurons are firing at a high rate, as in states of high arousal[42,43]. In keeping with this, ATD affects responses in laboratory tests of aggression that incorporate an element of provocation[44,45], but not in the absence of an arousing stimulus[46,47]. The present study was designed to test the hypothesis that ATD would induce behavioral disinhibition and increase aggressive responding in MPFH men, relative to age/sex matched controls. Disinhibition was measured by commission errors in a go/no-go learning task. A modified Taylor Aggression task, used to quantify aggression, was included before the go/no-go task to increase arousal.

METHODS

Selection of Participants and Baseline Testing

Males, ages 18 to 25, were recruited through local newspaper advertisements. An initial telephone screen excluded those with significant present or past alcohol abuse or dependence, evidence of a present DSM-III-R[48] Axis I diagnosis, significant medical illness, and lack of knowledge of their family psychiatric histories. Individuals passing this screen and providing informed consent underwent the Structured Clinical Interview for the DSM-III-R, non-patient version (SCID-NP)[49-51] and the Family History Assessment Module[52]. If necessary, participants were asked to contact family members to obtain more information. Family History Research Diagnostic Criteria[53,54] were used to make retrospective diagnoses of alcoholism in family members up to second degree relatives. This method has a satisfactory specificity for alcoholism in first-degree relatives, but is less sensitive than direct interviews[55-57].

The inclusion criterion for individuals at risk for alcoholism was a multigenerational family history of paternal alcoholism, as defined by at least two male alcoholics on the father's side of the family in two different generations. The inclusion criterion for individuals at low risk for alcoholism was the absence of documented cases of alcoholism in all known first, second and third-degree relatives (family history negative, or FH-). FH- individuals with multigenerational family histories of any other Axis I disorder were excluded from the study.

Individuals with abnormal electrocardiograms were excluded from some parts of the study. Participants were administered eight

Wechsler Adult Intelligence Scale-Revised (WAIS-R)[58] subtests: Information, Arithmetic, Similarities, Picture Completion, Digit Span, Picture Arrangement, Block Design, and Digit Symbol. Seven subtests (excluding Picture Arrangement) were used to estimate IQ[59]. This IQ estimate is highly correlated with WAIS-R full scale IQs in psychiatric inpatients[60].

A modified Personal Drinking Habits Questionnaire[61] (including questions concerning nicotine and drug use) estimated current alcohol and drug use; a caffeine intake survey assessed weekly caffeine intake[62,63], and the Michigan Alcoholism Screening Test (MAST)[64] assessed possible consequences of excessive alcohol intake. The Beck Depression Inventory (BDI)[65] provided a baseline measure of depressed mood.

Amino Acid Administration

The day preceding a test day, participants ate a low protein diet[66,67], and were asked to refrain from alcohol or illegal drug use. On the test day, fasting participants completed the BDI[65], the Profile of Mood States (POMS)[68,69], the Visual Analogue Mood Scale (VAMS)[70], and the state version of the State-Trait Anxiety Inventory (STAI)[71], produced a urine sample to screen for drugs of abuse (Triage™ Panel from Biosite Diagnostics), and provided a blood sample for the measurement of tryptophan levels. The participants received (double-blind) either a tryptophan-free (T-) or nutritionally balanced (B) AA mixture in a between-subjects design. The exact procedure has been described previously[66,72]. For both MPFH and FH- groups, administration of AA treatments was randomized in blocks of ten.

For the next 4.25 hours, participants read magazines, watched television, or watched movies (all confined to relatively affectively neutral material). They drank water ad libitum, and could smoke a limited amount if they desired. No sleeping was allowed.

Taylor Aggression Task

Participants did the Taylor aggression task[73] (described fully elsewhere[74]) to measure aggression and increase participants' arousal levels. Briefly, each participant's pain threshold was determined by presenting a series of increasing shocks. The task itself was introduced as a competitive reaction time task. Each participant was instructed to first select a shock level (that he would deliver to his opponent should he win the reaction time trial) on a panel of eight buttons in front of him, each numbered consecutively from one to eight. Shock levels 1-8 increased linearly from 15% to 100% of the person's given pain threshold. Following the reaction-time trial, the participant was informed of the opponent's shock choice by the appearance of one of eight red lights on the panel above each numbered button. The appearance of lights five to eight signified a loss, following which the participant received a shock. Lights one through four signified a win, and the participant administered the previously chosen shock intensity to his opponent by pressing a button. Participants could monitor shock administrations to their opponent using a direct current ammeter to his immediate left. After receiving these instructions, the participant viewed, on a television connected to a VCR in the adjacent room, a pre-recorded videotape of a fictitious opponent receiving the same instructions. This tape served to review the instructions, reinforce the nature of the competition, and present the situation more realistically.

The task consisted of 26 consecutive trials, the first half under low provocation (shocks administered to the participant ranging from 1 to 4), the second under high provocation (shocks from 5 to 8). The order of wins and losses as well as the opponent's shock choices within the provocation blocks were randomly selected by the computer. All participants received three shocks at each level, alternately winning one trial and losing two trials or winning two trials and losing one trial. Participants won and lost half of the trials in both provocation conditions. Dependent variables included the shock intensity chosen before each reaction time trial, the shock duration and latency to shock delivery on those trials in which the participant administered a shock to his opponent, and the reaction time to the stimulus by provocation level (low and high). The first shock intensity, chosen before the first reaction time test, was analyzed separately as a measure of unprovoked aggression.

Go/No-go Learning Task

Following the Taylor task, participants were administered the go/no-go discrimination task[75,76]. Participants learned by trial-and-error to press a button to "active" stimuli and to not press to "passive" stimuli. Stimuli consisted of eight two-digit numbers (four active, four passive, ranging from 03 to 99) repeated 10 times in different, randomized orders for 80 total trials. Additional stimulus characteristics have been presented elsewhere[75]. Four different sets of eight stimulus numbers were employed (one per condition). Correct responses were rewarded with a high-pitched tone, presentation of the word "CORRECT" on the computer screen, and the addition of 10 cents to an on-screen running tally of the participant's earnings. Incorrect

responses were punished by a low-pitched tone, presentation of the word "WRONG" and subtraction of 10 cents from the participant's earnings.

All participants did four conditions. In the reward-punishment (Rew-Pun) condition, participants began with $1.00. Responses to active numbers were reinforced, and responses to passive numbers punished. In the punishment-only (Pun-Pun) condition, participants began with $4.00. Responses to passive numbers and nonresponses to active numbers were punished. In the reward-only (Rew-Rew) condition, participants started with no money. Responses to active numbers and nonresponses to passive numbers were rewarded. In the punishment-reward (Pun-Rew) condition[77], participants began with $1.00; nonresponses to active numbers were punished, and nonresponses to passive number rewarded (see[77], Table 2). Each condition was preceded by a twelve trial reward pretreatment, in which the ratio of active to passive numbers was 2:1. This pretreatment hypothetically served to establish a dominant response set for reward[76,78].

Participants were given instructions on the go/no-go task, the reinforcement contingencies and the process of trial and error learning. With the experimenter present, they received eight practice trials involving four presentations of each of two practice stimuli (01 as an active number; 02 as a passive number). The experimenter answered any questions the participant had but was not present during testing. Participants were randomly assigned to one of the 24 possible orders of presentation of the four conditions. The experimenter re-entered the room between conditions to explain the demands of the next condition. Dependent measures for this task included commission errors (CEs; failures to inhibit responses to passive numbers) and omission errors (OEs; failures to respond to active numbers).

Adolescent and adult psychopaths[75,76] and extraverts[78,79], and children with attention deficit hyperactivity disorder[77] make more CEs compared to controls, (depending on reinforcement condition), with no differences in OEs. These findings suggest that CEs on the go/no-go learning task represent a valid measure of disinhibition.

Participants completed a short interview to verify the success of the Taylor task deception. The experimenter rated the degree to which the participant was deceived, and he was encouraged to voice his feelings concerning the deception. Next, participants were given a high protein snack and a 1 g L-tryptophan tablet to normalize plasma tryptophan levels (if the individual was tryptophan-depleted), or to maintain the double-blind status of the study (if the individual received the B AA mixture). The tryptophan preparation used is available by prescription in Canada and has not been associated with eosinophilia-myalgia syndrome[80]. The participant was debriefed on the procedure, provided with a detailed information sheet on the study, and had any questions answered.

Determination of Plasma Tryptophan Concentrations

Plasma free and total tryptophan were measured in blood samples prior to and five hours following ATD, as described previously[66].

Data Analysis

Variables were inspected by group for normality, homogeneity of variance and outliers. Appropriate transformations were applied to

correct for violations of these assumptions[81], and where employed, are specified. Demographic characteristics of MPFH and FH- participants were compared using t-tests. Plasma free tryptophan levels were analyzed using a 2 (risk; MPFH, FH-) X 2 (treatment; T-, B) X 2 (time; pre, five hours post AA consumption) between-within ANOVA. For the go/no-go discrimination task, an initial 2 (risk) X 2 (treatment) X 4 (condition; Rew-Pun, Pun-Pun, Rew-Rew, Pun-Rew) X 2 (type of error; OE, CE) between-within ANOVA on square root-corrected errors was followed by separate 2 (risk) X 2 (treatment) X 4 (condition) between-within ANOVAs on square root OEs and CEs. Dependent measures on the Taylor aggression task were analyzed using separate 2 (risk) X 2 (treatment) X 2 (provocation level; low, high) between-within ANOVAs. The mood data were analyzed using separate 2 (risk) X 2 (treatment) X 2 (time) between-within ANOVAs. Statistically significant interactions were further analyzed using simple interaction effects tests followed by pairwise comparisons using the Newman-Keuls procedure. Geisser-Greenhouse (G-G) corrections were used for all main effects and interactions involving repeated measures. Multiple regression analyses were performed to identify variables significantly predicting CEs.

ETHICS

All participants provided written informed consent. The study was approved by the Research Ethics Board of the Department of Psychiatry, McGill University. Participants were compensated for lost time.

RESULTS

DEMOGRAPHIC DATA

Reasons for four dropouts were: lost contact with participant, noncompliance, busy schedule, and nonspecific desire to discontinue. Three MPFH participants who completed the entire study were subsequently dropped from further analyses when the multigenerational nature of their family history of paternal alcoholism could not be confirmed.

MPFH and FH- participants did not differ significantly on demographic measures, with the exception of square root MAST scores ($t[55]=-3.19$, $P<.003$) (Table 1).

Insert Table 1 about here

Groups differed by definition with respect to their family histories of paternal alcoholism, but also according to their family histories of maternal alcoholism and major affective disorders. Three MPFH men met criteria for past alcohol abuse, and one met criteria for dependence for a six month period, three years before testing. Two MPFH participants had past histories of major depression, one had a past history of major depression and substance dependence, and one of cannabis dependence.

Six FH- (three T-, three B) and 14 MPFH men (nine T-, five B) tested positive for recent use of various drugs of abuse (primarily amphetamine or cannabis) on the Triage™ Panel (Biosite Diagnostics).

Nausea subsequent to AA consumption was reported by three FH- individuals (one T-, two B). Additionally, two FH- individuals

(one T-, one B) and eight MPFH individuals (seven T-, one B) vomited following AA consumption. Significantly more MPFH participants vomited following T- than B (Fisher's Exact Test, one-tailed, P<.03). Of these, one FH- participant (who received the B mixture) and three MPFH participants (all of whom received the T- mixture) were sent home and rerun (without vomiting) on another day. Thus, five MPFH participants (four T-, one B), in spite of emesis following AA administration, were retained for testing (a nonsignificant difference; Fisher's Exact Test, one-tailed, P=.22). Substantial decreases in plasma total and free tryptophan were noted in these participants (mean = 88.6% depletion of total tryptophan, 87.6% depletion of free tryptophan).

ANALYSIS OF SERUM FREE AND TOTAL TRYPTOPHAN LEVELS

A 2 (risk) X 2 (treatment) X 2 (time) ANOVA, with time a repeated-measures factor, on square root plasma free tryptophan concentrations revealed a highly significant treatment by time interaction (F[1,53]=449.41, P<.0001) (Table 2). The tryptophan-depleted AA mixture resulted in a decline in free and total plasma tryptophan of 89% across groups.

Insert Table 2 about here

MODIFIED TAYLOR AGGRESSION TASK

One MPFH individual who received the B mixture did not participate in the Taylor task due to an abnormally short PR interval

on his electrocardiogram. A 2 (risk) X 2 (treatment) ANOVA performed on log pain threshold levels revealed a significant main effect of treatment (F[1,52]=6.99, P=.01). Pain thresholds were lower following T- (i.e., greater pain sensitivity) compared to B.

For the Taylor task itself, twelve individuals (3 FH-, B; 1 MPFH, B; 4 FH-, T-; 4 MPFH, T-) were excluded from the following analyses, as they were judged to have had either doubt about the presence of their opponent, or to not have been deceived at all. Thus, the cell sample sizes for these analyses are 15 FH-, B; 9 MPFH, B; 11 FH-, T-; 9 MPFH, T-. A 2 (risk) X 2 (treatment) ANOVA on intensity of first shock chosen (unprovoked aggression) revealed a significant risk main effect (F[1,40]=4.06, P=.05), with MPFH participants choosing higher initial shock levels. A 2 (risk) X 2 (treatment) X 2 (provocation) ANOVA on shock intensity revealed a risk by provocation interaction (F[1,40]=10.14, P=.002). MPFH men chose significantly higher shock intensities compared to FH- men under low provocation, whereas under high provocation, FH- men chose slightly (but significantly) higher shock levels (see Figure 1).

Insert Figure 1 about here

Analysis of log shock duration revealed only a trend for a provocation main effect (F[1,40]=3.05, P<.09). All participants tended to administer longer shocks under high provocation. Analysis of log latency to shock revealed a significant treatment by provocation interaction (F[1,40]=4.37, P=.04). Under low provocation, latencies to shock were significantly greater in T- participants. Under high provocation, latencies to shock in both groups were significantly lower and not different in magnitude (Figure 1). Finally, analysis of reaction time

revealed a significant three-way risk by treatment by provocation interaction (F[1,40]=4.17, P=.05). Further analyses demonstrated that the FH-, B group tended to react slower under low provocation compared to FH-, T- group, with the former group quickening their reaction times to the level of the latter under high provocation.

The results of all analyses were similar when performed on the full sample, suggesting that the degree of belief in the deception (as determined during the post-experimental interview) did not affect the results. In summary, ATD did not markedly affect aggressive responding in MPFH participants, as compared to controls.

GO/NO-GO TASK

OEs and CEs were summed across the eight blocks of ten trials within each condition. Errors within the 12 trial reward pretreatment were not included because participants had to be exposed to the stimuli at least once in order to learn which were active and passive. An initial 2 (risk) X 2 (treatment) X 4 (condition) X 2 (type of error) ANOVA on square root OEs and CEs revealed a significant risk X treatment X error interaction (F[1,53]=3.95, P=.05). (see Figure 2).

Insert Figure 2 about here

A 2 (risk) X 2 (treatment) X 4 (condition) ANOVA on square root OEs revealed a significant condition main effect (G-G F[2.7,143.13]=16.02, P<.0001). Participants made significantly more OEs in the Pun-Rew condition compared to the other three conditions. Analysis of square root CEs revealed a significant risk X treatment interaction (F[1,53]=3.94, P=.05). MPFH individuals made significantly more square root CEs

after T- compared to the FH-, B and MPFH, B groups, and near significantly more than the FH-, T- group (MPFH, T-: mean = 3.03, 95% confidence interval [CI] 2.34-3.72; MPFH, B: mean = 2.09, 95% CI 1.29-2.90; FH-, T-: mean = 2.06, 95% CI 1.49-2.62; FH-, B: mean = 2.19, 95% CI 1.83-2.56). Effect sizes (differences between the mean of the MPFH, T- group and each of the other groups divided by respective pooled estimates of the population standard deviation) range from 0.81 to 0.91, large effect sizes according to Cohen[82]. There was also a significant condition main effect (G-G F[2.94,155.57]=4.15, P=.008). All participants made significantly more square root CEs in the Pun-Rew condition than in the Pun-Pun and Rew-Rew conditions. There were no interactions involving the condition factor, indicating that tryptophan-depleted MPFH participants made more square root CEs compared to the other three groups across conditions.

CHANGES IN MOOD

The mood questionnaires were analyzed using separate three-way mixed 2 (risk) X 2 (treatment) X 2 (time) ANOVAs. In general, significant treatment by time interactions were found on many of the mood variables, with post-hoc tests demonstrating significant increases in the negative mood state in the T- group from pre to five hours post AA consumption, while the B group showed no changes or slight improvements in mood. This held true for the (square root reflected) composed-anxious (F[1,52]=10.85, P<.01), agreeable-hostile (F[1,52]=6.44, P<.02), and clearheaded-confused (F[1,52]=6.44, P<.02) bipolar subscales of the POMS, the log state version of the STAI (F[1,52]=11.30, P<.01), and the lethargic-energetic (F[1,52]=6.49, P<.02), contented-discontented (F[1,52]=5.86, P<.02), mentally slow-quickwitted (F[1,52]=8.17, P<.01),

incompetent-proficient ($F[1,52]=6.48$, $P<.02$), happy-sad ($F[1,52]=5.83$, $P<.02$), antagonistic-amicable ($F[1,52]=5.02$, $P<.03$), and interested-bored ($F[1,52]=5.09$, $P<.03$) subscales of the VAMS. For the treatment by time interaction on the muzzy-clearheaded ($F[1,52]=15.19$, $P<.001$), troubled-tranquil ($F[1,52]=4.80$, $P<.04$) and tense-relaxed ($F[1,52]=8.67$, $P<.01$) subscales of the VAMS, T- individuals started with a more positive baseline mood state, which then became significantly worse at five hours following ATD. On the (square root reflected) elated-depressed ($F[1,52]=4.29$, $P<.05$) and confident-unsure ($F[1,52]=4.93$, $P<.04$) POMS subscales, and the strong-feeble ($F[1,52]=3.98$, $P=.05$), well-coordinated-clumsy ($F[1,52]=5.51$, $P<.03$) and attentive-dreamy ($F[1,52]=5.91$, $P<.02$) subscales of the VAMS, post-hoc testing failed to reveal significant increases in the negative mood state in T- participants. The changes were in the expected direction, however.

VARIABLES PREDICTING COMMISSION ERRORS

Multiple regression analyses were performed to identify variables that significantly predicted CEs. The presence of nausea and/or vomiting following AA consumption, a positive urine test for recent drug use, and whether the participant slept during the five hour wait time, were entered into an equation to predict average square root CEs (i.e., square root CEs averaged across the four go/no-go conditions). Recent drug use might reasonably be expected to affect go/no-go performance; similarly, sleep might affect arousal levels and thus the degree of change in serotonergic neurotransmission. The regression equation predicting total square root CEs was nonsignificant, with simple r^2's for the variables ranging from .005 to .02. Presence of symptoms or diagnoses of alcohol or drug abuse/dependence, major

depression, and/or anxiety disorders in the participants, coded from the SCID-NP, failed to predict total square root CEs, with simple r^2's again very low. Familial psychopathology, coded from the family history interviews, also did not significantly predict total square root CEs. A multiple regression analysis using paternal alcoholism family history, maternal alcoholism family history, familial drug abuse/dependence, familial depression, familial anxiety and familial antisocial personality to predict total square root CEs was nonsignificant ($F[6,49]=1.57$, $P=.18$). Separate regression analyses predicting total square root CEs using change scores (post *minus* pre) for those POMS and VAMS subscales in which ATD effects were found, did not reach significance.

COMMENT

The primary finding of this study is that ATD increased CEs on a passive avoidance learning task in young men at risk for alcoholism, reflecting increased behavioral disinhibition (i.e., increased responding in the presence of stimuli associated with prior punishment or loss of reward). This result supports the hypothesis that, at least in some groups of individuals, lowered serotonergic functioning may lead to increased impulsivity. In this regard, it complements previous research demonstrating that impulsive violent behavior is negatively associated with serotonin-related measures[11,13,14], and positively related to blunted neuroendocrine responses to serotonin agonists[15].

While ATD significantly increased CEs on a go/no-go task, it did not affect measures of aggressive responding. In this study, the Taylor task was used primarily to increase arousal, and was not executed to maximize the chances of seeing an ATD effect: the study compared only T- and B mixtures, instead of also including a mixture containing

excess tryptophan[44,45]. The fact that positive results were obtained for impulsivity, but not aggression, suggests that the laboratory test of impulsivity is more sensitive, or that impulsive responding is more sensitive to serotonergic modulation when it is devoid of an important affective component as in aggressive responding.

Acute tryptophan depletion selectively enhanced CEs in MPFH participants, suggesting these men are more susceptible than FH- individuals to manipulation of their serotonin systems. Whether this is due to a pre-existing abnormality in serotonergic neurotransmission, or to some differences in other neurotransmitter systems modulating impulsivity, is not known. Preliminary evidence obtained from measurements of platelets suggests that nonalcoholic sons of male alcoholics may have altered serotonin functioning[83,84].

A substantial proportion of the vulnerability to alcoholism is believed to be genetically mediated[33], particularly in early-onset, male-limited type 2 alcoholism[36]; indeed, early onset alcoholics have been reported to have lower CSF 5-HIAA than late-onset alcoholics[19]. Human[85,86] and primate[87] studies suggest a significant genetic component in serotonin-related measures. Also, mice with genetic alterations affecting serotonergic neurotransmission show increased aggression[88-90] and alcohol intake[91]. However, environmental factors may also be important. Early stressors lead to greater developmental declines in CSF 5-HIAA in monkeys relative to unstressed animals[92]. The extent to which low serotonin function contributes to the genetic risk for alcoholism remains to be determined. The present results, if replicated, suggest that the propensity for disinhibited behavior in response to ATD might be a potential marker for the future development of alcoholism.

Newman and associates found that psychopaths and extraverts make more CEs in the Rew-Pun condition, but not in the other conditions of the go/no-go task[75,79]. Patterson and Newman[93] suggested that when both reward and response costs are present, these individuals form a dominant response set for reward which is resistant to modulation by response cost. In the absence of the two competing outcomes, disinhibition is not noted in these groups, ruling out a generalized inhibitory and generalized reward-seeking difficulties. In contrast, in the MPFH individuals, ATD appears to induce a generalized disinhibitory state, as the they made more CEs in all four condition of the go/no-go task. In this respect, MPFH men after ATD exhibit disinhibited behavior similar to children with attention deficit hyperactivity disorder[77].

In this study, ATD caused an increase in negative mood. This change in mood is unlikely to be responsible for the alteration in passive avoidance response because (i) it was seen in both MPFH and FH- individuals, (ii) mood did not predict CEs, and (iii) response in the go/no-go task is not influenced by modest changes in mood[94]. It is noteworthy that in this study, the ability of ATD to elicit a "depressive" effect was far less prominent than in unaffected men at high risk for the development of mood disorders[66].

A few methodological aspects deserve attention. The fact that some of the participants, particularly those with MPFH, tested positive for recent use of drugs of abuse is a concern, as is the fact that a number of MPFH individuals felt nauseous and vomited after ATD. However, regression analyses indicated that these variable did not affect the go/no-go response.

Family histories were collected from the individuals rather than directly from the relatives themselves. This method has a high

specificity but a low sensitivity (correctly identifying only some of the alcoholic relatives)[55,56]. Thus, there were probably additional unidentified cases of alcoholism in the relatives of both MPFH and FH- individuals. However, misclassification of a MPFH individual into the FH- group would work against our hypothesis, and so does not pose a major problem for interpreting the results. Systematic classification of the type of alcoholism in the fathers of MPFH individuals (i.e., type 1 or 2) was not accomplished in the present study, but should be considered in future studies given recent results highlighting its importance[95].

Also of concern is the high failure rate in producing deception in the Taylor Aggression Task. However, the fact that similar results were obtained when undeceived participants were included in the analyses indicates that deception may not be essential in the Taylor test, and increases the credibility of our data.

A final factor to consider when interpreting the data is the nature of the physiological changes induced by ATD. Recent results suggest that ATD produces a substantial decrease in brain serotonin synthesis[41]. However, while a decline in serotonin synthesis may produce a decline in serotonergic neurotransmission, this remains a working hypothesis. Furthermore, lowered levels of tryptophan may lower the levels of other potentially psychoactive tryptophan metabolites, such as tryptamine[96], melatonin[97], quinolinic acid and kynurenic acid, as well as brain protein synthesis. However, the fact that results obtained using other experimental approaches also link low serotonin to increased impulsivity, suggests that the increase in CEs seen in MPFH individuals in this study was due to lowered serotonin function.

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Table 1. Demographic and Family History Characteristics of Participants at Risk for Alcoholism and Normal Controls*

	MPFH	FH-
Demographic Characteristics		
Number	24	33
Age, y	21.6 ± 2.6	21.3 ± 2.3
Weight, lbs	169 ± 27	161 ± 26†
Education, y	13.7 ± 1.7	14.5 ± 1.8†
IQ (WAIS-R short form)	110 ± 11.5	113 ± 13.4
MAST	5.0 ± 4.8	1.9 ± 1.8‡
Drinks per week	7.5 ± 7.9	6.4 ± 6.2
Caffeine, g/wk	1100 ± 842	840 ± 1269
Baseline Depression (BDI)	2.7 ± 3.1	2.8 ± 3.2
Mean number of paternal male alcoholics per participant	2.8 ± 1.1	0.1 ± 0.3†‡
Psychiatric Disorders in Relatives		
Paternal Alcohol Abuse and Dependence		
First-degree relatives, No. (%)**	27 (28.4)	1 (0.9)†
Second-degree relatives, No. (%)	48 (16.2)	2 (0.6)†
Maternal Alcohol Abuse and Dependence		
First-degree relatives, No. (%)	5 (5.3)	0 (0)†

Second-degree relatives, No. (%)	14 (4.7)	1 (0.3)†
Drug Abuse and Dependence		
First-degree relatives, No. (%)	6 (6.3)	0 (0)†
Second-degree relatives, No. (%)	7 (2.4)	2 (0.6)†
Major Affective Disorder		
First-degree relatives, No. (%)	23 (24.2)	4 (3.4)†
Second-degree relatives, No. (%)	27 (9.1)	13 (4.1)†
Antisocial Personality Disorder		
First-degree relatives, No. (%)	12 (12.6)	0 (0)†
Second-degree relatives, No. (%)	7 (2.4)	1 (0.3)†
Anxiety Disorders (panic, agoraphobia)		
First-degree relatives, No. (%)	4 (4.2)	3 (2.6)†
Second-degree relatives, No. (%)	2 (0.7)	1 (0.3)†

*MPFH indicates participants with a multigenerational paternal family history of alcoholism; FH-, participants with no family history of alcoholism; IQ, intelligence quotient; WAIS-R, Wechsler Adult Intelligence Scale - Revised; MAST, Michigan Alcoholism Screening Test; BDI, Beck Depression Inventory. Values represent raw data and are expressed as mean ± SD.

**Percentages of affected relatives were calculated by dividing the total number of affected relatives by the total number of relatives at each degree level.

†n=32.

‡p<.006

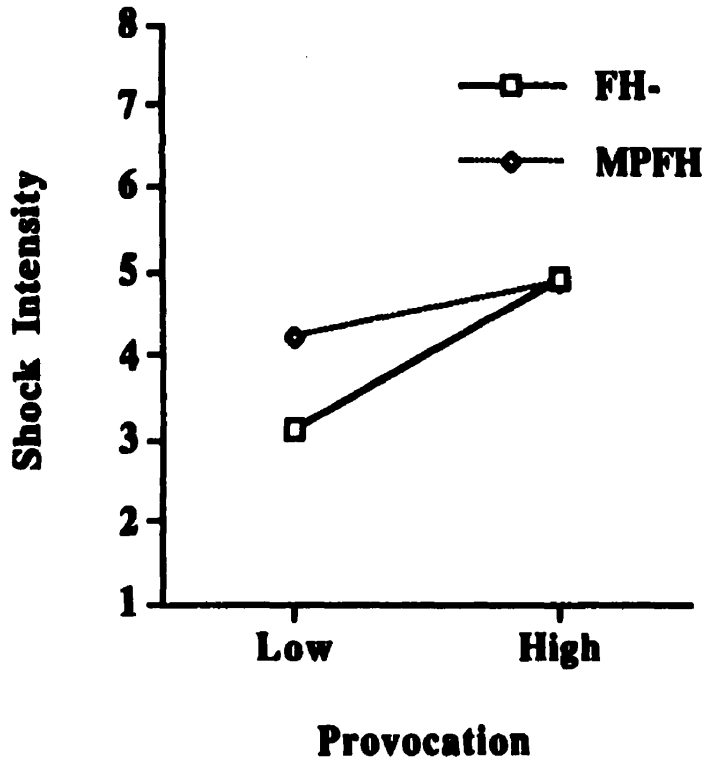
Table 2. Total and Free Plasma Tryptophan Levels Before and Five Hours Following the Ingestion of a Balanced and Tryptophan-Depleted Amino Acid Load in MPFH and FH- Participants*

	Balanced Mixture		Tryptophan-Depleted Mixture	
Time of Blood Draw	MPFH (n=11)	FH- (n=18)	MPFH (n=13)	FH- (n=15)
Total Plasma Tryptophan				
Pretreatment, μg/mL	10.8 ± 1.8	11.5 ± 1.4	11.1 ± 2.1	10.7 ± 1.5
Posttreatment, μg/mL	15.3 ± 4.2	17.9 ± 6.3	1.3 ± 0.5	1.1 ± 0.6
Percentage change	41.5	56.1	-88.2	-90.0
Free Plasma Tryptophan				
Pretreatment, μg/mL	1.6 ± 0.5	1.6 ± 0.3	1.4 ± 0.3	1.4 ± 0.2
Posttreatment, μg/mL	2.3 ± 0.7	2.7 ± 1.1	0.2 ± 0.1	0.2 ± 0.1
Percentage change	39.3	70.0	-87.6	-89.6

*MPFH indicates participants with a multigenerational paternal family history of alcoholism; FH-, participants with no family history of alcoholism. Values represent raw data and are expressed as mean ± standard deviation.

Figure 1. Results on the modified Taylor aggression task: a) Mean (± standard error) shock intensities chosen, by risk group and provocation level; b) Mean (± standard error) latencies to shock administration by amino acid status and provocation level. MPFH indicates participants with a multigenerational family history of paternal alcoholism; FH-, participants with no family history of alcoholism; T- indicates tryptophan-depleted amino acid mixture; B, balanced amino acid mixture. Raw data are depicted.

a)


Shock Intensity
8
7
6
5
4
3
2
1
FH-
MPFH
Low
High
Provocation

b)

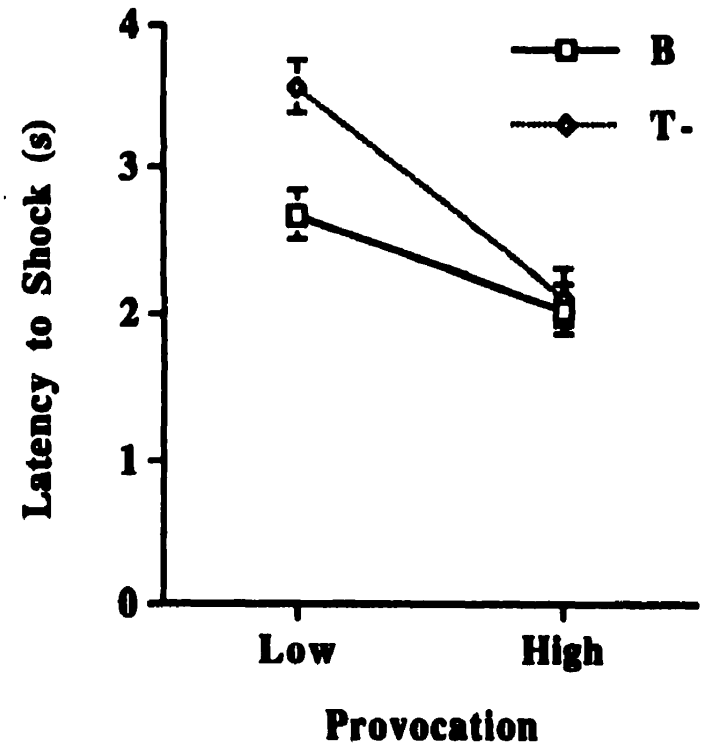
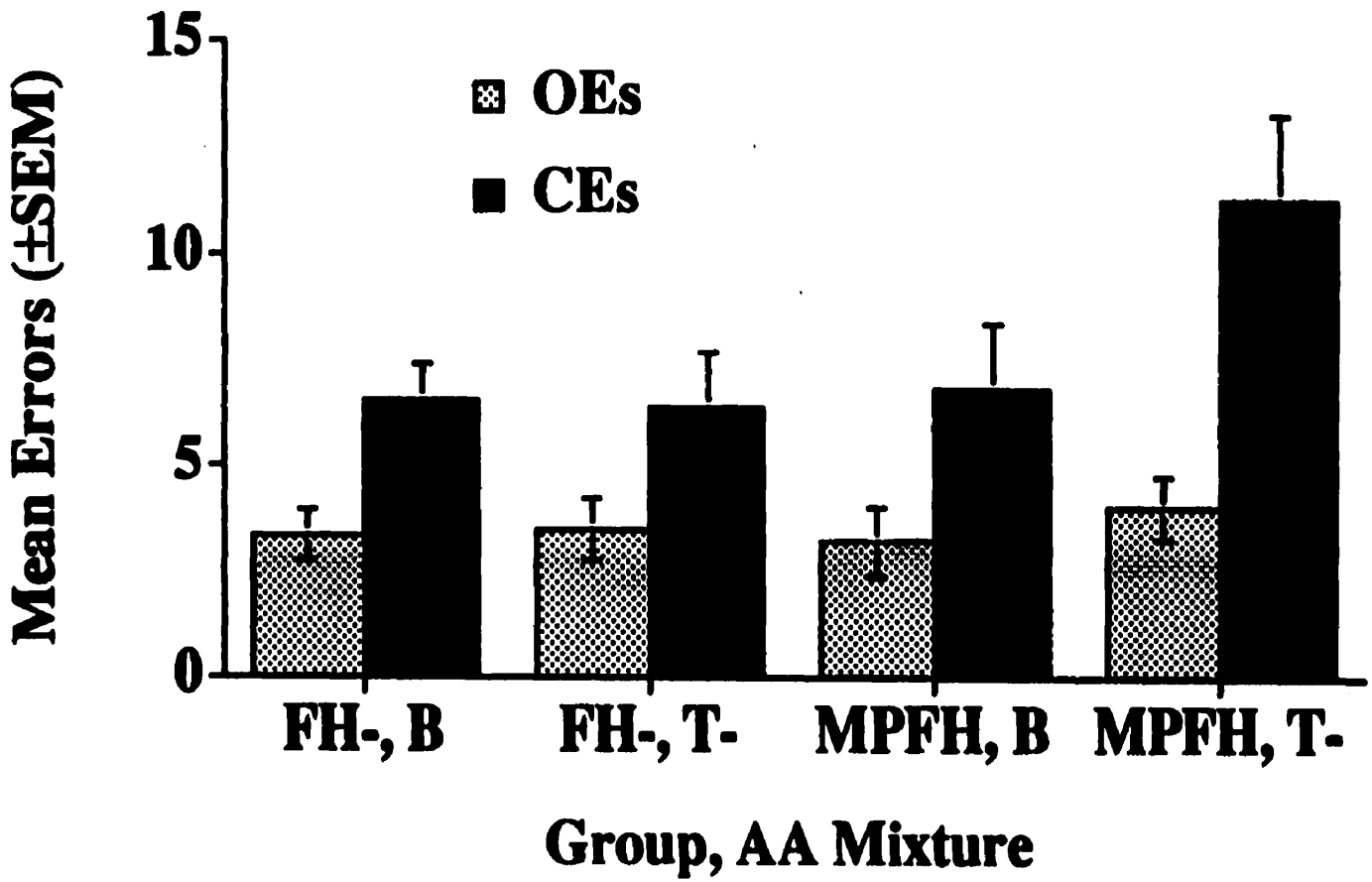

Latency to Shock (s)
4
3
2
1
0
B
T-
Low
High
Provocation

Figure 2. Mean (± standard error) omission (OEs) and commission errors (CEs) across conditions of the go/no-go learning task in the four groups of participants. MPFH indicates participants with a multigenerational family history of paternal alcoholism; FH-, participants with no family history of alcoholism; T-, tryptophan-depleted amino acid mixture; B, balanced amino acid mixture. Cell sizes for the four groups are 18, 11, 16, and 12, respectively. Raw data are depicted.


15
10
5
0
Mean Errors (±SEM)
OEs
CEs
FH-, B
FH-, T-
MPFH, B
MPFH, T-
Group, AA Mixture

The first study demonstrated that ATD induced an increase in disinhibition (commission errors) on a go/no-go task specifically in nonalcoholic young men with a multigenerational paternal family history of alcoholism. A concomitant increase in aggression on the modified Taylor task was not found. The effects of ATD on mood appeared to be unrelated to its effects on disinhibition in MPFH young men.

A number of questions were raised by these results. First, is the effect of ATD on commission errors specific to MPFH individuals? It may be that another group of individuals, similarly at heightened risk for future disinhibited behavior, might demonstrate increased disinhibition on the go/no-go task after ATD. Young men rated by their teachers as consistently high in physical aggression behavior might be such a group. As reviewed above, aggression, and particularly impulsive aggression, has been inversely related to peripheral measures of central serotonergic functioning in impulsive, violent adults (Virkkunen, Rawlings, et al., 1994) as well as in children with disruptive behavior disorders (Kruesi et al., 1990). Stably aggressive adolescent males, having already exhibited outwardly aggressive behavior, and presumably at risk for exhibiting further aggressive behavior, might be susceptible to an ATD-induced increase in disinhibition.

Second, what might be the mechanism producing the ATD-induced increase in commission errors on the go/no-go task in MPFH men? Specific abilities appear necessary for optimal performance on the go/no-go task. Motivation, attention to the stimuli, concentration, the ability to hold in short-term memory at least a subset of the stimuli (e.g., the active numbers), the ability to actively monitor the numbers held in memory and compare them to subsequent stimuli, the ability

to learn the association between a stimulus, one's response and the outcome (e.g., reward, punishment, etc.), and the ability to withhold a response to avoid punishment or nonreward appear essential for optimal go/no-go performance. ATD could be affect any combination or all of these processes in increasing commission errors on the go/no-go task in MPFH men.

Some of the cognitive abilities listed above have been termed *executive functions*. Executive functions describe capacities for the initiation and maintenance of efficient goal attainment (Lezak, 1985). They include: abstract reasoning, problem solving, sustained attention, concentration, programming and planning of goal-oriented motor behavior skills, modulation of behavior in light of expected future consequences, anticipation of events in the regulation of behavior, learning of contingency rules and the ability to use feedback cues, and inhibition and response flexibility (versus perseveration) (Séguin, Harden, Pihl, Tremblay, & Boulerice, 1995). Executive functions operate within working memory and require active monitoring (Petrides, Alivisatos, Evans, & Meyer, 1993). They have been attributed to the proper functioning of the prefrontal cortex (Lezak, 1985). There is preliminary evidence that the prefrontal cortex is critically involved in passive avoidance learning in humans. Activity of the right prefrontal cortex was associated with the ability to withhold responding in a go/no-go task in a recent positron emission tomography study with healthy males (Kawashima et al., 1996). Executive functions have been inversely related to physical aggression (Séguin et al., 1995), laboratory aggression (Lau, Pihl, & Peterson, 1995; Giancola & Zeichner, 1994), impulsive reactive aggression in sons of individuals abusing/dependent on a substance (Giancola, Moss, Martin, Kirisci, &

Tarter, 1996) and the adverse consequences of excessive alcohol use (Giancola, Zeichner, Yarnell, & Dickson, 1996).

In order to demonstrate that an ATD-induced increase in commission errors on the go/no-go task is mediated by decreased executive functioning, it is necessary to demonstrate that 1) ATD interferes with executive functions, and 2) disrupting executive functions leads to increased disinhibition. In the second study, a hypothesized association between executive functions and disinhibition is tested. Cognitive test factor scores derived in an earlier study using this sample (Séguin et al., 1995) were used to relate executive functioning to disinhibition (commission errors) on the go/no-go. As emphasized by Séguin et al. (1995), basic memory functioning was controlled in order to dissociate the role of executive functions in disinhibition from the role of more basic memory processes.

Preliminary evidence suggests that ATD does not interfere with cognitive abilities associated with prefrontal cortical functioning. Park et al. (1994) concluded that ATD impaired memory and learning processes but not measures sensitive to prefrontal dysfunction. In that study, ATD impaired the ability to learn spatial associations between abstract patterns, and the ability to learn a visual discrimination to criterion, then upon an unannounced change in the rule, display cognitive flexibility to deduce the new rule. Impairment was not seen following ATD on tasks involving planning and spatial working memory, which were suggested by Park et al. (1994) to require proper "Central Executive" function. Since there was some evidence that ATD affects cognitive processes that might be involved in go/no-go performance (e.g., the learning of associations), it may yet still be demonstrated that ATD affects cognitive processes necessary for go/no-

go performance, including some "executive functions" subsumed by the prefrontal cortex. (It should be noted that one study (LeMarquand, Peterson, Roth, Young, & Pihl, 1994) found preliminary evidence that tryptophan depletion affects executive functioning, including the ability to form spatial associations and maintain these associations in working memory, however methodological irregularities limit the interpretation of these findings). One of the difficulties noted in this literature is the wide variation in operational definitions of executive functions, and in the tests used to assess executive functions, making interpretation of these studies difficult.

Two notable changes were made to the methodology of the second study. First, a within-subjects design was used to reduce the number of participants needed, to increase the sensitivity to detect an effect of ATD on disinhibition, and to observe if an effect of ATD on disinhibition could be demonstrated in a within-subjects context. Second, the go/no-go was not carried out following an aggression task, as in the first study. Despite the hypothesis that changes in serotonin synthesis are most likely to alter serotonin release and postsynaptic function when serotonin neurons are firing at a high rate, as in states of high arousal (Young, 1986; Young et al., 1988), it was decided not to include the modified Taylor Aggression task before the go/no-go due to concerns about maintaining the deception across experimental days.

Tryptophan Depletion, Executive Functions, and Disinhibition in Aggressive Adolescent Males

by

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ABSTRACT

Low serotonin has been linked to aggressive behavior, and to behavioral dishibition. Executive functions (cognitive abilities involved in the initiation/maintenance of goal attainment) have also been implicated in aggressive behavior. We tested whether lowering central serotonin synthesis via a dietary lowering of tryptophan (the amino acid precursor of serotonin) would increase disinhibition in aggressive adolescent men. Cognitive-neuropsychological variables predictive of disinhibition were also explored, with the hypothesis that executive functions would be significantly related to disinhibition. Stable aggressive and nonaggressive young men received balanced and tryptophan-depleted amino acid mixtures separately (counterbalanced and double-blind). Commission errors on a go/no-go learning task (i.e., failures to inhibit responding to stimuli associated with punishment/nonreward) measured disinhibition. Aggressive adolescent males made more commission errors compared to nonaggressives. Lower executive functioning was significantly related to commission errors over and above conventional memory abilities. Tryptophan depletion had no effect on commission errors in either group, but tended to increase omission errors (failures to respond to stimuli associated with reward) in aggressive adolescents in the reward-punishment condition of the go/no-go task. The failure of tryptophan depletion to increase commission errors in this population may have been due to a ceiling effect.

INTRODUCTION

Serotonin (5-HT) has been linked to aggression in animals (Pucilowski and Kostowski 1980) and humans (Tuinier et al 1995). Clinically, studies with adults (Linnoila et al 1983; Virkkunen and Linnoila 1993; Virkkunen et al 1987, 1994) and children (Halperin et al 1994; Kruesi et al 1990) suggest that reduced baseline functioning of the central 5-HT system is associated with aggressive/violent behavior. Additionally, dietary depletion of tryptophan, the amino acid precursor of 5-HT, increases aggressive responding on a laboratory task in young men with high trait aggression (assessed by the Buss-Durkee Hostility Inventory) (Cleare and Bond 1995).

At a more fundamental level, 5-HT may be controlling the inhibition of behavior (Soubrié 1986). The first goal of the present study was to test the hypothesis that lowered 5-HT synthesis (and presumably function) might increase disinhibition, defined as behavior committed in the presence of stimuli previously associated with punishment or loss of potential reward. We studied the effect of tryptophan depletion on disinhibition in stable aggressive young men, a population that *a priori* might be expected to possess low baseline 5-HT functioning. This sample was part of a large cohort followed longitudinally since the age of five. Biochemical, cognitive/neuropsychological, behavioral, personality and family history assessments have been made of this cohort over the last 12 years. Stable aggressive young men have exhibited high teacher-rated physical aggression from childhood to mid-adolescence (Tremblay et al 1991).

The tryptophan depletion procedure has been used to investigate the consequences of lowered central 5-HT functioning in humans. In

this procedure, participants consume a mixture of amino acids devoid of tryptophan. Consumption of this mixture results in the lowering of plasma tryptophan, brain tryptophan and brain 5-HT in rats and primates (Biggio et al 1974; Gessa et al 1974; Moja et al 1989; Young et al 1989), as well as plasma free and total tryptophan (Benkelfat et al 1994) and brain 5-HT synthesis (Nishizawa et al 1997) in humans.

A go/no-go passive avoidance learning task previously shown to assess disinhibition in extraverted college students (Newman et al 1985; Patterson et al 1987), adolescent and adult male psychopaths (Newman and Kosson 1986; Newman et al 1990), and children with attention deficit and hyperactivity disorder (ADHD; Iaboni et al 1995) was used in the present study to assess disinhibition. In this task, participants must respond to "active" stimuli to gain or avoid the loss of monetary reward and withhold responses to "passive" stimuli to avoid punishment or the loss of potential reward. Commission errors, or failures to withhold responses to passive stimuli (i.e., failures to display passive avoidance) represent a measure of disinhibition.

The second goal of the present study was to assess the relationship between disinhibition and cognitive functioning. Cognitive-neuropsychological processes have been implicated in the regulation of aggressive behavior (Kandel and Freed 1989; Giancola 1995; Moffitt 1993; Pennington and Ozonoff 1996). Specifically, selective deficits in executive functions have been correlated with physical aggression (Séguin et al 1995). Executive functions subsume the capacities for initiation and maintenance of goal attainment (Lezak 1985). These include the planning of motor skills, modulation of behavior in light of expected future consequences, learning to contingencies, ability to use feedback, abstract reasoning, problem

solving, and sustained attention and concentration (Séguin et al 1995). Given the association between aggression and impulsivity, one might expect decreased executive functioning to be associated with increased disinhibition. In addition to executive functioning, measures of conventional memory processes were also included in order to examine if the hypothesized relationship between disinhibition and executive functioning would hold after controlling for conventional memory functioning. Cognitive functioning was measured by a neuropsychological battery administered to this sample four years earlier.

Additional measures were included before and after amino acid mixture consumption to assess the effects of tryptophan depletion. A supplementary measure of disinhibition, the Draw-a-Line Slowly (DALS) test, assessed the inhibition of motor activity (Rohrbeck and Twentyman 1986). Mood variables were included, as the mood-lowering effect of tryptophan depletion is well-documented (Benkelfat et al 1994; Young et al 1985). State sensation seeking was assessed using the Sensation Seeking State questionnaire (SSS; Zuckerman 1979). Additional baseline measures (assessed in previous years) were utilized to investigate their potential relationships with go/no-go performance. An IQ estimate was used, as global intellectual functioning has been associated with go/no-go performance (Helmers et al 1995). Frequencies of parent- and self-rated childhood externalizing psychopathology were employed, as the presence of ADHD has been associated with poorer passive avoidance learning (Iaboni et al 1995). Family histories of alcoholism and depression may also be important predictors of passive avoidance learning (LeMarquand et al 1997), and thus were included in this report.

METHODS AND MATERIALS

Participants

Participants were selected from a sample of adolescents followed since kindergarten. One thousand and thirty-seven boys from 53 schools with the lowest socioeconomic index in the Montreal Catholic School Commission were initially selected for study. To control for cultural factors, boys were included only if both their biological parents were born in Canada and their mother tongue was French. All boys were Caucasian. They were 17 years old when tested.

Physically aggressive behavior was rated by teachers when the boys were 6, 10, 11 and 12 using the fighting subscale of the Social Behavior Questionnaire (Tremblay et al 1991). This subscale is comprised of three items: 1) fights with other children; 2) kicks, bites and hits other children; and 3) bullies or intimidates other children. Subscale ratings for 893 boys were available (see Séguin et al 1995 for additional sample details). Those boys scoring above the 70th percentile at age 6 and at least two of the three additional assessment points were classified as stable aggressive (SA), while those below the 70th percentile at all assessment points were classified nonaggressive (NA). From pools of 63 potential SA and 59 potential NA participants, 18 and 20 took part in the present study, respectively.

Procedure and Instruments

DEMOGRAPHIC VARIABLES. A number of variables were selected from the longitudinal data set to compare the SA and NA samples demographically. IQ was estimated according to Sattler (1988) using the

Vocabulary and Block Design subtests of Weschler Intelligence Scale for Children-Revised (WISC-R) (Wechsler 1974) administered at age 15. Self-reported number of years in school, assessed in 1995, was included. A family adversity index (Tremblay et al 1991) was constructed using parental age at the birth of the first child, parental education, parental occupational status (Blishen et al 1987), and family structure, all assessed when the participant was in kindergarten. Participant-reported fathers' and mothers' occupational status (average of 1994 and 1995 assessments) (Blishen et al 1987) and total family revenue (in 1993) provided a more recent assessment of the participants' family socioeconomic status. For total family revenue, units represent income increments of $5000, beginning at one (i.e., 2=$5000 to $9999; 3=$10000 to $14999, etc.).

Teacher-rated aggression and anxiety represent the average of participants' ratings at ages 6, 10, 11 and 12 on the fighting and anxiety subscales of the Social Behavior Questionnaire (Tremblay et al 1991). Parent- (usually mother) and self-rated frequencies of ADHD, oppositional defiant disorder (ODD) and conduct disorder were evaluated using the Diagnostic Interview Schedule for Children (DISC-2; Shaffer et al 1991) when the participants were between 14 and 16 years old. The DISC-2 is a structured interview designed to assess symptoms over the past six months. An earlier version of the DISC-2 has proven valid (Costello et al 1985). Paternal and maternal alcoholism risk were estimated using the Short Michigan Alcoholism Screening Test (SMAST; Selzer et al 1975). Mothers were interviewed by telephone and asked questions on the SMAST for each of their sons' first and second degree relatives. Paternal pedigrees were classified as high risk if both the father and paternal grandfather were alcoholic;

medium risk if only the father was alcoholic, and low risk if neither the father or paternal grandfather were alcoholic. Similar pedigree classification was achieved for maternal alcoholism using alcoholism in the mother and maternal grandmother. Frequencies of parental depression were estimated over a three-year period using an abridged version of the Diagnostic Interview Schedule - Revised (Robins et al 1981).

COGNITIVE/NEUROPSYCHOLOGICAL VARIABLES. At ages 13 and 14 (1991/92), participants were administered a neuropsychological test battery, described previously (Séguin et al 1995), composed of the Dichaptic Lateralization (DL) (Witelson 1974, 1976), Digit Span (DS) and Paired Associates (PASS) (Wechsler 1987), Nonspatial Conditional Association (NSP) (Petrides 1990), Self-Ordered Pointing (SOP) (Milner et al 1985), Spatial Memory (SM) (Smith and Milner 1981, 1989), Strategic Problem Solving (SPS) (Becker et al 1986), Subjective Ordering (Number Randomization, NR) (Wiegersma et al 1990), and Semantic (SFL) and Letter Fluency (LFL) (Lezak 1983) tests. Séguin et al (1995) factor analyzed the tests results on a larger sample (N=177) and found four factors accounting for 58% of the variance: Verbal Learning (composed of the SFL, LFL, PASS and DS tests), Incidental Spatial Learning (composed of the SM subtests), Tactile Lateralization (composed of the DL subtests) and Executive Function (composed of the NSP, NR, SOP, SPS tests). Participants' scores on three of the four factors were used in the present study to assess cognitive-neuropsychological correlates of disinhibition on the go/no-go task. Verbal and Spatial Learning were included to assess conventional memory processes (Séguin et al 1995). (Tactile Lateralization was not included in these analyses because it did not differentiate stable

aggressive from unstable and nonaggressive boys, and was not of theoretical interest).

ACUTE TRYPTOPHAN DEPLETION. Prospective participants were mailed an information sheet outlining the study, and parental and participant consent forms. Potential participants were contacted by telephone by trained research assistants who had had previous contact with the boys. Those boys interested in participating were asked to sign the consent form and obtain parental consent. They were scheduled for the first lab test day, and asked to avoid consumption of certain foods high in protein (e.g., meats), abstain from alcohol and/or recreational drug use the day before each lab session, and refrain from eating breakfast on test days.

A 2 (group; SA, NA) X 2 (amino acid administration; tryptophan depletion
[T-] and balanced amino acid mixture [B]) between-/within-subjects design was employed. Each participant was tested on two days, separated by at least one week. On each day, participants consumed an amino acid mixture administered double-blind. Assignment to order of amino acid administration (T- and B, or B and T-) was counterbalanced within groups. Research assistants who administered the amino acid mixtures, tests, questionnaires, and other procedures were blind to the young mens' behaviour ratings.

One or two participants were scheduled per test day. Early in the morning, the boys were transported by car from their homes to the laboratory. Testing commenced at approximately 9:00 am. Upon arrival at the lab, adherence to the previous day's specified menu and the prohibitions against recreational drug/alcohol use and breakfast consumption were assessed (via self-report). Mood was assessed using

the Beck Depression Inventory (BDI; Beck et al 1961), the Profile of Mood States (POMS; Lorr et al 1982; McNair et al 1988), the "State" version of the State-Trait Anxiety Inventory (STAI; Spielberger et al 1970), and the Visual Analogue Mood Scales (VAMS; Bond and Lader 1974). State sensation seeking was assessed using the Sensation Seeking State questionnaire (SSS; Zuckerman 1979). After the mood assessment, participants did the Draw-a-Line Slowly (DALS) test. In this test, participants were asked to draw a line as slowly as possible from the top to the bottom of a 9" x 1" column without crossing the boundaries. Following this test, ten milliliters (ml) of venous blood were drawn from each participant to obtain a measure of pre-treatment plasma total and free (non-albumin-bound) tryptophan levels.

AMINO ACID ADMINISTRATION. The T- amino acid mixture was the same as that employed by Young et al (1985) except that 11.0 g L-lysine monohydrochloride was employed in lieu of 8.9 g L-lysine. The B mixture contained the same amino acids plus 2.3 g L-tryptophan. The amino acids were combined with 150 ml orange juice and 0.8 g artificial sweetener (sodium cyclamate) to improve taste. An alternate combination consisting of 150 ml water and 40 ml chocolate syrup (in lieu of the orange juice) was offered to guard against the development of a conditioned taste aversion. Participants were additionally required to swallow twelve capsules containing three amino acids (4.9 g L-arginine, 2.7 g L-cysteine, and 3.0 g L-methionine) not included in the mixture due to their bitter taste. They were allowed ad libitum water to accomplish this. Chewing gum was provided to participants to remove the aftertaste.

Immediately following amino acid administration, on the first test day only, paper-and-pencil questionnaires measuring various

personality dimensions were administered. Participants were weighed and their height was measured. During the ensuing four to five hour waiting period, participants were allowed to read or watch one or two movies. They were prohibited from sleeping. Five hours after amino acid administration, a second 10 ml blood sample was drawn from each participant for analysis of the effects of the amino acid mixtures on plasma tryptophan levels. Mood and state-impulsivity were reassessed, and the DALS test was re-administered.

ASSESSMENT OF DISINHIBITION: THE GO/NO-GO TASK. Participants were required to learn, by trial-and-error, to respond (press a button) to "active" stimuli (two-digit numbers paired with reward) and withhold responses to "passive" stimuli (two-digit numbers paired with punishment). For the first session, eight numbers (four active, four passive) were repeated ten times in different, randomized orders for a total of 80 trials. For the second session, ten different numbers (five active, five passive) were repeated eight times in randomized orders, again for a total of 80 trials. Four different sets of stimuli were employed per session, one for each condition. Additional characteristics of the stimuli have been presented elsewhere (Newman and Kosson 1986).

Visual, auditory and monetary feedback followed each response. Correct responses were rewarded with a high-pitched tone, presentation of the word "CORRECT" on the computer screen, and the addition of ten cents to a running tally of the participant's earnings presented on screen. Incorrect responses were punished by a low-pitched tone, the word "WRONG", and subtraction of ten cents from the participant's earnings.

Each participant did four conditions of the go/no-go task. In the reward-punishment (Rew-Pun) condition, participants started with one dollar. Responses to active stimuli were rewarded, and responses to passive stimuli punished. In the punishment-only (Pun-Pun) condition, participants began with four dollars and had no opportunity to win more money. Responses to passive stimuli and failures to respond to active stimuli were punished. In the reward-only (Rew-Rew) condition, participants began with no money and could not lose money. Responses to active stimuli and withholding responses to passive stimuli were rewarded. In the final punishment-reward (Pun-Rew) condition, participants started with one dollar; failures to respond to active stimuli were punished, and non-responses to passive stimuli were rewarded. (For a tabular summary of the four conditions, see Iaboni et al 1995). Each condition was preceded by a reward pretreatment (twelve [first session] or fifteen [second session] trials presented in the format described above with the frequency of active and passive stimuli in the ratio of 2:1) before the standard 80 trials of the condition. This pretreatment served to establish a dominant response set for reward (Newman et al 1990 ; Patterson et al 1987).

Participants received instructions concerning the nature of go/no-go task, the reinforcement contingencies, and the process of trial and error learning. In the presence of the experimenter, they received eight practice trials involving four presentations of each of two practice stimuli (01 as an active stimulus; 02 as a passive stimulus). The experimenter answered any questions the participant had, but was not present during actual testing. Participants were randomly assigned to one of the 24 possible orders of presentation of the four conditions. At the conclusion of each condition, the experimenter re-entered the

room to explain the demands of the next condition. Dependent measures for this task included commission error (CEs; failures to inhibit responses to passive stimuli) and omission errors (OEs; failures to respond to active stimuli) for each condition.

TRYPTOPHAN REPLETION. Following completion of the go/no-go task, participants were provided with a high protein snack and a 1 g L-tryptophan tablet to normalize plasma tryptophan levels if the individual was tryptophan-depleted, or to maintain the double-blind status of the study if the individual received the B amino acid mixture. The tryptophan preparation used (Tryptan) is available by prescription in Canada and has not been associated with any cases of eosinophilia-myalgia syndrome (Wilkins 1990). One hour following the start of meal consumption, a final 10 ml blood sample was drawn for analysis of the effects of the amino acid mixtures following repletion. The participants were remunerated for their time and given their winnings on the go/no-go task. After completing both amino acid administrations, participants were debriefed. They were provided with an information sheet outlining the basic goals of the study, and any questions they had were answered.

Determination of Plasma Tryptophan Concentrations

Plasma free and total tryptophan was measured in all blood samples as an index of tryptophan depletion. This procedure has been fully detailed previously (Benkelfat et al 1994).

Data Analysis

Variables were initially inspected by group for normality, homogeneity of variance and outliers. Appropriate transformations or

treatment of outliers were applied to correct for violations of these assumptions (Tabachnick and Fidell 1989), and where employed, are specified. Demographic characteristics of SA and NA participants were compared using t-tests for continuous variables or Fisher's Exact Test (two-tailed) for frequencies. Plasma free tryptophan levels were analyzed using a 2 (group; SA, NA) X 2 (treatment; T-, B) X 3 (time; pre, five hours post amino acid consumption, one hour post repletion) between-within ANOVA. For the go/no-go discrimination task, separate 2 (group) X 2 (treatment) X 4 (condition; Rew-Pun, Pun-Pun, Rew-Rew, Pun-Rew) mixed-model analyses of variance (ANOVAs) were performed on omission and commission errors. The DALS and mood data were analyzed using separate 2 (risk) X 2 (treatment) X 2 (time; pre, five hours post amino acid consumption) between-within ANOVAs. Statistically significant interactions were further analyzed using simple interaction effects tests followed by pairwise comparisons using the Newman-Keuls procedure. Geisser-Greenhouse (G-G) corrections were used for all main effects and interactions involving repeated measures. Relationships between cognitive/neuropsychological functioning and disinhibition on the go/no-go were explored using multiple regression.

Ethical Approval

All participants involved in this study, as well as their parents, gave written informed consent. The study was approved by the Research Ethics Board of the Department of Psychiatry, McGill University.

RESULTS

Six participants (three SA, three NA) completed only one of the two amino acid test days. Go/no-go data for the missing test day for these participants was estimated using group means. Additionally, three participants (one SA, two NA), who completed both amino acid test days, came for cognitive testing at age 13 but not at age 14. Factor scores for the two missing factors (Verbal Learning and Executive Function) were estimated using multiple regression to predict missing test data within each factor, then multiplying the predicted test scores by the factor weights to estimate the factor scores.

An additional three NA and two SA participants vomited during one of the test days, were retained for testing on that day, and subsequently completed the entire experiment. In four cases, emesis occurred during the T- amino acid session.

Demographic Data

Demographic characteristics of the study sample are presented in Table 1.

Insert Table 1 about here

SA participants had lower estimated IQs [t (23.14) = -2.90, p = .008], fewer years of education [t (17) = -3.42, p = .003], lower family revenues in 1993 [t (36) = -2.17, p = .037], and higher (square root) teacher-rated averaged aggression [t (36) = 19.62, p < .001] and averaged anxiety [t (36) = 2.94, p = .006]. There tended to be a higher frequency of parent-reported ADHD in the SA group (p = .08).

Serum Free And Total Tryptophan Levels

Plasma free tryptophan concentrations were square root transformed to correct for positive skewness and violations of the homogeneity of variance assumption. Plasma free tryptophan concentration for one case five hours post amino acid administration was identified as an outlier, and brought into the next nearest value. This individual's plasma free tryptophan did not decrease following tryptophan depletion, despite a substantial lowering in plasma total tryptophan. A 2 (group) X 2 (treatment) X 2 (time) ANOVA, with treatment and time repeated-measures factors, on plasma free tryptophan concentrations revealed a highly significant treatment by time interaction [G-G F (1.11,39.80) = 28.47, $p < .001$]. The T- amino acid mixture significantly decreased, while the B mixture significantly increased, plasma free tryptophan levels five hours post-consumption across groups. The T- mixture led to a decline in plasma free tryptophan of 81% across groups, whereas the B mixture led to, on average, a 95% increase in plasma free tryptophan concentration. In those four individuals (1 SA, 3 NA) who vomited in the T- session and were retained for testing, plasma total and free tryptophan dropped 64.8% and 48.2% respectively.

Consumption of the snack and the 1 g tryptophan supplement led to a 353% increase in plasma free tryptophan in the B condition and a 269% increase in the T- condition relative to pre-amino acid administration levels (see Table 2). Levels of total and free tryptophan were significantly lower in those who received the T- mixture compared to the B mixture following meal consumption and tryptophan supplementation.

Insert Table 2 about here

Go/No-Go Task

Errors (omission and commission) were summed separately across the eighty trials within each condition. Errors within the reward pretreatment were not included because participants had to be exposed to the stimuli at least once in order to learn which were active and passive. Square root transformations were applied to normalize the positively-skewed distributions of the omission and commission errors. A 2 (group) X 2 (treatment) X 4 (condition) ANOVAs on square root OEs revealed a significant group X treatment X condition interaction [G-G F (2.81,101.15) = 3.51, p = .02] (see Figure 1).

Insert Figure 1 about here

Further analysis revealed a significant group X treatment interaction in the Rew-Pun condition [F (1,36) = 5.66, p < .03]. Newman-Keuls post-hoc tests failed to show significant differences between any of the means, however square root omission errors were near significantly increased following tryptophan depletion in the SA group relative to their (square root) omission errors following the balanced amino acid mixture, and relative to (square root) omission errors following the T-mixture in the NA group.

Analysis of square root CEs revealed a significant group [F (1,36) = 8.96, p = .005] and condition [G-G F (2.67,96.07) = 5.07, p < .01] main effects. SA participants made more (square root) CEs compared to NA

participants, and all participants made fewer (square root) CEs in the Rew-Pun condition relative to the Pun-Rew condition. No main effects or interactions involving treatment were significant, indicating that tryptophan depletion had no effect on square root CEs by group or condition (see Figure 1).

Square root omission and commission errors were reanalyzed (separately) using estimated IQ, years of education, family revenue, average teacher-rated anxiety, and parent-rated ADHD diagnosis as covariates in separate ANCOVAs. In the analyses of square root OEs, none of the covariates altered the significant group X treatment X condition interaction. In the analyses of square root CEs, estimated IQ was a marginally significant covariate [F (1,35) = 4.04, p = .052], reducing the group main effect to a trend [F (1,35) = 3.56, p = .068]. Average teacher-rated anxiety was a significant covariate [F (1,35) = 6.22, p = .02], similarly reducing the group main effect to a trend [F (1,35) = 3.16, p = .08]. Years of education, family revenue and parent-rated ADHD diagnosis were not significant covariates, and did not affect the group difference in commission errors.

Draw-a-Line Slowly Task

For the DALS test, all four variables (pre- and posttreatment, T- and B amino acid mixtures) for one case were identified as outliers and brought in to the next nearest values. These measures were square root transformed to normalize moderate positive skewness. A 2 (group) X 2 (treatment) X 2 (time) ANOVA revealed a trend for a group X treatment X time interaction [F (1,36) = 3.45, p = .072]. Inspection of the means revealed that the SA group drew slightly quicker five hours post-consumption of the T- mixture relative to pre-amino acid

consumption, whereas the NA group drew slightly slower (raw means [seconds] ± standard deviations: Pretreatment: T-, SA 16.3 ± 8.6; T-, NA 28.7 ± 30.4; Posttreatment: T-, SA 15.4 ± 9.9; T-, NA 32.9 ± 37.8).

Go/No-Go and Cognitive Variables: Interrelationships

In order to explore relationships between disinhibition on the go/no-go task and cognitive functioning, square root omission and commission errors were averaged (separately) across conditions then treatments and used as dependent variables in separate multiple regression analyses. Estimated IQ was employed as a measure of general intellectual ability, and the factor scores for the Verbal Learning, Incidental Spatial Learning, and Executive Function factors were used as indicators of cognitive functioning. These variables were entered on separate steps, in that order, to test whether executive function was associated with disinhibition over and above IQ, spatial memory and verbal abilities, the latter two assessing conventional memory processes. Group membership (stable aggressive versus nonaggressive) was added on the last step to see if aggressive status was related to disinhibition over and above cognitive functioning. Executive Function significantly predicted average square root commission errors [B (unstandardized)= -0.50, t = -3.07, p = .004] over and above IQ, spatial memory and verbal skill. Aggressive group status did not predict (square root) commission errors [B= 0.34,t = -1.08, p = .29] over and above cognitive functioning. The final equation accounted for 39% of the variance [adjusted R^2; F (5,32) = 5.72, p = .0007]. Addition of the Executive Function factor accounted for 21% of the variance in (square root) commission errors over and above the 18% accounted for by estimated IQ and the Spatial and Verbal factors. Figure 2 portrays the

relationship between commission errors (by group, averaged across conditions and treatments) and executive function factor scores.

Insert Figure 2 about here

None of the cognitive variables, nor group membership, predicted average square root omission errors.

Mood Variables

Separate 2 (group) X 2 (treatment) X 2 (time) ANOVAs were performed on the BDI, the state STAI, the anxiety and state sensation seeking subscales of the SSS, the POMS subscales and the VAMS items. Some variables were transformed to normalize skewed distributions. Only significant effects involving the time factor (pre, five hours post amino acid consumption) are reported in order to assess group or amino acid effects, or the interaction of these, across time. There were no such effects on the anxiety or state sensation seeking subscales of the SSS scale, the state STAI, or on any of the POMS subscales. In fact, there was scant evidence of an effect of the tryptophan-depleted mixture on mood across time. The only such effect was a treatment X time interaction on the contented-discontented scale of the VAMS [F (1,36) = 7.22, p = .01], resulting from all participants indicating greater feelings of discontent following tryptophan depletion relative to the B amino acid mixture posttreatment. Group effects across time primarily involved the NA group, as they reported feeling more feeble at posttest on the strong-feeble scale on the VAMS [group X time F (1,36) = 4.65, p < .04] relative to the SA group, and they tended towards less hunger at post-test on the hungry-full scale [group X time trend F (1,36) = 3.81, p =

.059] relative to pre, and to SA participants both pre and post amino acid administration. Finally, on the BDI, a group X time interaction [$F(1,36) = 4.65, p < .04$] resulted from the SA group showing a greater decrease in self-report depressive symptoms across time relative to the NA group across amino acid conditions.

DISCUSSION

The effect of tryptophan depletion on disinhibition (commission errors), and the relationship between executive functions and disinhibition, were investigated in this sample of stable aggressive and nonaggressive adolescent males, a subsample of a larger, well-defined, longitudinal cohort followed for the last twelve years. There are two primary findings in the present study. The first is that SA participants made more commission errors than NA participants across go/no-go and amino acid conditions. This is congruent with previous work demonstrating increased commission errors (but similar omission errors) in incarcerated psychopaths, extraverts, and juvenile delinquents (Newman and Kosson 1986; Newman et al 1985, 1990; Patterson et al 1987) and children with attention deficit hyperactivity disorder (Iaboni et al 1995). Increased commission errors in psychopaths, extraverts and juvenile delinquents were found in the reward-punishment condition only (not in the reward-reward or punishment-punishment conditions), leading to the hypothesis that, in situations with competing reward and response cost, a dominant response set for reward is formed making response inhibition difficult when confronted with stimuli associated with response cost (Newman and Wallace 1993). In the present study, commission errors were

increased across go/no-go conditions in SA participants (as well as in ADHD children; Iaboni et al 1995), suggesting a more global impairment in behavioral inhibition in SA young men. Alternatively, the fact that participants in the present study and in that of Iaboni et al. (1995) did all four conditions of the go/no-go whereas participants in the studies by Newman and his associates (Newman and Wallace 1993) did the go/no-go conditions between-subjects may have had an impact on the findings. Taken together, these studies suggest that disinhibition is an important characteristic of individuals with a history of aggressive behavior.

The second important finding of the present study is the association between executive functions and disinhibition (commission errors on the go/no-go). This association was robust even after controlling for IQ and conventional memory processes, and it accounted for the difference in commission errors between the SA and NA participants, as group membership was no longer associated with commission errors after controlling for executive functions. These findings are consistent with the association between physical aggression and executive functions (Séguin et al 1995). This association has been hypothesized to reflect "an inability to organize several parameters simultaneously, uncover complex rules, anticipate consequences of choices and actions, and reflect abstractly (verbally or otherwise) in order to solve interpersonal and social problems" (p. 621, Séguin et al 1995). The association between commission errors on the go/no-go and executive functions may represent a difficulty in anticipating the consequences of choices and actions on a moment-to-moment basis, and thus reflect an underlying process in the executive functions/aggression relationship.

Neuroimaging studies have implicated the dorsolateral prefrontal cortex in the performance of neuropsychological tests tapping executive functions (tests similar to those used to derive the executive functions factor of the present study) (Petrides et al 1993a, b). Executive functions have been found to be related to aggressive behavior on a laboratory task (Giancola and Zeichner 1994; Lau et al 1995). Furthermore, neuropsychological tests associated with areas 9 and 46 of the dorsolateral prefrontal cortex are most associated with physical aggression after controlling for attention deficit hyperactivity disorder and IQ (Séguin et al 1997). Giancola (1995) has hypothesized that the dorsolateral prefrontal cortex may be involved in physical aggression, while the orbitofrontal cortex may be associated with "disinhibited-nonaggressive" behavior. Future investigation might focus on which specific executive functions and which neuroanatomical areas in the frontal cortex are most highly correlated with commission errors. A recent positron emission tomography study found that no-go responses (inhibition of thumb flexing) were associated with activation in the right prefrontal cortex (approximately area 46) in healthy males (Kawashima et al 1996).

Tryptophan depletion had no effect on disinhibition on the go/no-go task in aggressive, disruptive young men, in contrast to an earlier study in which tryptophan depletion increased commission errors in young men with family histories of alcoholism (LeMarquand et al 1997). Tryptophan depletion did tend however to increase drawing speed (slightly) in the DALS test in the SA group, and decreased it in the NA group, suggesting a weak effect on disinhibition in this task. As well, tryptophan depletion increased omission errors in the reward-

punishment condition, an effect that could be attributed to reduced attention or motivation.

The absence of a tryptophan depletion effect on disinhibition may have been due to a ceiling effect: SA participants made more commission errors compared to NA participants in the B amino acid condition as well as the T- condition. This suggests that the SA group was disinhibited at baseline (i.e., after the B amino acid mixture), washing out a potential T- effect. Altering the go/no-go task to facilitate behavioral inhibition (e.g., adding a brief time period after stimulus presentation where no response is possible) might lower the number of CEs in the B condition, allowing for the demonstration of a T- effect.

Stable aggressive participants made more CEs following the B amino acid mixture, which may indicate reduced baseline serotonergic functioning in these individuals. Reduced baseline serotonin levels in aggressive children and adolescents have been suggested by a number of studies. Cerebrospinal fluid 5-hydroxyindoleacetic acid, a major metabolite of 5-HT, was inversely correlated with aggressive behavior in 6 to 17 year old boys with disruptive behavior disorders (Kruesi et al 1990), and predicted aggressive ratings two years later (Kruesi et al 1992). Halperin et al (1994, 1997) found age-related changes in prolactin response to fenfluramine challenge. Younger aggressive boys (< 9.1 years) demonstrated a greater prolactin response compared to age-matched controls. In the older cohort (> 9.1 years), prolactin response to fenfluramine was slightly higher in the nonaggressive boys, suggesting that normal boys may undergo a developmental increase in serotonergic functioning, while aggressive boys do not, subsequently leading to a blunted prolactin response in aggressive boys relative to controls. In the present study, SA and NA participants did not differ on

one possible factor influencing serotonin synthesis: baseline plasma tryptophan levels. (Interestingly, however, plasma tryptophan levels in SA participants after repletion did not increase to the level of NA participants following tryptophan depletion, possibly suggesting a lag in the availability of tryptophan for 5-HT synthesis in some circumstances; Buydens-Branchey et al 1989). If aggressive young men do have somewhat lower baseline serotonergic functioning, augmenting baseline serotonin levels should decrease disinhibition (commission errors).

Alternatively, the present sample of aggressive young men may not represent individuals with the greatest susceptibility to the effects of tryptophan depletion. Previous research has shown that it is individuals with psychiatric disorders (Barr et al 1994; Delgado et al 1990) , and those at risk by virtue of a family history of a disorder (Benkelfat et al 1994; LeMarquand et al 1997) that demonstrate behavioral effects of tryptophan depletion, while healthy individuals, by and large, do not (Young 1992). In the present study, 16 of the 18 SA adolescent males were also rated by their teachers as high in anxiety (i.e., greater than the 70th percentile on the anxiety subscale of the Social Behavior Questionnaire (Tremblay et al 1991) at age 6 and at least two of the three other assessment points). Eight additional *nonanxious,* aggressive young men declined to participate when contacted. Thus we were unable to test a subgroup of individuals who, *a priori,* might be most likely to show increased disinhibition following tryptophan depletion. It is also important to note that the SA and NA groups were well-matched in terms of paternal and maternal alcoholism family history; it may be that increased disinhibition following tryptophan

depletion is relatively specific to young men with family histories of alcoholism (LeMarquand et al 1997).

Young et al (1986, 1988) have hypothesized that changes in 5-HT synthesis may have the greatest effect on 5-HT release and postsynaptic function when 5-HT neurons are firing at a high rate. A state of behavioral arousal might facilitate higher firing rates in 5-HT neurons (Trulson and Jacobs 1979) relative to an unaroused state, creating a greater differential in 5-HT release and post-synaptic function between the balanced and tryptophan-depleted amino acid administrations. In the current study, participants did the go/no-go task after completion of the mood questionnaires, so arousal levels may have been low in these participants. In contrast, tryptophan-depleted young men with a paternal family history of alcoholism demonstrated increased commission errors when the go/no-go followed an aggression task (LeMarquand et al 1997), possibly as a result of increased arousal.

We did not require participants to adhere to a specified low protein diet in the present study, as has been done in previous studies (Benkelfat et al 1994; Delgado et al 1990), due to concerns of differential adherence to the diet between groups (i.e., that SA participants would not adhere to the diet). The T- mixture depleted plasma free tryptophan by 81%, on average, between groups in this study. This is slightly lower, although comparable to the degree of depletion of plasma free tryptophan achieved in other studies in our and other's laboratories (approximately 88% in Benkelfat et al 1994, LeMarquand et al 1997 and Leyton et al 1997; 83% in Delgado et al 1994 and Ellenbogen et al 1996; and 91% in Delgado et al 1990). It is possible, however, that the absence of an effect of tryptophan depletion on disinhibition was due to an inadequate lowering of plasma free tryptophan availability.

The lack of a prominent effect of tryptophan depletion on mood is intriguing. The mood-lowering effect of tryptophan depletion is a well-replicated phenomenon, noted in healthy controls with high normal baseline depression scores (Smith et al 1987; Young et al 1985), individuals at risk for affective disorder (Benkelfat et al 1994), and clinical groups (Barr et al 1994; Delgado et al 1990; Smith et al 1997), but not in healthy controls with low normal baseline depression scores (Abbott et al 1992). The weak T- effect on mood in the present study is congruent with the absence of an effect on disinhibition, perhaps for the reasons detailed above.

In summary, stable aggressive adolescent males were more disinhibited (i.e., made more commission errors) compared to nonaggressive young men on a go/no-go task. Moreover, executive functions accounted for a significant proportion of the variance in commission errors in the entire sample, over and above IQ, memory abilities and group membership (stable aggressive versus nonaggressive). Tryptophan depletion had no effect on disinhibition in stable aggressive young men, possibly due to a ceiling effect.

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Table 1. Demographic Characteristics of Stable Aggressive (SA) and Nonaggressive (NA) Participants*

Measure (Year of Assessment)	SA	NA
Number	18	20
Age, y	17.2 ± 0.4	17.0 ± 0.6
Height, cm	177 ± 7.1	175 ± 5.2
Weight, lbs	158 ± 36.9	147 ± 17.1
IQ, (WISC-R short form)	93 ± 14.9	104 ± 6.7‡
Education, years (1995)	10.3 ± 0.9	11.0 ± 0.0‡
Family Social		
Family Adversity (1984)	0.4 ± 0.2	0.4 ± 0.2
Family Revenue (1993)	5.8 ± 2.7	8.0 ± 3.4†
Mother's Occupational Prestige (1994-95)	34.1 ± 6.9	38.1 ± 11.6
Father's Occupational Prestige (1994-95)	40.9 ± 10.2	46.2 ± 11.3
Personal Behavior		
Teacher-rated Aggression	2.9 ± 0.9	0.1 ± 0.1‡
Teacher-rated Anxiety	4.8 ± 1.7	2.9 ± 2.1‡
Parent-rated ADHD (1992-94)	3 (18.8; n=16)	0 (0.0)††
Parent-rated ODD (1992-94)	2 (12.5; n=16)	0 (0.0)
Parent-rated Conduct Disorder (1992-94)	2 (11.8; n=17)	0 (0.0)
Self-rated ADHD (1992-94)	1 (5.6)	1 (5.0)

Self-rated ODD (1992-94)	0 (0.0)	0 (0.0)
Self-rated Conduct Problems (1992-94)	1 (5.6)	1 (5.0)
Parent Psychiatric		
Paternal Alcoholism Pedigree (1990)		
Neither Father, Pat. Grandfather Alcoholic	13 (76.5) (n=17)	14 (87.5) (n=16)
Father Alcoholic	2 (11.8)	0 (0.0)
Father, Paternal Grandfather Alcoholic	2 (11.8)	2 (12.5)
Maternal Alcoholism Pedigree (1990)		
Neither Mother, Mat. Grandmother Alcoholic	15 (88.2) (n=17)	16 (100.0) (n=16)
Mother Alcoholic	0 (0.0)	0 (0.0)
Mother, Maternal Grandmother Alcoholic	2 (11.8)	0 (0.0)
Parental Depression (1992-94)	2 (11.8; n=17)	4 (20.0)

*Values represent raw data and are expressed as mean ± SD, or frequency (percentage).

†$p < .05$

‡$p < .01$

††$p = .08$

Table 2. Total and Free Plasma Tryptophan Levels (mean ± standard deviation) at Baseline and Five Hours Following the Ingestion of a Balanced and Tryptophan-Depleted Amino Acid (AA) Load, and Following Tryptophan Repletion, in SA (Stable Aggressive) and NA (Nonaggressive) Participants

	SA (n=18)		NA (n=20)	
Time of Blood Draw	B Mixture	T- Mixture	B Mixture	T- Mixture
Total Tryptophan				
Baseline, μg/mL	10.8 ± 2.3	11.1 ± 2.9	11.6 ± 2.1	11.6 ± 2.4
5 h Post AA Mixture, μg/mL	15.6 ± 6.8 (+42.4%)	1.4 ± 0.5 (-87.0%)	18.9 ± 3.1 (+65.8%)	2.0 ± 1.5 (-82.1%)
Repletion, μg/mL	25.9 ± 10.9 (+147%)	18.7 ± 13.9 (+78%)	35.3 ± 11.7 (+206%)	26.2 ± 16.3 (+136%)
Free Tryptophan				
Baseline, μg/mL	1.3 ± 0.3	1.5 ± 0.3	1.5 ± 0.4	1.5 ± 0.3
5 h Post AA Mixture, μg/mL	2.3 ± 1.0 (+76.9%)	0.2 ± 0.1 (-85.3%)	3.0 ± 0.8 (+114%)	0.3 ± 0.3 (-76.9%)
Repletion, μg/mL	5.1 ± 3.0 (+279%)	4.6 ± 3.6 (+220%)	7.3 ± 3.2 (+428%)	5.7 ± 4.7 (+317%)

Figure 1. Mean (± standard error) omission and commission errors by condition in each of the two groups following consumption of the two amino acid loads. Rew-Pun indicates the reward-punishment go/no-go condition; Pun-Pun, punishment-punishment; Rew-Rew, reward-reward; Pun-Rew, punishment-reward. T- indicates tryptophan-depleted amino acid mixture; B, balanced amino acid mixture; SA, stable aggressive participants; NA, nonaggressive participants.

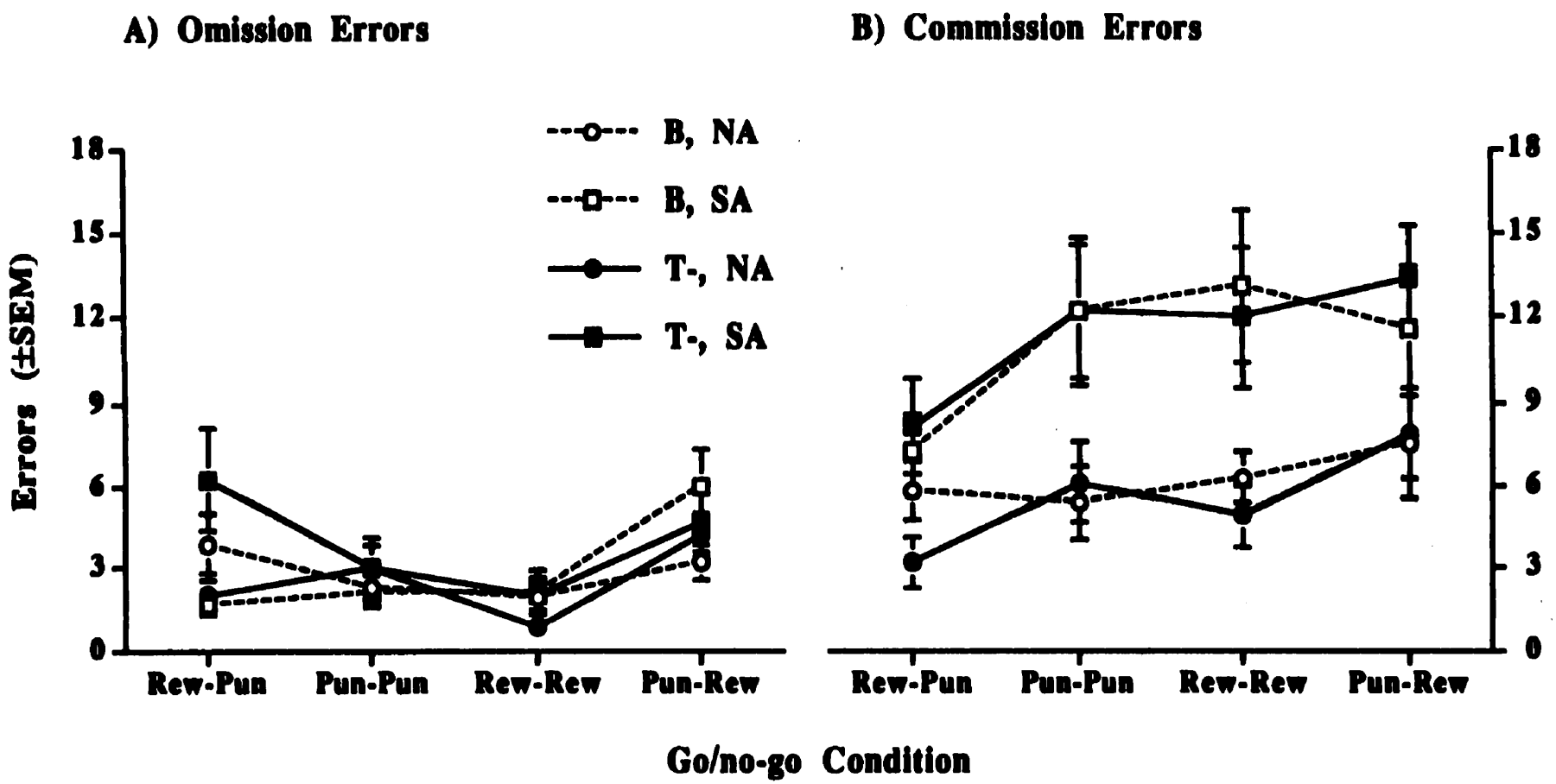
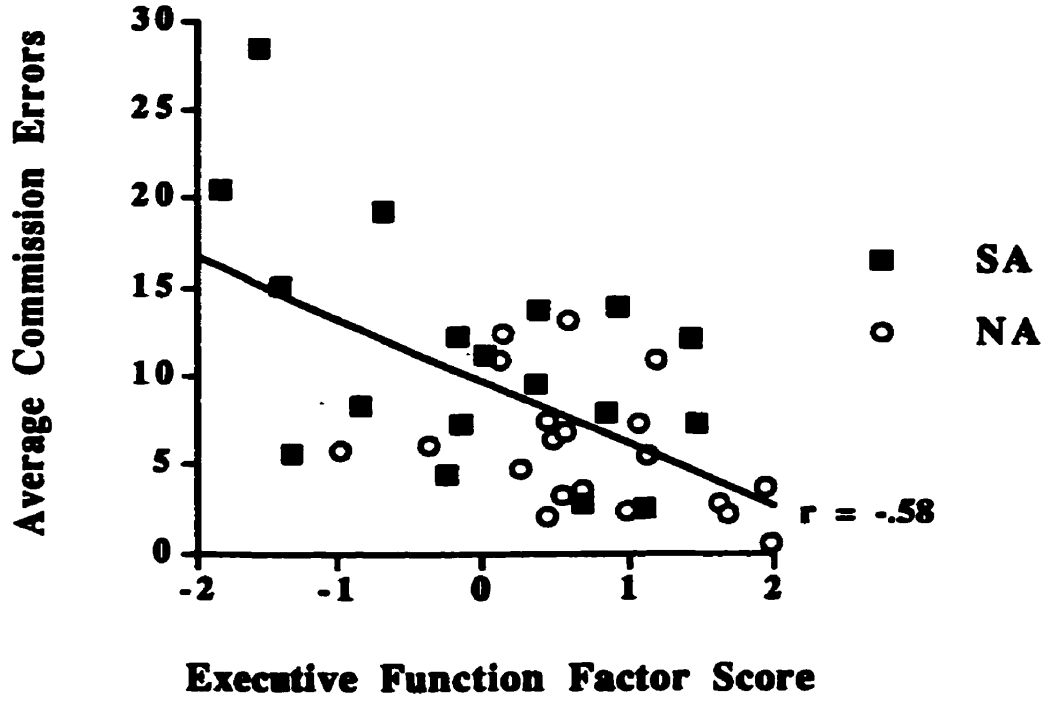

A) Omission Errors
B) Commission Errors
B, NA
B, SA
T-, NA
T-, SA
Errors (±SEM)
0
3
6
9
12
15
18
Rew-Pun
Pun-Pun
Rew-Rew
Pun-Rew
Go/no-go Condition

Figure 2. Correlation between commission errors on the go/no-go (averaged across conditions and treatments) and executive function factor scores. SA indicates stable aggressive participants; NA, nonaggressive participants.


Average Commission Errors
30
25
20
15
10
5
0
-2
-1
0
1
2
SA
NA
r = -.58
Executive Function Factor Score

GENERAL DISCUSSION

Acute tryptophan depletion increased disinhibition (commission errors), but not aggression, in nonalcoholic young men with a multigenerational paternal family history of alcoholism in the first study. This study provides the first demonstration that an experimental reduction of tryptophan availability, and presumably a reduction if the synthesis and post-synaptic function of central 5-HT, leads to increased behavioral disinhibition on a go/no-go learning task. It provides strong evidence supporting the hypothesis that central serotonergic functioning is inversely related to impulsivity (Virkkunen, Goldman, Nielsen, & Linnoila, 1995). In contrast, ATD had no effect on disinhibition in stable aggressive adolescent males in study two, however it did affect omission errors in the reward-punishment condition of the go/no-go. The differential response between the two "at-risk" groups on commission errors may have been due to differences in susceptibility to the neurochemical effects of acute tryptophan depletion and/or differences in methodologies between the studies.

Concerning the first hypothesis, it appears that the ATD-induced increase in commission errors on the go/no-go is specific to MPFH individuals, and not aggressive, disruptive adolescents. This may suggest a neurochemical susceptibility to the effects of ATD relatively specific to individuals with a family history of alcoholism. This is congruent with studies showing that low 5-HIAA is strongly associated with a family history of alcoholism in male alcoholic violent offenders and fire setters (Virkkunen et al., 1996). It is interesting to note that relatively few SA or NA participants had family histories of paternal or maternal alcoholism, providing circumstantial evidence supporting

this hypothesis. Of course, a replication of this effect is needed, preferably employing a within-subjects design to maximize power to detect an effect.

Methodological differences between the studies may also account for the lack of an ATD effect on commission errors in SA participants. There was no additional task administered before the go/no-go in the second study, as the Taylor aggression task was in the first study. An arousing stimulus may be necessary to facilitate a difference in 5-HT release and post-synaptic function between the T- and B amino acid conditions (Young, 1986; Young et al., 1988). As detailed earlier, participants in study two did not receive a standardized meal the day prior to amino acid administration. Although there were comparable decreases in plasma total and free tryptophan levels, it is important to remember that a secondary mechanism determining the levels of brain tryptophan following ATD involves the competition among the large neutral amino acids for brain uptake on the same carrier system. This is dependent on the *ratio* of tryptophan to the other large neutral amino acids that compete for brain uptake (Krahn et al., 1996; Weltzin et al., 1994). Administration of the standardized meal followed by the balanced amino acid mixture (with 2.3 g tryptophan, as was used in these two studies) has been shown to *decrease* the ratio of tryptophan to other large neutral amino acids, perhaps decreasing brain tryptophan and reducing the likelihood of observing differences between the ATD and B conditions (Weltzin et al., 1994). It may be that the absence of the standard meal prior to amino acid administration in study two systematically reduced group differences in plasma tryptophan availability, leading to the lack of an effect. Previous studies using similar amino acid mixtures without the standard meal have found behavioral differences, however (Smith et al., 1987a; Young et al., 1985).

Group differences in IQ in the two studies may partly account for baseline differences in CEs on the go/no-go task. SA and NA participants in the second study had mean IQs of 93 and 104, respectively, which are somewhat lower than the mean IQs of the MPFH and FH- participants in the first study, at 110 and 113. SA participants, in particular, had lower IQs, which may account for the greater CEs seen at baseline (i.e., following the balanced amino acid mixture) in this group. In Newman's early work, there were no group differences in IQ despite differences in CEs (Newman et al., 1985; Newman & Kosson, 1986; Newman, Patterson, Howland, & Nichols, 1990). IQ was uncorrelated with go/no-go errors in ADHD boys and non-ADHD controls (Iaboni et al., 1995). In fact, only one study (Helmers et al., 1995) found IQ to be inversely related to CEs in the Pun-Pun and Rew-Rew conditions, and to OEs in the Rew-Pun and Pun-Pun conditions as well, in normal male volunteers.

The inverse relationship between executive functioning and commission errors on the go/no-go found in the second study suggest a mechanism by which ATD may have increased commission errors in the first study. The executive functions factor utilized in study two consisted of tests that involved the active monitoring of working memory, the maintenance and retrieval of recently acquired information, forming associations between stimuli, responses and feedback, motor response and inhibition, and problem-solving abilities. Many of these cognitive functions are necessary for successful performance on the go/no-go task. ATD may have interfered with any combination of these abilities in increasing commission errors in MPFH men in study one.

In fact, the exact processes affected by ATD that resulted in increased CEs in MPFH men in study one are unknown. Similarly, the

processes that led to increased commission errors in SA relative to NA men at baseline in study two are also not clearly understood. The notion of impulsivity, or behavioral disinhibition, could imply difficulties at a number of levels, as outline in the introduction: a lack of forethought, a difficulty learning from the consequences of one's actions (acquiring, storing, or retrieving associations), and/or a quickened behavioral tempo. Dissociation between these processes with the primary dependent measure used in these studies (commission errors on the go/no-go task) is difficult.

This is underscored by the results of a third preliminary study (see Appendix). In this study, the hypothesis that a polymorphism of the D4 dopamine receptor gene would be related to behavioral disinhibition (go/no-go commission errors) was tested. Variation exists in the number of repeats of a specific section of the D4 dopamine receptor gene, with the most frequent alleles in the normal population being the 4 and 7 repeat (Ebstein et al., 1996). Presence of the 7 repeat allele has been associated with the personality construct of novelty seeking in healthy individuals (Benjamin et al., 1996; Ebstein et al., 1996). Individuals high in novelty seeking have been characterized as impulsive, explorative, excitable, quick-tempered, fickle, and extravagant (Cloninger, 1987a). No association between presence of the 7-repeat allele and commission errors on the go/no-go was found (see Appendix). D4 dopamine polymorphisms may yet be found to be related to behavioral impulsivity, but not to the component(s) of behavioral disinhibition tapped by go/no-go commission errors. Commission error performance may be related more to learning and memory functions (e.g., forming associations between stimuli, responses and feedback, maintaining these associations in working

memory), whereas D4 dopamine polymorphisms may be related to motor impulsivity (e.g., quickened behavioral tempo).

Of what practical importance is the finding of an ATD-induced increase in disinhibition (commission errors) in MPFH men? Although depletions of plasma free and total tryptophan of the magnitude induced by ATD do not occur naturally, smaller variations in tryptophan availability may be enough to affect central serotonergic synthesis and function. These variations may be sufficient, in turn, to have a significant impact on behavior, perhaps leading to transient increases in behavioral disinhibition in MPFH men. Seasonal variation in plasma tryptophan in a sample of healthy volunteers has been inversely related to the seasonal variation of violent suicide in a population sample (Maes et al., 1995).

Whether the increased disinhibition (commission errors) following ATD in MPFH men is a marker for the future development of alcoholism remains to be explored. The original thesis of this dissertation concerned the existence of a causal pathway leading from low central serotonergic functioning to increased disinhibition, and ultimately to increased alcohol consumption and the development of alcoholism in individuals at heightened risk for alcoholism. Only long-term follow-up of a large sample of MPFH men following ATD and testing on the go/no-go will determine whether it is those MPFH individuals who demonstrate an ATD-induced increase in disinhibition that subsequently develop alcoholism. This type of long-term follow-up would be costly, however it is feasible. Schuckit and Smith (1996) have completed an eight-year follow-up of their cohort of sons of male alcoholics, finding that a low level of behavioral response to alcohol challenge in these individuals is related to the development of alcoholism eight years later.

Clinically, the results of these two studies have two implications. The results of the first study suggest that increasing serotonergic function might lead to reduced disinhibition in impulsive individuals, and that pharmacological interventions could be developed with specific serotonergic agonist actions to decrease impulsivity. As mentioned in the introduction, tryptophan (Morand et al., 1983) and the SSRI citalopram (Vartiainen et al., 1995) have been used to treat aggressive inpatients with some success. It is unlikely, however, 5-HT agonists could decrease impulsivity in the long-term, due to tolerance effects.

The results of study two, however, suggest an alternate method of facilitating behavioral inhibition in impulsive individuals. Therapeutic techniques emphasizing pausing and attending to feedback, and using that feedback to modify future behavior, might reduced disinhibition in impulsive individuals. In an empirical investigation, Arnett, Howland, Smith and Newman (1993) demonstrated that by introducing an eight second post-feedback period after each go/no-go response, previous elevations in commission errors in psychopaths versus controls were eliminated. Thus allowing disinhibited individuals the time to process feedback facilitates behavioral inhibition.

Finally, what do the results of these two studies suggest for the role of serotonin in impulsivity? As stated earlier, the findings of the first study represent the first demonstration that depleting the amino acid precursor of serotonin induces a selective increase in commission errors on a passive avoidance learning task in men at risk for alcoholism. Thus they provide preliminary evidence that serotonin is causally involved in impulsivity, in some individuals. Further specification of the brain neuroanatomical and biochemical pathways

involved in the production of disinhibited behavior is not possible at this time. While more precise theories of the biochemistry of other psychiatric disorders have been produced (Duman, Heninger, & Nestler, 1997), theoretical models specifying the neurochemistry of impulsivity and aggression, and more specifically the role of serotonin in the production of these behaviors, are less well developed. Schreiber and De Vry (1993) suggest that impulsivity/inhibition is mediated through activation of postsynaptic 5-HT_{1A} receptors in as yet unspecified brain regions.

Linnoila and Virkkunen (1992) have a somewhat more intricate model, based on their research with impulsive, alcoholic violent offenders. They posit that reduced serotonergic innervation from the dorsal and median raphe nuclei to the suprachiasmatic nucleus leads to a disturbance in circadian rhythms, resulting in increased dysphoria or dysthymia, which prompts excessive alcohol use (and the acute release of serotonin) to ameliorate this subjective state. Secondly, reduced suprachiasmatic serotonergic functioning disturbs glucose metabolism, resulting in lowered blood glucose levels and an increased propensity for impulsive, aggressive behavior. Excessive alcohol use subsequently lowers serotonergic functioning, which further increases the propensity for impulsivity. This model is intriguing and provides a number of testable hypotheses, which are receiving empirical support (Matykiewicz, Lagrange, Reyes, Vance, & Wang, 1997; Virkkunen, De Jong, Bartko, Goodwin, et al., 1989).

The data in the present thesis support the causal pathway leading from reduced serotonergic function to increased impulsivity, but cannot test any of the mediating factors hypothesized in Linnoila and Virkkunen's (1992) model. The acute tryptophan depletion paradigm can, at best, only effect a global depletion of brain serotonergic

synthesis, and presumably function. A full specification of the neuroanatomical structures and neurochemical pathways involved in producing impulsive behavior is needed. Research toward this end will necessarily involve animal models of disinhibited behavior, as well as neuroimaging techniques and pharmacological challenges with increasingly more specific serotonin receptor agonists and antagonists in humans.

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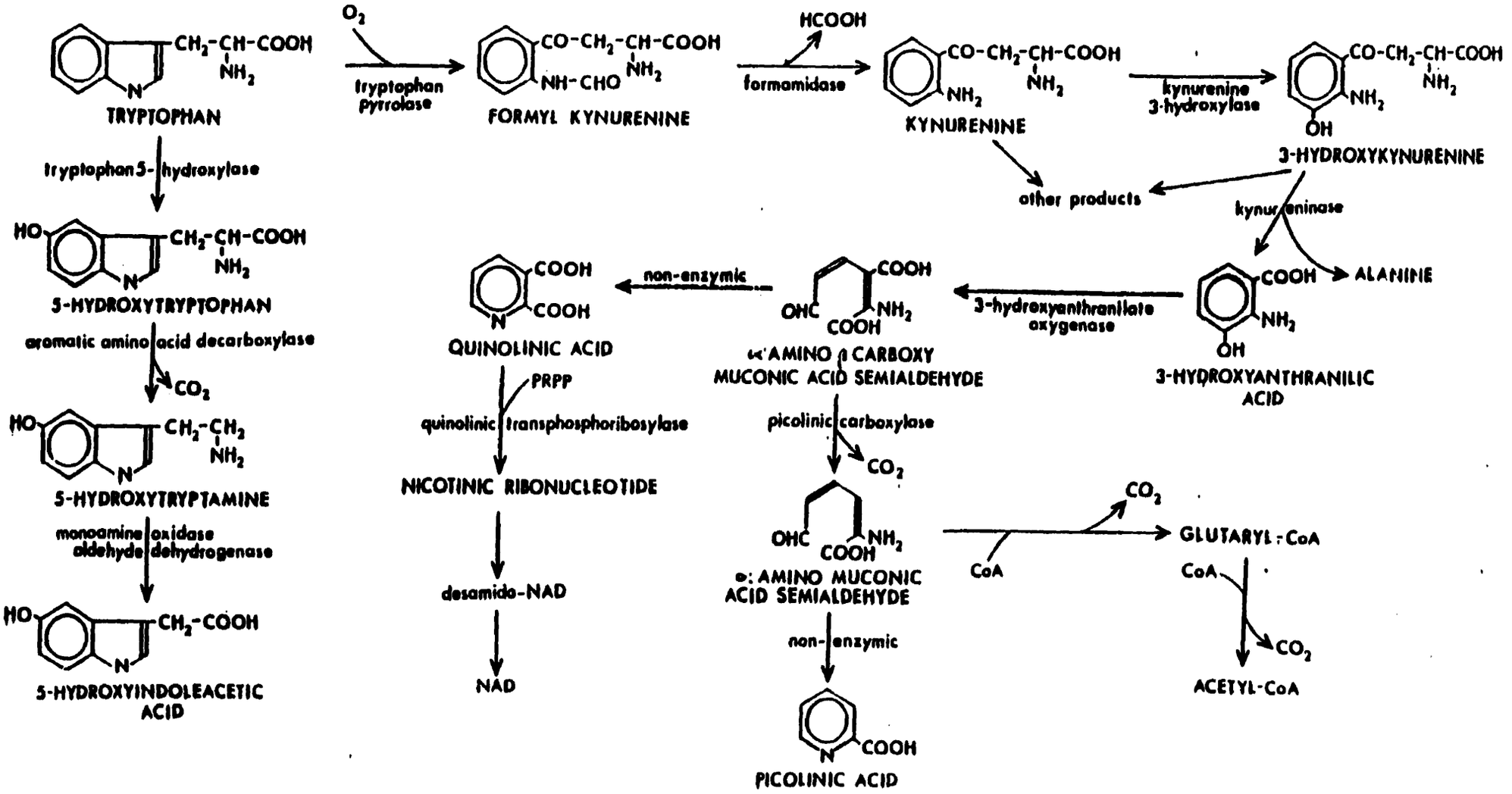
Table 1. **Reinforcement Contingencies in Effect for the Reward-Punishment (Rew-Pun), Punishment-Reward (Pun-Rew), Reward-Only (Rew-Rew) and Punishment-Only (Pun-Pun) Conditions of the Go/No-Go Discrimination Learning Task** (adapted from Iaboni et al., 1995)

		Reinforcement Contingency			
Stimulus	Response	Rew-Pun	Pun-Rew	Rew-Rew	Pun-Pun
Active[a]	yes	WIN[c]	—	WIN	—
	no	—[d]	LOSE	—	LOSE
Passive[b]	yes	LOSE[e]	—	—	LOSE
	no	—	WIN	WIN	—

[a]Stimulus to which participant should respond; [b]stimulus to which participant should not respond; [c]participant won $.10; [d]participant did not win or lose $.10; [e]participant lost $.10.

Figure 1. The pathways of the synthesis and metabolism of tryptophan and serotonin


TRYPTOPHAN
tryptophan 5-hydroxylase
5-HYDROXYTRYPTOPHAN
aromatic amino acid decarboxylase
CO2
5-HYDROXYTRYPTAMINE
monoamine oxidase
aldehyde dehydrogenase
5-HYDROXYINDOLEACETIC ACID
O2
tryptophan pyrrolase
FORMYL KYNURENINE
HCOOH
formamidase
KYNURENINE
kynurenine 3-hydroxylase
3-HYDROXYKYNURENINE
other products
kynureninase
ALANINE
3-HYDROXYANTHRANILIC ACID
3-hydroxyanthranilate oxygenase
α-AMINO β-CARBOXY MUCONIC ACID SEMIALDEHYDE
non-enzymic
QUINOLINIC ACID
PRPP
quinolinic transphosphoribosylase
NICOTINIC RIBONUCLEOTIDE
desamido-NAD
NAD
picolinic carboxylase
CO2
ε-AMINO MUCONIC ACID SEMIALDEHYDE
non-enzymic
PICOLINIC ACID
CO2
CoA
GLUTARYL-CoA
CoA
CO2
ACETYL-CoA

APPENDIX

Associations Between Polymorphisms of the Dopamine D4 Receptor (D4DR) Exon III, Extraversion and Behavioral Impulsivity[2]

by

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ABSTRACT

Two recent reports have demonstrated that healthy volunteers who score higher than average on novelty seeking (i.e., are impulsive, exploratory, fickle, excitable, quick-tempered and extravagant) show a higher frequency of a specific exonic polymorphism, the 7 repeat allele in the locus for the D4 dopamine receptor gene (D4DR). In the present study, a possible association between the D4DR repeat 7 allele and commission errors on a go/no-go learning task was tested. Commission errors represented failures to inhibit responses to stimuli previously associated with punishment or loss of potential reward. As well, possible associations between the D4DR repeat 7 allele and questionnaire measures of sensation seeking and extraversion were tested. The sample of young men included a group with multigenerational family histories of paternal alcoholism, as well as adolescents high on teacher-rated aggression. Results demonstrated no significant associations between the presence/absence of the D4DR repeat 7 allele and go/no-go commission errors, sensation seeking, or extraversion. Presence of the repeat 7 allele was associated with fewer go/no-go omission errors (failures to respond to stimuli associated with reward or avoidance of punishment). Possible reasons for the absence of the predicted associations are explored.

INTRODUCTION

Two recent reports have demonstrated that the 7 repeat allele of exon III of the D4 dopamine receptor gene (D4DR) is positively associated with novelty seeking traits (impulsivity, exploration, excitability, quick-temperedness, fickleness, and extravagance) in healthy individuals (Benjamin et al., 1996; Ebstein et al., 1996). The D4DR receptor gene contains a polymorphic 16-amino acid repeat region in the putative third cytoplasmic loop (Lichter et al., 1993; Van Tol et al., 1992); the most frequent alleles of the D4DR exon III repeat polymorphism are the 4 repeat and the 7 repeat (Ebstein et al., 1996). The finding of an association between the 7 repeat allele and novelty seeking is particularly significant given that the affinity of the D4 receptor for dopaminergic ligands is influenced by the number of repeats at this particular site (Asghari et al., 1994; Van Tol et al., 1992). This finding may reinforce the notion put forward by Cloninger (1987) that novelty seeking is mediated by dopaminergic neurotransmission, independent from two other dimensions of personality, harm avoidance and reward dependence, which are hypothetically mediated by the serotonergic and noradrenergic neurotransmitter systems, respectively. In the association studies cited above, novelty seeking was assessed using the Tridimensional Personality Questionnaire (TPQ) (Cloninger, Svrakic, & Przybeck, 1993) or the NEO Personality Inventory (NEO-PI-R) (Costa & McCrae, 1992). More recent studies have not replicated the initial findings, using the impulsiveness and monotony avoidance subscales of the Karolinska Scales of Personality (Jönsson et al., 1997), or the novelty seeking scale from the TPQ (Gelernter, Kranzler, & Mulgrew, 1996).

Due to the hypothesized presence of an impulsivity component in the novelty seeking factor, the present study tested whether the long allele of polymorphic exon III repeat sequence of the D4DR gene might also be associated with a behavioral measure of disinhibition. The go/no-go learning task has been used to investigate disinhibition in a variety of populations (Patterson & Newman, 1993). In this task, participants learn by trial-and-error to respond (press a button) to "active" stimuli and withhold their responses to "passive" stimuli (two-digit numbers presented on a computer screen). Correct responses to active stimuli lead to reward (accumulation of money) or avoidance of punishment (loss of money), while incorrect responses to passive stimuli lead to punishment or failure to obtain potential reward. Commission errors, or failures to withhold responses to passive stimuli, function as a measure of disinhibition. College students who score high on extraversion as measured by Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975) make more commission errors in certain conditions of the go/no-go task compared to those scoring low. As well, certain clinical groups, such as adolescent and adult psychopaths, and children with attention deficit hyperactivity disorder, make more commission errors compared to controls, depending on reinforcement condition of the go/no-go (Iaboni, Douglas, & Baker, 1995; Newman, Patterson, Howland, & Nichols, 1990) . Additionally, the present study addresses whether the long allele of polymorphic exon III repeat sequence of the D4DR is associated with other measures which may tap into the personality dimension of novelty seeking: sensation seeking, as assessed by Zuckerman's Sensation Seeking Scale (Zuckerman, 1979), and extraversion, from the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975).

The sample in the current study is composed of young men with a multigenerational paternal family history of alcoholism and those without, and adolescent males previously rated high or low on aggressiveness (Séguin, Harden, Pihl, Tremblay, & Boulerice, 1995) previously studied on the go/no-go paradigm (LeMarquand, Benkelfat, Pihl, Palmour, & Young, 1997a; LeMarquand et al., 1997b). The primary hypothesis was that individuals with the long allele of the D4DR gene would make more commission errors on the go/no-go task and would score higher on the Sensation Seeking scale and on Eysenck's extraversion dimension.

METHODS

Participants

Participants included 59 healthy males, mean age 21, and 39 adolescent males, mean age 17, who participated in earlier studies on the effects of acute tryptophan depletion on disinhibition (LeMarquand et al., 1997a, b). The sample from the first study was recruited from the community and screened to be free of DSM-III-R (American Psychiatric Association, 1987) Axis I disorders. Twenty-three men in the former sample were selected on the basis of having a multigenerational paternal family history of alcoholism (MPFH; typically father and paternal grandfather, at minimum), while the remainder (n=36) had no family history of alcoholism in their previous two generations (FH-). The sample from the second study was recruited from a larger cohort of 1037 boys followed longitudinally from age 6. These boys were originally recruited from 53 schools with the lowest socioeconomic index in the Montreal Catholic School Commission in 1984. They were

rated by their teachers at ages 6, 10, 11 and 12 on the fighting subscale of the teacher form of a French Canadian version of the Social Behaviour Questionnaire (Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987). Those boys scoring above the 70th percentile at age 6 and at least two of the three additional assessment points were classified as stable aggressive (SA), while those below the 70th percentile at all assessment points were classified nonaggressive (NA) (Séguin et al., 1995). Eighteen SA and 20 NA adolescent males participated in the tryptophan depletion study. An additional participant who took part in the second study (LeMarquand et al., 1997b) but was not included in data analysis, was included in the present study.

Procedure

After providing informed consent, initial screening included the completion of the Sensation Seeking (SS) scale (Zuckerman, 1979) and the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975). Participants provided a blood sample on the morning of the day on which they participated in the tryptophan depletion procedure. The go/no-go task was completed approximately 5.5 to 7 hours following consumption of the amino acid mixture. Participants in the first sample received either a tryptophan-depleted or balanced amino acid mixture (between-subjects design), while those in the second sample received both a tryptophan-depleted and balanced amino acid mixture on separate days (within-subjects design). As tryptophan depletion affected commission errors in the first sample (LeMarquand et al., 1997a), only those individuals who received the balanced amino acid mixture were included in this analysis. This included 18 FH-

participants and 11 MPFH participants (see (LeMarquand et al., 1997a, b) for procedural details).

For participants who took part in the first study (LeMarquand et al., 1997a), IQ was estimated using a seven-subtlest Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) short form (including Information, Arithmetic, Similarities, Picture Completion, Digit Span, Block Design, and Digit Symbol) (Ward, 1990). This IQ estimate is highly correlated with WAIS-R full scale IQs in psychiatric inpatients (Benedict, Schretlen, & Bobholz, 1992). For those who participated in the second study (LeMarquand et al., 1997b), IQ was estimated using a two-subtest Weschler Intelligence Scale for Children-Revised (Wechsler, 1974) short form (Sattler, 1988), including the Vocabulary and Block Design subtests, administered when the participants were age 15.

The go/no-go task has been described in detail elsewhere (LeMarquand et al., 1997a). Briefly, participants must respond (press a button) to "active" stimuli and withhold their responses to "passive" stimuli. Stimuli consist of two-digit numbers presented on a computer screen. Correct responses were rewarded with a high-pitched tone, presentation of the word "CORRECT" on the computer screen, and addition of ten cents to a running tally of the participant's earnings, also presented on the screen. Incorrect responses were punished with a low-pitched tone, presentation of the word "WRONG" on the computer screen, and subtraction of ten cents from the running tally of the participant's earnings.

Participants completed four conditions on the go/no-go task, presented in a counterbalanced order. In the reward-punishment (Rew-Pun) condition, responses to active numbers were reinforced, and responses to passive numbers punished. Participants started with

one dollar in this condition. In the punishment-punishment (Pun-Pun) condition, responses to passive numbers were punished, as were nonresponses to active numbers. In this condition, participants started with four dollars, as they could only lose money. In the reward-reward (Rew-Rew) condition, responses to active numbers and nonresponses to passive numbers were reinforced. Participants started with no money in this condition, as they could only win. In the punishment-reward (Pun-Rew) condition, nonresponses to active stimuli were punished, and nonresponses to passive stimuli were rewarded. As in the Rew-Pun condition, participants started with one dollar in the Pun-Rew condition. Dependent measures include commission errors (CEs; failures to withhold responses to passive numbers) reflecting disinhibition, and omission errors (OEs; failures to respond to active numbers).

Genotyping

DNA was isolated from peripheral leukocytes by phenol/chloroform extraction, and genotyped following amplification of a region in the third exon of the D4DR gene containing a 48bp VNTR (Lichter et al., 1993). The forward and backward primers were: D4-3 (5π-GCGACTACGTGGTCTACTCG-3π) and D4-42 (5π-AGGACCCTCATGGCCTTG-3π). The PCR reaction was performed in 25 ml final volume of mix [10% DMSO, 200 mM of dATP, dCTP, cTTP; 100 mM dCTP; 100 mM deaza-dGTP, 500 ng each primer; 1.5 U Taq polymerase; 1x Taq polymerase buffer (50mM KCl, 10 mM tis-HCL ph9, 1 mM MgCl and 1% Triton x-100)]. Conditions for amplification were: 40 cycles of 20≤ @ 95 c, 20≤ @ 54 C, and 40≤ @ 72 C followed by a final extension of 4π @ 72 C, using an MJ Research Inc. PT-100 thermocycler. After electrophoresis (70π in a 10% non-denaturing polyacrylamide gel), bands containing DNA were stained with ethidium bromide,

photographed under UV light and typed by comparison to molecular weight markers and reference standards. Each gel was read independently by two observers; disagreements were resolved by reanalysis of the sample or by a third reader.

Data Analysis

All personality and go/no-go variables were inspected for normality (skewness, kurtosis). Appropriate transformations were performed when necessary (Tabachnick & Fidell, 1989) and are specified below. Genotypes were stratified according to Ebstein et al. (Ebstein et al., 1996) by the presence or absence of allele 7. Separate independent samples t-tests (by polymorphism) were performed on the Extraversion subscale of the EPQ, as well as on the Psychoticism and Neuroticism subscales. Separate t-tests were performed on the total score of the SS scale, as well as on the four subscales: Boredom Susceptibility, Disinhibition, Excitement Seeking, and Thrill and Adventure Seeking. Estimated IQ was analyzed using an independent samples t-test. Two-tailed P values were chosen, due to the exploratory nature of these analyses. The criterion for significance (alpha level) was not adjusted for the number of comparisons, as a heightened probability of Type I errors (false positives) is thought to be justified when conducted exploratory association studies (Ebstein et al., 1997; see also Lander & Kruglyak, 1995).

Separate 2 (polymorphism) X 4 (condition) between/within-subjects ANOVAs on omission and commission errors were performed. Statistically significant interactions were further analyzed by pairwise comparisons using the Newman-Keuls procedure. Geisser-Greenhouse (G-G) corrections were used for all main effects and interactions involving repeated measures.

RESULTS

Presence/Absence of Repeat 7 Polymorphism and Sensation Seeking, Extraversion, and IQ

Of the 98 total participants across the two studies, blood was obtained and genotyped for 78 participants. Twenty participants' blood samples were not genotyped due to difficulties isolating viable DNA. (Of these 20 individuals, six were MPFH and 12 FH- in the first study, and two were NA from the second study). Of the remaining 78 participants, 14 were positive for the repeat 7 polymorphism. Additionally, some data was missing for some participants on the questionnaire and IQ measures. One NA participant from the second study did not complete the SS and EPQ scales; one FH- participant from study one did not complete the EPQ; one SA participant from study two did not complete the EPQ or IQ measures, and three additional participants in study two (one SA and two NA) did not complete the IQ measures. Of the individuals that did not complete the questionnaire measures, all were repeat 7 negative.

T-tests demonstrated that repeat 7 present individuals were not higher in Extraversion on the EPQ ($t[73]=-.27$, $P=.78$), or sensation seeking as indexed by the (log) total score on the SS scale ($t[75]=-1.51$, $P=.14$). Repeat 7 present participants were not higher on any of the SS subscales (Boredom Susceptibility ($t[75]=-.53$, $P=.60$), Disinhibition ($t[75]=1.53$, $P=.13$), Excitement Seeking ($t[75]=-.59$, $P=.56$), and Thrill and Adventure Seeking ($t[75]=1.64$, $P=.11$)), nor were they different from repeat 7 absent individuals on the Psychoticism ($t[73]=.06$, $P=.95$) or Neuroticism ($t[73]=-.88$, $P=.38$) subscales of the EPQ. Group means and

standard deviations by repeat 7 status (present or absent) are presented in Table 1.

Insert Table 1 about here

In terms of estimated IQ, there were no differences between repeat 7 absent (n=60, mean=105.3, SD=14.9) and repeat 7 present (n=14, mean=106.5, SD=9.9) individuals (t[72]=-.29, P=.77).

Presence/Absence of Repeat 7 Polymorphism and Go/no-go Performance

Thirty-three participants who received only the T- mixture were excluded from the present analysis due to the effects of the T- amino acid mixture on go/no-go CEs. Only those participants who received the balanced (placebo) mixture were included in the analysis. Of the 65 remaining participants, 10 (six FH-, three MPFH from study one, one NA from study two) were not genotyped due to difficulties isolating viable DNA. Nine of the remaining total sample of 55 participants were positive for the repeat 7 allele. A polymorphism X go/no-go condition ANOVA on log transformed OEs revealed a significant main effect of polymorphism (F[1,53]=4.47, P=.04), and a weak trend for a polymorphism X condition interaction (G-G F[2.59,159]=2.22, P=.098). Repeat 7 present individuals made significantly fewer (log) OEs relative to repeat 7 absent individuals (raw means ± standard deviations: repeat 7 present, 1.8 ± 1.4; repeat 7 absent, 3.3 ± 2.4). Inspection of the means by polymorphism and go/no-go condition revealed that repeat 7 present individuals tended to make fewer omission errors in the reward-punishment and punishment-punishment go/no-go conditions. A

polymorphism X go/no-go condition ANOVA on square root transformed CEs revealed no main effects or interactions involving the polymorphism factor. Repeat 7 absent individuals made 8.9 ± 6.1 commission errors (mean ± SD), while repeat 7 present individuals made 6.3 ± 3.6.

DISCUSSION

This preliminary study represents the first attempt to associate D4DR receptor polymorphisms, previously reported to be associated with novelty seeking in population samples (Benjamin et al., 1996; Ebstein et al., 1996), with a well-validated behavioral measure of disinhibition, commission errors on a go/no-go task. Results suggest no association between the presence of the 7 repeat polymorphism and commission errors. Furthermore, in a slightly larger sample, no associations between D4DR polymorphisms and extraversion on the EPQ or sensation seeking on the SS scale were found.

The present data does not replicate the association between novelty seeking and D4DR polymorphisms (Benjamin et al., 1996; Ebstein et al., 1996), possibly for a number of reasons. The sample size of the present study was smaller than those typically found in gene association studies. Alternatively, extraversion on the EPQ and sensation seeking on the SS scale may not sufficient estimates of the trait of novelty seeking (as measured by the TPQ or estimated from the NEO-PI-R). In the study by Benjamin et al. (1996) however, extraversion and conscientiousness on the NEO-PI-R are the two factors specifically associated with longer and shorter (respectively) repeat sequences (long D4DR alleles containing 6 to 8 exon III repeats, short alleles containing 2 to 5 repeats). Within the extraversion factor,

higher scores on the warmth, excitement seeking, and positive emotions subfactors were found in long allele individuals. At face value therefore, one might expect that EPQ extraversion and Zuckerman's SS would be associated with the number of exon III repeats.

Jönsson et al. (1997) suggest that the genetic basis for the same personality trait (novelty seeking) might different across populations, being present in Israeli and American but not Swedish populations. A failure to replicate the association in another American sample (Gelernter et al., 1996), as well as the present failure to replicate, question the existence of the association in the North American population.

Jönsson et al. (1997) also note that the results of the first two studies (Benjamin et al., 1996; Ebstein et al., 1996) may represent false positives. The present study, however, may represent a false negative. The power to detect a large difference (effect size [d]=.80) between repeat 7 absent and present groups on commission errors with the group sizes used in the present study (and with alpha set at 0.05, two-tailed) is .58, somewhat lower than the accepted standard of .80 (Cohen, 1977; Kirk, 1984). Eighty-four participants would be needed to detect a large effect size given these parameters. The possibility that significant associations between the presence of 7 repeat sequences of the D4DR allele and extraversion or CEs on the go/no-go task might emerge with a larger sample can not be ruled out in the present study.

Another possibility is that the association between novelty seeking and the number of repeat sequences of the D4DR gene may be restricted to women, and that the failure to detect this association in the present study is a product of the lack of inclusion of women in the sample. (Men were only included in these studies because they were

selected to address other research questions). This is unlikely, however, as the sample of 315 American participants in the Benjamin et al. (1996) study were 95% male.

An association between go/no-go omission errors and the D4DR repeat 7 allele was found, with repeat 7 allele present individuals making fewer omission errors compared to repeat 7 absent individuals across conditions of the go/no-go. Omission errors represent failures to respond to stimuli previously associated with reward or avoidance of punishment. This difference appeared to be unrelated to intelligence, as there no were no group differences on estimated IQ. It is difficult at this point to interpret this difference, which may involve motivation or attentional processes. Replication with a larger sample is necessary.

In summary, go/no-go commission errors, a putative measure of behavioral disinhibition, were unrelated to the presence/absence of the D4DR repeat 7 allele, despite this allele's previous association with novelty seeking, of which impulsivity is purportedly one dimension. Additionally, the D4DR polymorphisms were unrelated to questionnaire measures of sensation seeking and extraversion, dimensions which one might hypothesize to be related to the construct of novelty seeking. The lack of these expected associations awaits confirmation with a larger sample.

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Table 1. Sensation Seeking Scale and Eysenck Personality Questionnaire Results by D4DR Allele*

Measure	7 allele absent	7 allele present
Sensation Seeking Scale		
	n=63	n=14
Boredom Susceptibility	3.8 ± 2.1	4.1 ± 1.8
Disinhibition	6.5 ± 2.1	5.6 ± 1.5
Excitement Seeking	6.6 ± 2.1	7.0 ± 2.0
Thrill and Adventure Seeking	8.6 ± 1.9	7.6 ± 2.6
Total Score	25.6 ± 4.8	24.4 ± 5.0
Eysenck Personality Questionnaire		
	n=61	n=14
Extraversion	14.8 ± 4.0	15.1 ± 3.6
Psychoticism	6.0 ± 3.0	5.9 ± 3.2
Neuroticism	7.1 ± 4.1	8.2 ± 4.2
Lie	7.6 ± 2.9	6.4 ± 3.6

*Values represent raw data and are expressed as mean ± SD