CHAPTER 8

Nicotine

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A. Introduction

Tobacco use is a form of drug dependence, pharmacologically mediated by the actions of nicotine at central and peripheral receptors. Nonpharmacological factors are also important in determining patterns of tobacco use and the prevalence of use but it is the pharmacologic factors which define tobacco use as a form of psychoactive drug dependence and which will be the focus of this review. The dependence process involves psychoactive and reinforcing effects of nicotine, tolerance and physical dependence to nicotine, as well as effects produced by nicotine that some users feel is useful if not indispensable. The neuropharmacological underpinnings of the dependence process have been the subject of considerable research in recent years and may pave the way towards more effective treatments. The goal of this review is to provide an overview of major findings and contemporary theory regarding the dependence producing actions of nicotine so as to provide a useful guide to further research. Our approach will be to provide an overview of the clinical phenomena of nicotine dependence and the general pharmacology of nicotine as well as to highlight recent research on the cellular and molecular basis of these effects.

B. Abuse and Dependence in Humans

I. Epidemiology

There are more than 1 billion cigarette smokers worldwide and of these, approximately one half billion will be killed by tobacco (Connolly and Chen 1993; Peto et al. 1994). In fact, approximately one half of continuing smokers will die prematurely as a result or their tobacco use (Peto et al. 1994). This will amount to approximately 3 million deaths per year throughout the 1990s and 10 million deaths per year by the 2020s. About 400 000 deaths per year occur in the U.S. and this will remain generally stable if current smoking trends persist (McGinnis and Foege 1993).

It has been estimated that more than one in three people who continue to smoke will die prematurely because of their tobacco exposure and that

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approximately 20% of all deaths occurring each year in the United States are attributable to cigarette smoking; however, cigarette smoking caused mortality can be significantly reduced by cessation of smoking at any age (US DHHS 1990). The causes of death in order of incidence are cardiovascular disease (43%); all forms of tobacco-caused cancer (36%), respiratory diseases (20%), and all other smoking-caused deaths (1%) (Centers for Disease Control 1993). Cigarette smoking is an important contributor to the fact that the three primary causes of mortality are similar for men and women: heart disease, cancer, and stroke.

The spread of nicotine dependence follows the course of an infectious disease, with transmission being largely by person to person exposure to cigarettes. Frequently, this is augmented by tobacco company promotions, free sampling campaigns and other marketing efforts. The absence of active public health and educational campaigns against smoking apparently leaves populations highly vulnerable to developing dependence. For example, RUSSELL (1990) has reported that a survey of adults in the Great Britain in the early 1960s indicated that 94% of those who smoked more than three cigarettes became "long term regular smokers." More recently collected data in the United States and Great Britain suggest that between 30% and 50% of people who try smoking cigarettes escalate to regular patterns of use (MCNEILL 1991; HENNINGFIELD et al. 1991; HIRSCHMAN et al. 1984). Consistent with these observations, data from the 1991 National Health Survey indicate that approximately 70% of adolescents tried smoking, whereas approximately 25% were smoking every day of the 30 days prior to the survey. Since it is unlikely that cigarettes have become substantially less addictive or that people have become biologically less vulnerable in two to three decades, it would appear that educational efforts and social factors and smoking policies have decreased the likelihood of progression from use to dependence.

The United States provides an interesting case history for why continued research on the pharmacology of nicotine is needed. The prevalence of smoking declined form 42% of adults in 1965 to approximately 25% in 1990. Unfortunately, there has been no decline since 1990, either in adult prevalence or in smoking prevalence by the primary source of adult smokers, i.e., adolescent and preadolescent smokers (GIOVINO et al. 1995). Approximately one half of young smokers try to quit smoking by age 18 and approximately one third of all smokers attempt to quit each year by quitting for at least one day. It is not clear how many more people attempt to quit but relapse within 24 h and thus are not even counted as attempted quitters. It is clear that only about 2.5% of all smokers become nonsmokers each year, leaving much room for improvement.

The foregoing statistics illustrate the important intersection of population based public health efforts and individually driven treatment efforts. The population targeted efforts are presumably most important in pressuring people to quit smoking and in providing support to those attempting to sustain abstinence; however, the limitations on treatment efficacy, accept-

ability and availability mean that the vast majority of quitting efforts are short-lived. Biomedical research may be the key to new treatments that could reverse this situation.

II. Clinical Aspects and Pathophysiology of Nicotine Dependence

The pathophysiological consequences of tobacco smoke exposure include destructive tissue effects that contribute to pulmonary disease, cellular changes that contribute to cancer, and the neuronal changes produced by nicotine exposure and reinforcing effects of nicotine that lead to addiction. Without the pathophysiologic changes leading to nicotine addiction, there would not be enormous public health toll and cost to our health care system because most people would be more readily able to stop smoking or at least to smoke at substantially lower levels. That goal is the expressed desire of the vast majority of smokers, but only a minority of these smokers ever achieve lasting abstinence. Those who do achieve lasting abstinence greatly reduce their risk of premature death and significantly lengthen their lives (US DHHS 1990). The pathophysiology of the nicotine dependence process has been reviewed in detail elsewhere and will only be summarized here (see Henningfield et al. 1995a).

A variety of surveys and clinical studies indicate that the vast majority of cigarette smokers are nicotine-dependent, an observation consistent with the remarkably short-lived success of more than 90% of most self-managed cessation attempts. In the United States, approximately 90% of cigarette smokers smoke more than five cigarettes per day, and the majority have tried to reduce their tobacco intake or report various symptoms of dependence (Henningfield et al. 1990). By contrast, among people who had consumed five or more alcoholic drinks in the past 30 days only 17% reported feeling a need to drink or dependence; among people who had used cocaine in the previous year, only 16% had used it in the previous week with only less than 10% feeling they needed the drug or were dependent (Henningfield 1992).

The tobacco dependence process, like other pathogenically induced disorders, involves host or individual factors, environmental factors, and the level of exposure to the pathogen itself. Initiation is often mediated by a variety of social and cultural factors, much as other forms of psychoactive drug use. However, over time, the reinforcing effects of the drug strengthen and the individual's control over use is lessened. Whereas a variety of social and other factors may continue to be operative, cigarette addiction is powerfully and critically driven by the positively and negatively reinforcing actions of nicotine, as will be discussed further on in this review.

Nicotine dependence shares many critical features in common with other drug dependencies (Schuster et al., this volume). The role of nicotine in the use of tobacco products is functionally similar to the role of cocaine, morphine and ethanol in the use of coca and opiate-derived products and alcoholic beverages, respectively. While certain commonalties in the effects

of these drugs lead to their being categorized similarly, as dependence producing psychoactive drugs that lead to harmful use and abuse, the pharmacology of these substances differs in many respects (Henningfield et al. 1995a). Like other drug dependencies, nicotine dependence is a "progressive," "chronic", "relapsing" disorder. In the United States, the mean age of onset of cigarette smoking is 13–14 years (US DHHS 1994; Gallup 1992). It is older in some populations in the U.S. (e.g., African Americans) and in many countries where access to cigarettes to children is highly restricted. No age level appears to confer invulnerability to dependence; however, the level of dependence to nicotine observed in adults has been found to be inversely related to the age of initiation of smoking when measured by diagnostic criteria of the American Psychiatric Association (Berslau et al. 1992).

The progression of increased tobacco intake is accompanied by the development of tolerance and physiological dependence. In the United States, the average cigarette smoker consumes approximately 20 cigarettes per day (Centers for Disease Control 1994). The actual number of cigarettes smoked per day appears to be influenced by factors such as cigarette nicotine delivery, price, the restrictions on smoking (US DHHS 1988; Burns et al. 1992; Sweanor et al. 1992). Thus, cigarette smokers with less dispensable income might smoke a smaller number of cigarettes but extract more nicotine per cigarette, thereby sustaining a high dependence level. Such considerations are important in cross-cultural and cross-national comparisons of smoking rates.

Tobacco use tends to be chronic with many people attempting to quit but persistent remission only occurring in the minority of cases. In fact, studies by Ravies and Kandel (1987) showed that whereas the use of cocaine, heroin and alcohol all declined sharply with age, the progression of cigarette smoking was slowed but not reversed as individuals aged. The chronic phase of the addictive process is highly resistant to substantial modification. For example, efforts to reduce tobacco smoke and nicotine exposure by smoking cigarettes with lower nicotine delivery ratings or to smoke fewer cigarettes are usually partially or completely thwarted by compensatory changes in how the cigarettes are smoked (Benowitz et al. 1983; Benowitz and Jacob 1984; Kozlowski 1981, 1982; US DHHS 1988).

Efforts to achieve and sustain abstinence are generally short lived with the majority of individuals who quit on their own relapsing within a few days (Hughes et al. 1992). Providing some level of medical support extends the mean period of remission by a week or more (Kottke et al. 1988), and providing nicotine replacement in addition to adjunctive therapy can extend the mean duration of remission by 6 months or more (Foulds et al. 1993).

III. Tolerance and Physical Dependence

Tolerance refers to the decreased responsiveness to the same dose of the drug as a function of repeated drug exposure (Jaffe 1985; US DHHS 1988).

It is often demonstrated by the observation that increased doses of a drug are required to obtain pharmacologic effects formerly produced by lower doses. Nicotine tolerance appears to be substantially acquired during youth as people progress from a few cigarettes upon initial exposure to higher levels (US DHHS 1988; McNeil et al. 1989). Administering nicotine to a tobacco deprived smoker can substantially increase heart rate and euphoria measures and decrease knee reflex strength (US DHHS 1988). However, with repeated doses, heart rate stabilizes at a level intermediate to that produced by the first dose and that occurring when nicotine deprived. In addition, subjective effects are minimal, and the knee reflex may appear normal (US DHHS 1988; Domino and von Baumgarten 1969; Swedberg et al. 1990). Tolerance to a variety of the behavioral, physiologic, and subjective effects of nicotine has been stuided (US DHHS 1988). There are several physiologic mechanisms of nicotine tolerance including decreased responsiveness to the drug at the site of drug action and possibly increased metabolism in chronic smokers (US DHHS 1988). It is possible that the development of tolerance is related to up-regulation of nicotine receptors, as will be discussed in Sect. C.

Tolerance resulting from nicotine exposure has been measured using various pharmacodynamic assays. For example, Perkins et al. (1991a) demonstrated that acute tolerance to the pressor effect of intranasal nicotine develops rapidly in smokers and nonsmokers. In a series of investigations in smokers and nonsmokers, repeated exposure to the same dose of nasal nicotine administered over several days produced progressively decreased subjective, physiological and behavioral responses over time (Perkins et al. 1990a,b, 1991a,b).

Like morphine and alcohol, chronic nicotine administration leads to physiologic or physical dependence such that abrupt abstinence is accompanied by a syndrome of signs and symptoms. The severity of the withdrawal syndrome can range from unpleasant to debilitating (US DHHS 1988). The clinical course has been described in detail elsewhere (American Psychiatric Association 1987). In brief, the syndrome includes increased craving, anxiety, irritability, appetite, and decreased cognitive capabilites and heart rate. Onset is within approximately 8 h after the last cigarette; the symptoms peak within the first few days, then subside over the next few weeks. Symptoms may persist for months or more in some individuals. The magnitude of the withdrawal syndrome is directly related to the level of nicotine dependence, and measured by cotinine concentration or the Fagerstrom Tolerance Questionnaire score (Fagerstrom and Schneider 1989; Heatherton et al. 1991), although there is considerable variability within and across individuals (US DHHS 1988).

The tobacco withdrawal syndrome is pharmacologically mediated by nicotine deprivation, although behavioral conditioning factors are certainly important (Henningfield and Nemeth-Coslett 1988; US DHHS 1988). Nicotine withdrawal has been observed in abstinent cigarette smokers, smokeless tobacco users, and chronic users of nicotine gum (Hatsukami et

al. 1987, 1991). Furthermore, many abstinent smokers complain about cognitive deficits. Because the tobacco withdrawal syndrome is associated with moderate to severe levels of physical/psychological discomfort, it is difficult for tobacco users to abstain from cigarette use for any extended period (see Hughes et al. 1990). It is a commonly held belief that people continue to use tobacco and fail at cessation in order to avoid any or all of the above-mentioned withdrawal symptoms associated with abstinence (Stolerman 1991). One of the most important and probably least understood features of the nicotine withdrawal syndrome is "craving for tobacco." Cravings and urges to smoke cigarettes and/or use smokeless tobacco have been described as major obstacles confronting tobacco users attempting to quit. Craving for tobacco has been identified as one of the most prominent symptoms of nicotine withdrawal (see Hughes et al. 1990; Tiffany and Drobes 1990, 1991). Abstinent cigarette smokers report that craving for cigarettes is the most troublesome symptom they experience over the first month of quitting (West et al. 1989), and there is evidence that the intensity of urges and cravings associated with cigarette smoking is comparable in magnitude with the craving associated with other addictive disorders (Kozlowski et al. 1989). Animal models of nicotine dependence have also been developed as will be discussed further on in this review (Sect. BIV).

C. General Pharmacology

Nicotine and its metabolites exert a multitude of pharmacologic effects, including reinforcement of tobacco use. Understanding these effects is critical to understanding the underpinnings of the dependence process.

I. Chemistry and Pharmacokinetics

1. Absorption

Nicotine is a tertiary amine existing in both isomeric forms, but tobacco contains only the levo-rotary form, (*S*)-nicotine, which has greater pharmacologic activity (Pool et al. 1985). It is a water- and lipid-soluble weak base with an 8.0 index of ionization (Lide 1991). Thus, the nicotine present in the mildly alkaline smoke of cigars, pipes, chewing tobacco and snuff, is readily absorbed across mucosal membranes of the mouth and nose (Russell et al. 1980; Svensson 1987). Cigarette smoke, in contrast, is mildly acidic and is absorbed in the lungs, where the massive area of distribution renders pH less important (Gori et al. 1986). Smokeless tobacco products vary widely in their pH levels and this appears to be the primary means by which nicotine dosage is controlled by tobacco manufacturers (Henningfield et al. 1995; Djordjevic et al. 1995).

Studying nicotine dose-response relationships with commercially marketed cigarettes is complicated by the fact that cigarettes contain a range of

6–11 mg of nicotine of which up to 40% is bioavailable to the cigarette smoker (Benowitz and Henningfield 1994; Henningfield et al. 1994). There is little direct relationship between advertised cigarette nicotine yield levels and absorbed nicotine when people smoke cigarettes ad libitum (Henningfield et al. 1994; US DHHS 1988). Thus, the intent of researchers to manipulate nicotine dose by simply giving volunteers cigarettes with varying estimated yields may have been thwarted by subtle changes in smoking topography which allowed the volunteer to obtain lower than expected doses from the cigarettes rated most highly, and higher than expected doses for the low rated cigarettes.

The tobacco cigarette is the most toxic and addictive widely used vehicle for nicotine delivery. Nicotine is volatilized at the tip of a burning cigarette where it is carried by particulate matter ("tar" droplets) deep into the lungs with inspired air. The approximately 800°C pyrolysis at the tip of the cigarette is also the source of carbon monoxide and many other toxicologically significant products.

Nicotine is rapidly absorbed through tissue barriers and pulmonary alveoli following smoke inhalation into the lungs. Intravenous and inhaled nicotine produce an almost instantaneous nicotine bolus in arterial blood pumped from the heart which is delivered to the brain within 10 s (US DHHS 1988). Available data from studies of nicotine distribution in arterial blood (Henningfield et al. 1990, 1993) and studies of the absorption of radiolabeled nicotine (Armitage et al. 1975) suggest that absorption characteristics are similar to those of gases such as oxygen which are exchanged in the lung from inspired air to venous blood (Kety 1951). Thus, smoke inhalation produces arterial boli which may be ten times more concentrated than the levels meausred in venous blood (Henningfield et al. 1990, 1993). A similar phenomenon of arterial boli occurs when cocaine is smoked, adding to the addictiveness and toxicity of "crack" cocaine (Evans et al. 1995).

Following oral smokeless tobacco use, venous blood nicotine concentration peaks in 15 min (Benowitz et al. 1988). Time to peak blood nicotine concentration may be 30 min or longer following nicotine gum use (Benowitz et al. 1988) and several hours for transdermally delivered nicotine (Palmer et al. 1992).

a. Nicotine Delivery Kinetics May Determine Effects of Alternate Nicotine Delivery Systems

It is now clear that the vehicle of nicotine delivery is a determinant of not only toxicity, but also of the nature and magnitude of the effects produced by nicotine due to its control over the nicotine concentrations in the blood over time. Addictive and cardioactive effects are generally directly related to the speed of delivery of nicotine and other drugs (Henningfield and Keenan 1993; Benowitz 1993). For example, smoke inhalation essentially mimics the effects of a rapid intravenous injection and exposes the

heart, brain, and fetus to high concentrations which dissipate within a few minutes. Conversely, nicotine polacrilex gum and transdermal patch systems are of low abuse liability and weak cardiovascular effects, in part because rapid absorption of high dose is not possible from either system. Moreover, release of nicotine from polacrilex requires a substantial work effort (chewing) (Henningfield and Keenan 1993; US DHHS 1988). Smokeless tobacco systems similarly vary widely in their impact in accordance with their pH (Freedman 1994; Henningfield et al. 1995; Djordjevic et al. 1995). The delivery system also helps to determine the nature and quantity of other toxic substances to which the user is exposed.

These issues are not unique to nicotine. The drug dosage form affects the acceptability of a medication to patients, and compliance with instructions for medication use: similarly the drug dosage form is a determinant of the addiction potential of substances of abuse (Farre and Cami 1991; Sellers et al. 1991; US DHHS 1988). The drug delivery system determines ease and convenience of use as well as the speed and amount of drug that is absorbed. For example, tobacco and coca leaves are rarely swallowed and addiction to swallowed formulations are uncommon, presumably because the bioavailability of the nicotine and cocaine is so poor via the gastrointestinal system; furthermore, cocaine or nicotine absorbed via this route do not produce the rapid onsetting and offsetting effects which characterize the most powerfully addicting drugs and drug forms (Henningfield and Keenan 1993; Jaffe 1985; US DHHS 1988).

2. Distribution

Following absorption of nicotine into the body, about two thirds of the drug is present in the ionized form. Less than 5% of nicotine is bound to plasma proteins. Thus, nicotine is widely distributed in all body tissues and organs with the highest concentrations observed in brain, lungs, heart, kidneys, adrenal glands, liver and spleen. The steady state volume of distribution for nicotine is 180 liters which indicates extensive distribution. Following intravenous nicotine administration, the blood nicotine concentration declines rapidly due to uptake by the various organ tissues of the body. Nicotine freely crosses the placenta and has been found in amniotic fluid and breast milk of cigarette smokers.

3. Systemic Metabolism

In the earliest work on nicotine metabolism, Lautenbach (1886–1887) macerated liver tissue from dogs and rabbits with a nicotine solution. The tissue extract was then injected into dogs with no symptoms of nicotine poisoning noted. Conversely, the tissue extract of nicotine macerated with kidney produced death in all animals following injection. Lautenbach hypothesized that nicotine detoxification was occurring in the liver, but not

the kidney. Subsequent research has demonstrated that nicotine undergoes extensive metabolism, primarily in the liver, but also to a lesser extent in lung and brain (US DHHS 1988). Systemic metabolism of nicotine produces several compounds in differing amounts and biologic activity. Cotinine, the major metabolite of nicotine (about 85% of ingested nicotine), is produced via a two-step oxidation in the liver. Cotinine is then further metabolized to several other compounds including cotinine-*N*-oxide, norcotinine, and hydroxycotinine, with only 17% of cotinine excreted unchanged in urine. Nicotine is also metabolized to nornicotine and nicotine-*N*-oxide.

For most routes of administration, the $t_{1/2}$ of nicotine is 2 h following an initial redistribution "half-life" phase of about 20 min (Benowitz 1988). The *t*1/2 of transdermally delivered nicotine is 4 h (Palmer et al. 1992), probably reflecting the continued release of some nicotine absorbed by the dermal tissues at the site of application. Using radiolabeled nicotine administered to cigarette smokers, the average nicotine intake per cigarette (FTC yield 1.1 mg) was estimated to be 2.3 mg, while the bioavailability of oral nicotine capsules and transdermally delivered nicotine were 44% and 82%, respectively (Benowitz et al. 1991a,b).

4. Brain Metabolic Activity

Efforts to understand the effects of nicotine on the regional metabolism of glucose emanated from studies of the distribution of nicotine binding sites in the brain. The 2-deoyx-D-[1–14 C]glucose method (Sokoloff et al. 1977) has been used to map the areas of the brain that respond metabolically to acute and chronic nicotine administration. The acute administration of nicotine in rats leads to a significant increase in cerebral glucose utilization (London et al. 1985a,b, 1988; Grunwald et al. 1987) that is related to the distribution of nicotine binding sites (London et al. 1985b). After chronic (twice daily, 10 days nicotine treatment) acute stimulatory effects of nicotine on glucose metabolism were still obtained. In the lateral geniculate and the superior colliculus tolerance to nicotine-induced stimulation was reported; sensitization was never seen (London 1990). Chronic nicotine infusion (Grunwald et al. 1987) did not change the characteristic nicotine-induced stimulatory effect in most brain ares, but in the lateral geniculate body an increased response was reported. In general, animal stuides indicate that nicotine increases glucose utilization and the effect persists after chronic exposure.

In contrast to the findings with animals, that nicotine increases glucose utilization in certain regions of the brain, preliminary clinical data from a study of smokers and nonsmokers showed that intravenous nicotine decreased glucose metabolism in both groups of subjects (Stapleton et al. 1992). Euphorigenic doses of abused drugs including cocaine (London et al. 1990a) and morphine (London et al. 1990b) also decreased cerebral glucose metabolism in humans. In line with a model of drug-induced euphoria (Swerdlow

and Koob 1987), it has been proposed that a decrease in cortical glucose metabolism may reflect changes in dopaminergic modulation of the nucleus accumbens causing a decrease in thalamic activity (London 1990).

5. Drug Interactions

Cigarette smoking is known to alter the metabolism of many medications used in the treatment of various medical disorders (US DHHS 1988). As a consequence, the effect of nicotine on hepatic drug metabolism has received significant experimental attention. In clinical practice, higher doses of a broad range of medications are given to cigarette smokers than to nonsmokers and tobacco cessation can result in increased plasma levels of these medications (Benowitz 1988; Kyerematen et al. 1983; Kyerematen and Vesell 1991; Sevnsson 1987).

Nicotine replacement medications may not produce the same level of hepatic induction that cigarette smoke does. For example, one study found that theophylline half-life increased by 36% within 1 week of smoking cessation, but there was no apparent effect of nicotine polacrilex on theophylline metabolism (Lee et al. 1987). Consistent with these observations, caffeine concentrations can increase by more than 250% when people quit smoking, mainly due to decreased metabolism (Benowitz et al. 1989). Certain adverse effects of acute caffeine overdose are similar to those of nicotine withdrawal (e.g., anxiety and sleep disturbance) (Sachs and Benowitz 1988). These findings suggest that patients in treatment for nicotine addiction should be warned not to increase their caffeine intake, and possibly to decrease it by about one third. Follow-up evaluations of patient status should include questions about caffeine and all other drug intake to determine if intake should be adjusted. With respect to the methylxanthines, it is also worth noting that acute caffeine abstinence results in its own withdrawal syndrome (Silverman et al. 1992) that might complicate simultaneous tobacco withdrawal. Furthermore, some caffeine intake may produce a small degree of relief of nicotine withdrawal symptoms (Cohen et al. 1994; Oliveto et al. 1991).

Although the mechanism is not understood, chronic use of a variety of dependence producing drugs is positively associated with higher levels of tobacco use and dependence (Kozlowski et al. 1993). Acute exposure to alcohol (Griffiths et al. 1976; Henningfield et al. 1984; Nil et al. 1984; Mello et al. 1980; Keenan et al. 1990), pentobarbital (Henningfield et al. 1984), opioids (Mello et al. 1980a; Chait and Griffiths 1984), and amphetamine (Henningfield and Griffiths 1981; Chait and Griffiths 1983) increase cigarette smoking and tobacco intake. Caffeine and marijuana produce weak and unreliable effects on smoking across studies (Chait and Griffiths 1983; Nil et al. 1984; Kozlowski 1976; Ossip and Epstein 1981; Mello et al. 1980; Nemeth-Coslett et al. 1986a). Acute administration of the centrally distributed ganglionic blocker mecamylamine produced increased

cigarette smoking (Stolerman et al. 1973; Nemeth-Coslett et al. 1986b), whereas the noncentrally acting blocker pentolinium did not (Stolerman et al. 1973). The opioid antagonist naloxone produced a small reduction of smoking in one study (Karras and Kane 1980) and no effect over a wide dose range in another study (Nemeth-Coslett et al. 1986a).

II. Pharmacodynamics

Nicotine acts at nicotinic receptors and has mixed pharmacologic effects depending upon the dose, the interval since prior administration, and the time following administration at which the measurement is taken. Thus, the pharmacodynamic effects of nicotine vary widely and, in part, are determined by the conditions under which it is administered. This section will review some of these effecs.

1. Cardiovascular Effects

Upon acute administration, nicotine produces potent pressor effects in animals and humans (US DHHS 1988). Nicotine has been shown to produce dose-related increases in heart rate and blood pressure which last over several minutes and then diminish. With each subsequent nicotine administration, the peak cardiovascular effect is diminished. This is an example of a phenomenon known as tachyphylaxis (i.e., acute tolerance). Within the cardiovascular system, tachyphylaxis is protective against nicotine toxicity. The mechanism of tachyphylaxis is not well understood, but it may be related to neurotransmitter depletion or to the formation of antagonistic-like metabolites and/or receptor desensitization.

Cigarette smokers who chronically abuse nicotine have a higher resting heart rate than nonsmokers. Furthermore, past research has shown that cigarette smokers have modestly, but significantly, lower blood pressure than nonsmokers (Larson et al. 1961). Within a large group of cigarette smokers, Benowitz and Sharp (1989) noted a significant inverse correlation between serum cotinine concentration and blood pressure and suggested that this relationship could be secondary to the pharmacologic effects of cotinine and/or nicotine exposure.

While the mechanism of action underlying nicotine's effect of decreasing blood pressure is unknown, data regarding the effect of nicotine and cotinine on blood pressure have been accrued. For example, Borzelleca et al. (1962) found that intravenous nicotine base (0.125 mg/kg) induced a potent pressor response in anesthetized dogs, whereas equivalent doses of intravenous cotinine produced no response. Conversely, at higher doses (10–500 mg/kg), intravenous cotinine transiently lowered blood pressure in a dose-dependent manner. Cotinine's depressor effect was not appreciably altered in either the decerebrate or spinal dog preparation, suggesting that the pharmacologic mechanism of action was not dependent upon intact

central nervous system function. Pretreatment with atropine (a cholinergic muscarinic receptor antagonist) or diphenhydramine (a nonspecific histaminic receptor antagonist) had no effect on the depressor activity. Hence, cotinine's depressor effect was not mediated by cholinergic muscarinic and/or histaminic receptors. The authors concluded that the depressor effect of cotinine was secondary to the induction of vascular smooth muscle relaxation. Another interesting result of this experiment was that high dose cotinine pretreatment completely antagonized the potent pressor effects of intravenous nicotine. Consequently, high doses of cotinine in the presence of nicotine may serve as a pharmacologic nicotinic antagonist either directly or indirectly within the cardiovascular system.

Cigarette smoking is the greatest preventable risk factor for cardiovascular disease. Carbon monoxide exposure and the rapid high dose delivery of nicotine produced by cigarette smoking inhalation appear to be major determinants of this increased risk (see US DHHS 1983). In addition, nicotine and cotinine influence prostaglandin biosynthesis of prostacyclin (PGI2), which could have adverse cardiovascular consequences. Decreased levels of PGI2 are thought to increase atherogenesis progression. Using horse aorta and platelet preparations, the effects of nicotine and cotinine on the biosynthesis of PGI2 in vitro were examined (Chahine et al. 1990, 1991). Nicotine significantly decreased PGI2 synthetase activity which led to a decreased PGI2 concentration, while cotinine stimulated PGI2 synthetase activity resulting in increased PGI2 levels. Moreover, cotinine significantly attenuated the inhibitory effect of nicotine on PGI2 synthetase activity. Thus, nicotine's effect on PGI2 levels is thought play a role in the atherosclerosis noted in smokers. Furthermore, cotinine may serve to defend the cardiovascular system from atherosclerosis by antagonizing the effects of nicotine resulting in decreased PGI2 levels within the arterial system.

2. Electroencephalograph Effects

The spontaneous electroencephalogram (EEG) recorded from scalp electrodes is a convenient, noninvasive measure of drug action in the brain. Golding (1988) reported that tobacco but not sham smoking increased power in the β-band, reduced α and θ activity and had no effect on δ power; α frequency increased after smoking. Intravenous nicotine increased α power in discrete bursts that were correlated with subject-reported euphoria (Lukas et al. 1990). Knott and Venables (1977) reported that smoking caused a decrease in α and θ power and increased β and α frequencies.

In several experiments, the EEG effects of nicotine have been measured in smokers deprived of tobacco. Nicotine adminstration in the form of smoked tobacco increased EEG α frequency (Ulett and Itil 1969) and decreased α and θ power (Herning et al. 1983). The EEG consequences of overnight (Pickworth et al. 1986) and extended (Pickworth et al. 1989) abstinence were reversed by nicotine polacrilex and these effects were prevented by pretreatment with mecamylamine (Pickworth et al. 1988), Fur-

thermore, the EEG effects of overnight abstinence were accompanied by a slowing of cognitive performance that was also reversed by nicotine gum (Snyder and Henningfield 1989). Robinson et al. (1992) reported that a low nicotine yield cigarette decreased δ power and increased β power but a cigarette from which the nicotine had been extracted caused no significant changes in the EEG.

The EEG synchrony that persistently follows nicotine deprivation in smokers has been temporally linked to changes in performance and subjective complaints of inability to concentrate (Conrin 1980; Edwards and Warburton 1983). Revell (1988) found that performance changes occur on a puff-by-puff basis, and Knott (1988) reported that EEG changes associated with arousal also occur while smoking a single cigarette. In most EEG studies, however, the EEG arousal effects are only apparent when the EEG is collected in a low arousal situation. For example, Pickworth et al. (1986, 1989) found that the EEG effects of nicotine and the effects of nicotine abstinence were most apparent in subjects at rest with eyes closed. In situations in which the subjects concentrated on a task or simply opened their eyes, the EEG effects of nicotine were diminished, confirming the importance of behavioral context in the effects of EEG effects of nicotine.

III. Systemic Effects

1. Immunologic Effects

Nicotine may act to regulate endocrine systems resulting in decreased immune competency. Increased glucocorticoid secretion resulting from adrenergic stimulation of the adrenal gland produces immune suppression through a reduction in thymus-dependent responses (Munck et al. 1984). However, nicotine-induced autonomic activation and the release of other pituitary hormones may serve to counteract the immunosuppressive actions of the glucocorticoids. For example, cholinergic stimulation itself may increase immune function (Atweh et al. 1984). Vasopressin release increases the mitogenic activity of thymocytes (Whitfield et al. 1970) and enhances lymphocyte production of interferon (Johnson and Torres 1985). Nicotine-induced endorphin release enhances lymphocytic function (Wybran 1985a,b). Thus, like morphine (a tumorogenic and immunosuppressive agent), endorphin may have inhibitory and/or facilitatory effects on the immune system (Shavit et al. 1985). Prolactin is an immunomodulatory hormone and the nicotine-induced decrease in its release may be immunosuppressive (see Fuxe et al. 1989). A decrease in natural killer cell activity of monkey spleen cells, and a decrease white blood cell response to concanvalin (Sopori et al. 1985) were reported after exposure of the animals to high doses of cigarette smoke. In view of the hypothesis that natural killer cells may play a protective role in the immune defense against cancer, reductions in natural killer cell activity could lead to increased susceptibility for many malignant diseases (see Fuxe et al. 1989).

2. Hormonal Effects

Female cigarette smokers experience more infertility than do non-smokers. In fact, women who smoke cigarettes have lower endogenous estrogen levels than nonsmokers (US DHHS 1988). Barbieri et al. (1986) determined that nicotine inhibits estrogen formation without affecting progesterone biosynthesis in human choriocarcinoma cell cultures and term placental microsomes. Nicotine prevented the conversion of androstenedione to estradiol in a dose-dependent fashion. The observed effect on estrogen formation was mediated through aromatase enzyme inhibition. These findings may explain, in part, the decreased estrogen levels observed in women who smoke cigarettes and potentially the difference in fertility between smokers and nonsmokers.

Male cigarette smokers are also prone to sex hormone abnormalities compared to nonsmokers. Meikle et al. (1988) investigated the effects of nicotine on testosterone metabolism using isolated canine prostate cells. Nicotine competitively inhibited 3-α-hydroxysteroid dehydrogenase (3-α-HSD) activity which is involved in the enzymatic metabolism of 5-α-dihydrotestosterone (5-α-DHT) and results in altered testosterone production. Using the Leydig cells of the rat testis, Yeh et al. (1989) found that nicotine competitively inhibited multiple steps in testosterone biosynthesis. Patterson et al. (1990) performed similar androgen biosynthesis research with nicotine on mouse Leydig cells. Again, nicotine inhibited LH-stimulated testosterone production. The mechanism of inhibition was thought to involve calcium or a calcium-mediated metabolic pathway. These data demonstrate the ability of nicotine to alter testosterone biosynthesis and metabolism. The observed alterations in testosterone biosynthesis could impact upon androgen action in several tissues including skin, prostate or testis.

Nicotine has been observed to affect other endocrine systems. In a study of nicotine on pancreatic functioning, Tjälve and Popov (1973) found that nicotine at low concentrations stimulated and at high concentrations inhibited glucose-induced insulin secretion in isolated rabbit pancreas. The differential effects of nicotine on insulin secretion at all doses were attenuated by atropine and/or hexamethonium pretreatment. Thus, the effects of nicotine on insulin secretion are mediated through mechanisms involving both muscarinic and nicotinic cholinergic receptors. Humans, dogs and rabbits that are chronically exposed to nicotine have increased plasma levels of thyroid hormones. In male rats, however, nicotine decreases the release of thyroid hormones (see Fuxe et al. 1989) and this effect is more evident after intermittent than after chronic nicotine exposure.

3. Toxicity

Nicotine is a potent, highly toxic substance which has been routinely used as a pesticide for many years. In rats, the LD_{50} for intraperitoneally administered nicotine is 10 mg/kg (Kitamura 1958). Nicotine derives its toxicity and potential lethality from its ability to act as a potent cholinergic nicotinic

receptor antagonist which inhibits the activity of the sympathetic and parasympathetic nervous systems. In spite of its potential toxicity, nicotine poisoning deaths are rare, with none reported to the U.S. poison control centers in recent years. This is despite the fact that in addition to the several million replacement prescriptions written each year, more than 25 billion packages of cigarettes are distributed, each of which contains approximately 160 mg nicotine. The reasons include the poor bioavailability of orally ingested nicotine and the remarkable degree of tolerance that begins to develop even during a single nicotine use episode (Benowitz 1993).

Nicotine is psychotoxic at high doses and even at doses readily supplied by one cigarette in nontolerant persons, who may exhibit severe behavioral disruption, confusion and intoxication (US DHHS 1988, Appendix B; Henningfield and Heishman 1995). In fact, certain South American populations have used tobacco ritualistically to produce altered states of consciousness including hallucinations (Wilbert 1987; Jarvik 1995). Intoxication is rare in tolerant smokers, however, and tobacco associated antisocial behavior appears to be a more prominent feature of nicotine deprivation than of the acute effects of nicotine.

IV. Abuse Liability and Dependence Potential

1. Discriminative Effects

Human studies of the subjective effects of several forms of nicotine delivery and animal studies of the discriminative effects of parenterally administered nicotine have demonstrated that nicotine's psychoactive effects partially generalize to prototypic drugs of abuse. For example, nicotine produces dose-related discriminable effects in animals and subjective responses in humans that generalize more to stimulants such as amphetamine and cocaine than to depressants and opioids (US DHHS 1988). These effects can be blocked or at least reduced by pretreatment with centrally acting nicotinic antagonists (e.g., mecamylamine) but not by antagonists which do not penetrate the central nervous system (e.g., pentolinium, hexamethonium) (Stolerman 1991). Similarly, partial blockade of nicotine's effects by increasing doses of mecamylamine led smokers to rate the delivered tobacco smoke as weaker and to show a preference for higher nicotine concentrations of smoke (Rose et al. 1989). This effect and other effects on brain neurotransmitters that might mediate the psychoactive effects of nicotine will be discussed in Sect. C of this chapter.

Psychoactive drugs which produce elevations in scores on drug-liking scales and other indices of mood elevation are often abused by humans and self-administered by animals (Jasinski 1977; Griffiths et al. 1980). Nicotine has been shown to produce such elevations in mood in humans when given by intravenous injection (Jones et al. 1978; Henningfield et al. 1985; Keenan et al. 1994a) by nasal nicotine administration (Perkins et al. 1992,

1994; Sutherland et al. 1992a,b), and by cigarette smoke administration (Henningfield et al. 1985; Pomerleau and Pomerleau 1992). Delivery of nicotine via the slow release polacrilex and transdermal medications produces little if any such elevations in mood (Henningfield and Keenan 1993). Interestingly, nicotine may produce discriminative effects which would facilitate its ability to modify behavior at very low doses and not produce distinct changes in mood (Perkins et al. 1994). Nicotine and other drugs abused by humans increase extrasynaptic dopamine concentrations in the mesolimbic system of the brain in rats (Di Chiara and Imperato 1988). Additional findings regarding the literature on the discriminative and psychoactive effects of nicotine have been reviewed in greater detail elsewhere (Rosencrans and Meltzer 1981; Henningfield 1984; Stolerman and Reavill 1989; Stolerman 1991).

An emerging research issue of relevance to developing medications for treating tobacco dependence is the role of nicotine's metabolites in mediating its dependence producing effects. For example, whereas the psychoactivity of nicotine has been well characterized in animals and tobacco users, there has been much less study of the psychoactivity, or pharmacology in general, of nicotine's metabolites. Cotinine has received the most attention, with studies demonstrating that intravenous and oral cotinine produces subjective and other behavioral effects in abstinent cigarette smokers at blood levels similar to those achieved through daily smoking (Benowitz et al. 1983; Keenan et al. 1994b, 1995; Schuh et al. 1995). Studies of continine's behavioral effects in animals have demonstrated dose-related changes in arrousal (Yamamoto and Domino 1965), food-reinforced rates of responding (Risner et al. 1985; Goldberg et al. 1983), and nicotine discrimination (Takada et al. 1989; Goldberg et al. 1981a). These data suggest that cotinine and possibly other nicotine metabolites have significant pharmacologic activity which needs further elucidation in preclinical and clinical investigation.

2. Reinforcing Effects

The potential of nicotine to serve as a reinforcer and thereby strengthen behaviors leading to its ingestion has been explored and confirmed in a variety of animal and human models (Swedberg et al. 1990). Although the reinforcing effects of intravenous nicotine were demonstrated by Deneau and Inoki in 1967, it was not until the research of Goldberg et al. (1981b) that a robust nonhuman primate model of nicotine self-administration was established. Henningfield and colleagues studied human nicotine self-administration in the early 1980s (Henningfield et al. 1984; Henningfield and Goldberg 1983). This work was extended by Corrigall (1991a,b) who used procedures analogous to those of Goldberg to develop a rat model of nicotine self-administration. In brief, it has now been demonstrated that, in the absence of the tobacco vehicle or the taste and other sensory effects of

tobacco use, nicotine can serve as a positive reinforcer for five animal species in addition to humans (SWEDBERG et al. 1990).

Both the CORRIGALL and GOLDBERG procedures utilized small, rapidly delivered doses of intermittently available nicotine; in addition, the GOLDBERG procedure added paired stimuli, which further increased the amount of behavior sustained ultimately by nicotine injections and provide paired environmental stimuli with the injections. These procedures appear to model key features of cigarette-delivered nicotine and led to the establishment of strong reinforcing effects in animals. Cigarettes also enable people to easily provide themselves with rapid delivery of small intermittent doses and salient sensory stimuli. The importance of rate of delivery of nicotine to the reinforcing effects of the substance has not been adequately studied; however, it appears that rate of delivery is directly related to the subjective effects of the nicotine delivery system (HENNINGFIELD and KEENAN 1993). For example, whereas rapid intravenous injections or cigarette smoke inhalation produce psychoactive effects that may be pleasurable, slow infusions or delivery by the transdermal systems produce little if any discriminable psychoactive response (HENNINGFIELD and KEENAN 1993), and blunted or eliminated physiologic responses (BENOWITZ 1988; PALMER et al. 1992). Analogously, BALSTER and SCHUSTER (1973) found that the reinforcing effects of cocaine in rhesus monkeys were directly related to infusion rate, and DE WIT, BODKER and AMBRE (1992) showed that the subjective effects of pentobarbital in humans were directly related to the rate of drug administration. The role of infusion rate as a determinant of the reinforcing and other effects of nicotine is clearly a factor meriting further study, because this appears to be one means by which both the qualitative and the quantitative effects of nicotine are determined. Additional findings regarding the reinforcing effects of nicotine have been reviewed in detail elsewhere (GOLDBERG and HENNINGFIELD 1988; SWEDBERG et al. 1990; CORRIGALL 1991b).

3. Physical Dependence

As discussed earlier, nicotine produces physical dependence such that acute deprivation leads to a well defined withdrawal syndrome (AMERICAN PSYCHIATRIC ASSOCIATION 1994; HUGHES et al. 1990). Several promising animal models of various features of nicotine withdrawal have also been developed in animals that have been chronically maintained on nicotine for 10 days or longer. For example, a rat drug discrimination model revealed that nicotine deprivation produces an interoceptive state that generalizes to the presumably anxiogenic cue produced by pentylenetetrazol administration (HARRIS et al. 1986).

Two models of behavioral performance revealed the behaviorally disrupting effects of acute nicotine deprivation (CARROLL et al. 1989; CORRIGALL et al. 1988a). Another model of clinical relevance found that rats showed increased sensorimotor reactivity in an auditory startle paradigm (HELTON et

al. 1993). The animal models should be useful for drug development research and for exploring the mechanisms of nicotine withdrawal (Maultsby et al. 1991). For example, it appears that both mecamylamine (Malin et al. 1994) and naloxone (Malin et al. 1993) administration can precipitate EEG and/or behavioral signs of withdrawal in rats maintained on nicotine, thus, suggesting the involvement of opioid and nicotinic components in nicotine dependence.

D. Neuropharmacology

The neuronal mechanisms underlying the pharmacological effects of nicotine have been the subject of intense study in recent years. This had led to a broader understanding of how nicotine produces receptor up-regulation, differentially activates receptor subpopulations, and releases a variety of neurohormones – actions that may contribute to the resultant dependence disorder. Recent and important neuropharmacological research on nicotine which have led to these conclusions will be summarized below.

I. Nicotinic Receptors

1. Receptor Diversity

Virtually all the known actions of nicotine appear to be mediated by nicotinic receptors (Clarke 1987a; US DHHS 1988). It is believed that most, and perhaps all, nicotinic receptors are acetylcholine (ACh)-gated cation channels, permitting the influx of sodium and to some extent calcium. Nicotinic receptors form an extended family, as revealed principally by molecular genetic approaches (Sargent 1993). All such receptors are probably composed of five protein subunits arranged around a central ionophore (Anand et al. 1991; Cooper et al. 1991). Each subunit protein is encoded by a distinct gene; neuronal receptors appear to consist only of α subunits (that provide the principal binding sites for agonists) and β ("structural") subunits. To date, at least five α and three β subunit genes have been shown to be expressed in the central or peripheral nervous systems (Sargent 1993).

Assuming that each neuronal receptor subtype is made up of a unique permutation of α and β subunits, there is considerable potential for receptor diversity. However, expression studies in *Xenopus* oocytes indicate that not all subunit combinations can function as nicotinic receptors (Deneris et al. 1991). There are also indications from studies employing in situ hybridization histochemistry or protein isolation that certain receptor subunits may be preferentially coexpressed and coassemble to form functional receptors (Wada et al. 1989; Whiting et al. 1991). However, the prevalence of most nicotine ACh receptor (nAChR) subunits cannot be measured at the protein level because specific and quantifiable probes are lacking.

Receptors for nicotine are widely distributed in the CNS and in the periphery. In the CNS, nicotinic receptors are present in virtually every

brain region (Clarke and Pert 1985) and in the spinal cord (Gillberg et al. 1988). Peripheral receptors are located mainly on autonomic ganglion cells, adrenal chromaffin cells, primary sensory neurons, and on skeletal muscle fibers. Doses of nicotine relevant to smoking exert actions in the CNS and at several peripheral sites, but muscle nAChRs appear unaffected at such doses.

Radioligand binding studies have identified two principal populations of nAChRs in mammalian brain, labeled with nanomolar affinity by ^{3}H-agonists and ^{125}I-labeled α-bungarotoxin, respectively (Clarke et al. 1985b). The former are associated with receptors containing $\alpha 4$ and $\beta 2$ subunits (Whiting and Lindstrom 1986; Swanson et al. 1987; Whiting et al. 1991; Flores et al. 1992), the latter with receptors containing $\alpha 7$ subunits (Schoepfer et al. 1990; Couturier et al. 1990; Seguela et al. 1993). A third, less prevalent, subtype of putative receptors that may contain $\alpha 3$ subunits has been identified by ^{125}I-labeled neuronal bungarotoxin binding in rat brain (Schulz et al. 1991). Nicotinic receptors in the brain that contain $\alpha 4$ and $\beta 2$ subunits are widely believed to represent important pharmacological targets for behaviorally active doses of nicotine that might be relevant to smoking (Clarke 1987a). However, the evidence is rather indirect and largely correlational (London et al. 1988; Benwell et al. 1988; Grady et al. 1992). The possibility therefore remains that other receptor subtypes play a greater role in behavioral responses to nicotine.

2. Receptor Regulation

Chronic in vivo treatment with nicotine, in sufficient doses, leads to an increase in [^{3}H]nicotine and ^{125}I-labeled α-bungarotoxin binding site density in rodent brain (Marks et al. 1983a; Schwartz and Kellar 1983; El-Bizri and Clarke 1994b). This effect has been termed "paradoxical" because chronic agonist treatment typically leads to a down-regulation of receptors. It has been proposed that nicotine up-regulates its receptors by acting as a "time-averaged" antagonist (Hulihan-Giblin et al. 1990). Thus, nicotine treatment would produce a transition of the receptor to a desensitized state or to a more persistent "inactivated" state (Marks et al. 1983b; Schwartz and Kellar 1985). Although there is ample evidence that nicotine can indeed produce acute and chronic tolerance in the CNS (Lapchak et al. 1989a; Hulihan-Giblin et al. 1990; Benwell et al. 1994; Marks et al. 1993), there is some evidence to suggest that loss of receptor function per se may not be the stimulus leading to up-regulation (El-Bizri and Clarke 1994b).

II. Cellular Mechanisms

At the cellular level, nicotine can be considered as an excitatory agent, since, when nicotinic receptors are present, acute administration tends to

result in depolarization. If this occurs at the somatodendritic level, cell firing may increase, whereas acute depolarization of the nerve terminal tends to increase transmitter release.

With prolonged or repeated administration, tolerance may occur. Tolerance to nicotine may reflect a number of cellular processes with different dose relationships and time courses. Nevertheless, it is useful to distinguish acute tolerance (also known as tachyphylaxis), which occurs over a period of seconds to hours, from chronic tolerance, which may last for several weeks or longer. Acute tolerance could conceivably occur, for example, through receptor desensitization (Grady et al. 1994) or as a result of inactivation of voltage-gated ion channels. Chronic exposure to high doses of nicotine can result in a loss of sensitivity to nicotine lasting a number of days (Hulihan-Giblin et al. 1990; Lapchak et al. 1989a). The mechanisms underlying chronic tolerance remain largely unexplored.

Tolerance to nicotine can also be induced by concomitantly administered substances. Animals chronically exposed to ethanol exhibit a lessened response to the effects of nicotine thereby demonstrating cross-tolerance (Collins 1990). In mice, chronic exogenous corticosterone exposure decreases the sensitivity and density of cholinergic nicotinic receptors, which mimics tolerance to nicotine (Pauly et al. 1990a,b).

1. Effects of Nicotine on Cell Firing

A large number of electrophysiological studies have demonstrated that nicotine can alter neuronal firing in many brain regions (Clarke 1990). Most of this work is based upon extracellular recordings of single neurons in anesthetized animals and on the local application of drugs, given either by microiontophoresis or by pressure ejection. In only a few recent studies has it been possible to demonstrate unequivocally the occurrence of direct drug actions on the neuron under study. The sole dependent measure in almost all studies has been neuronal firing rate; drug-induced changes in the pattern of firing have received little attention (Grenhoff et al. 1986; Tung et al. 1989).

The preponderant electrophysiological effect of nicotine reported in the literature is one of excitation, but there are numerous examples of inhibitory effects. However, among those reports likely to reflect a direct drug action, inhibition has only been clearly shown in two brain areas – the cerebellum (De la Garza et al. 1987a,b) and dorsolateral septum (Wong and Gallagher 1989, 1991) of the rat. The latter action appears to be mediated by a calcium-dependent potassium conductance. The receptor subtype(s) associated with these inhibitory actions is not known, nor is it clear how widespread such actions might be in the brain.

2. Effect of Nicotine on Nerve Terminals

Nicotine has been reported to modulate the release of a number of brain transmitters in vitro. In some cases, direct presynaptic actions have been

demonstrated, through the use of superfused synaptosomes or of brain slices superfused with tetrodotoxin. Several neurotransmitters and brain areas have been examined. Direct actions of nicotine on the nerve terminal have generally been found to be stimulatory. This is not surprising, since it appears that most, and perhaps all, nicotinic receptors in the brain function as ligand-gated cation channels. Neurochemical evidence for nicotine-induced depolarization of isolated nerve terminals has been provided (Hillard and Pounds 1991); however, such a depolarizing action may reduce rather than increase *impulse-dependent* transmitter release.

3. Effects of Nicotine on Transmitter Release in the Whole Animal

For numerous reasons, the effects of a drug on a given neurotransmitter system in vivo may differ markedly from those seen in isolated tissues in vitro. All attempts to demonstrate drug-induced transmitter release in the living animal are by their nature indirect and thus introduce problems of interpretation. In some early studies, tissue levels of transmitter were found to be decreased by nicotine, but this is at best an insensitive guide to release and usually required massive doses of the drug. Drug-induced changes in metabolite/transmitter ratios have also been reported; since considerable intraneuronal metabolism can take place, it is not clear what these changes represent. Inhibition of synthetic enzymes prior to nicotine administration can provide a measure of transmitter utilization, but here the relationship to release is presumed rather than demonstrated. More recently, in vivo microdialysis has provided a method for sampling the extracellular milieu in the brain region of interest. This approach is potentially problematic, not least because it usually leads to a local depletion of transmitter and, quite possibly, of other unidentified neuromodulators. Finally, in vivo electrochemistry can provide a less invasive means of measuring transmitters that are electroactive (such as dopamine, noradrenaline and 5-HT); the challenge with this approach is to demonstrate chemical selectivity.

III. Neuronal Activity and Mechanisms of Reinforcement

The search for mechanisms underlying the reinforcing actions of nicotine has been largely confined to the brain. There are two principal reasons for this. Firstly, cigarette smoking in human subjects was found early on to be influenced by acute administration of the centrally active nicotinic antagonist mecamylamine, but not by the nicotinic antagonist pentolinium, which does not readily pass into the CNS (Stolerman et al. 1973). Secondly, virtually all of the behavioral effects of nicotine in animals have, where tested, been found to result from direct central effects of the drug (Clarke 1987b). Of particular relevance, the voluntary self-administration of intravenous nicotine is reduced by prior central administration of the quasi-irreversible nicotinic antagonist chlorisondamine (Corrigall et al. 1992). Clearly, nicotine is likely to exert many actions in the brain and not all will contribute a

reinforcing effect. In the following discussion, emphasis is placed on neuronal systems that may be relevant to nicotine dependence in humans.

1. Mesolimbic Dopamine

Several drugs of abuse appear to derive their reinforcing properties in animals from their ability to stimulate the mesolimbic dopamine (DA) system (WISE and HOFFMAN 1992). This neuronal system is widely thought to represent part of the reinforcement circuitry of the brain. Convergent evidence is now reviewed which indicates that it is also a target for nicotine.

Mesolimbic dopamine neurons form a pathway that ascends in parallel with the adjacent nigrostriatal dopamine system. Both neuronal populations express nAChRs on their cell bodies and/or dendrites and on terminals (CLARKE and PERT 1985). They also appear to synthesize the same types of nAChR subunit (WADA et al. 1989; WADA et al. 1990). In anesthetized rats, systemic administration of nicotine increased cell firing of nigrostriatal DA neurons via a central mechanism (CLARKE et al. 1985a); burst firing was also facilitated (GRENHOFF et al. 1986). Nicotine did not, however, stimulate mesolimbic DA neurons in rats under general anesthesia (GRENHOFF et al. 1986; MEREU et al. 1987); a stimulant action did occur in locally anesthetized, paralyzed animals (MEREU et al. 1987), but this action is likely to have been complicated by the stress imposed on the animals. However, intracellular recordings in rat midbrain slices have shown that nicotine (10 and 100 μM) depolarizes presumed mesolimbic DA cells via a direct action mediated by nAChRs (CALABRESI et al. 1989). Nicotine-induced excitation of mesolimbic DA neurons has also been reported to occur in vitro at considerably lower concentrations (EC_{50} approximately 170 nM), more clearly relevant to cigarette smoking (BRODIE 1991). Unlike nicotine-evoked DA release from synaptosomes (see below), this action did not manifest desensitization upon prolonged application of agonist.

Of all transmitters in the brain whose release is modulated by nicotine, DA has been the most extensively investigated in vitro. The majority of studies have used synaptosomes prepared from rat caudate-putamen, representing the nigrostriatal terminal field. DA release has also been demonstrated in other species (mice and cats), in brain slice preparations, and in the nucleus accumbens, which represents the principal terminal field of the mesolimbic DA system.

At least two DA releasing actions of nicotine have been identified in the striatum in vitro (WESTFALL et al. 1987). At high concentrations that are highly unlikely to occur in vivo (e.g., 1 mM), nicotine-induced DA release is associated with a "tyramine-like" effect. However, at lower concentrations, evoked release is concentration-dependent, mimicked by other nicotinic agonists, stereoselective, blocked by a number of nicotinic receptor antagonists, and dependent on external calcium (GIORGUIEFF-CHESSELET et al. 1979; RAPIER et al. 1988, 1990; GRADY et al. 1992; EL-BIZRI and CLARKE

1994a). This second action of nicotine is typically associated with an EC50 of around 1 μM, suggesting that it may be pharmacologically relevant in vivo. However, it is also susceptible to profound desensitization in vitro (Rapier et al. 1988; Grady et al. 1994). Thus, declining effects have been seen with brief nicotine (1μM) challenges given as much as 30 min apart (Rapier et al. 1988), and a near-total attenuation has been noted after continuous superfusion with low nanomolar concentrations of the agonist (Grady et al. 1994; Rowell and Hillebrand 1994). Tests with other secretagogues suggest that desensitization occurs at the nicotinic receptor rather than on the transmitter release mechanism. It should also be noted that nicotine, in concentrations as low as 1 nM, has been reported to inhibit [^{3}H]DA uptake in rat striatal tissue (Izenwasser et al. 1991). This action appeared to be receptor-mediated but was probably not mediated by a direct action on DA terminals.

Convergent evidence indicates that acute administration of nicotine to freely moving rats can increase DA release in both the nigrostriatal and mesolimbic systems. In this regard, the mesolimbic system appears the more susceptible to doses of nicotine that might be relevant to tobacco smoking. Indeed, a fivefold difference in sensitivity has been reported between the two projections (Imperato et al. 1986). In another study, nicotine (0.1–0.4 mg/kg sc) increased DA utilization in a dose-dependent, stereoselective manner; significant effects were observed at 0.2 and 0.4 mg/kg and were confined to mesolimbic terminal fields (Clarke et al. 1988).

The possible development of tolerance or sensitization has also been examined in rats implanted with microdialysis probes in the nucleus accumbens. In one such study (Damsma et al. 1989), DA release evoked by nicotine (0.35 mg/kg sc) was not significantly altered by administration of the same dose 1 h before; the data suggest that some tolerance may nevertheless have occurred. When release of mesolimbic DA was repeatedly evoked by giving nicotine (0.35 mg/kg sc) once daily, nicotine-evoked release was comparable in size to that obtained in drug-naive animals. However, other investigators have reported that daily nicotine injections lead to a sensitized DA response under similar conditions (Benwell and Balfour 1992). In contrast, chronic continuous infusion of nicotine abolished the release of nucleus accumbens DA evoked by acute nicotine challenge, as measured by intracerebral dialysis (Benwell et al. 1994). The occurrence of receptor desensitization is likely to have contributed to the latter result.

Nicotinic receptors are present at both the somatodendritic and terminal levels of mesolimbic DA neurons (see above). In the whole animal, local application of nicotine into cell body or terminal regions can result in activation (Lichtensteiger et al. 1982; Mifsud et al. 1989). However, two studies suggest that DA release induced by *systemic* nicotine administration results mainly or exclusively from a somatodendritic action. In the first, nicotine-evoked DA release was found to be impulse-dependent, as shown by the intra-accumbens infusion of tetrodotoxin via the dialysis probe

(BENWELL et al. 1993). In the second study, accumbens DA release resulting from systemic nicotine administration was attenuated by local infusion of the nicotinic antagonist into the mesolimbic cell body region but not into the nucleus accumbens (NISELL et al. 1994).

It is not known why systemic nicotine stimulates the mesolimbic DA system more readily than the nigrostriatal system. It is also unclear why somatodendritic nAChRs appear more important than terminal-located receptors. However, it may be significant that, in vitro, somatodendritic nAChRs located on mesolimbic DA neurons appear to desensitize much less readily than nAChRs located on terminals of the nigrostriatal pathway (BRODIE 1991; RAPIER et al. 1988; GRADY et al. 1994).

2. Dorsal Noradrenergic Bundle

Neurons arising from the locus coeruleus (LC) form the dorsal noradrenergic bundle, providing a widespread innervation of much of the forebrain, including the hippocampus and cerebral cortex. Many functions have been proposed for this neuronal population, including arousal and vigilance. Noradrenergic (NA) neurons orginating in the LC have also been implicated in the physical aspects of opiate withdrawal (NESTLER 1992).

Nicotinic receptors are present at both the somatodendritic and terminal levels of NA neurons. Nicotine appears to excite NA cell bodies of the LC via two mechanisms. One excitatory effect occurs via a peripheral action and is discussed below. An additional, centrally derived excitation has been observed at higher doses (ENGBERG and HAJOS 1994). In vitro electrophysiological experiments have implicated a direct action that is susceptible to prolonged desensitization (EGAN and NORTH 1986).

Nicotine stimulates the release of NA in a number of isolated preparations and brain areas in vitro (BALFOUR 1982). However, not infrequently, the concentrations of nicotine studied have been outside the pharmacological range. In superfused hippocampal slices, nicotine (10 and 100 μM) produced a small and transient increase in [^{3}H]NA release; this action was significantly attenuated by mecamylamine (10 μM) (SNELL and JOHNSON 1989). Nicotine has proved to be of greater potency in, synaptosomal preparations. possibly because the agonist reaches the receptors more rapidly, with less opportunity for desensitization to occur. In synaptosomes prepared from rat hippocampus or hypothalamus and incubated with [^{3}H]NA, nicotine (5 and 50 μM) increased both uptake and release of the neurotransmitter (BALFOUR 1973). Subsequently, [^{3}H]NA release evoked from a hypothalamic synaptosomal preparation by nicotine (1 and 10 μM) was shown to be mecamylamine-sensitive, indicative of a probable receptor-mediated action (YOSHIDA et al. 1980). In the whole animal, nicotine acutely increases NA release. As with DA release, it appears that NA release promoted by systemic nicotine results mainly or exclusively from a somatodendritic action (MITCHELL 1993).

3. Thalamocortical Projections

Thalamocortical relay neurons process and convey sensory signals to the neocortex. Drugs that modulate this flow of information may conceivably affect such central processes as arousal, attention, and memory. There are reports from animal and human studies suggesting that nicotine can affect all three processes (Levin 1992; Jones et al. 1992). The rat thalamus contains abundant [^{3}H]nicotine binding sites and nAChR-related mRNA, particularly in the anterior nuclei and in "specific" thalamic relay nuclei (Wada et al. 1989; Clarke et al. 1984). As far as known, a similar pattern exists in human thalamus (Rubboli et al. 1994; Perry et al. 1989; Adem et al. 1988). Electrophysiological studies have identified direct excitatory actions of nicotine on thalamocortical relay neurons in the dorsolateral and medial geniculate nuclei (Andersen and Curtis 1964; McCormick and Prince 1987a). The association of [^{3}H]nicotine binding sites with the corresponding projection areas in cortex (Prusky et al. 1987; Clarke 1991) suggests that nicotine may modulate thalamocortical transmission at the somatodendritic and terminal levels.

4. Habenulo-Interpeduncular System

The medial habenula and its principal projection target, the interpeduncular nucleus (IPN), represent a major target for nicotine in the brain. The relevance of this pathway to drug dependence is not clear. Both structures possess very dense [^{3}H]nicotine binding and abundant nAChR-related mRNAs in the rat (Wada et al. 1989; Clarke et al. 1984). Many neurons within these nuclei are directly excited by nicotine and nicotinic agonists (Brown et al. 1983; McCormick and Prince 1987b; Mulle and Changeux 1990; Mulle et al. 1991), and presynaptic modulation by nicotine has also been demonstrated within the IPN (Brown et al. 1984; Mulle et al. 1991). In vivo, the IPN evinces one of the largest increases in expression of the immediate early gene c-*fos* after systemic administration of nicotine (Pang et al. 1993).

5. 5-HT Release

Serotoninergic (5-HT) afferents from the midbrain raphé nuclei innervate much of the neuraxis. Serotoninergic interactions with the ascending DA systems have been noted at different anatomical sites (Hagan et al. 1993), and there are indications that 5-HT tone modulates the reinforcing effects of cocaine (Richardson and Roberts 1991). Nicotinic receptor mRNA has been detected in raphe nuclei (Wada et al. 1989, 1990), but to date no electrophysiological data are available that might point to a direct somatodendritic action of nicotine. Lesion evidence suggests that some nicotinic receptors reside on 5-HT terminals in rat striatum and hypothalamus (Schwartz et al. 1984), but there have been a few attempts to demonstrate

presynaptic control of 5-HT release by nicotine in the brain (HERY et al. 1977; BALFOUR 1973; BECQUET et al. 1988; FUXE et al. 1979). Although the majority of these results suggest that nicotine exerts little if any direct effect, the procedures used to data may not have been optimal for observing such effects. Although nicotine can clearly alter 5-HT utilization when administered in vivo, the mechanisms involved remain obscure (BALFOUR 1982).

The nicotine metabolite cotinine also has neuropharmacologic activity in the serotonergic system (ESSMAN 1973; FUXE et al. 1979). ESSMAN (1973) examined the influence of cotinine and nicotine on 5-HT activity in the cerebral cortex, mesencephalon and diencephalon of the rat brain. Nicotine slightly decreased the 5-HT turnover rate in all brain regions, while cotinine markedly increased 5-HT turnover rate (approximately six- to eightfold) in the mesencephalon and diencephalon without significantly affecting activity in the cerebral cortex. In other work, cotinine increased spontaneous release of 5-HT and inhibited neuronal 5-HT uptake and release from rat brain neurons, thereby increasing 5-HT turnover, while nicotine had no systematic effect (FUXE et al. 1979). Further, cotinine and nicotine given concomitantly with α-propyldopacetamide, a drug which depletes 5-HT in the brain, reduced whole brain 5-HT depletion compared to saline. Pretreatment with mecamylamine had no effect on the 5-HT depletion reduction induced by cotinine or nicotine. It was concluded that the observed effects following nicotine administration were likely due to the presence of the nicotine metabolite cotinine. These studies demonstrate that the serotonergic system is acutely altered by the administration of cotinine and this could be a significant neuropharmacologic mechanism of action for cotinine in the CNS. Further, the majority of the observed pharmacologic effect related to the alteration of 5-HT activity of cotinine probably occurs within the mesencephalon and diencephalon.

6. Amino Acid Neurotransmitter Release

Although the amino acids, glutamate and γ-amino-butyric acid (GABA), are probably the most prevalent excitatory and inhibitory neurotransmitters in the brain, few studies have addressed the possiblity of a presynaptic control of release via nicotinic receptors. Nicotine was reported to inhibit glutamate release in rat striatal slices, an effect attributed to an indirect action mediated by interneurons (GODUHKIN et al. 1984). In contrast, direct nicotine-evoked [^{3}H]GABA release has been observed in superfused hippocampal synaptosomes; the EC_{50} was approximately $5\,\mu M$ and the effect was sensitive to nicotinic receptor blockers (WONNACOTT et al. 1989).

7. Acetylcholine Release

Nicotine has been reported to stimulate ACh release in several brain areas via a direct presynaptic action. Almost all studies to date have utilized [^{3}H] choline as a precursor, which is incorporated into the newly synthesized

ACh release pool. In mouse cerebral cortex synaptosomes, nicotine (0.1 μM and greater) increased ACh release in a concentration-dependent manner; this effect was mimicked by the nicotinic agonist DMPP, abolished by the antagonist hexamethonium, and was attenuated by removal of external calcium (Rowell and Winkler 1984). In rat cortical synaptosomes, in contrast, nicotine did not evoke ACh release (Meyer et al. 1987); however, the acetylcholinesterase inhibitor eserine was present in these experiments and has antagonistic activity at nAChRs (Clarke et al. 1994).

Nicotinic modulation of ACh release has also been studied in brain slices from cerebral cortex and hippocampus (Araujo et al. 1988). Significant stimulatory effects of nicotine were consistently observed at 0.1 and 1 μM. Nicotinic-evoked release was blocked by the nicotinic receptor antagonists DHBE and *d*-tubocurarine and was insensitive to tetrodotoxin. Similar findings have been obtained in rat cerebellum (Lapchak et al. 1989b). In contrast, nicotine-evoked ACh release was not detectable in rat striatum using the same approach (Araujo et al. 1988). In guinea pig cortical slices, nicotine-evoked ACh efflux was observed but was prevented by tetrodotoxin, indicating an indirect effect (Beani et al. 1985). Whether this represents a species difference or whether procedural differences are responsible is not clear. There are also reports of nicotine-induced cortical ACh release in freely moving animals (Quirion et al. 1994), but as yet the mechanisms involved have not been elucidated.

8. Other Measures of Neuronal Activity

a. 2-Deoxyglucose Uptake

Cellular uptake of radiolabeled 2-deoxyglucose (2-DG) has been widely used as a measure of neuronal activity in the rat brain. In all studies involving nicotine, animals have been partially immobilized during testing; this is an important caveat, in view of evidence that responses to nicotine can be attenuated by stress and/or circulating corticosteroids (Pauly et al. 1990a,b; Caggiula et al. 1993).

Acute systemic administration of nicotine produced a dose-dependent, mecamylamine-sensitive increase in 2-DG uptake in many brain areas in rats (Grunwald et al. 1987, 1988; London et al. 1988; McNamara et al. 1990). Typically, brain areas showing the greatest nicotine effect were those rich in [^{3}H]nicotine binding sites rather than ^{125}I-labeled α-bungarotoxin. The effects of chronic nicotine treatment have also been investigated. In one study, the acute response to an injection of nicotine (0.3 mg/kg sc) was blunted in several brain regions by prior subchronic nicotine administration (1 mg/kg sc bid for 11 days); no sensitization was seen (London 1990). Since the nicotine pretreatment resulted in significant residual plasma nicotine levels (12 ng/ml) at the time of testing, it is not clear whether the tolerance observed should be considered to be acute or chronic. In another study, nicotine (or saline) was infused chronically by osmotic minipump for 2 weeks, resulting in

plasma nicotine levels two to three times those typical of human cigarette smokers (Grunwald et al. 1988). 2-DG uptake, measured near the end of this period, was significantly increased in several brain areas, with a similar trend in many others. The pattern of effects resembled that obtained with an acute infusion of nicotine which achieved similar plasma levels. After 1 day of nicotine withdrawal, glucose utilization returned essentially to control levels (Schröck and Kuschinsky 1991).

b. C-fos Expression

Expression of the immediate early gene c-*fos* provides another measure of neuronal activation in the brain and can be mapped neuroanatomically in brain sections by in situ hybridization or immunocytochemistry. The pattern of nicotine-induced c-*fos* expression in rat brain (Ren and Sagar 1992; Pang et al. 1993) differs markedly from known nAChR distributions and does not resemble the distribution of nicotine-induced 2-DG uptake. This disparity is particularly striking in the ventral tegmental area, where it is the non-dopaminergic neurons that principally express c-*fos* (Pang et al. 1993).

9. Peripheral Effects

Whilst it is believed that the primary reinforcing actions of nicotine are largely of central origin, several observations suggest that peripheral actions of the drug may also play a role. Such actions may contribute to the primary reinforcing effects of nicotine, or act as secondary reinforcers by association.

Actions of nicotine in the mouth and respiratory tract may be particularly important. First, the immediate satisfaction of cigarette smoking is promoted by sensory cues that can be blunted by local anesthesia of the respiratory tract (Rose et al. 1985). Second, nicotine appears to be the most important component in tobacco smoke that causes airway irritation in humans (Lee et al. 1993). Third, nicotine can produce a burning sensation in the mouth which is blocked by mecamylamine (Jarvik and Assil 1988). Fourth, nicotinic receptors have been shown to reside on sensory nerve endings in several tissues (Suwandi and Bevan 1966; Tanelian 1991; Juan 1982). Fifth, mecamylamine can reduce subjective ratings of cigarette strength and harshness (Rose et al. 1989). Sixth, sensory cues associated with cigarette smoke appear to modulate smoke intake and craving (Rose et al. 1993). Lastly, inhalation of black pepper vapor, which irritates the respiratory airways, or of denicotinized cigarettes, can produce acute reduction of cigarette craving and certain other withdrawal symptoms (Butschky et al. 1995; Rose and Behm 1994).

Once nicotine has entered the bloodstream, it may exert additional peripheral effects that affect CNS activity. This is suggested by electrophysiologic experiments conducted in anaesthetized rats. In these studies, intravenous administration of nicotine resulted in an almost instantaneous

and transient excitation of neurons located in the substantia nigra pars reticulata (Clarke et al. 1985) or LC (Hajos and Engberg 1988; Engberg and Hajos 1994). These effects could be attenuated or blocked by peripherally active nicotinic antagonists. In one study, nicotine was found to be effective in a dose as low as 2 μg/kg, approximately equivalent to a single puff of tobacco smoke (Clarke et al. 1985). It appears that nicotine may activate primary sensory afferents to produce these indirect effects in the brain (Hajos and Engberg 1988).

E. Implications for Medications Development and Conclusions

The fundamental reason that tobacco dependence is a major concern secondary to no other form of drug abuse is that tobacco kills far more people than all other addictive drugs combined. In fact, the rates of tobacco-caused morbidity and mortality are accelerating rapidly world wide even though they are stabilizing in the United States. Simply put, this is because, except for a few countries such as Australia, Canada, the United States, and Sweden, demand reduction efforts (i.e., treatment and prevention) are not keeping pace with supply side efforts. Part of the problem is similar to that with other addictions, which is that current knowledge and treatment approaches which could help are not broadly available. Equally important, however, is that current treatment approaches leave much room for improvement with respect ot efficacy, acceptability to tobacco users, and cost. Improvements along these dimensions will require enhanced understanding of the pharmacology of nicotine and the pathophysiology of the dependence process. Such information should facilitate the development and administration of treatments which are selectively targeted to the clusters of symptoms that appear to distinguish various subpopulations of smokers.

The development of nicotine replacement medications in the 1980s and 1990s illustrated the important public health potential of medications for treating nicotine dependence as well as the limits of those medications. Many patients who were refractory to other approaches were able to give up smoking and sustain abstinence, and abstinence rates for those on the medications were often double those for persons treated with placebo (Fiore et al. 1992; Silagy et al. 1994; Henningfield 1994). However, the fact remains that, in most trials, the majority of persons treated resume smoking within days or weeks and show little evidence that the medication provided any meaningful benefit. Future research needs to determine which patients might benefit from repeated replacement therapy, higher doses, or fundamentally different approaches. Several avenues of research and development appear particularly promising. Identification of receptor subpopulations in the CNS that mediate various features of nicotine dependence is fundamental. Such information will facilitate the development of more effective

and selective nicotinic agonists, antagonists, and mixed agonist-antagonists, as well as nonnicotinic acting agents. In this regard, it is important to encourage approaches which are currently limited by lack of acceptable medications (e.g., antagonists), when the approach, in principle, could be quite useful (e.g., HENNINGFIELD 1984; CLARKE 1991).

Further information on the pathophysiologic underpinnings of nicotine dependence could also be critical in determining if there are subpopulations of people who are particularly vulnerable to nicotine dependence and may require prophylactic therapies. It is also plausible that some nicotine-dependent people might require extended, or even life long, administration of medications to sustain productive lives in the absence of tobacco delivered nicotine. Further, identification of similarities and differences in the mediation of nicotine dependence with other forms of drug dependence will also undoubtedly continue to contribute to the development of more effective behavioral and pharmacologic approaches to treatment. Thus, nicotine dependence researchers are clearly faced by many important challenges that could contribute significantly to our ability to prevent and treat this form of drug dependence.

References

Adem A, Jossan SS, d'Argy R, Brandt I, Winblad B, Nordberg A (1988) Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography. J Neural Transm 73:77–83

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd edn (revised). American Psychiatric Association, Washington

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. 4th edn. American Psychiatric Association, Washington DC

Anand R, Conroy WG, Schoepfer R, Whiting P, Lindstrom J (1991) Neuronal nicotinic acetylcholine receptors expressed in Xenopus oocytes have a pentameric quaternary structure J Biol Chem 266:11192–11198

Andersen P, Curtis DR (1964) The excitation of thalamic neurones by acetylcholine. Acta Physiol Scand 61:85–99

Araujo DM, Lapchak PA, Collier B, Quirion R (1988) Characterization of N-[3H]methylcarbamylcholine binding sites and effect of N-methylcarbamylcholine on acetylcholine release in rat brain. J Neurochem 51:292–299

Armitage AK, Dollery CT, George CF, Houseman TH, Lewis PJ, Turner DM (1975) Absorption and metabolism of nicotine from cigarettes. Br Med J 4: 313–316

Atweh SF, Grayhack MS, Richman DP (1984) A cholinergic receptor site on murine lymphocytes with novel binding characteristics. Life Sci 35:2459–2469

Balfour DJ (1982) The effects of nicotine on brain neurotransmitter systems. Pharmacol Ther 16:269–282

Balfour DJK (1973) Effects of nicotine on the uptake and retention of ^{14}C-noradrenaline and ^{14}C-5-hydroxytyramine by rat brain homogenates. Eur J Pharmacol 23:19–26

Balster RL, Schuster CR (1973) Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. J Exp Anal Behav 20:119–129

Barbieri RL, Gochberg J, Ryan KT (1986) Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast in vitro. J Clin Invest 77:1727–1733

Beani L, Bianchi C, Nilsson L, Nordberg A, Romanelli L, Sivilotti L (1985) The effect of nicotine and cytisine on 3H-acetylcholine release from cortical slices of guinea-pig brain. Naunyn Schmiedebergs Arch Pharmacol 331:293–296
Becquet D, Faudon M, Hery F (1988) In vivo evidence for acetylcholine control of serotonin release in the cat caudate nucleus: influence of halothane anaesthesia. Neuroscience 27:819–826
Benowitz NL (1988) Pharmacologic aspects of cigarette smoking and nicotine addiction. N Engl J Med 319:1318–1330
Benowitz NL (1993) Nicotine replacement therapy: What has been accomplished-can we do better? Drugs 45:157–170
Benowitz NL, Jacob P III (1984) Daily intake of nicotine during cigarette smoking. Clin Pharm Therap 35:499–504
Benowitz NL, Sharp DS (1989) Inverse relation between serum cotinine concentration and blood pressure in cigarette smokers. Circulation 80:1309–1312
Benowitz NL, Henningfield JE (1994) Establishing a nicotine threshold for addiction. N Engl J Med 331:123–125
Benowitz NL, Kuyt F, Jacob P, Jones RT, Osman AL (1983) Cotinine disposition and effects. Clin Pharmacol Ther 34:604–611
Benowitz NL, Porchet H, Sheiner L, Jacob P III (1988) Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 44:23–28
Benowitz NL, Hall SM, Modin G (1989) Persistent increase in caffeine concentrations in people who stop smoking. Br Med J 298:1075–1076
Benowitz NL, Chan K, Denaro CP, Jacob P III (1991a) Stable isotope method for studying transdermal drug absorption: the nicotine patch. Clin Pharmacol Ther 50:286–293
Benowitz NL, Jacob P III, Denaro C, Jenkins R (1991b) Stable isotope studies of nicotine kinetics and bioavailability. Clin Pharmacol Ther 49:270–277
Benwell MEM, Balfour DJK (1992) The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 105:849–856
Benwell MEM, Balfour DJ, Anderson JM (1988) Evidence that tobacco smoking increases the density of (−)-[^{3}H]nicotine binding sites in human brain. J Neurochem 50:1243–1247
Benwell MEM, Balfour DJK, Lucchi HM (1993) Influence of tetrodotoxin and calcium on changes in extracellular dopamine levels evoked by systemic nicotine. Psychopharmacology (Berl) 112:467–474
Benwell MEM, Balfour DJK, Khadra LF (1994) Studies on the influence of nicotine infusions on mesolimbic dopamine and locomotor responses to nicotine. J Clin Invest 72:233–239
Borzelleca JF, Bowman ER, Mckennis H (1962) Studies on the respiratory and cardiovascular effects of (−)-cotinine. J Pharmacol Exp Ther 137:313–318
Breslau N, Kilbey MM, Andreski P (1992) Nicotine withdrawal symptoms and psychiatric disorders: Findings from an epidemiologic study of young adults. Am J Psychiatry 149:464–469
Brodie MS (1991) Low concentrations of nicotine increase the firing rate of neurons of the rat ventral tegmental area in vitro. In: Adlkofer F, Thurau K (eds) Effects of nicotine on biological systems. Birkhäuser, Basel, p 373
Brown DA, Docherty RJ, Halliwell JV (1983) Chemical transmission in the rat interpeduncular nucleus in vitro. J Physiol (Lond) 341:655–670
Brown DA, Docherty RJ, Halliwell JV (1984) The action of cholinomimetic substances on impluse conduction in the habenulointerpedunculopontine pathway of the rat. J Physiol (Lond) 353:101–109
Burns DM, Axelrad R, Bal D, Carol J, Davis RM, Myers ML, Pinney JM, Rigotti NA, Shopland DR (1992) Report of the tobacco policy research study group on smoke-free indoor air policies. Tobacco Control 1 Suppl:S14–S18

Butschky MF, Bailey D, Henningfield JE, Pickworth WE (1995) Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. Pharmacol Biochem Behav 50:91–96

Caggiula AR, Epstein LH, Antelman SM, Saylor S, Knopf S, Perkins KA, Stiller R (1993) Acute stress or corticosterone administration reduces responsiveness to nicotine: implications for a mechanism of conditioned tolerance. Psychopharmacology (Berl) 111:499–507

Calabresi P, Lacey MG, North RA (1989) Nicotinic excitation of rat ventral tegmental neurones in vitro studied by intracellular recording. Br J Pharmacol 98:135–140

Carroll ME, Lac ST, Asencio M, Keenan RM (1989) Nicotine dependence in rats. Life Sci 45:1381–1388

Centers for Disease Control and Prevention (1993) Cigarette smoking-attributable mortality and years of potential life lost – United States. In: Chronic disease and health promotion. Adapted from the MMWR. tobacco topics 1990–1993. U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, pp 77–81

Centers for Disease Control (1994) Surveillance for selected tobacco-use behaviors–United States, 1900–1994. MMWR CDC Surveill Summ 43:11–15

Chahine R, Calderone A, Navarro-Delmasure C (1990) The in vitro effects of nicotine and cotinine on prostacyclin and thromboxane biosynthesis. Prostaglandins Leukot Essent Fatty Acids 40:261–266

Chahine R, Kaiser R, Pham Huu Chanh A (1991) Effects of nicotine and cotinine on prostacyclin biosynthesis. In: Adlkofer F, Thurau, K (eds) Effect of nicotine on biological systms. Birkhäuser, Basel, p 171

Chait LD, Griffiths RR (1983) Effects of caffeine on cigarette smoking and subjective response. Clin Pharmacol Ther 34:612–622

Chait LD, Griffiths RR (1984) Effects of methadone on human cigarette smoking and subjective ratings. J Pharmacol Exp Ther 229:636–640

Clarke PBS (1987a) Recent progress in identifying nicotinic cholinoceptors in mammalian brain. Trends Pharmacol Sci 8:32–35

Clarke PBS (1987b) Nicotine and smoking: a perspective from animal studies. Psychopharmacology (Berl) 92:135–143

Clarke PBS (1990) The central pharmacology of nicotine: electrophysiological approaches. In: Wonnacott S, Russell MAH, Stolerman IP (eds) Nicotine psychopharmacology: molecular, cellular, and behavioural aspects. Oxford University Press, Oxford, p 158

Clarke PBS (1991) Nicotinic receptors in rat cerebral cortex are associated with thalamocortical afferents. Soc Neurosci Abstr 17:384.18

Clarke PBS, Pert CB, Pert A (1984) Autoradiographic distribution of nicotine receptors in rat brain. Brain Res 323:390–395

Clarke PBS, Pert A (1985) Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res 348:355–358

Clarke PBS, Hommer DW, Pert A, Skirboll LR (1985a) Electrophysiological actions of nicotine on substantia nigra single units. Br J Pharmacol 85:827–835

Clarke PBS, Schwartz RD, Paul SM, Pert CB, and Pert A (1985b) Nicotinic binding in rat brain: autoradiographic comparison of ^{3}H-acetylcholine, ^{3}H-nicotine and ^{125}I-alpha-bungarotoxin. J Neurosci 5:1307–1315

Clarke PBS, Fu DS, Jakubovic A, Fibiger HC (1988) Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. J Pharmacol Exp Ther 246:701–708

Clarke PBS, Reuben M, El-Bizri H (1994) Blockade of nicotinic responses by physostigmine, tacrine and other cholinesterase inhibitors in rat striatum. Br J Pharmacol 111:695–702

Cohen C, Pickworth WB, Bunker EB, Henningfield JE (1994) Caffeine antagonizes EEG effects of tobacco withdrawal. Pharmacol Biochem Behav 40:919–926

Collins AC (1990) Interactions of ethanol and nicotine at the receptor level. Recent Dev Alcohol 8:221–231
Connolly G, Chen T (1993) International health and tobacco use. In: Houston TP (ed) Tobacco use: an American crisis. American Medical Association, Chicago, p 72
Conrin J (1980) The EEG effects of tobacco smoking – a review. Clin Electroencephalogr 11:180–187
Cooper E, Couturier S, Ballivet M (1991) Pentameric structure and subunit stoichiometry of a neuronal nicotinic acetylcholine receptor. Nature 350:235–238
Corrigall WA (1991a) A rodent model for nicotine self-administration. In: Boulton AA, Baker GB, Wu PH (eds) Animal models of drug addiction. Humana, Totawa, pp 315–344 (Neuromethods, vol 24)
Corrigall WA (1991b) Understanding brain mechanisms in nicotine reinforcement. Br J Addict 86:507–510
Corrigall WA, Herling S, Coen KM (1989) Evidence for a behavioral deficit during withdrawal from chronic nicotine treatment. Pharmacol Biochem Behav 33: 559–562
Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS (1992) The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl) 107:285–289
Couturier S, Bertrand D, Matter JM, Hernandez MC, Bertrand S, Millar N, Valera S, Barkas T, Ballivet M (1990) A neuronal nicotinic acetylcholine receptor subunit ($\alpha 7$) is developmentally regulated and forms a homo-oligomeric channel blocked by α-BTX. Neuron 5:847–856
Damsma G, Day J, Fibiger HC (1989) Lack of tolerance to nicotine-induced dopamine release in the nucleus accumbens. Eur J Pharmacol 168:363–368
De la Garza R, Bickford-Wimer PC, Hoffer BJ, Freedman R (1987a) Heterogeneity of nicotine actions in the rat cerebellum: an in vivo electrophysiologic study. J Pharmacol Exp Ther 240:689–695
De la Garza R, McGuire TJ, Freedman R, Hoffer BJ (1987b) The electrophysiological effects of nicotine in the rat cerebellum: evidence for direct postsynaptic actions. Neurosci Lett 80:303–308
De Wit H, Bodker B, Ambre J (1992) Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology (Berl) 107: 352–358
Deneau GA, Inoki R (1967) Nicotine self-administration in monkeys. Ann NY Acad Sci 142:277–279
Deneris ES, Connolly J, Rogers SW, Duvoisin R (1991) Pharmacological and functional diversity of neuronal nicotinic acetylcholine receptors. Trends Pharmacol Sci 12:34–40
Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 85:5274–5278
Djordjevic MV, Hoffmann D, Glynn T, Connolly GN (1995) US commercial brands of moist snuff, 1994: assessment of nicotine, moisture, and pH. Tobacco Control 4:62–66
Domino EF, von Baumgarten AM (1969) Tobacco cigarette smoking and patellar reflex depression. Clin Pharmacol Ther 10:72–79
Edwards JA, Warburton D (1983) Smoking, nicotine and electrocortical activity. Pharmacol Ther 19:147–164
Egan TM, North RA (1986) Actions of acetylcholine and nicotine on rat locus coeruleus neurons in vitro. Neuroscience 19:565–571
El-Bizri H, Clarke PBS (1994a) Blockade of nicotinic receptor-mediated release of dopamine from striatal synaptosomes by chlorisondamine and other nicotinic antagonists administered in vitro. Br J Pharmacol 111:406–413
El-Bizri H, Clarke PBS (1994b) Regulation of nicotinic receptors in rat brain following quasi-irreversible nicotinic blockade by chlorisondamine and chronic treatment with nicotine. Br J Pharmacol 113:917–925

Engberg G, Hajos M (1994) Nicotine-induced activation of locus coeruleus neurons–an analysis of peripheral versus central induction. Naunyn Schmiedebergs Arch Pharmacol 349:443–446

Essman WB (1973) Nicotine-related neurochemical changes: some implications for motivational mechanisms and differences. In: Dunn WL (ed) Smoking behavior: motives and incentives. Winston, Washington, p 51

Evans SM, Cone EJ, Henningfield JE (1995) Rapid arterial kinetics of intravenous and smoked cocaine; Relationship to subjective and cardiovascular effects. NIDA Research Monograph 153. US Dept of Health and Human Services, Public Health Service. National Institutes of Health, Rockville (NIH publication no. 95-3883)

Fagerstrom KO, Schneider NG (1989) Measuring nicotine dependence in tobacco smoking: a review of the Fagerstrom Tolerance Questionnaire. J Behav Med 12:159–182

Farre M, Cami J (1991) Pharmacokinetic considerations in abuse liability evaluation. Br J Addict 86:1601–1606

Fiore MC, Jorenby DE, Baker TB, Kenford SL (1992) Tobacco dependence and the nicotine patch: clinical guidelines for effective use. JAMA 268:2687–2694

Flores CM, Rogers SW, Pabreza LA, Wolfe BB, Kellar KJ (1992) A subtype of nicotinic cholinergic receptor in rat brain is composed of $\alpha 4$ and $\beta 2$ subunits and is up-regulated by chronic nicotine treatment. Mol Pharmacol 41:31–37

Foulds J, Stapleton J, Hayward M, Russell MAH, Feyerabend C, Fleming T, Costello J (1993) Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. Arch Fam Med 2:417–423

Freedman AM (1994) How tobacco giant doctors snuff brands to boost their "kick". Wall Street Journal 26 Oct; A1

Fuxe K, Everitt BJ, Hökfelt T (1979) On the action of nicotine and cotinine on central 5-hydroxytryptamine neurons. Pharmacol Biochem Behav 10:671–677

Fuxe K, Andersson K, Eneroth P, Harfstrand A, Agnati LF (1989) Neuroendocrine actions of nicotine and of exposure to cigarette smoke: Medical implications. Neuroendocrinology 13:19–41

Gallup GH (1992) Teen-age attitudes and behavior concerning tobacco. The George H. Gallup International Institute. GII 9104. Princeton, NJ

Gillberg PG, d'Argy R, Aquilonius SM (1988) Autoradiographic distribution of ^{3}H-acetylcholine binding sites in the cervical spinal cord of man and some other species. Neurosci Lett 90:197–202

Giorguieff-Chesselet MF, Kemel ML, Wandscheer D, Glowinski J (1979) Regulation of dopamine release by presynaptic nicotinic receptors in rat striatal slices: effect of nicotine in a low concentration. Life Sci 25:1257–1262

Giovino GA, Henningfield JE, Tomar SL, Escobedo LG, Slade J (1995) Epidemiology of tobacco use and dependence. Epidemiol Rev (in press)

Godukhin OV, Budantsev AY, Selifanova OV, Agapova VN (1984) Effect of cholinomimetics on the release and uptake of L-3H glutamic acid in rat neostriatum. Cell Mol Neurobiol 4:117–124

Golding JF (1988) Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving. Pharmacol Biochem Behav 29:23–32

Goldberg SR, Kelleher RT, Goldberg DM (1981a) Fixed-ratio responding under second-order schedules of food presentation or cocaine injection. J Pharm Exper Ther 218:271–281

Goldberg SR, Spealman RD, Goldberg DM (1981b) Persistent behavior at high rates maintained by intravenous nicotine self-adminstration. Science 214:573–575

Goldberg SR, Henningfield JE (1988) Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of IV drug injection. Pharmacol Biochem Behav 30:227–234

Goldberg SR, Risner ME, Stolerman IP, Reavill C, Garcha HS (1989) Nicotine and some related compounds: effects on schedule-controlled behavior and discriminative properties in rats. Psychopharmacology (Berl) 97:295–302

Gori GB, Benowitz NL, Lynch CJ (1986) Mouth versus deep airways absorption of nicotine in cigarette smokers. Pharmacol Biochem Behav 25:1181–1184
Grady SR, Marks MJ, Wonnacott S, Collins AC (1992) Characterization of nicotinic receptor-mediated [^{3}H]dopamine release from synaptosomes prepared from mouse striatum. J Neurochem 59:848–856
Grady SR, Marks MJ, Collins AC (1994) Desensitization of nicotine-stimulated [^{3}H]dopamine release from mouse striatal synaptosomes. J Neurochem 62: 1390–1398
Grenhoff J, Aston-Jones G, Svensson TH (1986) Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol Scand 128:351–358
Griffiths RR, Bigelow GE, Liebson I (1976) Facilitation of human tobacco self-administration by ethanol: A behavioral analysis. J Exp Anal Behav 25:279–292
Griffiths R, Bigelow GE, Liebson I, Kaliszak JE (1980) Drug preference in humans: Double-blind choice comparison of pentobarbital, diazepam and placebo. J Pharmacol Exp Ther 215:649–661
Grunwald F, Schrock H, Kuschinsky W (1987) The effect of an acute nicotine infusion on the local cerebral glucose utilization of the awake rat. Brain Res 400:232–238
Grunwald F, Schrock H, Theilen H, Biber A, Kuschinsky W (1988) Local cerebral glucose utilization of the awake rat during chronic administration of nicotine. Brain Res 456:350–356
Hagan RM, Kilpatrick GJ, Tyers MB (1993) Interactions between 5-HT_3 receptors and cerebral dopamine function: implications for the treatment of schizophrenia and psychoactive substance abuse. Psychopharmacology (Berl) 112 Suppl:S68–S75
Hajos M, Engberg G (1988) Role of primary sensory neurons in the central effects of nicotine. Psychopharmacology (Berl) 94:468–470
Harris CM, Emmett-Oglesby MW, Robinson NG, Lal H (1986) Withdrawal from chronic nicotine substitutes partially for the interoceptive stimulus produced by pentylenetetrazol (PTZ). Psychopharmacology (Berl) 90:85–89
Hatsukami DK, Gust SW, Keenan RM (1987) Physiological and subjective changes from smokeless tobacco withdrawal. Clin Pharmacol Ther 41:103–107
Hatsukami DK, Skoog K, Huber M, Hughes JR (1991) Signs and symptoms from nicotine gum abstinence. Psychopharmacology (Berl) 104:496–504
Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom Test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86:1119–1127
Helton DR, Modlin DL, Tizzano JP, Rasmussen K (1993) Nicotine withdrawal: a behavioral assessment using schedule controlled responding, locomotor activity, and sensorimotor reactivity. Psychopharmacology (Berl) 113:205–210
Henningfield JE (1984) Pharmacologic basis and treatment of cigarette smoking. J Clin Psychiatry 45:24–34
Henningfield JE (1992) Occasional drug use: Comparing nicotine with other addictive drugs. Tobacco Control 1:161–162
Henningfield JE (1994) Do nicotine replacement medications work? A unique standard for nicotine. Addiction 89:434–436
Henningfield JE, Griffiths RR (1981) Cigarette smoking and subjective response: Effects of d-amphetamine. Clin Pharm Ther 30:497–505
Henningfield JE, Goldberg SR (1983) Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19:989–992
Henningfield JE, Chait LD, Griffiths RR (1984) Effects of ethanol on cigarette smoking by volunteers without histories of alcoholism. Psychopharmacology 82:1–5
Henningfield JE, Miyasato K, Jasinski DR (1985) Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther 234:1–12

Henningfield JE, Nemeth-Coslett R (1988) Nicotine dependence, interface between tobacco and tobacco-related disease. Chest 93:37S–55S
Henningfield JE, London ED, Benowitz NL (1990) Arterio-venous differences in plasma concentration of nicotine after cigarette smoking. JAMA 263:2049–2050
Henningfield JE, Cohen C, Slade JD (1991) Is nicotine more addictive than cocaine? Br J Addict 86:565–569
Henningfield JE, Keenan RM (1993) Nicotine delivery kinetics and abuse liability. J Consul Clin Psychol 61:743–750
Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED (1993) Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend 33:23–29
Henningfield JE, Kozlowski LT, Benowitz NL (1994) A proposal to develop meaningful labeling for cigarettes. JAMA 272:312–314
Henningfield JE, Heishman SJ (1995) The addictive role of nicotine in tobacco use. Psychopharmacology 117:11–13
Henningfield JE, Schuh LM, Jarvik ME (1995a) Pathophysiology of tobacco dependence. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: the fourth generation of progress. Raven, New York, pp 1715–1729
Henningfield JE, Radzius A, Cone EJ (1995b) Estimation of available nicotine content of six smokeless tobacco products. Tobacco Control (in press)
Herning RI, Pickworth WB (1985) Nicotine gum improved stimulus processing during tobacco withdrawal. Psychohysiology 22:595
Herning RI, Jones RT, Bachman J (1983) EEG changes during tobacco withdrawal. Psychophysiology 20:507–512
Hery F, Bourgoin S, Hamon M, Ternaux JP, Glowinski J (1977) Control of the release of newly synthetized 3H-5-hydroxytryptamine by nicotinic and muscarinic receptors in rat hypothalamic slices. Naunyn Schmiedebergs Arch Pharmacol 296:91–97
Hillard CJ, Pounds JJ (1991) [^{3}H]Tetraphenylphosphonium accumulation in cerebral cortical synaptosomes as a measure of nicotine-induced changes in membrane potential. J Pharmacol Exp Ther 259:1118–1123
Hirschman RS, Leventhal H, Glynn K (1984) The development of smoking behavior: Conceptualization and supportive cross-sectional survey data. J Appl Social Psychol 14(3):184–206
Hughes JR, Higgins ST, Hatsukami DK (1990) Effects of abstinence from tobacco: a critical review. In: Kozlowski LT, Annis H, Cappell HD, Glaser F, Goodstadt M, Israel Y, Kalant H, Sellers EM, Vingilis J (eds) Research advances in alcohol and drug problems, vol 10. Plenum, New York, p 318
Hughes JR, Gulliver SB, Fenwick JW, Valliere WA, Cruser K, Pepper S, Shea P, Solomon LJ, Flynn BS (1992) Smoking cessation among self-quitters. Health Psychol 11:331–334
Hulihan-Giblin BA, Lumpkin MD, Kellar K (1990) Effects of chronic administration of nicotine on prolactin release in the rat: inactivation of prolactin response by repeated injections of nicotine. J Pharmacol Exp Ther 252:21–25
Imperato A, Mulas A, Di Chiara G (1986) Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 132: 337–338
Izenwasser S, Jacocks HM, Rosenberger JG, Cox BM (1991) Nicotine indirectly inhibits [^{3}H]dopamine uptake at concentrations that do not directly promote [^{3}H]dopamine release in rat striatum. J Neurochem 56:603–610
Jaffe JH (1985) Drug addiction and drug abuse. In: Gilman AG, Goodman LS, Rall TW, Murad F (eds) Goodman and Gilman's the pharmacologic basis of therapeutics, 7th edn. MacMillan, New York, pp 532–581
Jarvik ME, Assil KM (1988) Mecamylamine blocks the burning sensation of nicotine on the tongue. Chem Senses 13:213–217
Jarvik ME (1995) The addictive role of nicotine in tobacco use: commentary. Psychopharmacology 117:18–20

Jasinski DR (1977) Assessment of the abuse potentiality of morphinelike drugs (methods used in man). In: Martin WR (ed) Handbook of experimental pharmacology, vol 45. Springer, Berlin Heidelberg New York, pp 197–249
Johnson HM, Torres BA (1985) Regulation of lymphokine production by arginine vasopressin and oxytocin: modulation of lymphocyte function by neurohypophyseal hormones. J Immunol 135:773–775
Jones GMM, Sahakian BJ, Levy R, Warburton DM, Gray JA (1992) Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology (Berl) 108:485–494
Jones RT, Farrell TR III, Herning RI (1978) Tobacco smoking and nicotine tolerance. NIDA Res Monogr 20:202–208
Juan H (1982) Nicotinic nociceptors on perivascular sensory nerve endings. Pain 12:259–264
Karras A, Kane JM (1980) Naloxone reduces cigarette smoking. Life Sci 27:1541–1545
Keenan RM, Hatsukami DK, Pickens RW, Gust SW, Strelow LJ (1990) The relationship between chronic ethanol exposure and cigarette smoking in the laboratory and the natural environment. Psychopharmacology 100:77–83
Keenan RM, Jenkins AJ, Cone EJ, Henningfield JE (1994a) Smoked and iv nicotine, cocaine and heroin have similar abuse liability. J Addict Dis 13:259
Keenan RM, Hatsukami DK, Pentel P, Thompson T, Grillo MA (1994b) Pharmacodynamic effects of cotinine in abstinent cigarette smokers. Clin Pharmacol Ther 55:581–590
Keenan RM, Hatsukami DK, Pentel P, Thompson T, Grillo MA (1995) Reply to Mr. Foulds. Clin Pharmacol Ther 56:95–97
Kety SS (1951) The theory and application of the exchange of inert gas at the lungs and tissues. Pharmacol Rev 3:1–41
Kitamura T (1958) Studies on the pharmacological properties of nicotine related derivatives. Especially about the pharmacology of nornicotine. Folia Pharmacol Jpn 54:825–837
Knott VJ, Venables PH (1977) EEG alpha correlates of nonsmokers, smokers, smoking and smoking deprivation. Psychophysiology 14:150–156
Knott VJ (1988) Dynamic EEG changes during cigarette smoking. Neuropsychobiology 19:54–60
Kottke TE, Battista RN, DeFriese GH, Brekke ML (1988) Attributes of successful smoking cessation interventions in medical practice: a meta-analysis of 39 controlled trials. JAMA 259:2883–2889
Kozlowski LT (1976) Effects of caffeine consumption of nicotine consumption. Psychopharmacology 47:165–168
Kozlowski LT (1981) Tar and nicotine delivery of cigarettes: what a difference a puff makes. JAMA 245:158–159
Kozlowski LT (1982) The determinates of tobacco use: cigarette smoking in the context of other forms of tobacco use. Can J Pub Health 73:236–241
Kozlowski LT, Wilkinson DA, Skinner W, Kent C, Franklin T, Pope M (1989) Comparing tobacco cigarette dependence with other drug dependencies. JAMA 261:898–901
Kozlowski LT, Henningfield JE, Keenan RM, Lei H, Leigh G, Jelinek LC, Pope MA, Heartzen CA (1993) Patterns of alcohol, cigarette, and caffeine and other drug use in two drug abusing populations. J Subst Abuse Treat 10:171–179
Kyerematen GA, Dvorchik BH, Vesell ES (1983) Influence of different forms of tobacco intake on nicotine elimination in man. Pharmacology 26:205–209
Kyerematen GA, Vesell ES (1991) Metabolism of nicotine. Drug Metab Rev 23:3–41
Lapchak PA, Araujo DM, Quirion R, Collier B (1989a) Effect of chronic nicotine treatment on nicotinic autoreceptor function and N-3Hmethylcarbamylcholine binding sites in the rat brain. J Neurochem 52:483–491
Lapchak PA, Araujo DM, Quirion R, Collier B (1989b) Presynaptic cholinergic mechanisms in the rat cerebellum: evidence for nicotinic, but not muscarinic autoreceptors. J Neurochem 53:1843–1851

Larson PS, Haag HB, Silvette H (1961) Tobacco: experimental and clinical studies. Williams and Wilkins, Baltimore
Lautenbach BF (1886/1887) On a new function of the liver. Philadelphia Medical Times 7:387–394
Lee BL, Benowitz NL, Jacob P (1987) Cigarette abstinence, nicotine gum, and theophylline disposition. Ann Intern Med 106:553–555
Lee L-Y, Gerhardstein DC, Wang AL, Burki NK (1993) Nicotine is responsible for airway irritation evoked by cigarette smoke inhalation in men. J Appl Physiol 75:1955–1961
Levin ED (1992) Nicotinic systems and cognitive function. Psychopharmacology (Berl) 108:417–431
Lichtensteiger W, Hefti F, Felix D, Huwyler T, Melamed E, Schlumpf M (1982) Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 21:963–968
Lide DR (1991) CRC handbook of chemistry and physics, 72nd edn. CRC, Boca Raton
London ED (1990) Effects of nicotine on cerebral metabolism. In: Boch G, Marsh J (eds) The biology of nicotine dependence. Wiley, New York, p 131
London ED, Connolly RJ, Szikszay M, Wamsley JK (1985a) Distribution of cerebral metabolic effects of nicotine in the rat. Eur J Pharmacol 110:391
London ED, Waller SB, Wamsley JK (1985b) Autoradiographic localization of ^{3}H nicotine binding sites in the rat brain. Neurosci Lett 53:179–184
London ED, Connolly RJ, Szikszay M, Wamsley JK, Dam M (1988) Effects of nicotine on local cerebral glucose utilization in the rat. J Neurosci 8:3920–3928
London ED, Cascella NG, Wong DF, Phillips RL, Dannals RF, Links JM, Herning R, Grayson R, Jaffe JH, Wagner HN Jr (1990a) Cocaine-induced reduction of glucose utilization in human brain. Arch Gen Psychiaty 47:567–574
London ED, Broussolle EPM, Links JM, Wong DF, Cascella NG, Dannals DF, Sano M, Herning RI, Snyder FR, Rippetoe SK, Toung TJK, Jaffe JH, Wagner HN Jr (1990b) Morphine-induced metabolic changes in human brain: studies with positron emission tomography and ^{18}fluorine fluorodeoxyglucose. Arch Gen Psychiatry 47:73–81
Lukas SE, Mendelson JH, Amass L, Benedikt R (1990) Behavioral and EEG studies of acute cocaine administration: comparisons with morphine, amphetamine, pentobarbital, nicotine, ethanol and marijuana. NIDA Res Monogr 95:146–151
Malin DH, Lake JR, Carter VA, Cunningham JS, Wilson OB (1993) Naloxone precipitates nicotine abtinence syndrome in the rat. Psychopharmacology (Berl) 112:339–342
Malin DH, Lake JR, Carter VA, Cunningham JS, Hebert KM, Conrad DL, Wilson OB (1994) The nicotinic antagonist mecamylamine precipitates nicotine abstinence syndrome in the rat. Psychopharmacology 115:180–184
Marks MJ, Burch JB, Collins AC (1983a) Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. J Pharmacol Exp Ther 226: 817–825
Marks MJ, Burch JB, Collins AC (1983b) Genetics of nicotine response in four inbred strains of mice. J Pharmacol Exp Ther 226:291–302
Marks MJ, Grady SR, Collins AC (1993) Downregulation of nicotinic receptor function after chronic nicotine infusion. J Pharmacol Exp Ther 266:1268–1276
Maultsby PN, Lake JR, Cortes CW, Lanier JG, Roberts LK, Wilson OB, Malin DH (1991) Aminal model of nicotine dependence and abstinence syndrome. Soc Neurosci Abstr 17:1251
McCormick DA, Prince DA (1987a) Acetylcholine causes rapid nicotinic excitation in the medial habenular nucleus of guinea pig in vitro. J Neurosci 7: 742–752
McCormick DA, Prince DA (1987b) Actions of acetylcholine in the guinea-pig and cat medial and lateral geniculate nuclei, in vitro. J Physiol (Lond) 392:147–165
McGinnis JM, Foege WH (1993) Actual causes of death in the United States. JAMA 270:2207–2212

McNamara D, Larson DM, Rapoport SI, Soncrant TT (1990) Preferential metabolic activation of subcortical brain areaas by acute administration of nicotine to rats. J Cereb Blood Flow Metab 10:48–56
McNeill A (1991) The development of dependence on smoking in clildren. Br J Addict 86:589–592
McNeill AD, Jarvis MJ, Stapleton JA, West RJ, Bryant A, (1989) Nicotine intake in young smokers: longitudinal study of saliva cotinine concentrations. Am J Pub Health 79:172–175
Mello NK, Mendelson JH, Sellers ML, Kuehnle JC (1980) Effects of heroin self-administration on cigarette smoking. Psychopharmacology 67:45–52
Meikle AW, Liu XH, Taylor GN, Stringham JD (1988) Nicotine and cotinine effects on 3-alpha-hydroxysteroid dehydrogenase in canine prostate. Life Sci 43: 1845–1850
Mereu G, Yoon KW, Boi V, Gessa GL, Naes L, Westfall TC (1987) Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. Eur J Pharmacol 141:395–399
Meyer EM, Arendash GW, Judkins JH, Ying L, Wade C, Kem WR (1987) Effects of nucleus basalis lesions on the muscarinic and nicotinic modulation of [^{3}H] acetylcholine release in the rat cerebral cortex. J Neurochem 49:1758–1762
Mifsud JC, Hernandez L, Hoebel BG (1989) Nicotine infused into the nucleus accumbens increase synaptic dopamine as measured by in vivo microdialysis. Brain Res 478:365–367
Mitchell SN (1993) Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotne. Neuropharmacology 32:937–949
Mulle C, Changeux J-P (1990) A novel type of nicotinic receptor in the rat central nervous system characterized by patch-clamp techniques. J Neurosci 10:169–175
Mulle C, Vidal C, Benoit P, Changeux J-P (1991) Existence of different subtypes of nicotinic acetylcholine receptors in the rat habenulo-interpeduncular system. J Neurosci 11:2588–2597
Munck A, Guyre PM, Holbrook NJ (1984) Physiological function of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5:25–44
Nemeth-Coslett R, Henningfield JE, O'Keefe MK, Griffiths RR (1986a) Effects of marijuana smoking on subjective ratings and tobacco smoking. Pharmacol Biochem Behav 25:659–665
Nemeth-Coslett R, Henningfield JE, O'Keefe MK, Griffiths RR (1986b) Effects of mecamylamine on human cigarette smoking and subjective ratings. Psychopharmacology 88:420–425
Nestler EJ (1992) Molecular mechainsms of drug addiction. J Neurosci 12:2439–2450
Nil R, Buzzi R, Battig K (1984) Effects of single doses of alcohol and caffeine on cigarette smoke puffing behavior. Pharmacol Biochem Behav 20:583–590
Nisell M, Nomikos GGF, Svensson TH (1994) Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 16:36–44
Oliveto AH, Hughes JR, Terry SY (1991) Effects of caffeine on tobacco withdrawal. Clin Pharmacol Ther 50:157–164
Ossip, DJ, Epstein LH (1981) Relative effects of nicotine and coffee on cigarette smoking. Addict Behav 6:35–39
Palmer KJ, Buckley MM, Faulds D (1992) Transdermal nicotine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. Drugs 44:498–529
Pang Y, Kiba H, Jayaraman A (1993) Acute nicotine injections induce c-fos mostly in non-dopaminergic neurons of the midbrain of the rat. Brain Res Mol Brain Res 20:162–170
Patterson TR, Stringham JD, Meikle AW (1990) Nicotine and cotinine inhibit steroidogenesis in mouse Leydig cells. Life Sci 46:265–272
Pauly JR, Grün EU, Collins AC (1990a) Chronic corticosterone administration modulates nicotine sensitivity and brain nicotinic receptor binding in C3H mice. Psychopharmacology (Berl) 101:310–316

Pauly JR, Ullman EA, Collins AC (1990b) Strain differences in adrenalectomy-induced alterations in nicotine sensitivity in the mouse. Pharmacol Biochem Behav 35:171–179

Perkins KA, Epstein LH, Stiller RL, Sexton JE, Debske TD, Jacob RG (1990a) Behavioral performance effects of nicotine in smokers and nonsmokers. Pharmacol Briochem Behav 37:11–15

Perkins KA, Epstein LH, Stiller RL, Sexton JE, Fernstrom MH, Jacob RG, Solberg R (1990b) Metabolic effects of nicotine after consumption of a meal in smokers and nonsmokers. Am J Clin Nutr 52:228–233

Perkins KA, Epstein LH, Stiller RL, Fernstrom MH, Sexton JE, Jacob RG, Solberg R (1991a) Acute effects of nicotine on hunger and caloric intake in smokers and nonsmokers. Psychopharmacology (Berl) 103:103–109

Perkins KA, Stiller RL, Jennings JR (1991b) Acute tolerance to the cardiovascular effects of nicotine. Drug Alcohol Depend 29:77–85

Perkins KA, Grobe JE, Epstein LH, Caggiula AR, Stiller RL (1992) Effects of nicotine on subjective arousal may be dependent on baseline subjective state. J Subst Abuse 4:131–141

Perkins KA DiMarco A, Grobe JE, Scierka A, Stiller RL (1994) Nicotine discrimination in male and female smokers. Psychopharmacology 116:407–413

Perry EK, Smith CJ, Perry RH, Whitford C, Johnson M, Birdsall NJ (1989) Regional distribution of muscarinic and nicotinic cholinergic receptor binding activities in the human brain. J Chem Neuroanat 2:189–199

Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr (1994) Mortality from smoking in developed countries 1950–2000. Oxford University Press, New York

Pickworth WB, Herning RI, Henningfield JE (1986) Electroencephalographic effects of nicotine chewing gum in humans. Pharmacol Biochem Behav 25:879–882

Pickworth WB, Herning RI, Henningfield JE (1988) Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol Biochem Behav 30:149–153

Pickworth WB, Herning RI, Henningfield JE (1989) Spontaneous EEG changes during tobacco abstinence and nicotine substitution in human volunteers. J Pharmacol Exp Ther 251:976–982

Pomerleau CS, Pomerleau OF (1992) Euphoriant effects of nicotine in smokers. Phychopharmacology 108:460–465

Pool WF, Crooks PA (1985) Biotransformation of primary nicotine metabolites: In vivo metabolism of R-(+)-[14 C-NCH3]-N-methylnicotinium ion in the guinea-pig. Drug Metab Disposit 13:578–581

Prusky GT, Shaw C, Cynader MS (1987) Nicotine receptors are located on lateral geniculate nucleus terminals in cat visual cortex. Brain Res 412:131–138

Quirion R, Richard J, Wilson A (1994) Muscarinic and nicotinic modulation of cortical acetylcholine release monitored by in vivo microdialysis in freely moving adult rats. Synapse 17:92–100

Rapier C, Lunt GG, Wonnacott S (1988) Stereoselective nicotine-induced release of dopamine from striatal synaptosomes: concentration dependence and repetitive stimulation. J Neurochem 50:1123–1130

Rapier C, Lunt GG, Wonnacott S (1990) Nicotinic modulation of ^{3}H-dopamine release from striatal synaptosomes: pharmacological characteristation. J Neurochem 54:937–945

Raveis VH, Kandel DB (1987) Changes in drug behavior from the middle to the late twenties: Initiation, persistence, and cessation of use. Am J Pub Health 77:607–611

Ren T, Sagar SM (1992) Induction of c-fos immunostaining in the rat brain after the systemic administration of nicotine. Brain Res Bull 29:589–597

Revell AD (1988) Smoking and performance – a puff-by-puff analysis. Psychopharmacology (Berl) 96:563–565

Richardson NR, Roberts DCS (1991) Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. Life Sci 49:833–840

Risner MR, Goldberg SR, Prada JA, Cone EJ (1985) Effects of nicotine, cocaine, and some of their metabolites on schedule-controlled responding by beagle dogs and squirrel monkeys. J Pharmacol Exp Ther 234:113–119
Robinson JH, Pritchard WS, Davis RA (1992) Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. Psychopharmacology (Berl) 108:466–472
Rose JE, Behm FM (1994) Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. Drug Alcohol Depend 34:225–229
Rose JE, Tashkin DP, Ertle A, Zinser MC, Lafr R (1985) Sensory blockade of smoking satisfaction. Pharmacol Biochem Behav 23:289–293
Rose JE, Sampson A, Levin ED, Henningfield JE (1989) Mecamylamine increases nicotine preference and attenuates nicotine discrimination. Pharmacol Biochem Behav 32:933–938
Rose JE, Behm FM, Levin ED (1993) Role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacol Biochem Behav 44:891–900
Rosencrans JA, Meltzer LT (1981) Central sites and mechanisms of action of nicotine. Neurosci Biobehav Rev 5:497–501
Rowell PP, Winkler DL (1984) Nicotinic stimulation of [3h]acetylcholine release from mouse cerebral cortical synaptosomes. J Neurochem 43:1593–1598
Rowell PP, Hillebrand JA (1994) Characterization of nicotine-induced desensitization of evoked dopamine release from rat striatal synaptosomes. J Neurochem 63:561–569
Rubboli F, Court JA, Sala C, Morris C, Perry E, Clementi F (1994) Distribution of neuronal nicotinic receptor subunits in human brain. Neurochem Int 25:69–71
Russell MAH, Jarvis MJ, Feyerabend C (1980) A new age for snuff? Lancet 474–475
Russell MAH (1990) The nicotine addiction trap: A 40-year sentence for four cigarettes. Br J Addict 85:293–300
Sachs D, Benowitz N (1988) The nicotine withdrawal syndrome: Nicotine absence or caffeine excess? In: Harris LS (ed) Problems of drug dependence, 1988, NIDA research monograph 90, U.S. Government Printing Office, Washington DC, p 38 (DHHS publication no. (ADM) 89-1605)
Sargent PB (1993) The diversity of neuronal nicotinic acetylcholine receptors. Annu Rev Neurosci 16:403–443
Schoepfer R, Conroy WG, Whiting P, Gore M, Lindstrom J (1990) α-4 bungarotoxin binding protein cDNAs reveal subtypes of this branch of the ligand-gated ion channel gene superfamily. Neuron 5:35–48
Schröck H, Kuschinsky W (1991) Effects of nicotine withdrawal on the local cerebral glucose utilization in conscious rats. Brain Res 545:234–238
Schuh LM, Henningfield JE, Pickworth WB, Rothman R, Ohuoha D, Keenan RM (1995) Pharmacodynamic effects of cotinine. Annual Meeting of the Society for Research on Nicotine and Tobacco, San Diego
Schulz DW, Loring RH, Aizenman E, Zigmond RE (1991) Autoradiographic localization of putative nicotinic receptors in the rat brain using ^{125}I-neuronal bungarotoxin. J Neurosci 11:287–297
Schwartz RD, Kellar KJ (1983) Nicotinic cholinergic receptor binding sites in the brain: regulation in vivo. Science 220:214–216
Schwartz RD, Kellar KJ (1985) In vivo regulation of ^{3}H-acetylcholine recognition sites in brain by nicotinic cholinergic drugs. J Neurochem 45:427–433
Schwartz RD, Lehmann J, Kellar KJ (1984) Presynaptic nicotinic cholingeric receptors labeled by ^{3}H-acetylcholine on catecholamine and serotonin axons in brain. J Neurochem 42:1495–1498
Séguéla P, Wadiche J, Dineley-Miller K, Dani JA, Patrick JW (1993) Molecular cloning, functional properties, and distribution of rat brain α7: A nicotinic cation channel highly permeable to calcium. J Neurosci 13:596–604
Sellers EM, Otton SV, Busto UE (1991) Drug metabolism and interactions in abuse liability assessment. Brit J Addict 86:1607–1614
Shavit T, Terman GW, Martin FC, Lewis JW, Liebeskind JC, Gale RR (1985) Stress, opioid peptides, the immune system and cancer. J Immunol 135:834s–837s

Silagy C, Mant D, Fowler G, Lodge M (1994) Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 343:139–142

Silverman K, Evans SM, Strain EC, Grifiths RR (1992) Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 327:1109–1114

Snell LD, Johnson KM (1989) Effects of nicotinic agonists and antagonists on N-methyl-D-aspartate-induced 3H-norepinephrine release and 3H-(1-1-(2-thienyl) cyclohexyl-piperidine) binding in rat hippocampus. Synapse 3:129–135

Snyder FR, Henningfield JE (1989) Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. Psychopharmacology (Berl): 97:17–22

Sokoloff L, Reivich M, Kennedy C, DesRosiers MH, Patlak CS, Petigrew KD, Sakurad O, Shinohara M (1977) The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897–916

Sopori ML, Gairola CC, DeLucia A, Bryant L, Cherian S (1985) Immune responsiveness of monkeys exposed chronically to cigarette smoke. Clin Immunol Immunopathol 36:338–344

Stapleton JM, Henningfield JE, Wong DF, Phillips RL, Gilson SF, Grayson RF, Dannals RF, London ED (1992) Effects of nicotine on cerebral metabolism and subjective responses in human volunteers. Soc Neurosci Abst 18:1074

Stolerman IP (1991) Behavioural pharmacology of nicotine: multiple mechanisms. Br J Addict 86:533–536

Stolerman IP, Reavill C (1989) Primary cholinergic and indirect dopaminergic mediation of behavioural effects of nicotine. Prog Brain Res 79:227–237

Stolerman IP, Goldfarb T, Fink R, Jarvik ME (1973) Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia (Berl) 28:247–259

Sutherland G, Russell MAH, Stapleton J, Feyerbend C, Ferno O (1992a) Nasal nicotine spray: A rapid nicotine delivery system. Psychopharmacology 108: 512–518

Sutherland G, Stapleton JA, Russell MAH, Jarvis MJ, Hajek P, Belcher M, Feyerabend C (1992b) Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 340:324–329

Suwandi IS, Bevan JA (1966) Antagonism of lobeline by ganglion-blocking agents at afferent nerve endings. J Pharmacol Exp Ther 153:1–7

Svensson CK (1987) Clinical pharmacokinetics of nicotine. Clin Pharmacokinet 12:30–40

Swanson LW, Simmons DM, Whiting PJ, Lindstrom J (1987) Immunohistochemical localization of neuronal nicotinic receptors in the rodent central nervous system. J Neurosci 7:3334–3342

Sweanor D, Ballin S, Corcoran RD, Davis A, Deasy K, Ferrence RG, Lahey R, Lucido S, Nethery WJ, Wasserman J (1992) Report of the tobacco policy research study group on tobacco pricing and taxation in the United States. Tobacco Control 1 Suppl:S31–S36

Swedberg MDB, Henningfield JE, Goldberg SR (1990) Nicotine dependency: animal studies. In: Wonnacott S, Russell MAH, Stolerman IP (eds) Nicotine psychopharmacology: molecular, cellular and behavioural aspects. Oxford University Press, Oxford, p 38

Swerdlow NR, Koob GF (1987) Dopamine, schizophrenia, mania, and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function. Behav Brain Sci 10:197–245

Takada K, Swedberg MD, Goldberg SR, Katz JL (1989) Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys. Psychopharmacology (Berl) 99:208–212

Tanelian DL (1991) Cholinergic activation of population of corneal afferent nerves. Exp Brain Res 86:414–420

Tiffany ST, Drobes DJ (1990) Imagery and smoking urges: the manipulation of affective content. Addict Behave 15:531–539

Tiffany ST, Drobes DJ (1991) The development and initial validation of a questionnaire of smoking urges. Br J Addict 86:1467–1476
Tjälve H, Popov D (1973) Effect of nicotine and nicotine metabolites on insulin secretion from rabbit pancreas pieces. Endocrinology 92:1343–1348
Tung CS, Ugedo L, Grenhoff J, Engberg G, Svensson TH (1989) Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids. Synapse 4:313–318
Ulett JA, Itil TM (1969) Quantitative electroencephalogram in smoking and smoking deprivation. Science 164:969–970
US Department of Health and Human Services (1983) The health consequences of smoking: cardiovascular disease. A report of the Surgeon General. Public Health Service, Office on Smoking and Health, Rockville
US Department of Health and Human Services (1988) The health consequences of smoking: nicotine addiction. A report of the Surgeon General. Public Health Service, Office on Smoking and Health, Rockville
US Department of Health and Human Services (1990) The health benefits of smoking cessation. Public Health Service, Centers for Disease Control Center for chronic Disease Prevention and Health Promotion Office on Smoking and Health, Rockville DHHS publication no. (CDC) 90-8416
US Department of Health and Human Services (1994) Preventing tobacco use among young people: a report of the Surgeon General. US Department of Health and Human Services. Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Rockville
Wada E, Wada K, Boulter J, Deneris E, Heinemann S, Patrick J, Swanson LW (1989) Distribution of $\alpha 2$, $\alpha 3$, $\alpha 4$, and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J Comp Neurol 284:314–335
Wada E, McKinnon D, Heinemann S, Patrick J, Swanson LW (1990) The distribution of mRNA encoded by a new member of the neuronal nicotinic acetylcholine receptor gene family ($\alpha 5$) in the rat central nerous system. Brain Res 526:45–53
West R, Hajek P, Belcher M (1989) Time course of cigarette withdrawal symptoms while using nicotine gum. Psychopharmacology (Berl) 99:143–145
Westfall TC (1974) Effect of nicotine and other drugs on the release of 3H-norepinephrine and 3H-dopamine from rat brain slices. Neuropharmacology 13:693–700
Westfall TC, Perry H, Vickery L (1987) Mechanisms of nicotine regulation of dopamine. In: Martin WR, Van Loon GR, Iwamoto ET, Davis L (eds) Tobacco smoking and nicotine. Plenum, New York, p 209
Whitfield JP, MacManus JP, Gillan DJ (1970) The possible mediation by cyclic-AMP of the stimulation of thymocyte proliferation by vasopressin and the inhibition of this mitogenic action by thyrocalcitonin. J Cell Physiol 76:65–76
Whiting P, Lindstrom J (1986) Pharmacological properties of immuno-isolated neuronal nicotinic receptors. J Neurosci 6:3061–3069
Whiting P, Schoepfer R, Lindstrom J, Priestley T (1991) Structural and pharmacological characterization of the major brain nicotinic acetylcholine receptor subtype stably expressed in mouse fibroblasts. Mol Pharmacol 40:463–472
Wilbert J (1987) Tobacco and shamanisms in South America. Yale University Press, New Haven
Wise RA, Hoffman DC (1992) Localization of drug reward mechanisms by intracranial injections. Synapse 10:247–263
Wong LA, Gallagher JP (1989) A direct nicotinic receptor-mediated inhibition recorded intracellularly in vitro. Nature 341:439–444
Wong LA, Gallagher JP (1991) Pharmacology of nicotinic receptor-mediated inhibition in rat dorsolateral septal neurones. J Physiol (Lond) 436:325–346
Wonnacott S, Irons J, Rapier C, Thorne B, Lunt GG (1989) Presynaptic modulation of transmitter release by nicotine receptors. Prog Brain Res 79:157–163

Wybran J (1985a) Enkephalins and endorphins: activation molecules for the immune system and natural killer activity. Neuropeptides 5:371–374
Wybran J (1985b) Enkephalins and endorphins as modifiers of the immune system: Present and future. FEd Proc 44:92–94
Yamamoto K, Domino EF (1965) Nicotine-induced EEG and behavioral arousal. Int J Neuropharmacol 4:359–373
Yeh J, Barbieri RJ, Friedman AJ (1989) Nicotine and cotinine inhibit rat testes androgen biosynthesis in vitro. J Steroid Biochem 33:627–630
Yoshida K, Kato Y, Imura H (1980) Nicotine-induced release of noradrenaline from hypothalamic synaptosomes. Brain Res 182:361–368