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Pain Sensitivity in Females at Risk for Hypertension

Janis L. Krywiak
Department of Psychology
McGill University, Montreal
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Abstract

Hypertension is associated with a reduction in sensitivity to pain in both animals and humans. Changes in nociception pre-date elevations in blood pressure in animals genetically predisposed to hypertension, and preliminary findings with male offspring of hypertensives indicate that genetic risk for hypertension is related to decreased pain sensitivity in humans. Sensitivity to naturalistic and laboratory pain stimuli was compared in normotensive females with and without a parental history of hypertension in three studies. Genetic risk for hypertension was associated with decreased sensitivity for blood donation venipuncture pain and electric shock, but not for menstrual pain or the cold pressor test. These findings provide modest support for the notion that hypoalgesia is present in females at risk for hypertension. Issues for future research include extension of these findings to other pain stimuli, use of multiple indices of risk, assessment of the effects of cyclic hormonal changes on the relationship between pain sensitivity and risk for hypertension, and further study of the mechanisms and pathophysiological implications of this effect.

Résumé

L'hypertension est associée à une réduction de la sensibilité à la douleur chez les animaux comme chez les humains. Des changements de la perception de la douleur précèdent des élévations de la pression sanguine chez les animaux génétiquement prédisposés à l'hypertension. Des résultats préliminaires obtenus auprès d'hommes présentant une histoire parentale d'hypertension indiquent qu'une prédisposition génétique à l'hypertension est reliée à une diminution de la sensibilité à la douleur chez les humains. Trois études visent à comparer, chez des femmes ne souffrant pas d'hypertension et qui présentent ou ne présentent pas une histoire parentale d'hypertension, la sensibilité à la douleur causée par des stimuli naturalistes et de laboratoire. Une prédisposition génétique à l'hypertension est associée à une diminution de la sensibilité à la douleur causée par l'insertion de l'aiguille lors d'une prise de sang ou encore par une choc électrique, mais non pas à la douleur causée par les menstruations ou le test de l'eau glacée. Ces résultats offrent un appui modeste à la notion d'une hypoalgésie présente chez les femmes à risque pour l'hypertension. Les aspects à considérer lors de futures recherches incluent la généralisation de ces résultats à d'autres stimuli de la douleur, l'utilisation de multiples facteurs de risque, les effets de changements cycliques hormonaux sur la relation entre la sensibilité à la douleur

et la prédisposition génétique à l'hypertension ainsi qu'une étude plus poussée des mécanismes et des implications physiologiques de ces effets.

Statement of Original Contributions

The research presented in this thesis provides an original contribution to knowledge concerning the relationship between risk for hypertension and hypoalgesia. Previous research with animals has demonstrated that established hypertension is associated with decreases in nociception. Interestingly, hypertensive-prone animals also show evidence of hypoalgesia prior to the development of elevated blood pressure levels. Therefore, the mechanisms underlying these changes in nociception may have important implications for the pathogenesis of hypertension.

Although less extensively studied in humans, hypertension-related hypoalgesia has been reported in individuals with both established and borderline hypertension. To date, however, only one study has specifically examined the potential link between genetic risk for hypertension and pain sensitivity in humans. Although the results obtained in this study support the notion of decreased pain sensitivity in individuals at risk for hypertension, generalization of these findings is limited by 1) the exclusive focus on male subjects, and 2) the use of only one laboratory pain stimulus. In this regard, the present thesis provides a distinct contribution to the literature by focusing on sensitivity to diverse laboratory and naturalistic pain stimuli in females at risk for hypertension. Further, the present studies are the

first to examine a number of potential psychological and physiological mediators of group differences in pain sensitivity.

Results from this series of studies provide modest support for the notion that risk for hypertension is associated with hypoalgesia. Whereas female offspring of hypertensive parents experienced less venipuncture pain than offspring of normotensive parents and reported less pain in response to electric shock, they did not demonstrate less sensitivity for menstrual pain or the cold pressor test. Further, resting blood pressure (in the case of venipuncture pain) and blood pressure reactivity (with respect to electric shock sensitivity) were also found to be important in the association between parental history and sensitivity to pain. As such, this research provides the first evidence of hypoalgesia in females at risk for hypertension, and is the first report of such an effect in the context of a naturalistic pain stimulus. However, the mixed findings across pain stimuli suggest that there are important factors which require additional consideration. Enhancing the accuracy of establishing subject risk for hypertension appears to be one crucial element. Also, confirmation of whether this effect is elicited only by pain stimuli which are capable of engaging endogenous opiate activity will provide further information regarding potential mechanisms of hypertension-related hypoalgesia. Finally, these results

highlight the importance of further study of possible interactions between genetic risk for hypertension and physiological responses across the menstrual cycle, and the effect this may have on the occurrence of hypertension-related hypoalgesia.

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INTRODUCTION

Hypertension, or chronically elevated blood pressure, is present in about 33% of North American male adults and approximately 27% of adult females ("Hypertension Prevalence," 1985). This disorder may lead to a variety of serious medical complications such as coronary heart disease, cerebrovascular disease, and kidney disease, and is associated with shorter life expectancy (Shapiro & Goldstein, 1982). Although hypertension is typically defined in discrete categorical terms (currently agreed upon as blood pressure levels above 140 mmHg systolic and/or 90 mmHg diastolic), the relationship between blood pressure and risk for cardiovascular disease is a continuous function. Therefore, as blood pressure levels rise even within the normotensive range, risk for associated complications increases (Page, 1983; Peart, 1983).

Only 10 to 15% of all cases of hypertension are secondary to known medical conditions such as kidney disease, adrenal gland tumors, endocrine disorders, vascular diseases, and disorders of the central nervous system. The remaining large majority of cases of hypertension--referred to as essential, primary, or idiopathic hypertension--are of unknown etiology (Shapiro & Goldstein, 1982). Given its high prevalence rate and serious associated complications, much effort has been devoted to gaining a better understanding of factors that may contribute to the

development or exacerbation of essential hypertension.

It is generally believed that the development of essential hypertension is attributable to a complex interaction among many biological, psychological, and social variables. One major factor determining adult blood pressure level is heredity. Evidence supporting this includes the finding that correlations for resting blood pressure levels are approximately twice as high for monozygotic (e.g., r=.55) as compared to dizygotic (e.g., r=.25) twins (Page, 1983). Also, studies of natural and adopted children have revealed that there are significant correlations in blood pressure between parents and their biological offspring, but not with their adopted children (Biron, Mongeau, & Bertrand, 1976). In addition, a positive family history of hypertension is a significant predictor for the development of hypertension (Feinleib, 1979). Other biopsychosocial factors believed to mediate or moderate genetic predisposition include body mass and obesity, dietary sodium intake, oral contraceptive use, alcohol consumption, smoking, and stress (Page, 1983; Peart, 1983).

Gaining an understanding of the etiology of essential hypertension is complicated by the fact that sustained hypertension is a developmental disorder, and the physiological profile of the established disease may be radically different from that seen in the early stages (McCubbin, 1991). For instance, while increased cardiac

output has been observed in the early stages of hypertension, individuals with established hypertension appear to have normalized cardiac output with an upward structural adaptation in the systemic resistance vessels (Folkow, 1989). Folkow (1982, 1989) has outlined a possible etiology which is multifactorial and polygenetically linked to explain how these physiological changes may occur in the transition from a normotensive to a hypertensive state. One important aspect of this transition is believed to involve the defense reaction ("fight or flight" responses). Folkow has argued that even relatively mild psychosocial stressors are capable of eliciting this physiological response, which includes centrally elicited cardiovascular adjustments. While these adjustments are well-suited to support physical exertion, they lead to exaggerated pressor effects when such physical exertion is not required, as is often the case in present-day society. Thus, early stages of hypertension may involve repeated episodes of increased cardiac output in response to a variety of challenging or arousing situations. Over time, these repeated defense reactions are believed to lead to a gradual "structural autoregulation" involving thickening of the systemic vessel walls and upward resetting of the baroreceptors. At this point, even though cardiac output levels may be within normal limits, systemic changes maintain elevations in blood pressure. Thus, Folkow's model offers a possible explanation for how an individual with

borderline hypertension can develop more established high blood pressure levels. This model also offers insight as to how individuals at genetic risk for hypertension may be prone to develop the disorder. Offspring of hypertensives are known to exhibit greater cardiovascular reactivity under a variety of laboratory and naturalistic conditions than individuals who are not at genetic risk for hypertension (e.g., Ditto, 1986; Gintner, Hollandsworth, & Intrieri, 1986; Hastrup, Light, & Obrist, 1982; Jorgensen & Houston, 1981; Manuck, Proietti, Rader, & Polefrone, 1985). Over time, this tendency for repeated episodes of excessive physiological reactivity may provide the opportunity for the structural changes seen in established hypertensives to develop. Consistent with this notion, several prospective studies have shown an association between blood pressure reactivity to stress and the subsequent development of hypertension (e.g., Light, Dolan, Davis, & Sherwood, 1992; Matthews, Woodall, & Allen, 1993).

Although a variety of factors have been identified as playing an important role in the development of essential hypertension, much remains to be learned about the underlying pathology and course of the disorder. Interestingly, recent work with both animals and humans has provided considerable evidence indicating a relationship between cardiovascular and pain regulatory systems. In particular, hypertension has been shown to be associated

with increased thresholds for nociceptive stimuli. Further evidence of changes in nociceptive thresholds in those at risk for hypertension before the onset of elevated blood pressure levels has also been reported. These results are consonant with recent findings concerning endogenous opiates and hypertension (Szilagyi, 1989), and have lead to speculation that the pain regulatory system may be implicated in the development of hypertension. A greater understanding of the relationship between these two regulatory systems may offer important insight into the etiology of hypertension. This introduction will review research investigating the phenomenon of hypertension-related antinociception and discuss potential mechanisms of an interaction between the pain and cardiovascular systems.

Hypertension and Hypoalgesia

Increased tolerance for a nociceptive stimulus has been reported in both hypertensive animals and humans with hypertension. In the animal literature, both genetic models of hypertension and experimentally-induced hypertension have been used to study this phenomenon. While most work with humans has involved subjects with established essential hypertension, a few studies have examined tolerance for noxious stimuli in normotensive individuals with experimentally-induced increases in blood pressure. Nociceptive thresholds in individuals at genetic risk for

developing hypertension have also been examined. The following sections will review each of these areas of research.

Animal Studies

Genetic Hypertension

Many studies of the relationship between hypertension and nociceptive threshold have been conducted using animals genetically predisposed to develop hypertension, in particular the spontaneously hypertensive rat (SHR) and the Dahl salt-sensitive rat. These investigations have used a variety of noxious stimuli to measure nociceptive threshold, including the hot plate test, the tail flick test, the paw pinch test, and electric footshock. The hot plate test typically involves placing the animal on a rectangular flat surface heated to a temperature of 49 to 55 degrees Celsius and measuring latency to paw-licking or jumping behavior (Maixner, Touw, Brody, Gebhart, & Long, 1982; Sitsen & de Jong, 1983; Tsai & Lin, 1987; Wendel & Bennett, 1981; Zamir & Segal, 1979; Zamir, Simantov, & Segal, 1980). In the tail flick paradigm, the animal's tail is immersed in 50 degree Celsius water and latency to tail-flick withdrawal is recorded (Saavedra, 1981; Wendel & Bennett, 1981). The paw pinch task involves the application of a constantly increasing force to the hind paw, with grams of force necessary to elicit struggle or withdrawal of the paw being the dependent measure (Zamir et al., 1980). Finally, in the

electric footshock procedure, the animal is placed on an electrified grid floor and the number of microamperes required to elicit a run, jump, or a flinch response is recorded (Sitsen & de Jong, 1983).

The most commonly used model in animal studies of the relationship between hypertension and nociceptive threshold is the SHR model of hypertension. In one of the earliest studies, Saavedra (1981) compared responses to the tail flick test in SHR and age-matched controls from two normotensive strains (genetically similar Wistar-Kyoto and genetically dissimilar Sprague Dawley rats) between the ages of four and 24 weeks. A significantly longer latency to tail flick was evident in SHR compared to controls at all age levels. Wendel and Bennett (1981) examined the relationship between blood pressure and nociceptive threshold in SHR using both the hot plate and tail flick procedures. SHR between the ages of 30 and 55 days demonstrated significantly longer latencies to respond to the nociceptive stimuli than age-matched Wistar-Kyoto control rats. After the age of 55 days, response latencies demonstrated by SHR decreased until by the age of 70 days there was no significant difference between the groups. As a second control group, Sprague Dawley rats were also tested on the hot plate procedure and exhibited jump latencies that did not significantly differ from those of the Wistar-Kyoto rats. Maixner and colleagues (1982) also found significant

differences when comparing SHR and Wistar-Kyoto rats at four and 16 weeks of age on the hot plate test, with SHR demonstrating a longer latency to paw-licking or jumping behavior than their age-matched controls. Sitsen and de Jong (1983) compared SHR to Wistar-Kyoto controls between three and 12 weeks of age using both the hot plate and electric foot shock paradigms. Evidence of an increased nociceptive threshold in SHR compared to control animals was observed for both types of noxious stimuli--SHR had a significantly longer response latency to the hot plate test, and significantly more "no responses" and significantly fewer "flinch responses" to the electric foot shock procedure. Finally, using the hot plate task, Tsai and Lin (1987) also found a significantly longer latency to hind paw lick in SHR compared to age-matched Wistar-Kyoto controls.

Employing a different animal model of hypertension, Friedman, Murphy, Persons, and McCaughran (1984) studied nociceptive threshold using male Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats. In a 2 x 2 design, DS and DR animals were compared on their responses to the tail flick and electric foot shock tests after half of each group had been placed on a high-salt diet. DS rats on the high salt diet developed significantly higher mean blood pressures than each of the remaining groups. In addition, DS hypertensive rats demonstrated a significantly longer latency to tail flick withdrawal and showed a tendency for

longer latencies on the electric foot shock procedure than DS rats on the low salt diet or either group of DR rats.

Finally, Zamir and colleagues (1980) examined nociceptive thresholds for the hot plate and paw pinch tasks in three related strains of rats: (1) a parent strain of SABRA rats, (2) a descendent strain of rats prone to developing hypertension by DOCA-salt treatment (H), and (3) a descendent strain resistant to developing hypertension by DOCA-salt treatment (N). In DOCA-salt treatment, elevated blood pressure levels are induced by performing a unilateral nephrectomy, administering deoxycorticosterone acetate subcutaneously, and restricting fluid intake to a 0.9% saline solution (Sitsen & de Jong, 1983; Tsai & Lin, 1987; Zamir et al., 1980). Systolic and diastolic blood pressure levels of H rats were significantly higher than those of N and SABRA rats. Interestingly, both H and N rats were significantly less responsive to both types of noxious stimuli than the parent SABRA strain.

In sum, animal studies using various models of hypertension provide compelling evidence of an increased nociceptive threshold in hypertensive rats genetically predisposed to develop the disorder. These results have been consistently found using various genetic models of hypertension as well as a variety of nociceptive stimuli.

Experimentally-Induced Hypertension

Another line of investigation has focused on whether

elevated nociceptive thresholds are evident in rats with experimentally-induced hypertension. Although early studies reported results consistent with the findings in animals genetically predisposed to develop hypertension, more recent investigations have produced equivocal findings.

In one early study of this phenomenon, Dworkin, Filewich, Miller, Craigmyle, and Pickering (1979) utilized a procedure that produces transient hypertension. After Sprague-Dawley rats were trained to run on a treadmill to escape aversive stimulation of the trigeminal nerve, the rats were infused with phenylephrine, a peripheral vasoconstrictor, to induce transient hypertension. Escape behavior (running) decreased on phenylephrine versus saline-infusion days, leading the authors to speculate that experimentally-elevated blood pressure could also produce the increased nociceptive threshold present in genetically hypertensive rats. More recently, another research group has also reported that phenylephrine infusion leads to an increased latency to tail flick (Randich & Hartunian, 1983; Randich & Maixner, 1984).

In contrast to the phenylephrine procedure, most investigations of the effects of experimentally-induced hypertension have utilized methods which produce sustained elevations in blood pressure. One common technique used to induce hypertension in animals is the DOCA-salt treatment described above (Sitsen & de Jong, 1983; Tsai & Lin, 1987;

Zamir et al., 1980). Alternatively, elevated blood pressure levels may be induced by surgical application of a silver clip to a renal artery, which partially occludes blood flow and induces renal artery stenosis (Sitsen & de Jong, 1983; Tsai & Lin, 1987; Zamir & Segal, 1979; Zamir et al., 1980).

Using the renal clip procedure, Zamir and Segal (1979) compared paw lick latency to the hot plate test in renal hypertensive rats (Hebrew University strain) and two groups of control animals. One control group was sham-operated without renal clip application, while the other group had the left renal artery completely blocked following application of the clip, resulting in complete atrophy of the left kidney and no elevation in blood pressure. Blood pressure and paw lick latencies did not differ among groups before surgery. After surgery both control groups remained within a normal paw lick latency, while the experimental group demonstrated a significant increase in blood pressure and in latency to paw lick. In a further study, this group investigated the effects of both renal clip and DOCA-salt hypertension (Zamir et al., 1980). Results again revealed significantly longer latency to paw lick on the hot plate test in the renal hypertensive rats compared to control animals with a completely blocked renal artery. In addition, renal hypertensive rats tolerated a significantly greater mean threshold force before struggle or withdrawal of the paw on the paw pinch test than their normotensive

controls. Among the animals with DOCA-salt induced hypertension, a significantly longer latency to paw lick on the hot plate test was seen in those with severe hypertension, while animals with more moderate levels of hypertension had latencies similar to the control animals.

However, more recently, Sitsen and de Jong (1983) failed to demonstrate any differences in response to either the hot plate or electric foot shock procedures when they compared rats with experimentally-induced hypertension (using either the renal clip or DOCA-salt methods) to their appropriate sham-operated controls. Similar negative findings were reported by Tsai and Lin (1987) when they compared rats with renal clip or DOCA-salt hypertension and control animals with a completely blocked renal artery on response to the hot plate procedure.

As can be seen, findings involving animals with experimentally-induced elevations in blood pressure have been less consistent than results reported with genetic models of hypertension. Phenylephrine infusion has been found to lead to elevated nociceptive thresholds. However, the very brief nature of this type of induced hypertension may make it a poor model for understanding changes occurring with chronic elevations in blood pressure levels. In studies which have used induction techniques leading to chronic hypertension, only one research group has consistently found significant results. While Zamir and

colleagues have reported elevated nociceptive thresholds for a variety of noxious stimuli using both renal clip and DOCA-salt techniques, other researchers have been unable to replicate these findings.

Genetic Risk for Hypertension

The mixed findings of studies using animals with experimentally-induced hypertension suggests that an elevated blood pressure level per se may not be sufficient to reliably produce change in nociceptive threshold. In contrast, the highly convergent findings reported by investigators studying SHR suggests that some factor related to being at genetic risk for developing hypertension may play an important role in the relationship between blood pressure and antinociception. The notion that genetic risk for hypertension is an important factor in this relationship is further supported by evidence from investigations using young SHR.

In one of the first studies, Saavedra (1981) noted that differences in latency to tail flick withdrawal from a thermal stimulus in SHR versus age-matched controls were evident as early as three weeks of age, prior to any pronounced differences in blood pressure. Wendel and Bennett (1981) also noted that SHR in their study demonstrated longer response latencies on hot plate and tail flick tests than controls as early as 30 days of age, while significant elevations in blood pressure were not observed

for at least another ten days. Maixner and colleagues (1982) demonstrated hypoalgesia in response to the hot plate test in SHR at four weeks of age, when blood pressure levels did not differ from age-matched controls. Finally, Sitsen and de Jong (1983) reported the presence of hypoalgesia in response to the tail flick and electric foot shock tests in SHR at the age of three and a half weeks, before elevated blood pressure levels had developed.

Another attempt to examine the role of genetic predisposition to hypertension separate from elevated blood pressure levels was made by Friedman and colleagues (1984) in their study of Dahl salt-sensitive (DS) and salt-resistant (DR) rats. These researchers analyzed their data using resting blood pressure level as a covariate when comparing the effects of diet and strain on nociceptive threshold. They found no significant main or interaction effects after the effect of blood pressure had been partialled out. The authors therefore argued that the increased nociceptive threshold exhibited by DS/high salt rats was attributable solely to higher blood pressure levels. However, the control of blood pressure for these analyses was only statistical in nature. It would have been interesting if some blood pressure lowering agent had been given to the DS/high salt rats to see if their lower pain sensitivity was indeed due solely to the effect of blood pressure or to some interaction between genetic and dietary

risk.

Finally, Zamir and colleagues' (1980) findings regarding SABRA, H and N rats are also of note. In this instance, H and N rats were both less responsive to noxious stimuli than the parent SABRA strain, although only H rats had elevated blood pressure levels. These group differences provide further support for the hypothesis that genetic factors related to blood pressure may influence nociceptive threshold independent of current blood pressure level.

Thus, results from animal studies concerning hypertension-related antinociception are consistent with the notion of a link between the cardiovascular and pain regulatory systems. Further, findings of elevated nociceptive thresholds in normotensive animals genetically predisposed to hypertension, as well as inconsistent results in animals with experimentally-induced elevated blood pressure, suggest that blood pressure level per se is not the determining factor in hypertension-related hypoalgesia. Additional evidence from studies with human subjects that support the possibility of a link between the pain and cardiovascular systems will be reviewed next.

Human Studies

Established Hypertension

Although few in number, human studies have consistently confirmed the presence of an increased threshold for pain in individuals diagnosed with essential hypertension as

compared to normotensive controls. The pain stimulus most commonly utilized in these studies has been graded electrical stimulation of tooth pulp (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Rosa & Ghione, 1990; Rosa et al., 1988; Rosa, Ghione, Panattoni, Mezzasalma, & Giuliano, 1986; Zamir & Shuber, 1980). Tooth pulp contains only A-delta and C fibers and is thought to represent an exclusively nociceptive system (Ghione et al., 1988; Zamir & Shuber, 1980). In this procedure, a probe from a commercial non-invasive tooth pulp tester is applied to the tip of the tooth. Automatic intermittent bursts of electrical stimulation are applied to the tooth pulp in stepwise increments. Most typically, four healthy unfilled teeth (two incisors and two bicuspids) are tested and results are averaged across trials. Subjects are asked to indicate sensory and pain thresholds.

Using the tooth pulp stimulation procedure, Zamir and Shuber (1980) compared males diagnosed with essential hypertension and normotensive male controls on sensory and pain thresholds. Hypertensive males were found to have significantly higher sensory and pain thresholds for this pain task. In addition, a significant positive correlation was seen between both thresholds and systolic and diastolic blood pressure levels. In a series of investigations (Ghione et al., 1988; Ghione et al., 1985; Rosa et al., 1986), Ghione and colleagues have also examined sensory and

pain thresholds for tooth pulp stimulation. These researchers have compared responses of both established and borderline hypertensive subjects with a variety of control groups, including volunteers from hospital staff, medical students, and non-hypertensive outpatients. Although both genders were included in these studies, the majority of subjects were male. This series of investigations revealed that elevated sensory and pain thresholds are present not only in well-established hypertensives, but also in individuals with borderline hypertension. Ghione's group (1988) also reported a significant correlation between mean arterial pressure and both sensory and pain thresholds. These findings have also been generalized to a different pain task, with higher threshold and tolerance levels for painful thermal stimulation applied to the forearm reported for essential hypertensive subjects than controls (Maixner, 1991; Sheps et al., 1992).

Thus, studies with human hypertensive subjects are consistent with findings reported in the animal literature. Individuals diagnosed with essential hypertension, as well as those with borderline hypertension, report higher sensory and pain thresholds for at least two types of painful stimuli in comparison with a number of control groups.

Acute Hypertension

As in the animal literature, a few investigators have attempted to determine whether this hypoalgesic response can

be demonstrated in subjects who have experimentally-induced elevations in blood pressure. For obvious ethical reasons, the available studies have examined only the effects of short-term, reversible elevations in blood pressure.

In order to produce phasic increases in blood pressure in their sample of normotensive males, Larbig, Elbert, Rockstroh, Lutzenberger, and Birbaumer (1985) administered norfenefrin, an alpha-sympathomimetic drug with peripheral vasoconstrictive effects. Pain tolerance was measured as the latency until the subject terminated an electrical shock applied to the left calf. Using a placebo-controlled, double-blind, within-subject design, they found that subjects who reached the highest blood pressure levels following the drug injection showed increases in pain tolerance, while subjects who did not reach such extreme blood pressure levels following injection did not demonstrate an increased pain tolerance on norfenefrin versus placebo trials. The authors noted that for their sample, absolute blood pressure level achieved, rather than amount of change in blood pressure, determined whether the hypoalgesic response was observed. They therefore speculated that the hypoalgesic effect may have been limited to borderline hypertensive subjects who already had somewhat elevated baseline blood pressure levels.

Another procedure which produces reversible increases in resting blood pressure (e.g., Falkner & Kushner, 1990;

Mascioli et al., 1991) and blood pressure reactivity to stress (e.g., Haythornthwaite, Pratley, & Anderson, 1992; Miller & Friese, 1992) is dietary sodium loading. Using a within-subject design, Ditto, Edwards, Miller, D'Antono, and Blum (1993) studied the effect of increased dietary intake of sodium on pain tolerance in normotensive males. Subjects were compared on their responses to a cold pressor task following two weeks of sodium loading (daily increase of 10 g of salt to normal diet) and following two weeks of normal diet. Testing during the sodium loaded session revealed significantly greater diastolic blood pressure responses to the pain stimulus as compared with the control (normal diet) testing session. In addition, significantly lower pain ratings were associated with the increased diastolic blood pressure levels.

It is interesting to note that although the first study discussed (Larbig et al., 1985) attempted to examine whether experimentally-induced elevations in blood pressure would produce hypoalgesia, the results could be interpreted in terms of genetic risk for hypertension. That is, the investigators pointed out that the effects were primarily limited to individuals with pre-existing elevations in blood pressure. In regards to the second study (Ditto et al., 1993), while offspring of hypertensives were not tested, it is interesting to speculate if, like Dahl salt-sensitive rats, they might have displayed greater reductions in pain

sensitivity.

Genetic Risk for Hypertension

As in the animal literature, there is growing interest in the possibility that genetic risk for hypertension, rather than prevailing blood pressure level, is an important factor in hypertension-related hypoalgesia. Preliminary work in this area has focused on assessing pain thresholds in treated hypertensives, as well as in normotensive individuals at risk for the development of hypertension.

In a follow-up of their comparison of pain thresholds in hypertensive subjects and normotensive controls, Ghione and colleagues (1988) reassessed a subgroup of their hypertensive sample after three months of beta-blocker (n=7), diuretic (n=7), or sodium restriction (n=11) treatment. Despite significant reductions in arterial blood pressure, no significant changes were seen in sensory or pain thresholds for electrical tooth pulp stimulation. These findings support the notion that blood pressure level per se is not the mechanism responsible for hypertension-related hypoalgesia. However, with this study design it is unclear whether the original elevations in blood pressure were necessary to establish the increases in pain threshold. In order to truly assess the importance of pre-morbid risk for hypertension independent of elevated blood pressure, subjects must be tested prior to their development of the disorder.

Research examining whether a relationship between the cardiovascular and pain regulatory systems can be demonstrated in subjects at risk for developing hypertension is obviously more difficult with human subjects than with animals. In animal research, rats can be selectively bred to the point where the development of hypertension is a virtual certainty. In addition, confirmation of whether an animal at risk actually develops the disorder can be obtained within a short time. However, it is much more difficult to positively identify humans who will later develop hypertension. Several research designs have been used in an attempt to define a subject population that is truly at risk. One method has been to study normotensive individuals who are at risk for hypertension by virtue of elevated resting blood pressure or elevated blood pressure reactivity (Peart, 1983). An alternative has been to look at normotensive individuals who are at increased risk of developing hypertension due to a family history of the disorder (Feinleib, 1979). As in the animal literature, preliminary studies have yielded results which suggest that genetic risk for hypertension does play a role in hypertension-related hypoalgesia.

A number of previously described studies can be interpreted as providing some preliminary support for the notion that risk for hypertension is an important factor in this phenomenon. Investigations which have found that

borderline hypertensive subjects have elevated pain thresholds (Ghione et al., 1988; Larbig et al., 1985; Rosa et al., 1986) could be construed as evidence that hypoalgesia precedes the development of established hypertension. Other studies have attempted to more specifically assess the relationship between risk for hypertension and pain sensitivity in humans using individuals with elevated resting blood pressure levels that are not yet within the borderline hypertensive range. Rosa and colleagues (1988) related pain sensitivity with resting blood pressure levels and blood pressure reactivity in a small sample (n=10) of normotensive subjects. Blood pressure was assessed at rest and during a cold pressor stressor task. Subjects were categorized as having a high or low pain threshold based on their pain ratings in response to electric tooth pulp stimulation. Subjects with a high pain threshold had significantly higher diastolic blood pressure levels during the cold pressor task, as well as a tendency towards higher resting diastolic blood pressure levels. Using a larger sample of 60 normotensive males, Bruehl, Carlson, and McCubbin (1992) assessed resting blood pressure levels and pain ratings for a finger pressure pain task. Pain tolerance was assessed using a modification of the Forgione-Barber Finger Pressure Stimulator. Mean resting systolic blood pressure was found to be significantly negatively correlated with pain intensity

ratings throughout the one-minute pain task, although no significant relationship was seen between pain ratings and resting diastolic blood pressure. More recently, these researchers provided evidence that resting systolic blood pressure is a predictor of pain sensitivity to the cold pressor task in normotensive males (McCubbin & Bruehl, 1994). Thus, these studies support the notion that risk for hypertension by virtue of higher resting blood pressure or greater blood pressure reactivity may be associated with elevated pain thresholds.

Only two studies to date have attempted to examine this phenomenon in individuals at risk for hypertension due to a family history of the disorder. In their large study with multiple control groups, Ghione and colleagues (1988) included an analysis of pain ratings for electric tooth pulp stimulation for normotensive individuals who had a parental history of hypertension. No significant differences in pain ratings were found between normotensives with and without a self-reported parental history of hypertension. However, several problems with the sample may explain their failure to find significant differences. Subjects were not selected on the basis of family history of hypertension, and there were large differences in number, age, gender, and blood pressure levels of subjects in the family history positive and negative groups. An additional shortcoming was the failure to confirm parental blood pressure status. The

second study concerning family history of hypertension was specifically designed to compare normotensive offspring with and without a parental history of hypertension (France, Ditto, & Adler, 1991). Normotensive male offspring with and without a parental history of hypertension participated in a constrictive pressure task where a thigh cuff was inflated until the subject reported the stimulus to be painful. Parental blood pressure status was confirmed by contacting the biological parents of all subjects. With this more carefully selected at-risk sample, significantly lower pain sensitivity was seen in the group with a positive parental history of hypertension. Subjects with a hypertensive parent tolerated higher levels of constrictive pressure before reporting pain and gave lower subjective pain ratings at maximum constrictive pressure than subjects with normotensive parents.

Thus, as in the animal literature, there is at least preliminary support for the notion that some factor associated with being at risk for developing hypertension may be responsible for the observed hypoalgesia. Taken together, research with both animals and humans has provided substantial evidence for an association between the cardiovascular and pain regulatory systems. Possible mechanisms by which these systems interact will be reviewed in the following sections.

Postulated Mechanisms of Hypoalgesia

At present, it is not certain how the cardiovascular and pain systems interact to produce hypertension-related hypoalgesia, nor is it clear whether this relationship is implicated in the development of hypertension. However, investigators have begun to speculate on both physiological and psychological mechanisms which could be involved.

Physiological Mechanisms

Studies examining antinociception in hypertensive subjects add to a growing literature demonstrating close links between the systems controlling cardiovascular function and pain modulation. Two possible means (which are not mutually exclusive) by which these systems may interact are elevated levels of endogenous opiates and activation of baroreceptor reflex arcs.

Endogenous Opiates

A possible link between central cardiovascular control and endogenous opiate pain regulation is not unlikely since the regional distribution of opiate-like material parallels brain nuclei known to be involved in cardiovascular regulation (Szilagyi, 1989). Central nervous system loci that these regulatory systems are known to share include the nucleus of the solitary tract and nuclei of the vagus nerve. In addition, opiate precursors and their respective opiate receptors have been localized in areas within the central nervous system that are known to participate in

cardiovascular control--including the nucleus of the solitary tract, area postrema, hypothalamus, and locus coeruleus.

Animal studies using opiate blockers have provided experimental evidence supporting the notion that the endogenous opiate system is involved in hypertension-related antinociception. Opiate blockade is expected to decrease elevated thresholds where those elevations are related to endogenous opiate involvement. Several investigators have studied the effects of naloxone, a central nervous system opiate antagonist, in animals with experimentally-induced hypertension (Zamir & Segal, 1979; Zamir et al, 1980) and in SHR (Delbarre, Casset-Senon, Delbarre, Sestillange, & Christin, 1982; Maixner et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983; Wendel & Bennett, 1981). In all instances, a bolus injection of naloxone had no significant effect on blood pressure, but decreased nociceptive thresholds to normal levels. Naloxone administered to control animals failed to alter pain sensitivity. Interestingly, administration of N-methylnaloxone bromide, a naloxone derivative that does not cross the blood-brain barrier, does not appear to affect the elevated nociceptive threshold in SHR, supporting the argument that this is a centrally-mediated phenomenon (Sitsen & de Jong, 1984).

In a related study, Tsai and Lin (1987) assessed nociceptive threshold for the hot plate test after

administration of morphine. While control animals showed a dose-related decrease in sensitivity following injection, rats with experimentally-induced hypertension and SHR demonstrated no change in sensitivity. Since biochemical assays showed a significant decrease in 5-HTP, a serotonin precursor, in the hypothalamus and brainstem of hypertensive animals, the authors speculated that lower serotonin synthesis or turnover in the brain may be responsible for these results. However, the lack of change in sensitivity to the hot plate would also be expected if the opiate receptors of the hypertensive animals were flooded with endogenous opiates, preventing further stimulation of opiate receptors. Therefore, it is unclear which mechanism best explains these findings.

Additional support for the role of endogenous opiates is found in investigations directly assessing central opiate levels in hypertensive rats and control animals. Using radio-receptor assay to assess the level of endogenous opiates, Zamir and colleagues (1980) analyzed the cervical spinal cord, medulla oblongata, pons-midbrain, hypothalamus, hippocampus, and pituitary gland of renal hypertensive rats and sham-operated controls. A significant elevation (45%) of opiate content was found in the cervical spinal cord of the hypertensive animals. This research group also assessed central opiate levels in parent SABRA and descendent H and N strains. The H and N strains were found to have

significantly higher opiate content in the cervical spinal cord, hypothalamus, and pituitary gland than the SABRA strain.

Direct assessment of the role of endogenous opiates in hypertension-related hypoalgesia in humans has been less common. However, in one of the few available studies, Rosa and colleagues (1988) found that normotensive subjects with a high pain threshold for electric tooth pulp stimulation had higher plasma beta-endorphin levels during and following a cold pressor task than normotensives with low tolerance to electric tooth pulp stimulation. As was previously mentioned, subjects with high tolerance to tooth pulp stimulation had significantly higher diastolic blood pressure in response to the cold pressor task, as well as a tendency toward higher diastolic blood pressure in basal conditions. Also, Maixner (1991) reported elevated circulating levels of beta-endorphins and diminished pain sensitivity to a thermal stimulus in his group of subjects with essential hypertension compared with normotensive controls.

Further speculation has centered on the idea that elevated levels of endogenous opiates are not only present in conjunction with essential hypertension, but that they may play a role in the development of the disorder. Support for this notion is seen in the finding that elevated nociceptive thresholds are evident prior to the development

of high blood pressure levels for both animals (Maixner et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983; Wendel & Bennett, 1981) and humans (Bruehl, Carlson, & McCubbin, 1992; France et al., 1991). Also, use of central nervous system opiate antagonists appears to affect the course of essential hypertension. Decreases in blood pressure are seen in established hypertensive SHR following prolonged continuous naloxone administration, while prolonged administration to pre-hypertensive SHR attenuates the development of hypertension in a dose-related fashion (Delbarre et al., 1982; Szilagyi, 1989).

Thus, a number of lines of investigation provide convergent support for the notion that the endogenous opiate system is involved in hypertension-related elevations in nociceptive thresholds. Parallels in central nervous system distribution exist between the cardiovascular and pain regulatory systems, and direct assessment of endogenous opiate levels in hypertensive animals and humans show evidence of higher levels than controls. Results from studies using opiate blockers and morphine also suggest that endogenous opiates are a factor in hypertension-related hypoalgesia. Since there is some evidence that these elevations in endogenous opiates are present prior to the development of hypertension, it has been speculated that the endogenous opiate system may be involved in the pathogenesis of the disorder. However, one line of investigation into

this possibility has yielded some conflicting but intriguing results (McCubbin, 1991; McCubbin, Surwit, & Williams, 1985, 1988; McCubbin, Surwit, Williams, Nemeroff, & McNeilly, 1989). In a series of studies to examine the effects of opiate antagonism on cardiovascular responses to stress, naloxone was administered to block opiate action during a mental arithmetic stress task. Normotensive male undergraduate students were categorized into three groups on the basis of their resting blood pressure. While naloxone significantly increased responses to stress in the low resting blood pressure group, no effects were seen in the mid or high blood pressure groups. This differential effect of opiate antagonism suggests different levels of opiate tone during stress in the high and low resting blood pressure groups. Absence of a response to naloxone in the high blood pressure group may be interpreted as characteristic of a preexisting state of functional opiate blockade. These findings have led McCubbin (1993) to posit the opioid theory of stress hyperreactivity and cardiovascular risk. This theory suggests that endogenous opiates have an important inhibitory role during psychological stress, and that the efficacy of this inhibitory system appears to vary with the level of blood pressure and possibly other risk factors for hypertension. Stress hyperreactors are believed to show circulatory and neuroendocrine instability that may result from hypofunction

of opioid inhibitory mechanisms, placing these individuals at increased risk for cardiovascular disease. McCubbin and colleagues (1985, 1993) further speculate that this functional opiate blockade could reflect a defect in opiate biosynthesis, a deficiency in number or sensitivity of opiate receptors, or an overproduction of an endogenous opiate antagonist. However, these possibilities seem contradictory to the findings regarding decreases in pain sensitivity associated with high blood pressure and risk for hypertension. One potential reconciliation of these findings is the possibility that individuals at risk for hypertension exhibit differential sensitivity in those opiate receptors involved in pain regulation and those involved in blood pressure regulation. Alternatively, the relative insensitivity of some receptors involved in cardiovascular regulation may lead to compensatory up-regulation of opiate production in hypertensive-prone individuals, resulting in a greater availability of endogenous opiates for pain regulation. Finally, chronically elevated levels of endogenous opiates in individuals at risk for hypertension may render ineffective systems which normally respond to an increase in opiates with a decreased pressor response.

Needless to say, further research is required before the possible role of endogenous opiates in cardiovascular regulation is fully understood. Also of note, although the

body of research examining the potential importance of this system in hypertension-related hypoalgesia is growing, the endogenous opiate system is not the only physiological mechanism which has been considered. Evidence supporting the role of the baroreceptor reflex arcs will be reviewed next.

Baroreceptor Reflexes

Another recent line of investigation has focused on the potential role of the baroreceptor reflex arcs in hypertension-related antinociception (Randich & Maixner, 1984, 1986; Zamir & Maixner, 1986). Baroreceptor arcs maintain circulatory homeostasis via peripheral receptors and central nervous system components that act on sympathetic and parasympathetic efferents to the heart and blood vessels (Randich & Maixner, 1986). The sinoaortic baroreceptor reflex arc refers to the high pressure receptors located in the walls of the carotid sinuses, the aortic arch, the carotid arteries, and the bifurcation of the brachiocephalic and subclavian arteries. These baroreceptors primarily modulate arterial blood pressure, with mechanical distention leading to an increase in afferent activity in the carotid sinus nerves and the aortic depressor nerve. Therefore, increases in arterial blood pressure result in an increase in vagal tone and withdrawal of sympathetic tone. Low pressure receptors in the heart and lungs, referred to as the cardiopulmonary baroreceptor

reflex arc, appear important for regulating body fluid balance and stimulation leads to an increase in afferent activity in the vagi. Thus, any external stimulus capable of producing increases in blood pressure may stimulate the baroreceptor pathways, leading to bradycardia and vasodilation. Researchers are examining the possibility that when elevated blood pressure stimulates the baroreceptor reflex arcs, they may in turn engage endogenous central nervous system pain inhibitory mechanisms. This effect has been examined in models of both experimentally-induced and genetic hypertension.

Experimental manipulations in rats which activate the baroreceptors by increasing blood volume and hence blood pressure have been shown to produce decreased sensitivity to nociceptive stimuli (Randich & Maixner, 1986). For example, physiological activation of the cardiopulmonary baroreceptor afferents by increased central venous pressure has been shown to increase tail-flick latency (Maixner & Randich, 1984). Also, as was previously discussed, administration of phenylephrine to Sprague Dawley rats has been shown to lead to acute increases in blood pressure as well as increases in nociceptive threshold (Dworkin et al., 1979; Randich & Hartunian, 1983; Randich & Maixner, 1984). This antinociceptive effect is correlated with the degree of reflex bradycardia, suggesting the involvement of the baroreflex (Randich & Maixner, 1986). Supporting this

hypothesis, animals with bilaterally denervated sinoaortic baroreceptors fail to demonstrate changes in nociceptive threshold following phenylephrine-induced elevations in blood pressure (Dworkin et al., 1979). Interestingly, some intact rats also fail to show an increase in nociceptive threshold following phenylephrine infusion, despite the development of profound hypertension and bradycardia (Maixner et al., 1982). Taken together, these results suggest that stimulation of baroreceptor reflex arcs may elicit changes in nociception under some conditions.

The role of the baroreflex in antinociception associated with elevations in blood pressure in SHR has also been investigated. Expansion of blood volume results in a greater increase in central blood volume in SHR than in Wistar-Kyoto control animals due to a greater resistance of systemic veins in SHR. Blood volume expansion also results in higher nociceptive thresholds in SHR, suggesting that the greater central blood volume exerts greater pressure on the baroreceptors which in turn lead to elevations in nociceptive threshold (Randich, 1986). Further evidence of the importance of the integrity of the baroreflexes in hypertension-related antinociception in SHR includes the finding that an elevated nociceptive threshold for the hot plate test in SHR is attenuated by resecting the right cervical vagus, which diminishes cardiopulmonary baroreceptor afferent input (Maixner et al., 1982).

Denervation of the right cervical vagus in Wistar-Kyoto control animals also led to significant decreases in nociceptive threshold for the hot plate task. Maixner and colleagues (1982) also lowered mean arterial blood pressure by administering hexamethonium bromide to intact SHR and Wistar-Kyoto controls, thus decreasing baroreceptor stimulation. Following the drug administration, nociceptive threshold for the hot plate task returned to normal levels in SHR and fell to below normal levels in the control animals. This study therefore provides further support for the notion that the baroreflex arcs play a role in hypertension-related hypoalgesia.

While these studies are consistent with the hypothesis that the baroreflex arcs are involved in hypertension-related antinociception, they fail to explain why individuals at risk for hypertension would show an increase in nociceptive threshold prior to the development of elevated blood pressure levels. However, preliminary research with human subjects suggests one possibility. France and colleagues (1991) propose that individuals at risk for the development of hypertension may have enhanced baroreflex activity during painful stimulation, a hypothesis which is certainly consistent with the large literature indicating greater blood pressure responses to stress in offspring of hypertensive versus normotensive parents (e.g., Ditto, 1986; Gintner et al., 1986; Hastrup et al., 1982;

Jorgensen & Houston, 1981; Manuck et al., 1985). Results from a recent study by Elbert, Rockstroh, Lutzenberger, Kessler, Pietrowsky, and Birbaumer (1988) provide some support for this notion. The effects of mechanical stimulation of the carotid sinus baroreceptors on pain threshold was examined in normotensive and borderline hypertensive subjects. Baroreceptor activity was manipulated by varying the external cervical pressure within a cuff around the neck. Negative external cervical pressure would be expected to produce a stretching of the carotid sinus, and hence an increase in baroreceptor activity. Results indicated that baroreceptor stimulation produced elevated pain thresholds for electrical shock applied to the forearm, but only in the borderline hypertensive group. Since this group is at risk for developing hypertension by virtue of their elevated resting blood pressure levels, these results are consistent with the notion that baroreflex stimulation may be preferentially related to hypoalgesia among individuals at risk for hypertension. France and colleagues (1991) further examined this possibility in their study of normotensive offspring of hypertensives. As discussed earlier, risk for hypertension by virtue of a parental history of the disorder was associated with a higher pain threshold for a constrictive leg cuff task. In addition, the effect of baroreflex stimulation on pain threshold was assessed using the method of mechanical

manipulation of the carotid sinus baroreflex. As opposed to the findings reported by Elbert and colleagues (1988), baroreflex stimulation failed to elicit significant differences in pain sensitivity in either group. One possible limitation of this strategy, however, is the fact that the stretching of the carotid sinus baroreceptors produced in this manipulation is an unknown function of both the external negative pressure and the internal pressure produced by blood flow. Non-invasive assessment of baroreflex activity and sensitivity could be useful in the study of this effect.

As can be seen, there is a growing body of literature supporting the hypothesis that the baroreceptor reflex arcs play an important role in hypertension-related hyperalgesia. Activation of the baroreceptors has been shown to lead to decreased sensitivity to noxious stimuli and this effect can be abolished by denervation of the baroreceptors. Thus, at least two potential physiological mechanisms for hypertension-related hypoalgesia have been identified. The next section will briefly discuss how these mechanisms have also been postulated to play a joint role in the etiology of hypertension.

Pathophysiological Implications

Findings implicating the endogenous opiate system and the baroreceptor system in hypertension-related analgesia have led to speculation that these systems are jointly

involved in the development and course of hypertension. Some researchers have hypothesized that the endogenous opiate system may be involved in the etiology of hypertension via actions on the baroreflexes. Szilagyi (1989) notes that opiate administration has been shown to blunt the baroreflex response in both animal and human subjects. To examine the role of the endogenous opiate system in baroreceptor reflex function, Szilagyi evaluated baroreceptor reflex sensitivity in hypertensive and normotensive rats before and after administration of naloxone or naloxone methylbromide. As expected, hypertensive rats showed a tendency for baroreflex sensitivity to be reduced compared to normotensive animals under baseline conditions. Administration of naloxone significantly increased baroreflex sensitivity in both groups, indicating that endogenous opiates can suppress the baroreflex. This action appeared to be central in origin, since naloxone methylbromide had no effect on baroreflex sensitivity. Importantly, naloxone produced these effects on baroreflex sensitivity in the absence of any changes in baseline blood pressure or heart rate. Thus, Szilagyi's findings support the contention that centrally acting endogenous opiates can modify baroreceptor reflex function in both normal and hypertensive states, and that they may be a factor in the baroreceptor resetting process that occurs in the hypertensive condition. It is interesting to note

that the suppression of a reflex which operates to reduce stress-induced elevations of blood pressure could be viewed as an adaptive response for an animal that is under prolonged or frequent stress. Indeed, SHR have often been viewed as animals that are maintaining constant defense responses (Folkow, 1982).

A somewhat different perspective is offered by several others (Dworkin et al., 1979; Randich & Maixner, 1984). These researchers speculate that essential hypertension is a reinforced, conditioned autonomic response to environmental stressors. As Maixner (1991) outlines in a recent paper, the proposed model speculates that aversive environmental stimuli lead to increases in blood pressure which stimulate the baroreceptor pathways and the endogenous opiate system. As a result, the perceived unpleasantness of the aversive environmental stimuli is diminished. Furthermore, according to laws of conditioning, this pairing of acute elevations in blood pressure with diminished perception of unpleasantness of aversive environmental stimuli would lead to the acquisition of more enduring forms of hypertension such as essential hypertension. That is, baroreceptor stimulation and hypertension may produce "rewarding" properties to the organism under stress, and repeated pairings of stress and acute pressor responses may lead to more enduring forms of hypertension (Zamir & Maixner, 1986).

While it is interesting to speculate that the

endogenous opiate system and the baroreflexes may be jointly involved in the development of hypertension, further research is needed to determine their role in the etiology of the disorder, as well as to ascertain the exact role that either may play in the phenomenon of hypertension-related hypoalgesia. While the discussion thus far has focused on potential physiological mechanisms by which this antinociception might occur, it is also important to consider the potential role that psychological factors may play in this relationship.

Psychological Mechanisms

Personality factors such as suppressed anger and hostility have long been thought to be correlates of hypertension (e.g., Alexander, 1939). Some researchers are now speculating that psychological factors may also be related to hypoalgesia associated with hypertension. In particular, potential differences in coping style between normotensive individuals and individuals who are hypertensive or at risk for hypertension is a topic which is beginning to receive research attention. A small body of research has linked a repressive coping style with increased pain tolerance (Davidson & Bobey, 1970; Jamner & Schwartz, 1986). In addition, a few investigators have shown that hypertensive individuals (Cumes, 1983; Kahn, Medalie, Neufeld, Riss, & Goldbourt, 1972; McClelland, 1979) and their offspring (Baer, Vincent, Williams, Bourianoff, &

Bartlett, 1980; Semenchuk & Larkin, 1993) have a greater tendency to exhibit a repressive coping style. Therefore, the argument has been made that hypertension-related hypoalgesia may be related to a repressive coping style.

While a variety of personality factors have been postulated to play an important role in pain tolerance, repressive coping style has received the most attention with respect to hypertension-related hypoalgesia. In this literature, repression and defensiveness are conceptualized as a form of self-deception which is characterized by an avoidance of self-monitoring (Jamner & Schwartz, 1986). For instance, repressors deny feelings of anxiety in situations where their behavioral and physiological responses indicate otherwise (Weinberger, Schwartz, & Davidson, 1979). Repressors are thought to consistently avoid disturbing cognitions across a variety of situations by utilizing avoiding, denying, and repressing behaviors in response to threatening stimuli, including painful stimuli (Davidson & Bobey, 1970). Thus, this coping style allows the individual to reduce conscious awareness of painful and/or unpleasant experiences.

A variety of different instruments have been used to assess repressive coping tendencies. Scales which have been used to identify repressors typically consist of statements judged to be both universally true and psychologically threatening to respondents (Jamner & Schwartz, 1986).

Individuals with repressive coping styles tend to respond with false negatives to these types of items. That is, these individuals have high rates of denying statements universally judged to be psychologically threatening, and also report experiencing little distress or negative emotion in everyday situations.

Using different methods to operationalize repressive coping style, Davidson and Bobey (1970) and Jamner and Schwartz (1986) both found a higher pain tolerance among repressors than control subjects. Davidson and Bobey (1970) divided their sample of female students into two groups based on their scores on the Repression-Sensitization Scale, a measure derived from the Minnesota Multiphasic Personality Inventory. Assessment of pain tolerance included a radiant heat stimulus and a pressure stimulus applied to each subject's hand. The repressive coping group showed a higher pain tolerance than the sensitizers on first exposure to either type of pain stimulus. In contrast, Jamner and Schwartz (1986) used the Lie Scale of the Eysenck Personality Inventory to differentiate their subjects into High, Moderate, and Low Deceptive groups. Electrical stimulation was applied to the forearm in ascending steps of 0.1 mA until sensory threshold was reached, then continued in 0.3 mA increments until the subject indicated uncomfortable, painful, and tolerance thresholds. While the three groups did not differ in sensation threshold, the High

Deceptive group permitted significantly higher levels of shock than the Low Deceptors before reaching discomfort, pain, and tolerance levels. Thus, repressors identified using two different screening methods have been shown to have elevated pain thresholds.

In addition to being related to greater pain tolerance, repressive coping style has also been associated with the occurrence of hypertension. As in the pain tolerance literature, more than one method has been used to identify individuals with a repressive coping style. For instance, Cumes (1983) assessed degree of self-disclosure using a checklist of personal concerns. Results indicated that subjects with elevated blood pressure levels disclosed significantly fewer personal concerns than normotensive subjects. At least two investigations have employed a longitudinal design to investigate whether a repressive coping style is associated with increased risk for developing hypertension. Kahn and colleagues (1972) conducted a five-year prospective study which assessed 10,000 Israeli male civil service workers aged 40 and older. Interview data suggested that subjects who tended to restrain or repress feelings in response to conflict situations had a greater incidence of elevated blood pressure readings at subsequent testings. McClelland (1979) also found that his hypertensive-prone group had an increased tendency to use repressive coping. This study

investigated the potential role of suppressed anger in the development of essential hypertension. Results indicated that male subjects who tended to suppress anger when they were assessed in their early thirties were significantly more likely to have elevated diastolic blood pressure levels 20 years later. Suppressed anger predicted later elevated diastolic blood pressure even when the possible contribution of an earlier physiological predisposition was controlled by a multiple regression analysis. There is also suggestive evidence that offspring of hypertensives may show a greater propensity to use repressive coping strategies in times of conflict. Baer and colleagues (1980) videotaped family units (father, mother, and child) interacting under standardized conflict conditions. Behaviors exhibited by each family member were then coded into four categories: positive verbal, positive non-verbal, negative verbal, and negative non-verbal. Children of hypertensive fathers were found to exhibit significantly more negative non-verbal behavior under conditions of disagreement or conflict than children with normotensive fathers. The authors argue that these results are consistent with the hypothesis that there is a decreased self-awareness of negative attitudes in the offspring of hypertensives compared to those of normotensives. Semenchuk and Larkin (1993) used a similar behavior coding strategy with college-age males with or without hypertensive parents. Subjects were required to

self-report positive and negative cognitions and emotions that occurred during an interpersonal conflict situation with a confederate. Results indicated that offspring of hypertensives showed more negative verbal and non-verbal behavior than offspring of normotensives, yet their self-reports of negative cognitions and emotions did not differ. These findings were interpreted by the authors as indicating that offspring of hypertensives were utilizing repressive coping. Finally, Jorgensen, Gelling, & Kliner (1992) have identified two subgroups of male offspring of hypertensives which differ in their acknowledgment of angry feelings, overt expression of anger, and defensiveness. The subgroup that exhibited a high need for approval and low anger acknowledgement received higher scores on measures of denial but lower scores on angry temperament and overt anger expression than males with a parental history of hypertension who had low need for approval and high anger acknowledgment. Similar results were found when comparing the high approval/low anger acknowledgement subgroup with male offspring of normotensives. Of further interest, the high approval/low anger acknowledgement subgroup showed significantly greater blood pressure reactivity to laboratory stressors than either of the other two groups. These results suggest that although a repressive coping style may not be evident in all offspring of hypertensives, when present it appears to be related to cardiovascular

reactivity and may play an important role in the development of hypertension.

Thus, these lines of research provide suggestive evidence that a repressive coping style may be associated with hypertension-related hypoalgesia. Further, evidence from longitudinal studies and from research with offspring of hypertensives suggests that repressive coping may predate the development of hypertension, and may be a factor in the etiology of the disorder.

Limitations of the Existing Research

Research with animals and humans has provided evidence that there are changes in nociceptive threshold which accompany the condition of hypertension. Studies of subjects at genetic risk for hypertension appear to indicate that these changes in nociception are present prior to the development of the disorder. However, only a small number of studies have been conducted with human subjects at risk for developing hypertension, and only two studies have been reported where family history of the disorder was the criterion for establishing risk status. Thus, there are a number of issues which remain to be addressed concerning differences in nociception in individuals at risk for hypertension.

One limitation of the existing research is that this phenomenon has been studied using only a few specific

laboratory-type pain tasks. Therefore, it is unclear whether this antinociception generalizes to other types of laboratory pain stimuli, or whether the effect can be demonstrated in response to naturalistic or clinical pain. In addition, the few existing studies have used subject groups which were predominantly or exclusively male. As a result, it is not clear whether elevated pain thresholds are present in normotensive females at risk for the development of hypertension. Finally, potential mechanisms which may be responsible for this effect have not yet been positively identified. Both physiological and psychological mechanisms which may mediate this response require further study.

The series of studies presented here examined the hypothesis that genetic risk for hypertension by virtue of a parental history of the disorder is associated with decreased pain sensitivity. These studies attempted to address existing shortcomings in this research area in the following ways. First, in order to address the gender issue, each of the three studies focused on female subjects at risk for the development of hypertension. Second, a variety of pain tasks were used, including both naturalistic and laboratory pain stimuli, in an effort to determine whether the effect would generalize across different types of pain. Specifically, Study One and Study Two examined sensitivity to two different types of naturalistic pain, while Study Three included two laboratory pain tasks.

Third, to provide further information regarding the potential role of psychological mechanisms, each study included assessment of psychological factors which could mediate the relationship between hypertension and hypoalgesia. Finally, to further examine two possible physiological mechanisms which may play a role in hypertension-related hypoalgesia, Study Three included measurements which could reflect baroreceptor stimulation and sensitivity as well as the phenomenon of stress-induced analgesia.

STUDY 1

As was previously reviewed, animal studies (Friedman et al., 1984; Maixner et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983; Tsai & Lin, 1987, Wendel & Bennett, 1981; Zamir & Segal, 1979; Zamir et al., 1980) and research with humans (Ghione et al., 1988; Maixner, 1991; Rosa et al., 1986; Zamir & Shuber, 1980) have confirmed the presence of elevated pain thresholds in subjects with established hypertension. Further, the failure to consistently demonstrate elevated nociceptive thresholds in animals with experimentally induced hypertension (Sitsen & de Jong, 1983; Tsai & Lin, 1987) and evidence of changes in nociceptive threshold in young SHR prior to the development of elevated blood pressure (Maixner et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983; Wendel & Bennett, 1981) have led to speculation that some factor associated with being at genetic risk for hypertension may be more important in this relationship than prevailing blood pressure levels. Although little research has been conducted using human subjects at risk for hypertension, there is at least preliminary support for the notion that genetic risk for hypertension is an important factor in this hypoalgesia. For instance, normotensive males with high resting blood pressure have been shown to have decreased pain sensitivity compared to those with lower resting levels (Bruehl, Carlson, & McCubbin, 1992; McCubbin & Bruehl, 1994). In

addition, France and colleagues (1991) reported that normotensive males at risk for hypertension due to a parental history of the disorder had an elevated pain threshold for a constrictive leg cuff task compared to male offspring of normotensives.

The present study was designed to further examine the relationship between risk for hypertension and decreased pain sensitivity. Since previous research examining pain thresholds in both subjects with established hypertension and those at risk for the disorder have relied almost exclusively on male subjects, this project studied pain sensitivity in females at risk for hypertension. In addition, since another limitation of the existing literature has been the exclusive use of laboratory pain tasks, this study focused on the experience of menstrual pain as an example of a naturalistic pain.

Menstrual pain is commonly experienced by young women. Wilson and Keye (1989) reported the occurrence of at least mild menstrual cramps for 91% of their adolescent sample. In a college-age sample, Gruber and Wildman (1987) reported 94% of respondents complained of at least mild discomfort associated with menstruation. In a larger sample, Teperi and Rimpela (1989) reported a prevalence rate for menstrual pain among 18 year-olds of 79%. Thus, menstrual pain appears to commonly occur among college-age females, and may be experienced with varying degrees of severity. This study

examined whether some of the differences in reported severity of menstrual pain among normotensive, healthy, college-age females could be accounted for by parental history of hypertension.

Other research has indicated that additional factors which may moderate the severity of menstrual pain include oral contraceptive use (Avant, 1988) and duration of menstrual flow (Teperi & Rimpela, 1989). In addition, use of analgesic medication during menstruation may alter the amount of pain experienced. Personality factors such as the general tendency to report physical symptoms, as well as the manner of responding to self-report questionnaires, may also affect menstrual pain reports.

This study assessed whether there are differences in menstrual pain reports of normotensive females with and without hypertensive parents. Menstrual symptoms and medication use were monitored on a daily basis. Personality variables assessed included the tendency to respond in a socially desirable manner, the general tendency to report physical symptoms, and hypochondriasis.

Method

Subjects

Healthy, normotensive female undergraduates were recruited to participate in the study. Subjects received credit in an introductory psychology course in return for

their participation. Confirmation of parental blood pressure history was obtained through written communication with the biological parents of each subject. Subjects whose biological parents could not be contacted were excluded from the analyses. Subjects who had at least one parent with a history of hypertension without associated diabetes or kidney disease were assigned to the parental history positive (PH+) group. Subjects with both parents reporting no history of high blood pressure, diabetes, or kidney disease were assigned to the parental history negative (PH-) group. The final sample included 81 subjects in the PH+ group and 118 subjects in the PH- group. Descriptive characteristics of each group with respect to age, body mass index, and tobacco use are displayed in Table 1. There were no significant differences between the groups on any of these variables. In addition, there was no significant difference in the percentage of PH+ and PH- subjects who were smokers (16.0% and 15.3% respectively) or oral contraceptive users (37.0% vs 27.1% respectively). The overwhelming majority of the subjects were Caucasian (93%).

Questionnaires

Wahler Physical Symptoms Inventory. The Wahler Physical Symptoms Inventory (Wahler, 1983) is a 42-item inventory used to assess the frequency of occurrence of each of a wide variety of physical symptoms on a zero to five scale. A general physical symptom score is obtained by

Table 1

Mean (M) and standard deviation (SD) of various characteristics in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	PH+ (n=81)		PH- (n=118)	
	M	SD	M	SD
Age (years)	18.86	1.82	18.87	1.33
Body Mass Index (kg/m^2)	21.55	3.08	21.01	2.44
Tobacco Use (cigarettes/day)[a]	8.58	6.75	6.94	5.15

[a]there were 13 smokers in the PH+ group and 17 smokers in the PH- group

summing ratings for all items. In addition, for this study a general pain symptom score was obtained by summing the ratings for the six painful physical symptom items. This measure provides an indication of the general tendency to report painful symptoms.

Marlowe-Crowne Social Desirability Scale. The Marlowe-Crowne Social Desirability Scale (Crowne & Marlowe, 1960) is a 33-item true-false questionnaire widely used to assess the tendency of subjects to endorse infrequent, culturally-approved behaviors. It is considered to reflect subjects' manner of responding to self-report questionnaires.

Hypochondriasis Scale of the Minnesota Multiphasic Personality Inventory (MMPI). The Hypochondriasis Scale is a 33-item subscale of the MMPI (Hathaway & McKinley, 1967). This scale was included to provide an additional assessment of subjects' tendency to report physical symptoms.

Personal and Family Health History. A brief personal and family health history questionnaire was included to assess subjects' personal health status and medication use, as well as parental history of hypertension and other physical disorders (Appendix 1).

Daily Monitoring Form for Menstrual Symptoms. An 18-symptom checklist was adapted from the Menstrual Symptom Questionnaire (Chesney & Tasto, 1975). Eight painful symptom items are included. The subject indicated the occurrence of each symptom on a zero to four scale, with

zero meaning "not at all" and four meaning "continuously". Thus, total symptom scores for each day range from zero to 72, and total pain scores from zero to 32. Space was provided to record medication use each day (Appendix 2).

Parental Hypertension Questionnaire. Each biological parent completed a brief questionnaire concerning their current and past blood pressure status, whether they were prescribed any antihypertensive medications, and whether they suffered from diabetes or kidney disease. High blood pressure was defined for the respondents as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg (Appendix 3). Previous research suggests that such self-reports are highly correlated with physicians' reports (Ditto, 1986).

Procedure

Subjects were tested in classrooms in groups of 20 to 30 individuals. When subjects arrived they were given a description of the study protocol and informed consent was obtained. Subjects were blind to the hypothesis being tested and were told that the study involved identifying patterns of menstrual symptoms. Subjects then completed a series of questionnaires including a personal and family health history questionnaire, the Wahler Physical Symptoms Inventory, the Marlowe-Crowne Social Desirability Scale, and the Hypochondriasis Scale of the MMPI. Subjects were also asked to provide addresses and/or phone numbers of their

biological parents so that confirmation of parental blood pressure status could be made. These questionnaires required approximately 45 minutes to complete.

Before leaving the group testing session, subjects were given a packet of eight daily monitoring forms to use during their next menstrual cycle. Subjects were instructed to begin symptom recording two days prior to menstruation and to continue recording until the last day of menstruation. The forms were to be filled out at the end of each day. While at the group testing session, subjects were asked to predict the date of their next menstrual cycle. Subjects were contacted by telephone two days prior to their anticipated start date to remind them to begin symptom recording. Subjects were debriefed and received credit for participating in the study when they returned their daily recording forms.

Data Reduction and Analyses

A variety of measures were derived from the daily symptom reports. Scores were calculated for the menstrual and premenstrual phases of symptom recording, with separate scores for overall symptoms and pain-specific symptoms within each phase. Overall menstrual symptom scores were calculated using all 18 items on each day of menstrual recording. A menstrual symptom index was computed by determining the average total daily symptom score for each individual. The peak menstrual symptom score was determined

by the highest daily symptom score during the menstrual phase. Finally, the percentage of menstrual days where symptoms were reported was also calculated. Three similar measures were also derived to look specifically at painful menstrual symptoms using the eight pain-related items on each day of the menstrual phase of recording. A menstrual pain index was computed by determining the average total daily score of painful symptoms, while the peak menstrual pain score was determined by the highest daily pain report during the menstrual phase. In addition, the percentage of menstrual days where at least one pain item was endorsed was calculated. Finally, similar calculations were carried out to arrive at analogous measures for the premenstrual recording days. Again, overall symptom scores (premenstrual symptom index, peak premenstrual symptom score, and percent of premenstrual days with symptoms) and pain-specific symptom scores (premenstrual pain index, peak premenstrual pain score, and percent of premenstrual days with pain) were derived.

Social desirability scores, hypochondriasis scores, general physical symptom scores, age, body mass index, and tobacco use were examined as possible correlates of the overall symptom and pain measures for the menstrual and premenstrual recording phases. The number of days of recording provided by the subjects for the menstrual and premenstrual phases were also examined as possible

correlates for their respective overall symptom and pain measures. As can be seen in Table 2, significant positive correlations were observed between all three measures of menstrual symptoms (index, peak, and percent of days with symptoms) and both hypochondriasis scores and general physical symptom scores. Similarly, menstrual pain scores (index, peak, and percent of days with pain) were significantly correlated with both hypochondriasis scores and general physical symptom scores. With respect to the premenstrual data summarized in Table 3, hypochondriasis scores and general physical symptom scores were significantly positively correlated with the premenstrual symptom index and the premenstrual peak symptom score. Hypochondriasis scores and general physical symptom scores were also significantly correlated with premenstrual pain index and premenstrual peak pain scores. In addition, percent of premenstrual days with pain was significantly correlated with social desirability. Significant correlates were included as covariates in subsequent analyses involving the symptom and pain measures.

Possible group differences in general physical symptoms or pain symptoms, or in the tendency to respond to questionnaires in a socially desirable manner were examined using a series of one-way analyses of variance (ANOVAs). Separate 2 Group (PH+, PH-) ANOVAs were conducted on the measures of social desirability, general physical symptoms,

Table 2

Correlations between subject characteristics and menstrual symptom (Symp.) and pain scores

	Symp. Index	Peak Symp.	Percent Symp. Days	Pain Index	Peak Pain	Percent Pain Days
Social Desirability	-.12	-.14	-.14	-.08	-.09	-.13
Hypo-chondriasis	.45**	.44**	.22*	.40**	.39**	.25**
Physical Symptoms	.47**	.40**	.24**	.38**	.30**	.27**
Age	.02	.03	.01	.02	.02	-.02
Body Mass Index	.02	.08	-.12	.02	.05	-.07
Tobacco Use	.04	.05	.11	.05	.05	.05
# of Days Recorded	-.04	.09	-.12	-.08	.05	-.15

*p<.01, 2-tailed

**p<.001, 2-tailed

Table 3

Correlations between subject characteristics and premenstrual symptom (Symp.) and pain scores

	Symp. Index	Peak Symp.	Percent Symp. Days	Pain Index	Peak Pain	Percent Pain Days
Social Desirability	-.16	-.16	-.16	-.12	-.13	-.23*
Hypo-chondriasis	.48**	.47**	.12	.41**	.39**	.19
Physical Symptoms	.49**	.48**	.05	.39**	.38**	.20
Age	.11	.13	.02	.08	.08	.05
Body Mass Index	.03	.05	.08	-.05	-.05	.14
Tobacco Use	.04	.05	.07	.05	.07	-.02
# of Days Recorded	-.14	-.06	-.08	-.10	-.02	-.19

*p<.01, 2-tailed

**p<.001, 2-tailed

general pain symptoms, and hypochondriasis.

Chi-square analysis was used to determine whether the groups differed in their reported use of analgesic medications during their menstrual cycle. One-way ANOVAs were conducted to examine whether the groups differed in the number of days of premenstrual or menstrual recording that they provided.

Analysis of overall menstrual symptoms was conducted using a 2 Group (PH+, PH-) x 2 Oral Contraceptive Use (Yes, No) x 2 Analgesic Use (Yes, No) multivariate analysis of covariance (MANCOVA) conducted on the measures of menstrual symptom index, peak menstrual symptom score, and percent of days with symptoms. Hypochondriasis scores, general physical symptom scores, and length of recorded menstrual cycle were included as covariates. Significant effects observed in the overall MANCOVA were examined for each of the dependent measures using equivalent univariate analyses of covariance (ANCOVAs).

Differences in menstrual pain were examined using a 2 Group (PH+, PH-) x 2 Oral Contraceptive Use (Yes, No) x 2 Analgesic Use (Yes, No) MANCOVA conducted on the measures of menstrual pain index, peak menstrual pain score, and percent of menstrual days with pain. Hypochondriasis, general physical symptoms scores, and length of recorded menstrual cycle were included as covariates. Again, significant effects observed in the overall MANCOVA were examined for

each of the dependent measures using equivalent ANCOVAs.

Similar MANCOVAs were conducted to examine premenstrual symptoms and premenstrual pain scores. A 2 Group (PH+, PH-) x 2 Oral Contraceptive Use (Yes, No) x 2 Analgesic Use (Yes, No) MANCOVA was conducted on the dependent measures of premenstrual symptom index, peak symptom score, and percent of premenstrual days with symptoms. Hypochondriasis scores, general physical symptom scores, and number of recorded premenstrual days were included as covariates. Premenstrual pain reports were examined using a 2 Group (PH+, PH-) x 2 Oral Contraceptive Use (Yes, No) x 2 Analgesic Use (Yes, No) MANCOVA on premenstrual pain index, peak premenstrual pain score, and percent of premenstrual days with pain. Hypochondriasis, general physical symptoms, social desirability scores, and number of premenstrual days recorded were included as covariates in this analysis.

Results

Self-Report Measures

One-way ANOVAs were conducted on each of the self-report questionnaires completed in the group testing session. These analyses revealed no significant differences between the PH+ and PH- groups in scores on the Marlowe-Crowne Social Desirability Scale, the Hypochondriasis Scale of the MMPI, the Wahler Physical Symptom Inventory, or on the Wahler pain-specific items. Means and standard

deviations obtained by each group on each of these measures are presented in Table 4.

Daily Recording

A chi-square analysis revealed that there was no significant difference between the PH+ and PH- groups in reported use of analgesic medications during the period of symptom recording. However, an ANOVA did reveal a significantly longer menstrual recording phase for the PH- as compared to the PH+ group [5.05 vs 4.77 days, $F(1,197)=4.01$, $p<.05$]. In addition, the PH+ group provided a significantly longer premenstrual recording period than the PH- group [1.69 vs 1.49 days, $F(1,197)=4.35$, $p<.05$]. Therefore, length of menstrual cycle was included as a covariate in the analyses of menstrual symptoms and pain, and length of premenstrual recording as a covariate in the analyses involving premenstrual symptoms and pain.

Overall Menstrual Symptoms. Hypochondriasis and general physical symptom scores, as well as length of recorded menstrual cycle were included as covariates in these analyses. Results of the 2 Group x 2 Oral Contraceptive Use x 2 Analgesic Use MANCOVA for the dependent variables of menstrual symptom index, peak menstrual symptom score, and percent of menstrual days with symptoms revealed significant main effects of Group [$F(3,184)=3.32$, $p<.05$] and Oral Contraceptive Use [$F(3,184)=3.30$, $p<.05$], as well as a significant interaction

Table 4

Mean (M) and standard deviation (SD) of psychological self-report measures in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	PH+ (n=81)		PH- (n=118)	
	M	SD	M	SD
Social Desirability	15.26	5.19	15.20	5.53
Hypochondriasis	8.70	4.95	8.28	5.07
General Physical Symptoms	36.28	19.82	35.21	19.44
General Pain Symptoms	8.56	4.10	8.46	5.20

effect of Group x Contraceptive Use [$F(3,184)=3.47$, $p<.05$]. No other significant effects were observed. Given these results, the Group, Oral Contraceptive Use, and Group x Oral Contraceptive Use effects of the comparable univariate ANCOVAs were examined.

A significant interaction effect of Group x Contraceptive Use was observed for the menstrual symptom index, $F(1,187)=8.19$, $p<.01$. Follow-up simple main effects analyses indicated that among offspring of normotensives, oral contraceptive users received a significantly higher menstrual symptom index score than subjects not using oral contraceptives [18.31 vs. 12.85, $F(1,113)=5.55$, $p<.05$]. No significant group difference in menstrual symptom index was observed between oral contraceptive users and non-users with a positive parental history of hypertension (15.28 and 15.85, respectively).

Analysis of peak menstrual symptom scores also revealed a significant interaction effect of Group x Contraceptive Use, $F(1,186)=4.57$, $p<.05$. While follow-up analyses of the simple main effects failed to find significant differences between oral contraceptive users and non-users, examination of the group means revealed that among offspring of normotensives, peak symptom scores were higher in oral contraceptive users than for non-users (29.38 vs. 25.18), while among offspring of hypertensives the opposite relationship was observed (users: 27.57, non-users: 31.51).

The follow-up ANCOVA on percent of menstrual days with symptoms revealed no significant effect of Group, Contraceptive Use, or a Group x Contraceptive Use interaction.

Menstrual Pain. Hypochondriasis and general physical symptom scores, as well as length of recorded menstrual cycle were included in these analyses as covariates. Results of the 2 Group x 2 Oral Contraceptive Use x 2 Analgesic Use MANCOVA conducted with the dependent measures of menstrual pain index, peak menstrual pain score, and percent of menstrual days with pain indicated a significant main effect of Oral Contraceptive Use [$F(3,181)=3.34$, $p<.05$], and a significant interaction effect of Group x Contraceptive Use [$F(3,181)=2.93$, $p<.05$]. No other significant effects were observed. Subsequently, the Oral Contraceptive Use and Group x Oral Contraceptive Use effects were examined in the comparable univariate ANCOVAs.

A significant interaction effect of Group x Contraceptive Use was seen for the menstrual pain index, $F(1,187)=7.21$, $p<.01$. Follow-up analyses of the simple main effects revealed that oral contraceptive users with normotensive parents reported significantly more pain than offspring of normotensives who were not using oral contraceptives [7.92 vs. 5.25, $F(1,113)=8.19$, $p<.01$]. No significant oral contraceptive effect was seen among offspring of hypertensives (users: 7.38, non-users: 7.11).

A significant interaction effect of Group x Contraceptive Use was also observed for peak menstrual pain score, $F(1,183)=7.88$, $p<.01$. Follow-up analyses of the simple main effects indicated that among offspring of normotensives, oral contraceptive users reported higher peak menstrual pain scores than individuals not using oral contraceptives [15.33 vs. 12.02, $F(1,110)=5.98$, $p<.05$]. No significant effect of oral contraceptive use was seen for offspring of hypertensives (users: 13.87, non-users: 15.22).

The ANCOVA examining percent of menstrual days with pain revealed no significant effect of Oral Contraceptive Use and no significant interaction effect of Group x Contraceptive Use.

Overall Premenstrual Symptoms. Hypochondriasis and general physical symptom scores, as well as number of premenstrual days which were recorded were included as covariates in these analyses. A 2 Group x 2 Oral Contraceptive Use x 2 Analgesic Use MANCOVA for the dependent measures of premenstrual symptom index, peak premenstrual symptom score, and percent of premenstrual days with symptoms revealed no significant main or interaction effects.

Premenstrual Pain. Hypochondriasis, general physical symptom, and social desirability scores, as well as number of premenstrual days which were recorded were included in these analyses as covariates. A 2 Group x 2 Oral

Contraceptive Use x 2 Analgesic Use MANCOVA for the dependent measures of premenstrual pain index, peak premenstrual pain score, and percent of premenstrual days with pain indicated no significant main or interaction effects.

Discussion

This study revealed a significant interaction between parental history and oral contraceptive use on reports of menstrual pain and total menstrual symptoms. This interaction reflected the fact that among subjects without a parental history of hypertension, oral contraceptive users reported greater menstrual pain and total menstrual symptoms than those not using oral contraceptives. No effect of oral contraceptive use was seen among offspring of hypertensives. These findings fail to support the hypothesis that females at risk for hypertension due to a parental history of the disorder would report less menstrual pain than females with normotensive parents. Since oral contraceptive use is generally believed to reduce menstrual symptoms (e.g., Avant, 1988; Dawood, 1985), the tendency for greater severity of symptoms among oral contraceptive users, particularly among offspring of normotensives, is somewhat unexpected. It is possible that this group was experiencing even more severe symptoms prior to using oral contraceptives. Alternatively, the failure to find lower

menstrual pain in oral contraceptive users than non-users may be due to a short history of use in these college-age subjects (Teperi & Rimpela, 1989). In any case, this study design does not attempt to assess the efficacy of hormone therapy in reducing menstrual symptoms.

No significant effects of parental history, oral contraceptive use, or analgesic medication use were found when considering premenstrual pain and total premenstrual symptoms. However, in order to enhance compliance with recording requirements, subjects were asked to record for a limited number of premenstrual days. It is not possible to determine whether group differences would have emerged if subjects had been required to record all days on which they experienced premenstrual symptoms.

These results are inconsistent with previous findings using male subjects at risk for hypertension and laboratory pain stimuli (Bruehl, Carlson, & McCubbin, 1992; France et al., 1991, McCubbin & Bruehl, 1994). They are also inconsistent with the animal literature studying nociceptive threshold in young normotensive SHR (Maixner et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983; Wendel & Bennett, 1981). There are a number of reasons why this study may have failed to find decreased pain sensitivity in females at risk for hypertension. First, hypertension-related antinociception may not be due to some factor associated with genetic risk for hypertension. Existing studies with

human subjects are few, and provide only preliminary support for this notion. Nonetheless, animal studies provide a substantial body of evidence that genetic risk is sufficient to precipitate this effect. Alternatively, the relationship between risk for hypertension and decreased pain sensitivity may be exclusive to males. However, it would be premature to dismiss the possibility that this phenomenon also exists in females at risk for hypertension based on the results of a single study.

The discrepancy between findings in males and females at risk for hypertension may also reflect differences in levels of risk between these two groups. Not all offspring of hypertensives go on to develop hypertension themselves, although they are at an increased risk for developing the disease compared to offspring of normotensives (Feinleib, 1979). In addition, males show an overall higher prevalence of hypertension than females ("Hypertension Prevalence," 1985). Although it is not certain why fewer females develop hypertension, it has been speculated that some gender difference, such as estrogen level, may offset genetic risk in women. Thus, male offspring of hypertensives may be at higher risk for the development of hypertension than female offspring.

Another factor which may have contributed to the negative findings is the choice of pain stimulus. Previous research has been limited to the study of sensitivity to a

small number of laboratory stimuli (e.g., Bruehl, Carlson, & McCubbin, 1992, France et al., 1991; Ghione et al., 1988, McCubbin & Bruehl, 1994). This study addressed the important issue of whether this effect generalizes to a naturalistic pain stimulus. However, use of menstrual pain as a naturalistic stimulus introduced potential complications which were not a concern in the previous laboratory studies. One significant drawback with the use of menstrual pain is that it does not allow for standardized administration. Obviously, pain reports will be affected not only by the differences in pain sensitivity which were of interest in this study, but also by differences in the intensity or duration of the pain stimulus itself. Variables which may influence the experience of menstrual pain such as contraceptive use, analgesic use, and length of menstrual cycle were assessed in an attempt to control for their possible confounding effects. However, the issue of shorter menstrual recording periods in women with a parental history of hypertension remains particularly problematic in interpreting the results of the present study. While a greater total number of symptoms could be predicted to be associated with longer menstrual periods, it could also be argued that symptoms may be less common as the menstrual period progresses. Thus, with their shorter menstrual periods, women with a parental history of hypertension may not have had as much opportunity to record symptom-free

days.[1] Another potential problem with this study design is that other physiological variables which are believed to contribute to the severity of menstrual pain, such as level of prostaglandins or degree of uterine muscular contraction (Avant, 1988), were not assessed and could have contributed to the variability of the data. Finally, data collection was limited to one cycle, and results may not have been representative of symptom levels averaged across multiple cycles. As can be seen, examining the experience of menstrual pain introduces a number of issues that were not a concern in the previous laboratory studies involving hypoalgesia and risk for hypertension.

An additional important consideration is the potential effect of cyclic hormonal variation on blood pressure and blood pressure reactivity to stress. To date, conflicting findings have been reported concerning the influence of the menstrual cycle on cardiovascular activity (Kaplan, Whitsett, & Robinson, 1990; Plante & Denney, 1984; Sita, Miller, Giannini, & Caruso, 1992; Stoney, Owens, Matthews, Davis, & Caggiula, 1990; Tersman, Collins, & Eneroth, 1991). Further, there are few investigations concerning possible interactions between menstrual cycle and family history of

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[1]Some support for this hypothesis was seen in the present study. Examination of mean menstrual symptom and pain scores across menstrual recording days revealed peak scores for both measures on the first day of recording, with decreasing scores on each successive day.

hypertension (Miller & Sita, 1994; Polefrone & Manuck, 1988). However, there is some evidence that menstrual cycle effects interact with parental history of hypertension such that group differences in blood pressure reactivity are most pronounced during the luteal phase prior to menstruation. For instance, Miller and Sita (1994) found that cardiovascular reactivity to stress differed between offspring of normotensives and offspring of hypertensives in the luteal phase, but not in the follicular phase. As a result, the ability to elicit a hypertension-related effect on pain sensitivity may also vary with menstrual cycle phase. Since, by definition, all subjects in the present study were assessed during menstruation, it is not possible to determine whether group differences in pain sensitivity varied according to menstrual phase.

Although the results of this study failed to support the notion that females at risk for hypertension would demonstrate decreased pain sensitivity, there were a number of potential reasons for these findings. It was believed that further study was warranted in order to gain a better understanding of the phenomenon of hypertension-related hypoalgesia and to determine whether this effect is present in females.

STUDY 2

In Study 1, assessment of pain sensitivity to a naturalistic stimulus among female offspring of hypertensives and normotensives failed to demonstrate the expected group differences. However, it was unclear whether the findings reflected an absence of this effect in females at risk for hypertension or a problem inherent in the study design. One difficulty with the previous study may have been the choice of menstrual pain as a naturalistic stimulus. Further research is needed to determine whether hypertension-related hypoalgesia does exist in females at risk for the disorder, and to discover whether this effect can generalize to naturalistic types of pain. Examination of the role of possible psychological mediating variables, such as coping style, is also necessary. In order to address these questions, Study 2 assessed pain sensitivity to venipuncture during blood donation in normotensive females with and without a parental history of hypertension.

The selection of venipuncture as the naturalistic pain stimulus resolves several of the problems inherent in Study 1. For instance, the blood donation procedure is highly standardized so that each subject objectively experiences a very similar event which is commonly reported to be painful. The acute nature of the stimulus also eliminates the issue of possible moderating effects of analgesic use. Thus, for several reasons, venipuncture during blood donation appears

to offer a suitable opportunity to study pain sensitivity in a naturalistic setting. One potential disadvantage of using this naturalistic pain stimulus is that subjects are self-selected. Subjects who find or anticipate venipuncture to be extremely painful may be less likely to volunteer for blood donation. However, this selection bias may also be present in laboratory pain studies, since subjects who are particularly concerned about potentially painful stimuli would be unlikely to consent to participate in such projects.

Previous research on the relationship between risk for hypertension and hypoalgesia in humans provides little information on potential psychological mechanisms which may be involved. However, results from two areas of study suggest that coping style may play a role in this relationship. A few investigators have noted that individuals with a repressive coping style have a higher pain tolerance than control subjects (Davidson & Bobey, 1970; Jamner & Schwartz, 1986). Interestingly, other research has established an association between a repressive coping style and the development of hypertension (Baer et al., 1980; Kahn et al., 1972; McClelland, 1979). Together, these lines of research suggest that coping style may play a role in hypertension-related hypoalgesia. However, this possibility has not yet been studied in the research focusing on hypoalgesia and risk for hypertension.

The present study was designed to further examine whether hypoalgesia is present in normotensive females who are at genetic risk for hypertension. Female blood donors provided ratings of pain at various points during the donation process. Several personality characteristics which may influence pain sensitivity (subjective anxiety, tendency to respond to questionnaires in a socially desirable manner, and repressive coping style) were also assessed.

Method

Subjects

Subjects were recruited at Red Cross blood donor clinics in Montreal, Canada and in southeastern Ohio. Two hundred and seventy-five women completed the protocol in Montreal and 159 in Ohio, for a total of 434 subjects. All participants were asked to provide the names, addresses, and telephone numbers for both of their biological parents. All parents were contacted by mail to request information concerning their current and past blood pressure status and a brief medical history. If parental responses were not received within six weeks of the initial mailing, an attempt was made to acquire the needed information through telephone contact. Complete parental information was obtained from 66% of the sample (64% in Montreal, 71% in Ohio), which compares favorably with investigations of this type. It appeared that the largest percentage of lost data resulted

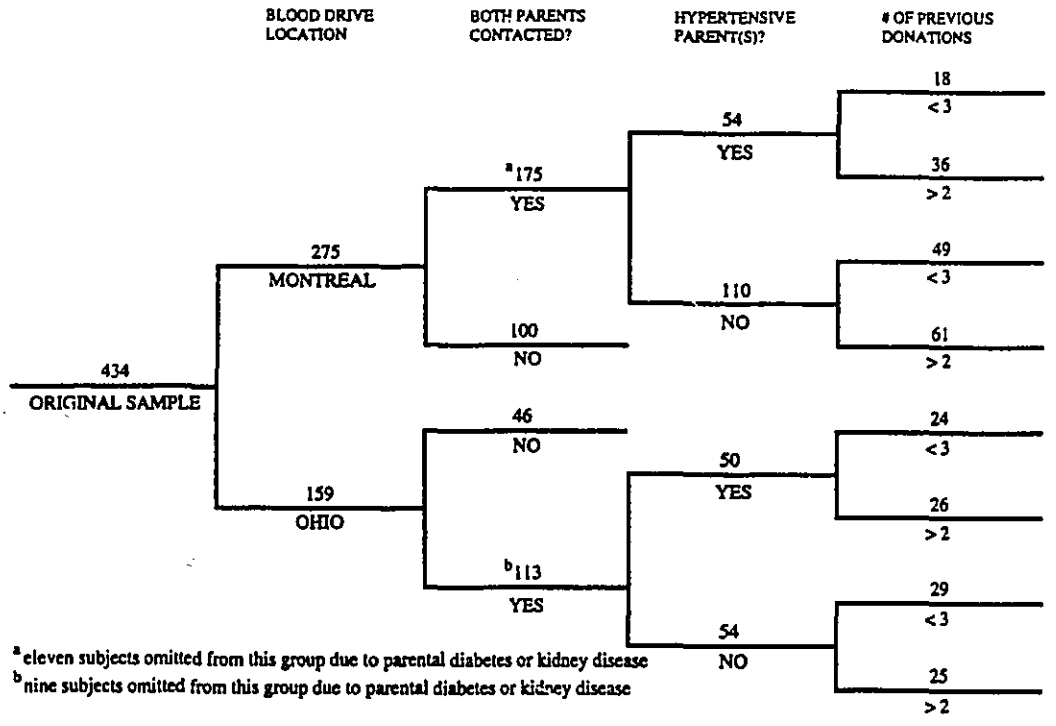
from the inability to contact the biological parents (due to adoption, death, or parental separation; or incomplete address and telephone information) rather than parents' unwillingness to respond to the questionnaire. Information provided on the 288 completed parental questionnaires was used to screen out 20 individuals who had a parental history of diabetes or kidney disease, since these disorders may lead to secondary hypertension. Of the remaining 268 subjects, 104 were found to have at least one parent with a history of hypertension (PH+) and 164 were classified as having no parental history of hypertension (PH-). Finally, since it is likely that donation experience affects pain ratings, the sample was divided based on the group median of three previous blood donations. There are several ways in which donation experience could tend to bias pain reports. First, experienced donors may be self-selected on the basis of greater tolerance for venipuncture pain and decreased arousal during blood donation procedures. Second, greater familiarity with the blood donation procedure is likely to be associated with habituation to various aspects of the procedure, and hence reduced anxiety and pain ratings. To verify that blood donation history could be a confound in pain and anxiety ratings, responses of individuals who had donated fewer than three times were compared with those who had previously donated blood on three or more occasions. These analyses revealed significantly higher pain

[$F(1,261)=8.59$, $p<.01$] and subjective anxiety [$F(1,261)=29.65$, $p<.001$] ratings for venipuncture among the novice donors. Therefore, donation experience was included as a factor in subsequent data analyses.

The final sample for analysis included 104 subjects with at least one parent with a history of hypertension and no associated diabetes or kidney disease, and 164 subjects with no parental history of hypertension, diabetes, or kidney disease. All subjects reported no personal history of hypertension or other physical illness. Figure 1 illustrates how the final sample was determined on the basis of location of blood drive, parental history of hypertension, and previous donation history. Due to higher donor turnout, 63% of the original subjects and 61% of the final sample were recruited at blood donation clinics held in Montreal. Table 5 provides descriptive characteristics of age, body mass index (kg/m^2), number of previous donations, Marlowe-Crowne Social Desirability scores, and Taylor Manifest Anxiety scores for the final sample. One-way ANOVAs revealed no significant parental history group differences on any of these variables. In addition, no significant differences in any of these variables were seen between subjects recruited in Montreal and those recruited in Ohio. Finally, 90% of the total sample was Caucasian, 2% were Black, and the remaining 8% of the subjects failed to provide this information. Chi-square analyses indicated

Figure 1

Number of subjects tested and included in the final sample on the basis of blood donor clinic location, parental history of hypertension, and number of previous donations



[a] eleven subjects omitted from this group due to parental diabetes or kidney disease
[b] nine subjects omitted from this group due to parental diabetes or kidney disease

Table 5

Mean (M) and standard deviation (SD) of various characteristics in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	PH+ (n=104)		PH- (n=164)	
	M	SD	M	SD
Age (years)	22.4	6.1	21.3	4.4
Body Mass Index (kg/m^2)	22.2	6.0	21.5	4.3
Previous Donations	4.5	5.3	3.8	4.9
Social Desirability	6.4	2.8	6.3	2.7
Manifest Anxiety	6.5	4.4	5.9	3.4

that there were no significant differences in ethnicity between parental history groups, or between the Montreal and Ohio samples.

Apparatus

Questionnaires

Parental History Questionnaire. Each biological parent received a brief questionnaire asking whether they had ever been diagnosed with hypertension, what, if any, antihypertensive medication they had been prescribed, and whether they suffered from diabetes or kidney disease. The questionnaire included a definition of hypertension as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg (Appendix 3). Although no attempt was made to confirm parental report by contacting family physicians, previous research has found personal and physician reports to be very highly correlated (Ditto, 1986).

Marlowe-Crowne Social Desirability Scale. The short form of the Marlowe-Crowne Social Desirability Scale (Reynolds, 1982) consists of 13 true/false items which assess the subject's tendency to report engaging in culturally-approved behaviors that have a low rate of occurrence. The short form has been shown to have a strong correlation with the original 33-item scale (r=.93, Reynolds, 1982).

Taylor Manifest Anxiety. The short form of the Taylor

Manifest Anxiety Scale (Bendig, 1956) consists of 20 true/false items concerning overt signs of anxiety and subjective reports of feeling nervous, and serves as a measure of trait anxiety. The short form is highly correlated with the original 50-item scale.

Repressive Coping Style. Individuals with a repressive coping style were identified using the combination of scores obtained on the Marlowe-Crowne Social Desirability and Taylor Manifest Anxiety scales, in accordance with the method proposed by Weinberger and colleagues (1979). This method is based on evidence that Marlowe-Crowne scores reflect a defensive or self-deceptive response style (Paulhus, 1984; Weinberger et al., 1979). Individuals who obtain a combination of low anxiety and high social desirability scores are therefore presumed to have a defensive tendency to deny, negate, or repress their true feelings of anxiety. Specifically, subjects were divided on the basis of scores above or below the median on each scale, to arrive at four distinct groups representing different coping styles: repressors (high Marlowe-Crowne, low Taylor), defensive high anxious (high Marlowe-Crowne, high Taylor), true high anxious (low Marlowe-Crowne, high Taylor), and true low anxious (low Marlowe-Crowne, low Taylor).

Physiological Measures

Systolic and diastolic blood pressure (in mmHg) and

heart rate (in beats per minute) measurements were taken prior to donation and at post-donation for a subset of the sample using a Lumiscope Model 1060 portable blood pressure monitor.

Procedure

Subject recruitment occurred while donors sat in a waiting area and completed paperwork for the Red Cross prior to being called for a health screening. If, following a brief overview of the study, she was interested in participating, the subject was given a more detailed explanation of the procedure and informed consent was obtained. No indication of the variables of interest was given at this time. The subject then completed a pre-donation questionnaire concerning recent food, drug, or alcohol intake; current anxiety level; and number of previous blood donations (Appendix 4). She was also familiarized with a numerical pain rating scale with anchors of zero ("not at all painful") and ten ("extremely painful"), and told that she would be asked to provide pain ratings immediately following the donation procedure. If time permitted, three blood pressure and heart rate readings were taken from the non-dominant arm at two-minute intervals. The subject was seated with her arm resting on a table at heart level for this procedure.

Subjects then proceeded through the standardized blood donation procedure adopted by the Canadian and American Red

Cross. Specifically, each subject completed a health screening during which a blood sample was obtained (via a fingerprick in Montreal and an earprick in Ohio). Once the subject passed the initial screening, she proceeded to the first available donation chair where 450 ml of blood was drawn. At the completion of the blood donation, the attending nurse or technician immediately completed a questionnaire ascertaining 1) the number of needle adjustments required, and 2) the degree of difficulty in needle insertion rated on a five-point scale.

After the donation procedure, subjects proceeded to a refreshment area where they completed the post-donation questionnaire packet. First, subjects were reminded of the zero to ten rating scale and ratings were obtained for the level of pain experienced during the initial blood sample (earprick or fingerprick), during venipuncture, and during blood drawing. These ratings followed the initial blood sample by approximately 20 minutes and venipuncture by approximately ten minutes. Although immediate pain ratings would have been preferable, this was not possible without interfering with the ongoing blood donation process. Therefore, the numerical rating scale was chosen as one which was sufficiently simple to allow it to be explained in advance and which could easily be recalled by the subjects for the duration of the procedure. Each set of pain ratings was found to be positively skewed: initial blood sample

pain ratings skew=1.06 (M=2.54, SD=2.23), venipuncture pain ratings skew=0.57 (M=3.39, SD=2.13), and blood drawing pain ratings skew=1.60 (M=1.54, SD=1.91). Ratings ranged from 0 to 10 for the initial blood sample and blood drawing, and from 0 to 9 for venipuncture.

Subjects provided four anxiety ratings in addition to the one obtained on the pre-donation questionnaire: immediately before the initial blood sample was taken, immediately before the blood donation needle was inserted, during blood drawing, and during completion of the post-donation questionnaire. Anxiety ratings were indicated on a five-point scale ranging from "not at all anxious or nervous" to "extremely anxious or nervous". These ratings were also positively skewed: pre-donation questionnaire skew=1.13 (M=1.84, SD=0.85), initial blood sample skew=0.93 (M=1.95, SD=0.92), venipuncture skew=0.73 (M=2.35, SD=1.08), blood drawing skew=1.37 (M=1.65, SD=0.87), and post-donation skew=2.45 (M=1.21, SD=0.48). Subjects endorsed the entire range of responses for the first four anxiety ratings (range=1 to 5), and endorsed anxiety ratings of 1 to 4 at the post-donation assessment.

Finally, subjects completed short forms of the Marlowe-Crowne Social Desirability and Taylor Manifest Anxiety scales, and were asked to provide the names and addresses of their biological parents. If blood pressure and heart rate data had been obtained prior to donation, three additional

readings were taken at this time. Subjects were then debriefed regarding the purpose of the study.

Data Reduction and Analyses

As mentioned above, significant positive skew was seen in the distributions of pain and anxiety ratings. Therefore, the original pain and anxiety ratings were log transformed, and the transformed data was used for all analyses.

Age, body mass index, Taylor Manifest Anxiety scores, Marlowe-Crowne Social Desirability scores, number of needle adjustments, and nurse's rating of difficulty of venipuncture were examined as possible correlates of pain and anxiety ratings. None of these variables were found to be significantly correlated with pain ratings for the initial blood sample. Age (r=-.17, p<.01) and nurse's rating of difficulty of venipuncture (r=.20, p<.01) were significantly correlated with venipuncture pain ratings. Pain ratings during blood drawing were also significantly correlated with age (r=-.14, p<.05) and nurse's rating of difficulty (r=.15, p<.05). For the subjective anxiety ratings, a significant positive correlation was seen between nurse's ratings of difficulty of venipuncture and state anxiety ratings on the pre-donation questionnaire (r=.12, p<.05), immediately prior to venipuncture (r=.18, p<.01), and during blood drawing (r=.11, p<.05). Age was significantly negatively correlated with anxiety immediately

prior to venipuncture (r=-.16, p<.01) and during blood drawing (r=-.12, p<.05). Finally, manifest anxiety was significantly correlated with anxiety ratings on the pre-donation questionnaire (r=.12, p<.05). Significant correlates were included as covariates in subsequent analyses involving pain or anxiety ratings. When these analyses were conducted without covariates, results were identical in all key respects.

Analysis of pain ratings for the initial blood sample was conducted using a 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) x 2 Testing Site (Montreal, Ohio) ANOVA. Venipuncture pain ratings were analyzed using a 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) x 2 Testing Site (Montreal, Ohio) ANCOVA with age and nurse's rating of venipuncture difficulty as covariates. Similarly, analysis of blood drawing pain ratings was conducted using a 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) x 2 Testing Site (Montreal, Ohio) ANCOVA with age and nurse's rating of venipuncture difficulty as covariates.

In order to maintain adequate cell sizes, testing site was used as a covariate rather than a factor in subsequent analyses. Analysis of the effect of coping style on pain ratings for the initial blood sample was conducted using a 2 Manifest Anxiety score (Below Median, Above Median) x 2 Social Desirability score (Below Median, Above Median) x 2

Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) ANCOVA with testing site as a covariate. For the analysis of the effect of coping style on venipuncture pain ratings a 2 Manifest Anxiety score (Below Median, Above Median) x 2 Social Desirability score (Below Median, Above Median) x 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) ANCOVA was performed with testing site, age, and nurse's ratings of venipuncture difficulty as a covariates. Finally, analysis of the effect of coping style on blood drawing pain ratings was conducted using a 2 Manifest Anxiety score (Below Median, Above Median) x 2 Social Desirability score (Below Median, Above Median) x 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) ANCOVA with testing site, age, and nurse's ratings of venipuncture difficulty as covariates.

Subjective anxiety ratings at different points throughout the donation procedure were examined using a 2 Group (PH+, PH-) x 5 Period (Pre-donation, Initial Blood Sample, Needle Insertion, During Blood Drawing, Post-donation) x 2 Donation Experience (Below Median, Above Median) MANCOVA approach to repeated measures analysis. Testing site, age, manifest anxiety score, and nurse's ratings of venipuncture difficulty were included as covariates.

Physiological data were obtained from 170 of the subjects (63% of the total sample). Systolic, diastolic,

and mean arterial blood pressure (computed as one-third the difference between systolic and diastolic levels plus the diastolic value) as well as heart rate readings were averaged to obtain single values for the pre-donation and post-donation periods. Since this information was available for only a subset of the sample, only preliminary analyses were conducted. Each measure was examined using a 2 Group (PH+, PH-) x 2 Period (Pre-donation, Post-donation) x 2 Donation Experience (Below Median, Above Median) MANCOVA approach to repeated measures with testing site as a covariate. Since these analyses revealed that blood pressure was significantly lower after donation, and thus closer to resting baseline values, the relationship of blood pressure level to pain sensitivity was investigated using three (one for each pain stimulus) 2 Group (PH+, PH-) x 2 Donation Experience (Below Median, Above Median) x 2 Post-Donation Mean Arterial Pressure (Below Median, Above Median) ANCOVAs, with testing site as a covariate.

Results

Pain Ratings

Original and log-transformed pain ratings are shown in Tables 6 and 7, respectively. The 2 Group x 2 Donation Experience x 2 Testing Site ANOVA for the initial blood sample revealed a significant Testing Site effect, $F(1,254)=112.9$, $p<.001$. This effect reflected significantly

Table 6

Mean (M) and standard deviation (SD) of original pain ratings in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	Less than 3 Previous Donations			3 or More Previous Donations		
	n	M	SD	n	M	SD
Montreal Sample						
Initial Blood Sample						
PH+	18	2.89	1.97	34	3.41	2.23
PH-	49	3.71	2.25	60	3.32	2.29
Venipuncture						
PH+	18	3.33	2.43	34	3.50	2.05
PH-	49	4.22	2.31	60	2.63	1.72
Blood Drawing						
PH+	18	1.67	2.14	34	1.97	2.28
PH-	49	1.71	1.70	60	0.65	0.97
Ohio Sample						
Initial Blood Sample						
PH+	24	1.04	1.16	24	1.00	1.02
PH-	28	1.14	1.08	25	1.44	2.10
Venipuncture						
PH+	24	2.71	1.85	24	2.67	1.88
PH-	29	4.34	2.16	25	3.60	2.04
Blood Drawing						
PH+	24	1.46	1.77	24	1.54	2.06
PH-	29	2.79	2.61	25	1.20	1.44

Table 7

Mean (M) and standard deviation (SD) of transformed pain ratings in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	Less than 3 Previous Donations			3 or More Previous Donations		
	n	M	SD	n	M	SD
Montreal Sample						
Initial Blood Sample						
PH+	18	0.54	0.21	34	0.59	0.24
PH-	49	0.63	0.21	60	0.57	0.24
Venipuncture						
PH+	18	0.56	0.29	34	0.60	0.24
PH-	49	0.67	0.20	60	0.51	0.22
Blood Drawing						
PH+	18	0.31	0.31	34	0.36	0.31
PH-	49	0.36	0.24	60	0.16	0.21
Ohio Sample						
Initial Blood Sample						
PH+	24	0.26	0.22	24	0.25	0.22
PH-	28	0.28	0.22	25	0.29	0.27
Venipuncture						
PH+	24	0.53	0.19	24	0.51	0.23
PH-	29	0.69	0.19	25	0.62	0.22
Blood Drawing						
PH+	24	0.29	0.30	24	0.28	0.32
PH-	29	0.47	0.32	25	0.26	0.27

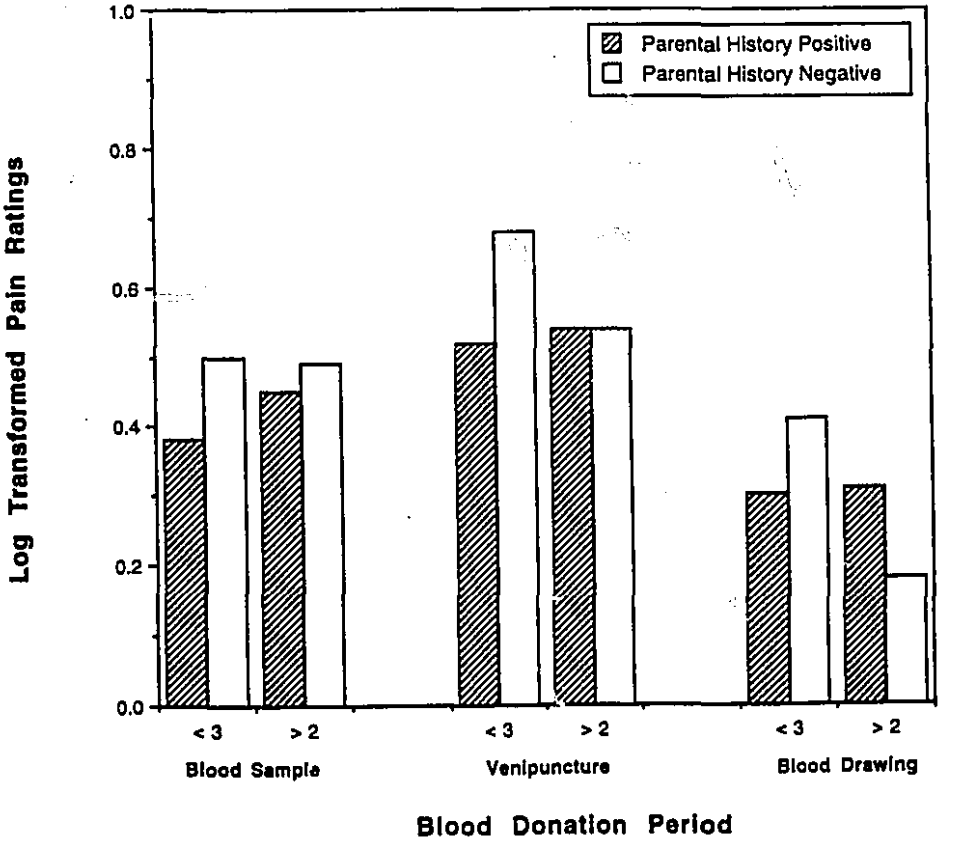
higher pain ratings in Montreal in response to the fingerprick than in Ohio where the earprick procedure was used (0.59 vs 0.27, respectively). No other significant main or interaction effects were seen.

Analysis of venipuncture pain ratings using a 2 Group x 2 Donation Experience x 2 Testing Site ANCOVA revealed significantly lower pain ratings in the PH+ (0.53) than the PH- group (0.61), $F(1,224)=4.73$, $p<.05$. In addition, a significant Group x Donation Experience interaction was seen, $F(1,224)=5.33$, $p<.05$. Follow-up analyses revealed that the PH+ group had significantly lower pain ratings than the PH- group when considering relatively novice donors [0.52 vs 0.68, $F(1,101)=13.75$, $p<.001$], but there was no significant Group effect among more experienced donors (Figure 2).

Results of the 2 Group x 2 Donation Experience x 2 Testing Site ANCOVA involving pain ratings for blood drawing indicated a significant effect of Donation Experience, with more experienced donors reporting less pain than novice donors (0.23 vs 0.37, respectively), $F(1,224)=9.62$, $p<.01$. A significant Group x Donation Experience interaction was also seen, $F(1,224)=9.20$, $p<.01$. Follow-up analyses revealed that pain ratings of the novice donors in the PH+ group (0.30) were marginally lower than those in the PH- group (0.41), $F(1,101)=3.89$, $p<.06$. However, among donors who were above the median for donation experience, the PH-

Figure 2

Transformed pain ratings in response to blood donation in novice (< 3 previous donations) and experienced (> 2 previous donations) donors with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)



group reported significantly less pain than the PH+ group, [0.18 vs 0.31, $F(1,125)=9.11$, $p<.01$]. As can be seen in Figure 2, these results reflect that donation experience did not affect pain ratings among PH+ subjects, while PH- subjects differed depending on whether or not they were experienced donors.

Coping Style

Analysis of the 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Donation Experience ANCOVA conducted on initial blood sample pain ratings revealed a significant effect of Manifest Anxiety, $F(1,245)=6.55$, $p<.05$. Individuals who were above the median in Manifest Anxiety scores reported more pain in response to the initial blood sample than those below the median (0.49 vs 0.44, respectively). In addition, a significant Social Desirability x Group interaction was seen, $F(1,245)=6.57$, $p<.05$. Follow-up analyses revealed significantly lower pain ratings in the PH+ (0.40) versus PH- (0.52) groups among subjects who were below the median on Social Desirability, $F(1,140)=5.57$, $p<.05$. No significant Group effect was observed among subjects who were above the median on Social Desirability.

The 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Donation Experience ANCOVA conducted on venipuncture pain ratings found significant main effects for Group [$F(1,215)=5.16$, $p<.05$], and Manifest Anxiety

[$F(1,215)=6.17$, $p<.05$]. The Group main effect revealed significantly lower pain ratings in the PH+ versus PH- group (0.53 vs 0.61), while the significant main effect of Manifest Anxiety reflected higher pain ratings among individuals who scored above the median on the Taylor Manifest Anxiety Scale than those falling below the median (0.62 vs 0.55). As before, a significant Group x Donation Experience interaction was seen, $F(1,215)=4.52$, $p<.05$. While PH+ subjects reported significantly less pain than PH- subjects in the novice donor sample, [0.52 vs 0.68, $F(1,100)=13.53$, $p<.001$], no significant Group effect was seen among experienced donors.

A significant main effect of Donation Experience was seen for the 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Donation Experience ANCOVA for blood drawing pain ratings. This effect reflected significantly lower pain ratings among experienced versus novice donors, [0.23 vs 0.37, $F(1,215)=10.54$, $p<.01$]. In addition, a significant Group x Donation Experience interaction was observed, $F(1,215)=6.33$, $p<.05$. Follow-up analyses revealed that PH+ subjects reported significantly lower pain ratings than PH- subjects in the novice donor sample [0.30 vs 0.41, $F(1,100)=4.44$, $p<.05$], while the reverse relationship was seen among experienced donors [PH+: 0.31, PH-: 0.18, $F(1,124)=8.73$, $p<.01$]. Finally, a significant Group x Manifest Anxiety x Social Desirability interaction was also

seen, $F(1,215)=4.95$, $p<.05$. Further analyses indicated that the Group x Social Desirability interaction was significant only among subjects who scored above the median on Manifest Anxiety, $F(1,107)=7.62$, $p<.01$. Further examination of these subjects revealed that the significant Group effect was limited to subjects who scored above the median on Social Desirability, i.e., defensive high-anxious subjects. Among this group, PH+ subjects had significantly higher pain ratings than PH- subjects, [0.47 vs 0.22, $F(1,36)=5.99$, $p<.05$].

Finally, a 2 Group x 4 Coping Style x 2 Donation Experience chi-square analysis indicated that subjects in the PH+ group were no more likely to exhibit a repressive coping style than those in the PH- group, among either the novice or experienced donors.

Anxiety Ratings

Original and log-transformed anxiety ratings are provided in Tables 8 and 9. The 2 Group x 5 Period x 2 Donation Experience repeated measures MANCOVA examining anxiety ratings throughout the donation procedure revealed that experienced donors reported significantly less anxiety than novice donors, $F(1,225)=22.14$, $p<.001$. A main effect of Period was also observed [$F(4,223)=8.21$, $p<.001$], reflecting significant changes in anxiety ratings at different points in the donation procedure. The highest anxiety ratings were seen just prior to needle insertion,

Table 8

Mean (M) and standard deviation (SD) of original state anxiety ratings in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	Less than 3 Previous Donations			3 or More Previous Donations		
	n	M	SD	n	M	SD
Pre-Donation						
PH+	42	2.00	0.77	58	1.62	0.59
PH-	78	2.21	1.02	85	1.56	0.73
Initial Blood Sample						
PH+	42	2.05	0.88	58	1.76	0.76
PH-	77	2.17	1.06	85	1.84	0.86
Venipuncture						
PH+	42	2.55	0.97	58	2.26	0.97
PH-	78	2.85	1.21	85	1.89	0.87
Blood Drawing						
PH+	42	1.60	0.70	58	1.62	0.77
PH-	78	2.05	1.12	85	1.34	0.61
Post-Donation						
PH+	42	1.17	0.38	58	1.17	0.42
PH-	78	1.38	0.65	85	1.11	0.31

Table 9

Mean (M) and standard deviation (SD) of transformed state anxiety ratings in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	Less than 3 Previous Donations			3 or More Previous Donations		
	n	M	SD	n	M	SD
Pre-Donation						
PH+	42	0.27	0.17	58	0.18	0.16
PH-	78	0.30	0.20	85	0.15	0.18
Initial Blood Sample						
PH+	42	0.27	0.19	58	0.21	0.18
PH-	77	0.28	0.22	85	0.22	0.20
Venipuncture						
PH+	42	0.37	0.18	58	0.31	0.20
PH-	78	0.41	0.20	85	0.24	0.19
Blood Drawing						
PH+	42	0.16	0.18	58	0.17	0.19
PH-	78	0.25	0.23	85	0.09	0.16
Post-Donation						
PH+	42	0.05	0.11	58	0.05	0.12
PH-	78	0.11	0.17	85	0.03	0.09

and the lowest were obtained at the time of the post-donation questionnaire. No other significant effects were seen. Finally, significant positive correlations were seen between subjective anxiety ratings at all time points and both venipuncture and blood drawing pain ratings (all *p*'s<.001). Subjective anxiety ratings at four of the five time points were also significantly positively correlated with the initial blood sample pain ratings (all *p*'s<.01).

Physiological Measures

Mean pre- and post-donation values for the physiological measures are reported in Table 10. The 2 Group x 2 Period x 2 Donation Experience repeated measures MANCOVA with testing site as a covariate conducted on systolic blood pressure found a significant main effect of Group [$F(1,162)=4.77$, $p<.05$], with the PH+ group having higher systolic blood pressure readings. A significant Period effect reflected lower systolic blood pressure levels at post-donation, $F(1,163)=84.56$, $p<.001$. A similar Period effect was seen for diastolic blood pressure, $F(1,163)=27.07$, $p<.001$. A significant effect of Group was also seen in the analysis of mean arterial pressure, with PH+ subjects having higher mean arterial pressure values, $F(1,162)=4.04$, $p<.05$. Again, a significant Period effect reflected lower mean arterial pressure values at post-donation, $F(1,163)=61.94$, $p<.001$. Finally, with respect to the heart rate data, a significant main effect of Period was

Table 10

Mean (M) and standard deviation (SD) of physiological measures at pre- and post-donation in offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	Less than 3 Previous Donations			3 or More Previous Donations		
	n	M	SD	n	M	SD
Systolic Blood Pressure (mmHg)						
Pre-Donation						
PH+	26	118.8	11.7	32	115.5	13.7
PH-	53	112.1	11.1	56	112.0	9.1
Post-Donation						
PH+	26	108.8	9.7	32	108.3	11.7
PH-	53	106.4	9.9	56	105.8	9.4
Diastolic Blood Pressure (mmHg)						
Pre-Donation						
PH+	26	75.4	9.6	32	73.3	10.2
PH-	53	72.0	9.4	56	71.4	7.4
Post-Donation						
PH+	26	70.3	9.9	32	71.7	10.4
PH-	53	68.7	8.6	56	69.1	7.2
Mean Arterial Pressure (mmHg)						
Pre-Donation						
PH+	26	89.9	9.3	32	87.3	10.6
PH-	53	85.4	9.0	56	84.9	7.3
Post-Donation						
PH+	26	83.1	8.8	32	83.9	10.5
PH-	53	81.3	8.2	56	81.4	7.2
Heart Rate (beats per minute)						
Pre-Donation						
PH+	25	82.4	14.2	32	76.0	12.7
PH-	53	80.8	12.4	56	77.1	14.4
Post-Donation						
PH+	26	85.7	15.3	32	80.6	12.0
PH-	53	81.2	11.1	56	78.9	13.5

found, [$F(1,162)=8.98$, $p<.01$], reflecting higher heart rate values at post-donation. In addition, novice donors had higher heart rates than more experienced donors, $F(1,161)=4.84$, $p<.05$.

The 2 Group x 2 Donation Experience x 2 Post-Donation Mean Arterial Pressure ANCOVA with testing site as a covariate conducted on pain ratings for the initial blood sample revealed a significant Group x Donation Experience interaction, $F(1,158)=4.22$, $p<.05$. Although follow-up analyses failed to reach significance, this interaction appeared to reflect that among novice donors parental history positive subjects reported less pain than offspring of normotensives (mean transformed ratings of .38 and .50, respectively), while pain ratings among experienced donors did not vary on the basis of parental history (PH+: .45, PH-: .49). Similar analysis of the pain ratings for venipuncture indicated that there was a significant main effect of Donation Experience, $F(1,158)=5.82$, $p<.05$, with experienced donors reporting less pain than novice donors (.54 vs .64). Significant interactions were also seen for Group x Donation Experience [$F(1,158)=10.75$, $p<.01$], and Group x Donation Experience x Mean Arterial Pressure [$F(1,158)=7.42$, $p<.01$]. Follow-up analyses of the two-way interaction revealed that parental history positive subjects had significantly lower pain ratings than offspring of normotensives among novice donors, [.54 vs .68,

$F(1,119)=11.32$, $p<.01$], while no effect was seen with experienced donors [PH+: .56, PH-: .54]. Analysis of the three-way interaction of Group x Donation Experience x Mean Arterial Pressure indicated that the significant Group x Mean Arterial Pressure interaction was limited to the novice donors, $F(1,74)=4.34$, $p<.05$. Further, in this group, offspring of hypertensives who were above the median for resting mean arterial pressure had significantly lower venipuncture pain ratings than offspring of normotensives (.46 vs .76, $F(1,36)=10.02$, $p<.001$]. Although also in the predicted direction, the difference in pain ratings in novice donors who were below the median for resting mean arterial pressure did not significantly differ between parental history groups [PH+: .55, PH-: .64]. Finally, the analysis of blood drawing pain ratings revealed significantly lower pain ratings in experienced as compared to novice donors [.24 vs .37, $F(1,158)=7.89$, $p<.01$]. In addition, a significant Group x Donation Experience interaction was seen, $F(1,158)=13.43$, $p<.001$. Again, among novice donors, offspring of hypertensives reported less pain than offspring of normotensives [.30 vs. .41, $F(1,117)=4.52$, $p<.05$]. Interestingly, for the experienced donors the reverse relationship was seen, with offspring of normotensives reporting less pain [.19 vs. .33, $F(1,140)=8.63$, $p<.01$]. Thus, results of these analyses are similar to the effects seen in the pain analyses previously

conducted using the full sample. In particular, the Group x Donation Experience effects reflect a similar pattern of results, with donation experience influencing pain ratings among offspring of normotensives but having little effect on pain ratings of offspring of hypertensives.

Discussion

The present study's main finding of lower venipuncture pain ratings among novice female donors with a hypertensive parent provides the first evidence of decreased pain sensitivity in females at risk for hypertension. However, the results of this study also emphasize that this is a complex phenomenon and various factors may affect this relationship. For instance, it may be necessary to use a pain stimulus of sufficient intensity in order to elicit this effect. This is consistent with the weaker group differences in pain ratings in response to the blood sample procedures, since these procedures were rated as less painful than venipuncture. However, pain ratings for blood drawing were also relatively low, yet novice donors with a parental history of hypertension did show differences from offspring of normotensives for this stimulus. This suggests that characteristics other than the intensity of the pain stimulus may also be important in determining whether reduced pain sensitivity is observed. The different results when considering novice versus experienced donors further

highlights that factors such as novelty of the situation may enhance the likelihood of eliciting this effect. It is interesting to note that the failure to find group effects among experienced donors reflected that parental history positive offspring had similar pain ratings regardless of donation history, while offspring of normotensive parents showed a decrease in pain sensitivity with increasing donation experience. Of course, the present data are cross-sectional in nature and do not address the reasons for such group differences. However, it is interesting to speculate that this pattern may reflect a self-selection bias over time such that offspring of normotensives who are more sensitive to pain do not return to donate blood on subsequent occasions. Pain is one of the main reasons donors cite for lack of participation in subsequent blood donation clinics (Piliavin, 1990). In any case, it appears that having a parental history of hypertension results in a level of pain sensitivity for venipuncture similar to that seen in experienced donors.

The present finding of lower sensitivity to pain among normotensive female novice donors who are offspring of hypertensives is consistent with an earlier report of a reduced sensitivity to pain among normotensive male offspring of hypertensives which used a leg constriction pain task (France et al., 1991). On the other hand, Ghione and colleagues (1988) were unable to demonstrate hypoalgesia

to electric tooth pulp stimulation in their "high-risk" sample. However, only a small subgroup of their sample was specifically selected on the basis of a positive or negative family history of hypertension and no attempt was made to confirm subjects' reports of parental hypertension. Thus, the lack of differences between the low-risk and high-risk groups in pain sensitivity may have been due to a failure to identify groups which were truly different in risk. The present finding suggesting that the effects of a parental history of hypertension on sensitivity to venipuncture may be most noticeable among individuals with moderately elevated blood pressure is consistent with this view.

Analysis of coping style effects failed to demonstrate that a repressive coping style mediated group differences in pain sensitivity between offspring of hypertensives and normotensives. Contrary to what other investigators have reported in hypertensive (e.g., Cumes, 1983), hypertension-prone (e.g., Kahn et al., 1972; McClelland, 1979), and parental history positive subjects (Baer et al., 1980; Semenchuk & Larkin, 1993), there was no evidence that the groups differed in preferred coping style. The failure to replicate earlier findings in this regard may reflect methodological differences between studies. Behavioral differences between offspring of hypertensives and normotensives that are related to the idea of repressive coping have mainly been noted when direct observational

methods have been employed.

Not only was there no evidence that a tendency towards a repressive coping style could explain differences in pain ratings between at-risk groups, this study also failed to find an overall relationship between repressive coping and pain ratings. No evidence was found for lower pain ratings among subjects who exhibited a combination of low anxiety and high defensiveness scores. This was somewhat surprising in light of previously reported findings. Davidson and Bobey (1970) found that repressors (as defined using the Repression-Sensitization Scale) showed a higher tolerance to pain on first exposure to a painful stimulus of heat or pressure. Similarly, Jamner and Schwartz (1986) found repressors (differentiated with the Lie Scale of the Eysenck Personality Inventory) permitted higher levels of shock before reaching discomfort, pain, and tolerance levels. The difference in findings between the present study and these earlier reports may be related to the nature of the pain stimuli used, or the manner in which repressors were defined. It is also interesting to note that Davidson and Bobey (1970) found a significant interaction between coping style and repeated trials of pain stimuli, with repressors showing a higher tolerance to pain than non-repressors on the first exposure to pain but not on the subsequent trial. Thus, we might not have expected to see a difference in pain reports between types of coping styles for all pain ratings,

but only for the initial pain stimulus.

Although these results failed to support the role of repressive coping as a moderator of pain reports, the findings regarding anxiety are more consistent with the existing literature. Elevated pain ratings in response to the initial blood sample and venipuncture among individuals with high trait anxiety are consistent with previous evidence of a relationship between trait anxiety and pain ratings. Many studies have reported that elevated trait anxiety is associated with higher levels of pain reports (e.g., Craig, 1989; Dougher, 1979; Sternbach, 1968, 1974; Weisenberg, 1977). State anxiety ratings were also significantly correlated with pain reports, consistent with previous research (e.g., Absi & Rokke, 1991; Merskey, 1980; Sternbach, 1986; Weisenberg, 1977; Weisenberg, Aviram, Wolf, & Raphaeli, 1984). However, there were no differences in anxiety between the parental history groups in this study. Therefore, it is unlikely that differences in anxiety could account for the differences in pain ratings between females with and without a parental history of hypertension.

It should be noted that, similar to the previous comments about stimulus parameters which might moderate the effect of family history, it is possible that coping style may affect the likelihood of observing an effect of family history. For instance, the analysis of coping style effects on initial blood sample pain ratings revealed a social

desirability by parental history interaction, with group differences only evident among subjects who received low social desirability scores. These results suggest that high social desirability may have obscured a relationship between initial blood sample pain ratings and parental history in the original pain analyses.

Thus, results from this study provide evidence of a reduced sensitivity to pain in females at genetic risk for hypertension. However, this phenomenon required further study to determine whether this effect could be elicited using other types of pain stimuli. In addition, further investigation of potential psychological or physiological mechanisms was needed.

STUDY 3

Results from the previous study provided the first evidence of decreased pain sensitivity in females at risk for hypertension. In addition, Study 2 demonstrated a reduced sensitivity to pain in humans at risk for hypertension using a naturalistic pain stimulus. However, to minimize disruption of Red Cross procedures, some limitations were placed on data collection. Therefore, a laboratory study was designed to gather further information concerning hypertension-related hypoalgesia in hypertensive-prone females. Study 3 examined pain sensitivity to two laboratory pain stimuli in females with and without a parental history of hypertension.

One advantage offered by a laboratory study is the greater degree of control over both subject- and stimulus-related variables. In Study 3, subjects were pre-screened to provide a homogeneous group in terms of age and health status. In addition, since inconsistent results have been reported concerning cyclic variation in pain thresholds (Amodei & Nelson-Gray, 1989; Hapidou & De Catanzaro, 1988) and physiological reactivity (Miller & Sita, 1994; Plante & Denney, 1984; Sita et al., 1992), all subjects were scheduled for testing at the same point in the menstrual cycle to remove any possible confounding effect. The follicular phase was chosen as the easiest to reliably identify without measuring serum estrogen and progesterone

levels. The laboratory setting also offered some advantages with respect to the administration of the pain stimuli. First, the procedure for administering the pain tasks was standardized. Second, it was possible to assess responses to two different pain stimuli. The cold pressor and electric shock were chosen as two commonly used laboratory pain tasks. Finally, more extensive self-report data regarding pain sensitivity were collected, as opposed to the single numerical rating scale used in Study 2. In addition, the potential role of psychological factors such as coping style was further examined by including a variety of self-report measures.

Another advantage of the laboratory setting is the opportunity to collect data which may shed light on possible physiological correlates or mechanisms of hypertension-related hypoalgesia. Research with normotensive males suggests that decreased pain sensitivity in hypertensive-prone individuals may be associated with higher resting blood pressure and/or greater blood pressure reactivity (Bruehl, Carlson, & McCubbin, 1992; Ditto et al., 1993; McCubbin & Bruehl, 1994). Of course, there may be no relationship other than the fact that both appear to be related to risk for hypertension. However, this increased blood pressure reactivity may be associated with or due to greater endogenous opiate activity, which also produces hypoalgesia. For example, baroreflex sensitivity appears to

be controlled in part by endogenous opiate activity, which is largely inhibitory in nature (Szilagyi, 1989). Alternatively, greater blood pressure reactivity may decrease pain sensitivity in some causal fashion, such as by increasing stimulation of the baroreceptors. Some previous work with males has shown that mechanical stimulation of the baroreceptors leads to decreased pain sensitivity (Elbert et al., 1988). However, this effect was seen only in individuals with borderline hypertension. This may or may not have been related to differences in baroreflex sensitivity between normotensive and borderline hypertensive individuals. The relationship between physiological reactivity and pain threshold has not been studied in hypertensive-prone females. Therefore, a variety of physiological measures were obtained in Study 3, including a non-invasive assessment of baroreflex sensitivity using continuous monitoring of blood pressure and interbeat interval. This non-invasive technique of assessing baroreflex sensitivity has not been previously applied in the study of pain sensitivity.

An additional advantage offered by a laboratory study is that the administration of the pain task is not limited to a single occurrence, as is often the case with naturalistic pain events. This provides an opportunity to study within-subject differences in pain sensitivity under varying circumstances, such as following stressful and non-

stressful tasks. The phenomenon of stress-induced analgesia has been extensively studied in animals, but much less researched in humans. Stress-induced analgesia is believed to be a reflection of the fact that non-painful behavioral demands may elicit many of the same physiological adaptations as pain stimuli. Evidence that this phenomenon is counteracted by the opiate antagonist naloxone (Bandura, Cioffi, Taylor, & Brouillard, 1988; Willer & Albe-Fessard, 1980; Willer, Dehen, & Cambier, 1981) supports the notion that stress-induced analgesia often involves endogenous opiates. Unfortunately, much of the existing research involves the use of physical, usually painful, stimuli as the analgesia-producing stressors (Kelley, 1986). This raises the possibility that the phenomenon is merely pain-induced analgesia, theoretically a much less interesting event. However, there are a number of animal studies which have found similar results with psychological stressors such as conditioned aversive stimuli (Chance, Krynock, & Rosecrans, 1978; Hayes, Bennett, Newlon, & Mayer, 1978; Oliverio & Castellano, 1982) or social isolation (Naranjo & Fuentes, 1985). Two studies have also looked at more purely psychological stressors with human subjects. Bandura and colleagues (1988) found that a difficult arithmetic task was capable of reducing pain sensitivity to the cold pressor test in both males and females. Using an all-male sample, a more extensive investigation examined this phenomenon using

two different psychological stressors (mental arithmetic and reaction time tasks) and assessing pain sensitivity to three types of laboratory pain tasks--cold pressor, finger pressure, and electric shock (Ditto, Edwards, & Spiegel, 1994). In general, pre-exposure to the non-painful stressors led to diminished pain sensitivity. In Study 3, a within-subjects design was used to further examine whether a reduced sensitivity to pain can be induced in females using a non-painful stressor. Pain sensitivity was assessed following stressful and non-stressful tasks in separate testing sessions. In addition to testing for stress-induced analgesia in females, this study allowed an examination of whether hypertensive-prone females would exhibit a greater tendency for stress-induced analgesia. Such an effect might be expected if hypertension-related hypoalgesia is related to an enhanced endogenous opiate response.

In this study, normotensive female offspring of hypertensives and normotensives participated in a two-session protocol assessing pain sensitivity to electric shock and cold pressor following stressful and non-stressful tasks. Various physiological measures were collected to examine possible mechanisms of hypertension-related hypoalgesia. Possible psychological mechanisms involved in this relationship were also assessed.

Method

Subjects

Healthy female undergraduates were administered a brief screening questionnaire assessing personal and parental history of hypertension. Subjects received partial credit in their introductory psychology course in return for their participation. Following the screening sessions, approximately equal numbers of females with and without a reported parental history of hypertension were contacted by telephone and invited to participate in the laboratory portion of the study. Their participation fulfilled the remainder of their required research participation credits. Subjects were unaware that they were selected on the basis of reported parental blood pressure status. Following the laboratory protocol, confirmation of parental blood pressure history was obtained through written communication with the biological parents. Subjects with at least one parent reporting a history of hypertension without associated diabetes or kidney disease were assigned to the parental history positive (PH+) group. Subjects with both parents reporting no history of high blood pressure, diabetes, or kidney disease were assigned to the parental history negative (PH-) group. The final sample included 24 subjects in each group. One individual failed to return for her second testing session and was replaced to maintain equal sample sizes between the groups. Descriptive

characteristics of age, body mass index (kg/m^2), number of cigarettes smoked, Marlowe-Crowne Social Desirability scores and Taylor Manifest Anxiety scores for each group are presented in Table 11. One-way ANOVAs revealed that there were no significant differences between the groups on any of these variables. Chi-square analysis indicated that there was no significant difference in the number of oral contraceptive users in the PH+ (9 out of 24) and PH- (8 out of 24) groups. The vast majority of the subjects (96%) were Caucasian.

Apparatus

Physiological Measures

Systolic and diastolic blood pressures (in mmHg) were measured using an Ohmeda Finapres 2300 continuous blood pressure monitor. Finger pulse amplitude (in units), finger pulse transit time (in msec), interbeat interval (in msec), and skin conductance level (in uSiemens) were obtained using a Contact Precision Instruments finger pulse amplifier, photoplethysmograph (model PT1), high-sensitivity bioamplifier, skin conductance amplifier, interval timers, Psylab version 3.0 software, and an NCR 386-SX computer. Disposable electrocardiograph electrodes (Marquette Electronics) and a silver earclip electrode (Sensor-Medics) were used to obtain electrocardiogram signals. Sensor-Medics 16 mm biopotential electrodes were used to collect skin conductance measures.

Table 11

Mean (M) and standard deviation (SD) of various characteristics of offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	PH+ (n=24)		PH- (n=24)	
	M	SD	M	SD
Age (years)	19.4	2.6	19.2	0.7
Body Mass Index (kg/m^2)	21.0	2.7	21.4	1.9
Cigarettes (#/Day)[a]	6.0	6.2	8.5	4.7
Social Desirability	16.8	5.2	17.3	6.5
Manifest Anxiety	19.4	7.1	16.3	9.3

[a]4 subjects in each group were smokers

Finger Pulse Transit Time. Finger pulse transit time, a measure of cardiac sympathetic activity, was calculated by measuring the time between the occurrence of the electrocardiogram R-wave and the upswing of the finger pulse wave using a Contact Precision interval timer.

Mean Arterial Pressure. Mean arterial pressure was computed as one-third the difference between systolic and diastolic blood pressure, plus the diastolic blood pressure value.

Baroreflex Sensitivity. Data obtained from the continuous monitoring of blood pressure and interbeat interval were used to assess baroreflex sensitivity following the procedures outlined by Steptoe and Sawada (1989). Ascending baroreflex sensitivity (in msec/mmHg) was determined by identifying sequences of at least three consecutive increases in interbeat interval that were associated with consecutive increases in systolic blood pressure. Descending baroreflex sensitivity was assessed in an analogous manner by identifying consecutive decreases in interbeat interval associated with decreases in systolic blood pressure. An average sensitivity value was obtained for ascending and descending sequences for each of the following periods: baseline, 20-minute task, electric shock, and cold pressor.

Electric Shock

Electric shocks were delivered using a 40 mm concentric

electrode. The shocks were generated by a constant current Digitimer Stimulator (model DS-7).

Psychological Measures

McGill Pain Questionnaire. The Present Pain Intensity scale and the Pain Rating Index of the McGill Pain Questionnaire (MPQ; Melzack, 1975) were completed following each pain task. The Present Pain Intensity scale involves rating the pain experienced on a six-level scale ranging from no pain to excruciating pain. The Pain Rating Index is derived from 20 subclasses of verbal descriptors. Subjects choose a maximum of one adjective from each of the subclasses of pain descriptors to provide a total Pain Rating Index score. The MPQ has been demonstrated to have strong test-retest reliability (Love, Loeboeuf, & Crisp, 1989) and acceptable discriminant validity (Melzack & Katz, 1992).

Profile of Mood States Questionnaire. The Anger and Anxiety subscales of the Profile of Mood States Questionnaire (POMS; McNair, Lorr, & Droppleman, 1971) were included to provide state measures of anxiety and anger at various points during the protocol. The anxiety subscale includes nine adjectives, while the anger subscale consists of 12 items. The subject is asked to indicate how self-descriptive each adjective is at the present time on a five-point scale (from 0=not at all to 4=extremely). Several studies have shown these POMS subscales to have excellent

internal consistency (.90 - .93) and acceptable test-retest coefficients. Construct and predictive validity have also been demonstrated (McNair et al., 1971).

Marlowe-Crowne Social Desirability Scale. The Marlowe-Crowne scale (Crowne & Marlowe, 1960) consists of 33 true-false items which assess the subject's tendency to report engaging in culturally-approved behaviors that have a low rate of occurrence. High scores on the Marlowe-Crowne have also been shown to reflect a defensive or self-deceptive response style (Paulhus, 1984; Weinberger et al., 1979). The Marlowe-Crowne scale has been used extensively in research (Reynolds, 1982) and has been shown to have adequate internal consistency and test-retest reliability (Crowne & Marlowe, 1960).

Taylor Manifest Anxiety Scale. The Taylor Manifest Anxiety scale (Taylor, 1953) is a 50 item true-false measure of trait anxiety. The items concern overt signs of anxiety and subjective reports of feeling nervous. Adequate split-half and test-retest reliability have been reported (Graham, 1987), and scores on the Taylor are positively correlated with other measures of anxiety (Byrne, 1974).

Coping Style. Coping style was identified using the combination of scores obtained on the Marlowe-Crowne Social Desirability and Taylor Manifest Anxiety scales, using the method proposed by Weinberger and colleagues (1979). Specifically, subjects were divided based on whether their

scores fell above or below the group median on each scale. The resulting four distinct groups represented the following coping styles: repressors (high Marlowe-Crowne, low Taylor), defensive high anxious (high Marlowe-Crowne, high Taylor), true high anxious (low Marlowe-Crowne, high Taylor), and true low anxious (low Marlowe-Crowne, low Taylor).

Personal and Family Health History. A brief personal and family health history questionnaire was included to assess personal health status and medication use, as well as parental history of hypertension and other physical disorders (Appendix 1).

Parental Hypertension Questionnaire. Each biological parent completed a brief questionnaire assessing whether they had ever been diagnosed with hypertension, whether they had ever been prescribed any antihypertensive medications, and whether they suffered from diabetes or kidney disease. The questionnaire included a definition of hypertension as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg (Appendix 3). Results from a previous study in this laboratory (Ditto, 1986) suggest that parental reports are highly accurate when compared with physician reports.

Procedure

Each subject participated in a 1.25 hour laboratory protocol on two consecutive days. Testing sessions were

scheduled to fall within the first four days following the last day of menstruation to control for possible menstrual cycle phase effects. Each session was conducted at approximately the same time of day.

When first entering the laboratory, the subject was given a written description of the procedures and informed consent was obtained. Electrocardiograph electrodes were then attached to the subject's left side approximately 2.5 cm above the base of the rib cage and on the subject's right back approximately 7.5 cm below the right shoulder and midway between the neck and shoulder tip. The reference electrode was attached to the subject's left earlobe. The remaining physiological recording equipment was attached to the subject's non-dominant hand. A digital blood pressure cuff was attached to the second phalange of the middle finger. A photoplethysmograph was attached to the distal phalange of the index finger. Skin conductance electrodes were attached to the second phalanges of the ring and small fingers. All physiological recordings were made on a continuous basis, with the exception of blood pressure. Although the Ohmeda Finapres 2300 monitor is designed to allow continuous blood pressure monitoring for up to several hours, prolonged monitoring may become uncomfortable due to sustained inflation of the finger cuff. To prevent the physiological recording equipment itself from becoming a noxious stimulus, the continuous blood pressure monitor was

turned off for the first and last five-minute intervals of the 20-minute task period. The finger cuff was also deflated during the five-minute recovery period between the pain tasks and during administration of psychological measures.

Each session began with the completion of the Anger and Anxiety subscales of the POMS questionnaire and a ten-minute resting baseline. This was followed by a 20-minute task period (see below). Following completion of the task, subjects participated in two pain sensitivity tasks (see below). Each pain task lasted two minutes, and the tasks were separated by a five-minute recovery period. Following each pain task, subjects were administered the Pain Rating Index of the MPQ and the Anger and Anxiety subscales of the POMS. After the pain tasks, a final ten-minute resting baseline was obtained and the Anger and Anxiety subscales of the POMS were administered for a final time. The remaining psychological questionnaires were completed by the subject before returning for the second testing session.

20-Minute Task

On one day subjects played a video game (Nintendo "Tetris") during this period, while on the other day they were asked to doodle with a pencil on a writing pad for 20 minutes to create a similar amount of hand movement. Due to the physiological recording equipment, subjects were limited to using only their dominant hand to manipulate the video

game control pad. To enhance motivation and maximize the stressfulness of the video game task, a $100 prize was offered to the individual who obtained the highest total point score in the 20-minute time period. Subjects were informed that the doodling task was designed merely to mimic the amount of hand movement required during the video game. The order of task presentation was counterbalanced across subjects.

Pain Tasks

The pain tasks included cold pressor and electric shock. For the cold pressor task, the subject was instructed to place her dominant hand up to the wrist in 4 degree Celsius water and to maintain her hand in the water for as much of the two-minute period as possible. If the subject removed her hand from the water before two minutes had elapsed, she was reminded to return her hand to the water as soon she felt able. The subject rated the sensation felt in her hand using an eleven-point scale (from 0=undetectable to 10=very painful). Ratings were obtained when the subject's hand was first submerged, and then at 15-second intervals. Pain measures obtained during the cold pressor task included average pain rating, maximum pain rating, and latency to hand withdrawal. Pain measures assessed following the cold pressor included the Present Pain Intensity scale and the Pain Rating Index score of the MPQ.

For the electric shock task, the shock electrode was attached to the ventral surface of the wrist of the dominant arm, just above the wrist fold. Subjects received a total of 16 mild electric shocks administered in alternating ascending (2.0 to 3.5 mA) and descending (3.5 to 2.0 mA) series at 0.5 mA increments. The pulse width of each shock was 1 msec. The subject rated the sensation associated with each shock using the same eleven-point scale used for the cold pressor task. Pain measures obtained during the shock task included the average pain rating across the 16 shock presentations and the maximum pain rating. Pain measures obtained following the shock task included the Present Pain Intensity scale and the Pain Rating Index score of the MPQ. Order of pain task presentation was consistent across days for each subject but was counterbalanced across subjects.

Data Reduction

Repeated measures of systolic blood pressure, diastolic blood pressure, finger pulse amplitude, finger pulse transit time, interbeat interval, and skin conductance level were averaged to obtain mean levels for each of the following periods on each day of testing: initial baseline, 20-minute task, electric shock, and cold pressor. Initial baseline values were used as covariates in all analyses involving these physiological measures.

Resting mean arterial pressure was calculated as the average initial baseline value across days. Mean arterial

pressure reactivity was computed as the change in mean arterial pressure from baseline to the 20-minute task on the video game day.

Data Analyses

Initial analysis of the effect of stress on the physiological measures was conducted using a 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) x 3 Period (20-Minute Task, Shock, Cold Pressor) repeated measures MANCOVA with initial baseline values as covariates and all six physiological measures as dependent variables. Significant effects observed in the overall MANCOVA were examined for each of the dependent measures using equivalent univariate MANCOVAs.

Since the pain stimuli were quite different, and not all measures were obtained in both instances (i.e., latency to hand withdrawal), pain measures for the two stimuli were analyzed separately. This was consistent with the procedure followed in Study 2. Further, pain measures obtained during the pain tasks were analyzed separately from those obtained following the pain tasks.

Pain sensitivity to the cold pressor was first examined using a 2 Group (PH+, PH-) x 2 Resting Mean Arterial Pressure (Below Median, Above Median) x 2 Day (Video Game, Doodling) repeated measures multivariate analysis of variance (MANOVA) with average pain rating, maximum pain rating, and latency to hand withdrawal as dependent

measures. To examine the possible influence of blood pressure reactivity on pain measures obtained during the cold pressor, a 2 Group (PH+, PH-) x 2 Mean Arterial Pressure Reactivity (Below Median, Above Median) x 2 Day (Video Game, Doodling) repeated measures MANOVA was conducted using average pain rating, maximum pain rating, and latency to hand withdrawal as dependent measures.

Similar analyses were conducted for the pain measures obtained during the shock task. Average pain rating for shock and maximum pain rating were included as dependent measures in a 2 Group (PH+, PH-) x 2 Resting Mean Arterial Pressure (Below Median, Above Median) x 2 Day (Video Game, Doodling) repeated measures MANOVA. Again, the same dependent measures were examined using a 2 Group (PH+, PH-) x 2 Mean Arterial Pressure Reactivity (Below Median, Above Median) x 2 Day (Video Game, Doodling) repeated measures MANOVA. Significant effects observed in the overall MANOVAs were examined for each of the dependent measures using equivalent univariate analyses.

Pain measures obtained after the cold pressor were analyzed using a 2 Group (PH+, PH-) x 2 Resting Mean Arterial Pressure (Below Median, Above Median) x 2 Day (Video Game, Doodling) MANOVA with Present Pain Intensity and Pain Rating Index scores as dependent variables. A similar analysis was conducted substituting Mean Arterial Pressure Reactivity for Resting Mean Arterial Pressure. Two

analogous analyses were conducted using Present Pain Intensity and Pain Rating Index scores obtained following the electric shock task.

Analyses of the effect of coping style on pain measures were conducted separately for each pain stimulus, and for measures obtained during and after the pain stimuli. A 2 Manifest Anxiety score (Below Median, Above Median) x 2 Social Desirability score (Below Median, Above Median) x 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) repeated measures MANOVA with average pain rating, maximum pain rating, and latency to hand withdrawal as dependent measures was used for the cold pressor test. A similar MANOVA using average pain rating and maximum pain rating was conducted for the electric shock task. Significant effects observed in the overall MANOVAs were examined for each of the dependent measures using equivalent univariate repeated measures MANOVAs. Pain measures obtained after the pain stimuli were analyzed using two separate 2 Manifest Anxiety score (Below Median, Above Median) x 2 Social Desirability score (Below Median, Above Median) x 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) repeated measures MANOVAs with Present Pain Intensity and Pain Rating Index scores as dependent measures for each pain stimulus.

Analyses of the effects of parental history on state anxiety and anger were examined using separate 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) x 3 Period (Baseline,

Shock, Cold Pressor) MANOVAs for each mood state.

Analyses of baroreflex sensitivity were conducted using a 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) x 4 Period (Baseline, 20-Minute Task, Shock, Cold Pressor) x 2 Direction (Up, Down) repeated measures ANOVA. Regression analyses were used to assess the possible relationship between baroreflex sensitivity and pain reports. The average pain rating and Pain Rating Index score for cold pressor and shock on each day were examined using eight separate regression analyses with ascending sensitivity, descending sensitivity, and parental history group included as possible predictor variables. A Bonferroni correction for multiple tests was conducted by dividing the alpha level by the number of tests (.05/8 = .006).

Results

Physiological Responses to Stress

Results of the 2 Group (PH+, PH-) x 2 Day (Video Game, Doodling) x 3 Period (20-Minute Task, Shock, Cold Pressor) MANCOVA for all six dependent variables revealed significant main effects of Day [$F(6,27)=4.30$, $p<.01$] and Period [$F(12,27)=31.55$, $p<.001$]. A significant Day x Period interaction [$F(12,27)=8.17$, $p<.001$] was also observed. Given these results, the Day, Period, and Day x Period effects of the comparable univariate MANCOVAs were examined and are presented in Table 12.

Table 12

Physiological responses to stress: Results of MANCOVAs of day and period with initial baseline covariates

	Day $F(1,43)^a$	Period $F(2,43)^a$	Day x Period $F(2,43)^a$
Systolic Blood Pressure	19.78***	32.78***	29.52***
Diastolic Blood Pressure	10.95**	62.63***	17.91***
Interbeat Interval	6.00*	37.52***	17.66***
Pulse Transit Time	9.85**	8.72**	0.40
Finger Pulse Amplitude	15.48***	43.73***	15.00***
Skin Conductance	5.06*	59.85***	0.96

[a]df of some analyses lower due to missing data

*$p<.05$

**$p<.01$

***$p<.001$

Blood Pressure

Significant effects of Day, Period, and Day x Period were observed for both systolic and diastolic blood pressure. As illustrated in Figures 3 and 4, the significant Day main effects indicated that significantly greater increases in systolic and diastolic blood pressure were observed on the video game day versus the doodling day. The significant Period main effects reflected significant differences in systolic and diastolic blood pressure across the stressor and pain tasks. The significant Day x Period interactions indicated that the day effect was restricted to particular periods. Specifically, follow-up simple main effects analyses revealed significantly higher systolic blood pressure on the video game day versus the doodling day during the 20-minute task [$F(1,44)=83.36$, $p<.001$], but not during shock or cold pressor. Similarly, follow-up simple main effects analyses for diastolic blood pressure revealed significantly higher values on the video game day versus the doodling day only during the 20-minute task period [$F(1,44)=54.40$, $p<.001$].

Interbeat Interval

Significant effects of Day, Period, and Day x Period were observed for interbeat interval. As illustrated in Figure 5, the significant Day effect revealed greater changes in interbeat interval on the video game day than the doodling day. The significant main effect of Period

Figure 3

Systolic blood pressure during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

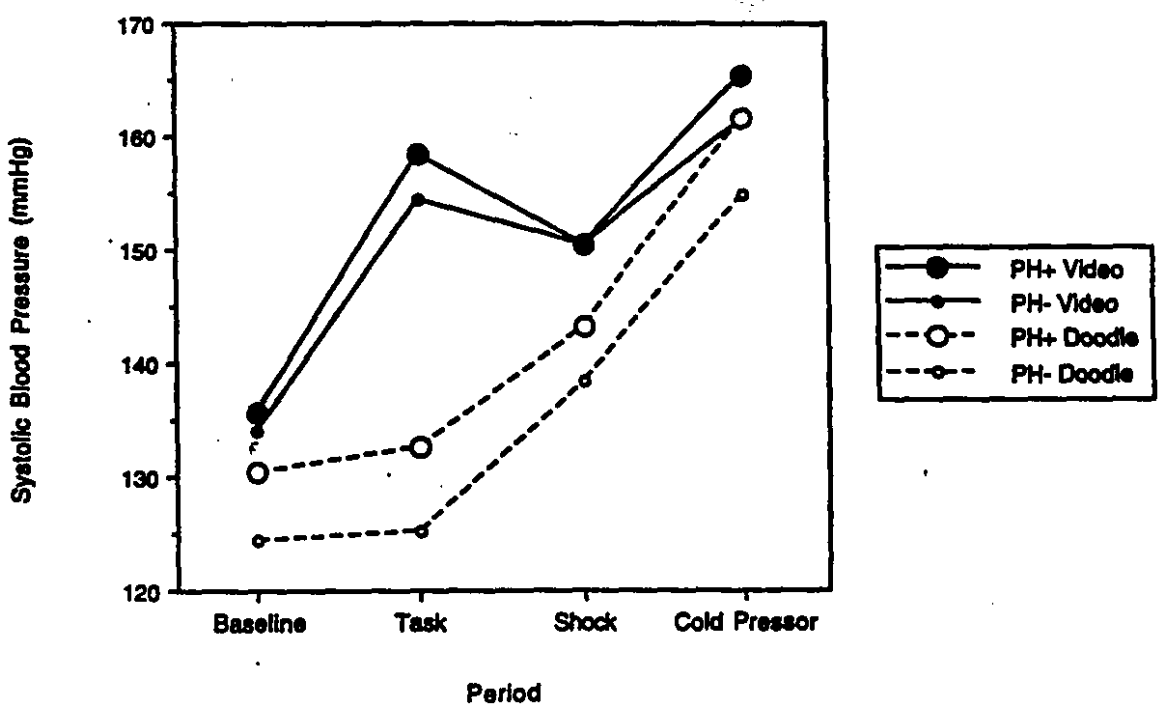


Figure 4

Diastolic blood pressure during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-).

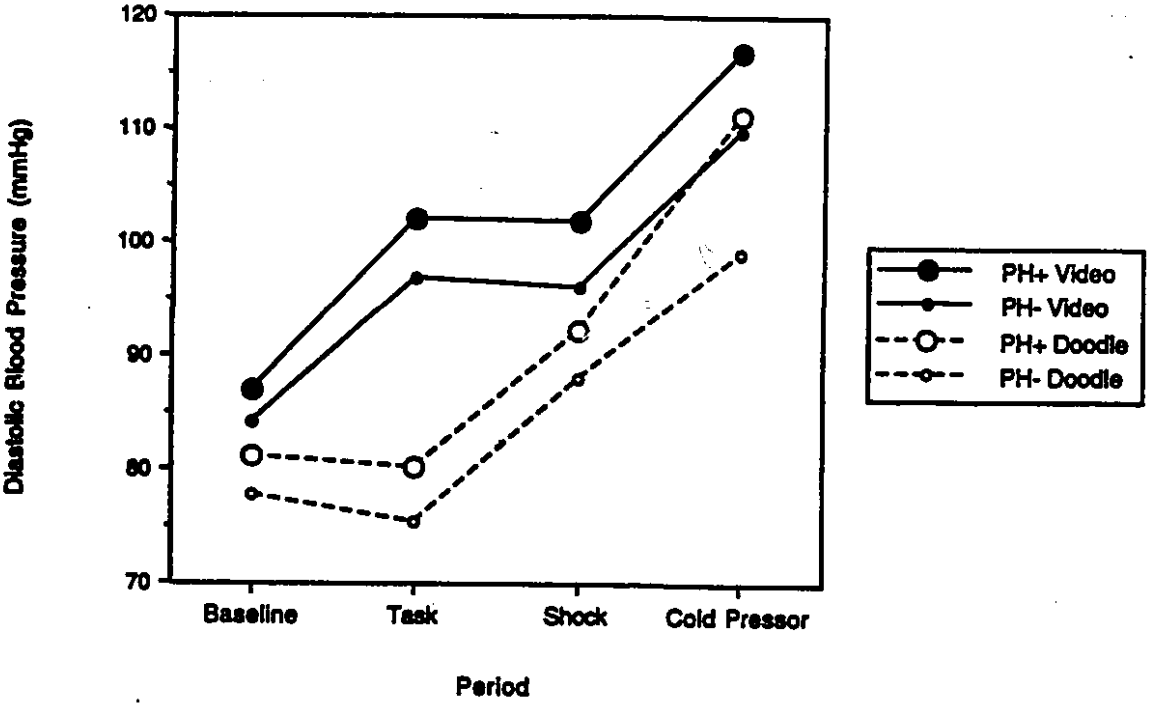
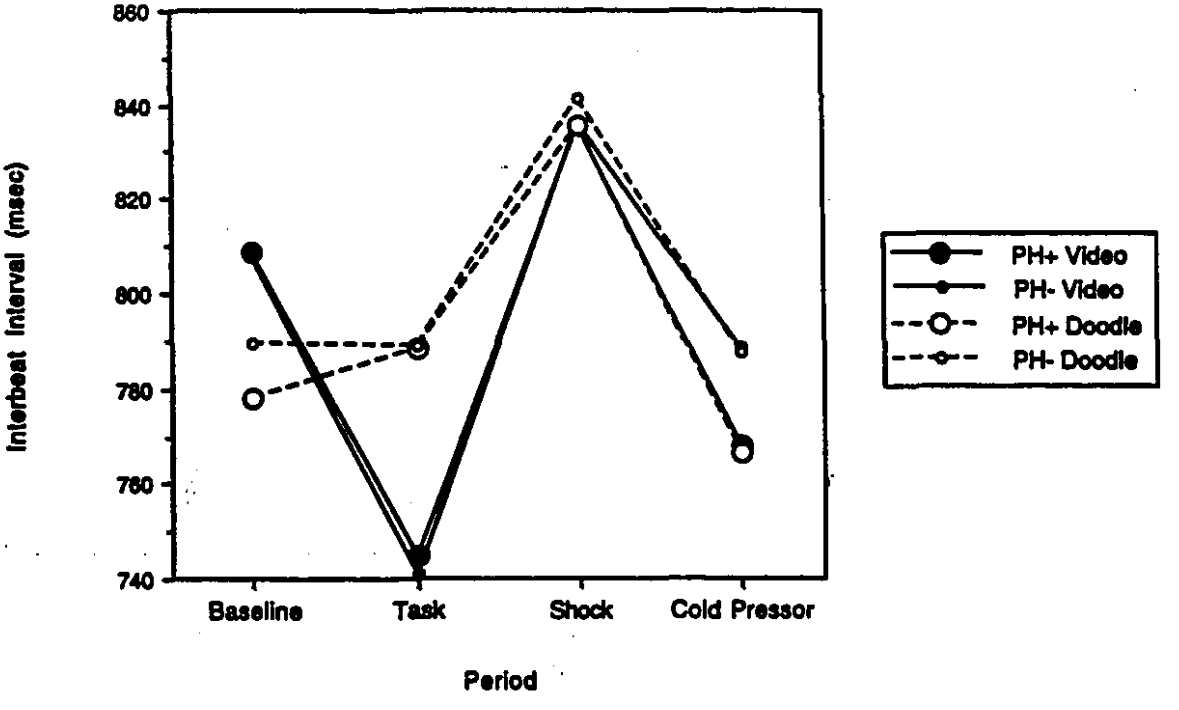


Figure 5

Interbeat interval during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)



indicated that the 20-minute task and the pain tasks were differentially stressful. The Day x Period interaction reflected significantly shorter interbeat intervals on the video game day as compared to the doodling day [$F(1,42)=28.87$, $p<.001$], but only during the 20-minute task.

Finger Pulse Transit Time

Significant main effects of Day and Period were observed for finger pulse transit time. As illustrated in Figure 6, the significant main effect of Day reflected significantly shorter pulse transit times on the video game versus doodling day. The significant Period main effect indicated significant changes in finger pulse transit time across the 20-minute task and the pain tasks.

Finger Pulse Amplitude

Significant effects of Day, Period, and Day x Period were observed for finger pulse amplitude (Figure 7). The main effect of Day reflected that overall, finger pulse amplitude tended to be smaller on the video game day than the doodling day. The Period main effect indicated that finger pulse amplitude significantly differed across the stressor and pain tasks. The stress-related decrease which was observed suggests an increase in digital vascular resistance. Further analysis of the Day x Period interaction indicated that finger pulse amplitude was significantly lower on the video game day versus the doodling day for the 20-minute task period [$F(1,42)=33.14$,

Figure 6

Finger pulse transit time during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

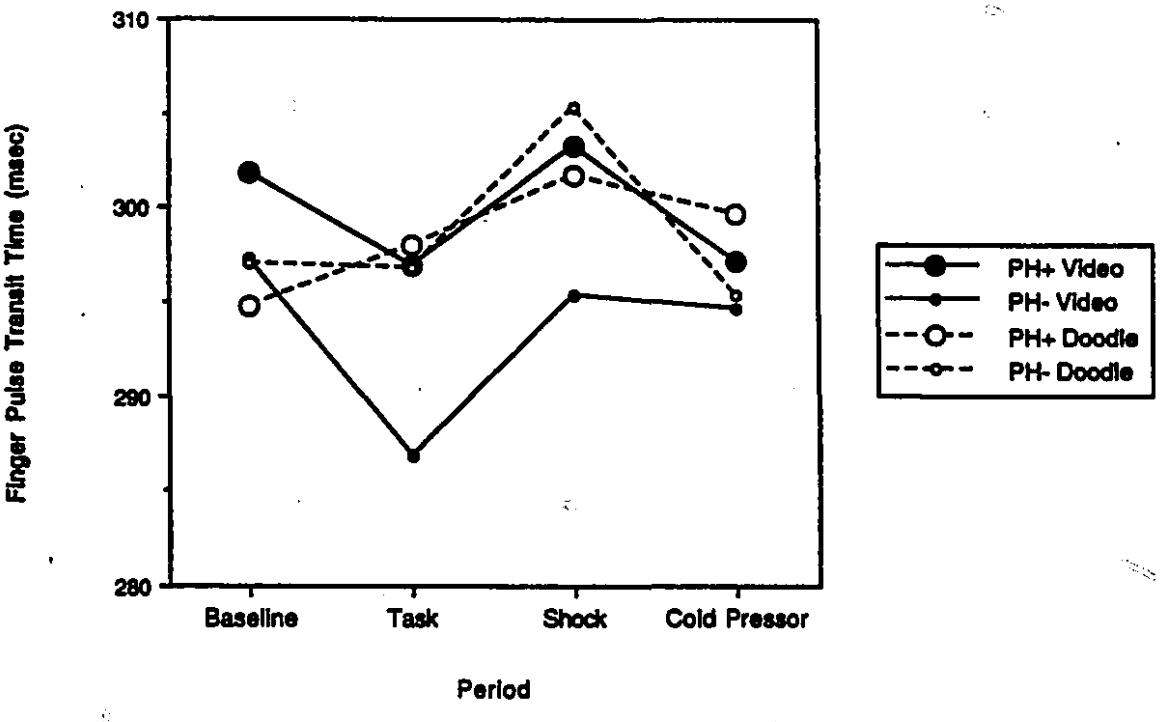
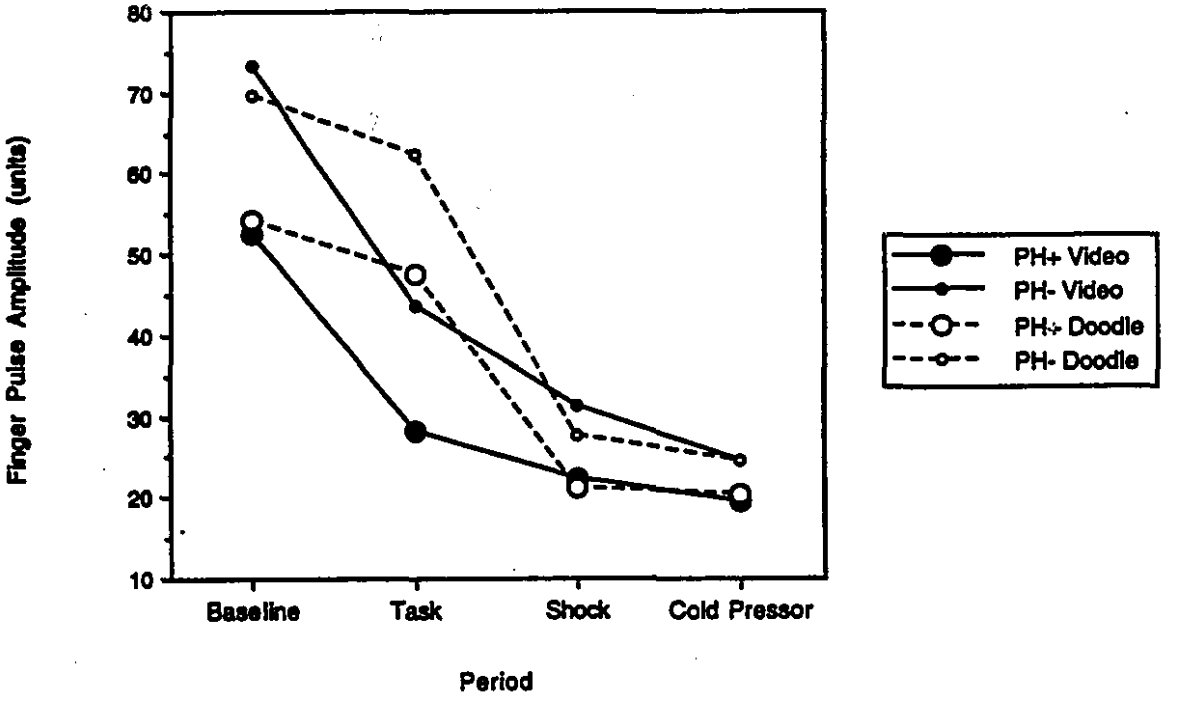


Figure 7

Finger pulse amplitude during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)



p<.001], but not during shock or cold pressor.

Skin Conductance Level

Significant effects of Day and Period were observed for skin conductance levels. As can be seen in Figure 8, the Day main effect reflected that significantly greater increases in skin conductance level were observed on the video game day as compared to the doodling day. The main effect of Period indicated that skin conductance levels were differentially affected by the stressor and pain tasks.

Pain Measures

Measures Obtained During Stimuli

Scores on the Taylor Manifest Anxiety Scale and the Marlowe-Crowne Social Desirability Scale were examined as possible correlates of the pain measures. No significant correlations were observed. Mean scores for the various pain measures obtained during each pain stimulus are presented in Table 13.

The pain measures obtained during the cold pressor test were analyzed using a 2 Group x 2 Resting Mean Arterial Pressure x 2 Day repeated measures MANOVA with the dependent measures of average pain rating, maximum pain rating, and latency to hand withdrawal. No significant main or interaction effects were seen. These results were unchanged by substitution of mean arterial pressure reactivity for resting mean arterial pressure.

The pain measures obtained during the electric shock

Figure 8

Skin conductance during each period on video game and doodling days for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

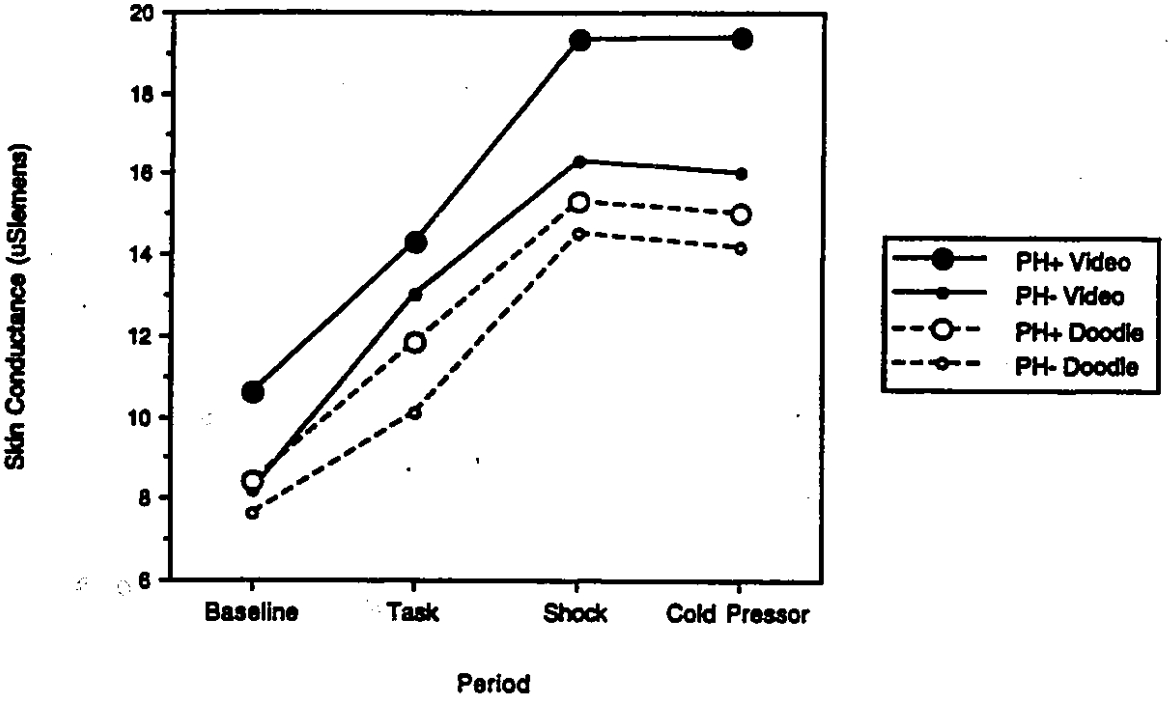


Table 13

Mean (M) and standard deviation (SD) of pain ratings on the video game and doodling day for offspring with at least one hypertensive parent (PH+) and with no hypertensive parent (PH-)

	PH+ (n=24)		PH- (n=24)	
	M	SD	M	SD
Video Game Day				
Cold Pressor				
Average Pain Rating	6.9	1.3	7.3	1.2
Maximum Pain Rating	8.5	1.4	8.9	1.2
Latency to Withdrawal	90.0	41.5	85.0	39.7
Shock				
Average Pain Rating	4.3	1.4	4.8	1.4
Maximum Pain Rating	5.4	1.7	6.5	2.0
Doodling Day				
Cold Pressor				
Average Pain Rating	7.0	1.3	7.3	1.4
Maximum Pain Rating	8.6	1.4	8.7	1.3
Latency to Withdrawal	84.4	41.0	82.5	41.7
Shock				
Average Pain Rating	4.6	1.3	4.6	1.5
Maximum Pain Rating	5.7	1.7	6.1	2.1

period were analyzed using a 2 Group x 2 Resting Mean Arterial Pressure x 2 Day repeated measures MANOVA with the dependent measures of average and maximum pain rating. The only significant effect was the main effect of Group, $F(2,40)=6.58$, $p<.01$. Equivalent follow-up univariate analyses failed to find a significant parental history effect for either average pain rating or maximum pain rating alone. However, inspection of the group means indicates that this multivariate effect was related to a general tendency of offspring of hypertensives to report less pain in response to shock.

A second MANOVA of pain measures obtained during the shock period was conducted substituting mean arterial pressure reactivity for resting mean arterial pressure. This also yielded a significant main effect of Group [$F(2,40)=5.32$, $p<.01$], as well as a significant Group x Mean Arterial Pressure Reactivity interaction [$F(2,40)=3.74$, $p<.05$]. Significant effects were then examined in equivalent univariate analyses. As before, the univariate analyses failed to detect a significant Group main effect in the individual pain measures, although the means indicated a tendency for offspring of hypertensives to report less pain. However, significant Group x Mean Arterial Pressure Reactivity interactions were seen for both the average pain rating for shock [$F(1,41)=7.48$, $p<.01$] and the maximum pain rating [$F(1,42)=9.18$, $p<.01$]. Further analyses revealed

that among subjects who were high mean arterial pressure reactors, offspring of hypertensives had significantly lower average pain ratings [PH+: 4.1, PH-: 5.2; $F(1,23)=5.18$, $p<.05$], and maximum pain ratings [PH+: 5.2, PH-: 7.1; $F(1,23)=9.26$, $p<.01$] in response to the shock task. No parental history effect was observed for subjects who were below the median for blood pressure reactivity (average rating PH+: 4.9, PH-: 3.9; maximum rating PH+: 6.0, PH-: 5.0).

In order to determine whether the reduced pain sensitivity to shock was associated specifically with blood pressure reactivity or to a general state of physiological arousal, a 2 Group x 2 Skin Conductance Reactivity x 2 Day repeated measures MANOVA was conducted for the dependent measures of average pain rating and maximum pain rating for shock. Skin conductance reactivity was computed as the change in skin conductance from baseline to the 20-minute task on the video game day, analogous to the mean arterial pressure reactivity measure. As before, the Group main effect was significant, $F(2,36)=7.16$, $p<.01$. However, the Group x Skin Conductance Reactivity interaction effect failed to reach significance, supporting the notion that the reduced pain sensitivity observed in the previous analysis was related more to cardiovascular reactivity than general physiological arousal.

Measures Obtained After Stimuli

Comparable MANOVAs were conducted for the MPQ data collected following the cold pressor test and the electric shock task. Present Pain Intensity and Pain Rating Index scores were used as the dependent measures. None of the effects were significant.

Coping Style and Pain

Results of the 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Day repeated measures MANOVA on the measures of average pain rating, maximum pain rating, and latency to hand withdrawal for the cold pressor test revealed a significant Manifest Anxiety x Social Desirability x Group interaction, $F(3,38)=3.21$, $p<.05$. No other significant effects were observed. Given these results, the Manifest Anxiety x Social Desirability x Group interaction effects of the comparable univariate analyses were examined. Univariate analyses for average pain rating and latency to hand withdrawal indicated that there was no significant three-way interaction for these measures. However, a significant Manifest Anxiety x Social Desirability x Group interaction was observed for maximum pain rating, $F(1,40)=7.01$, $p<.05$. Follow-up analyses of this three-way interaction revealed that a significant Manifest Anxiety x Social Desirability interaction was present only for the PH+ group, $F(1,20)=5.78$, $p<.05$. Further examination revealed that high manifest anxiety

scores were associated with significantly higher maximum pain ratings than the low manifest anxiety scores (9.6 and 7.8, respectively), but only in the group which fell below the median score on social desirability (i.e., the true high anxious group), $F(1,10)=6.80$, $p<.05$.

Results of the 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Day repeated measures MANOVA conducted using average pain rating and maximum pain rating for the shock task revealed a significant effect of Group, $F(2,36)=4.16$, $p<.05$. However, equivalent univariate analyses failed to detect a significant group effect when considering average pain rating and maximum pain rating individually.

The effect of coping style on pain measures obtained after the stimuli was examined using the MPQ data for each pain task. Present Pain Intensity and Pain Rating Index scores in response to each pain stimulus were used as dependent measures in two separate 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Day repeated measures MANOVAs. The overall MANOVA for the cold pressor test revealed a significant Manifest Anxiety x Group interaction effect, $F(2,39)=5.70$, $p<.01$. Comparable univariate analyses indicated a significant Manifest Anxiety x Group interaction for Present Pain Intensity scores [$F(1,40)=4.96$, $p<.05$], but not for Pain Rating Index scores. Further analysis of the significant interaction revealed that among offspring of

hypertensives, subjects who had high levels of anxiety had higher Present Pain Intensity scores than subjects with low levels of anxiety (3.0 vs 2.2). No effect of anxiety was seen in offspring of normotensives.

The 2 Manifest Anxiety x 2 Social Desirability x 2 Group x 2 Day repeated measures MANOVA with Present Pain Intensity and Pain Rating Index scores for the shock task as dependent measures also revealed a significant Manifest Anxiety x Group interaction [$F(2,39)=3.92$, $p<.05$], as well as a significant Manifest Anxiety x Day interaction [$F(2,39)=4.21$, $p<.05$] and a significant Manifest Anxiety x Social Desirability x Day interaction [$F(2,39)=4.68$, $p<.05$]. These interaction effects were then examined in the comparable univariate analyses. A significant Manifest Anxiety x Social Desirability x Day interaction was observed for Present Pain Intensity scores, $F(1,40)=5.25$, $p<.05$. No other effects were observed. Further analysis of this three-way interaction effect revealed that the Manifest Anxiety x Day interaction was restricted to the group which scored above the median on social desirability, $F(1,20)=4.75$, $p<.05$. This interaction reflected that while high anxious subjects did not differ in Present Pain Intensity scores for shock across the two days, low anxious subjects obtained higher scores on the doodling day compared to the video game day (1.44 vs. 0.67). With respect to the univariate analyses of Pain Rating Index scores, a

significant Manifest Anxiety x Group interaction was observed, $F(1,40)=7.92$, $p<.01$. No other significant effects were seen for Pain Rating Index scores. Examination of the significant interaction revealed that high anxious subjects received significantly higher Pain Rating Index scores in response to shock than low anxious subjects, but only among offspring of normotensives (high anxious: 18.9, low anxious: 11.0).

Finally, a 2 Group x 4 Coping Style chi-square analysis was conducted to assess whether offspring of hypertensives and offspring of normotensives differed in their coping styles. No significant effect was seen.

Mood States

Analyses of the effect of parental history on state measures of anger and anxiety during the protocol were conducted using separate MANOVAs for each mood state. No significant effects were observed for either of the 2 Group x 2 Day x 3 Period MANOVAs.

Correlations between state anxiety ratings at each time point and Pain Rating Index scores for the pain tasks were calculated for each day. State anxiety at all time points was highly correlated with Pain Rating Index scores for the cold pressor and shock on both the video game (r's ranging from .27 to .53, all p's<.05) and the doodling day (r's ranging from .22 to .48, all p's<.07).

Baroreflex Sensitivity

Results of the 2 Group x 2 Day x 4 Period x 2 Direction ANOVA of baroreflex sensitivity scores revealed a significant main effect of Period [$F(3,39)=13.63$, $p<.001$], reflecting a significant increase in baroreflex sensitivity during the shock task. A significant Group x Period interaction [$F(3,39)=4.41$, $p<.01$] revealed that the significant Period effect was limited to the PH+ group, [$F(3,17)=15.88$, $p<.001$]. A significant three-way interaction of Day x Period x Direction was also seen, $F(3,39)=3.79$, $p<.05$. Follow-up analyses indicated that the significant Period x Direction interaction was restricted to the video game day, $F(3,42)=6.83$, $p<.01$. Further examination of this effect showed that the significant Period effect was seen only for ascending sequences, $F(3,42)=6.17$, $p<.01$.

Regression analyses were conducted to examine whether ascending or descending baroreflex sensitivity or parental history were predictor variables for average pain rating or Pain Rating Index scores for either the cold pressor or electric shock pain stimuli. No significant effects were found at the adjusted alpha level.

Discussion

Pain Sensitivity

The present finding of reduced pain sensitivity to

electric shock in female offspring of hypertensives is consistent with the results of a laboratory study with male offspring of hypertensives (France et al., 1991), and the findings of the previous naturalistic study with females. However, there was no evidence that a parental history of hypertension was associated with reduced sensitivity for the cold pressor. Further, although previous work with normotensive males has suggested that a higher resting blood pressure level is associated with greater tolerance for a finger pressure pain task (Bruehl, Carlson, & McCubbin, 1992) and the cold pressor (McCubbin & Bruehl, 1994), high resting mean arterial pressure was not associated with lower pain ratings for cold pressor or electric shock in the present study.

One possible reason for some of the inconsistent results between studies is the use of different types of pain tasks. Previous investigations with established hypertensives have utilized an electric tooth pulp stimulation task, while positive findings among offspring of hypertensives have been seen with a constrictive pain task (male offspring) and venipuncture pain (female offspring). The positive effect involving parental history in the present study involved electric shock. There are a variety of ways in which the cold pressor may differ from the types of tasks which have shown positive results. For instance, it has been argued that tooth pulp stimulation represents an

exclusively nociceptive stimulus (Ghione et al., 1988), while the cold pressor could be considered to elicit a variety of sensations in addition to nociception. Additionally, qualities of the pain stimulus such as duration or intensity may play an important role in whether a hypoalgesic response will be observed among those at risk for hypertension. The social context or meaning of the stimulus may also be an important factor since other cues or associations with the environment in which the pain stimulus occurs may help elicit group differences in pain sensitivity. For instance, both electric tooth pulp stimulation (a procedure which takes place while sitting in a dentist's chair) and venipuncture (which takes place in a medical milieu with nurses, technicians, and medical equipment in the area) may elicit a different response than the administration of a pain task in a laboratory environment which has no previous associations for the subjects. One possible association to the medical or dental setting may be a perceived lack of personal control over the pain stimulus. In contrast, the majority of subjects withdrew their hand from the cold pressor prior to the maximum time limit, thus exercising control over the duration of the pain task. Although the physical environment for the administration of the cold pressor did not differ from that of the electric shock task, subjects expressed more misgivings prior to the administration of the

shocks than before the cold pressor. Thus, it is possible that it is easier to observe differences in pain sensitivity to tasks which are perceived as potentially harmful (or anticipated to be particularly painful) by the subject.

Another possible explanation for the inconsistent findings across pain tasks may relate to the restriction of testing sessions to the follicular phase of the menstrual cycle, when group differences may be minimal. Since some researchers have argued that there is no cyclic variation in pain thresholds of normally menstruating women (e.g., Veith et al., 1984), while others claim cyclic variations occur but have reported conflicting findings regarding the direction and timing of these changes (e.g., Goolkasian, 1980; Procacci, Zoppi, Maresca, & Romano, 1974; Tedford, Warren, & Flynn, 1977), the decision was made to control for menstrual phase between subjects. The follicular phase was chosen in the present study as it can be verified with reasonable accuracy without the need for costly and invasive estrogen and progesterone measurements. However, by restricting subject testing to this phase, we cannot determine whether group differences might have been more easily observed for the cold pressor at different phases of the menstrual cycle. There is at least some support for the argument that female offspring of normotensives and hypertensives may differ in their cardiovascular reactivity to stress during the luteal, but not the follicular, phase

of the menstrual cycle (Miller & Sita, 1994). Thus, hypertension-related hypoalgesia may be more easily observed during the luteal phase, and may be easier to elicit with a variety of pain tasks at that time.

Risk for Hypertension

The present results support the notion of a reduction in pain sensitivity in offspring of hypertensives, at least in response to electric shock. Findings regarding the interaction of family history and blood pressure reactivity provide further evidence that there is a relationship between pain sensitivity and risk for hypertension. That is, offspring of hypertensives who were identified as blood pressure reactors to the video game had lower average and maximum pain ratings for shock than offspring of normotensives. Interestingly, this occurred on both the video game day and the doodling day, when shock was not preceded by the game. As well, skin conductance reactivity was not associated with pain sensitivity. These findings have several implications. First, they are consistent with the initial analyses indicating the absence of stress-induced analgesia in the present study (i.e., no significant effect of day on the pain measures). While it is reasonable to expect that the effects of a non-pain stressor on pain sensitivity would be limited primarily to those who exhibited pronounced responses in peripheral measures such as blood pressure and skin conductance, the fact that blood

pressure reactors also reported less pain on the doodling day suggests that stress-induced analgesia did not occur. This does not eliminate the possibility that the relationship between risk for hypertension and pain sensitivity is mediated by differences in endogenous opiate levels or function, but it is inconsistent with the view that it is due to an association of risk with a general tendency towards greater peripheral arousal. Second, the apparently specific association between blood pressure reactivity and pain sensitivity was probably not related to baroreflex stimulation. The significantly higher blood pressure levels displayed during the video game compared to doodling suggest greater baroreflex stimulation on the video game day. However, pain sensitivity was unaffected by day. Admittedly, Elbert and colleagues (1988) found a reduction in pain sensitivity with baroreflex stimulation in borderline hypertensives, but the reactive offspring of hypertensives in the present study even displayed a reduced sensitivity to shock on the doodling day, in the absence of a stimulus for a large blood pressure response. In sum, it does not appear as if a reduced sensitivity to pain was the product of some form of exaggerated peripheral reactivity.

The joint effect of parental history and blood pressure reactivity on pain sensitivity seems, in contrast, to be more a reflection of elevated risk for hypertension among reactive parental history positive subjects. An elevated

blood pressure reactivity to stress is widely believed to be a pre-morbid indicator of risk for a sustained elevation in blood pressure. High blood pressure reactivity to stress has been associated with the subsequent development of hypertension in several prospective studies (e.g., Light et al., 1992; Matthews et al., 1993). The identification of reactive positive family history subjects may have improved the classification of the sample in regards to risk.

Psychological Mechanisms

Contrary to previous findings (Davidson & Bobey, 1970; Jamner & Schwartz, 1986), this study found no evidence that a repressive coping style was related to greater pain tolerance in either the hypertensive or normotensive offspring group. However, some evidence of a relationship between manifest anxiety and pain sensitivity was seen. This is consistent with existing evidence that elevated trait anxiety is associated with higher levels of reported pain across various pain stimuli (Craig, 1989, Dougher, 1979, Sternbach, 1968, 1974; Weisenberg, 1977).

As in Study 2, state anxiety at various time points was related to pain reports. It is possible that the laboratory pain tasks increased levels of state anxiety. However, since state anxiety at all time points, including preceding the pain tasks, was correlated with pain ratings, it seems plausible that anxiety led to higher pain reports.

Physiological Mechanisms

The present data do not provide much information concerning the central nervous system mechanisms responsible for the relationship between cardiovascular regulation and pain sensitivity. Endogenous opiates are known to be involved in the regulation of baroreflex sensitivity, but the differences between offspring of hypertensives and normotensive in the present study were minimal. Although offspring of hypertensives did show a significant increase in baroreflex sensitivity in response to shock, this was a somewhat unexpected finding, and they did not significantly differ from offspring of normotensives during any other period. A recent study also using continuous measurements of blood pressure provided by a Finapres monitor noted significantly lower baroreflex sensitivity in offspring of hypertensives (de Visser, 1994). In addition, regression analyses involving average pain rating and Pain Rating Index scores failed to find baroreflex sensitivity to be a significant predictor of pain reports when alpha levels were corrected for multiple tests. Therefore, these results provide little evidence to support speculation that baroreflex sensitivity differs between hypertensive-prone and normotensive individuals, or that differences in pain sensitivity can be attributed to baroreflex sensitivity.

GENERAL CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

As the results from each study have been discussed individually, this section will provide an overview and synthesis of these findings. In addition, some pertinent issues in this research area which remain to be addressed will be reviewed.

The most noteworthy finding from this series of studies is the fact that decreased pain sensitivity can be observed in normotensive females at genetic risk for hypertension, at least under some circumstances. Specifically, novice female donors at increased risk for the development of hypertension by virtue of a parental history of the disorder were found to have decreased pain sensitivity for venipuncture compared to female offspring of normotensives. In addition, female offspring of hypertensives were less sensitive to electric shock than offspring of normotensives. These are the first reported findings of a reduced sensitivity to pain in females at risk for hypertension, and extend the small body of research which has examined this phenomenon in males at risk for hypertension due to family history (France et al., 1991) or elevated resting blood pressure levels (Bruehl, Carlson, & McCubbin, 1992; McCubbin & Bruehl, 1994; Rosa et al., 1988). Of further interest, offspring of hypertensives who were at increased risk for the disorder by virtue of elevated resting blood pressure (in Study 2) or blood pressure reactivity (in Study 3) were particularly likely to

demonstrate reduced pain sensitivity.

Although these are interesting findings, hypertension-related hypoalgesia was not seen in response to cold pressor or in reports of menstrual pain. The failure to generalize this effect across different types of painful stimuli requires further consideration. One possible explanation is that not all the pain tasks tested in this series of studies were capable of triggering an endogenous opiate response to produce hypertension-related hypoalgesia. In support of this argument, evidence from some animal studies suggests that the endogenous opiate system may not be activated by noxious stimuli in general, but rather responds to highly specific stimuli. For instance, while response to brief front paw shock in rats appears to be opiate-mediated, hind paw shock and four paw shock do not seem to trigger an endogenous opiate response (Watkins & Mayer, 1982). In addition, there have been contradictory results reported in studies using naloxone to produce opiate blockade in human subjects. These findings have led to some debate whether commonly used laboratory pain tasks such as the cold pressor are capable of producing a significant release of endogenous opiates in humans (Grevert & Goldstein, 1978; Schull, Kaplan, & O'Brien, 1981). In contrast, intravenous catheterization has been shown to produce beta-endorphin release, and in fact has been found to lead to a greater release of endorphins in hypertensive adults than in a

normotensive control group (McNeilly & Zeichner, 1989). Thus, there is some support for the notion that in this series of studies not all the pain stimuli were likely to have triggered an endogenous opiate response.

Some investigators have argued that it may be difficult to engage the endogenous opiate system with any type of experimental pain task. Schull and colleagues (1981) note that experimental pain must mimic the severity, duration, and anxiety associated with clinical pain if endogenous opiate release is to be triggered. In humans, such painful and stressful stimuli may require the study of pain under more realistic conditions than can be obtained in the laboratory (Grevert & Goldstein, 1978), although it may be possible to choose types of pain tasks and modify experimental procedures so that they more closely resemble clinical pain (Schull et al., 1981). While this argument may also account for some of the inconsistent results across laboratory pain tasks, it fails to explain why the naturalistic stimulus of menstrual pain did not differentiate between parental history groups. One possibility is that this type of naturalistic pain does not trigger an endogenous opiate response. Alternatively, since subjects diagnosed with dysmenorrhea or receiving medical treatment for painful menstrual symptoms were excluded from the study, the sample may have been limited to individuals who experienced "sub-clinical" levels of menstrual pain

which were unlikely to elicit endogenous opiate activity. Of course, the difficulties associated with using menstrual pain as a noxious stimulus that were discussed in Study 1 (e.g., lack of standardized administration of the pain stimulus across subjects) also made it difficult to compare subjects' responses to this type of naturalistic pain.

Gender differences in hypertension-related hypoalgesia are another possible explanation for the difficulty in finding consistent differences in pain sensitivity between female offspring with and without a parental history of hypertension. The effects of gender on pain perception have been relatively well studied, with females typically reporting both lower pain threshold and pain tolerance for a variety of experimentally applied noxious stimuli compared to male subjects (e.g., Arendt-Nielsen & Bjerring, 1988; Buchanan & Midgley, 1987; Otto & Dougher, 1985; Rollman & Harris, 1987). However, only limited information is available concerning gender differences in physiological responses to noxious stimuli. There is some evidence that females show diminished blood pressure responses and elevated heart rate responses to psychological stressors compared to males (Girdler, Turner, Sherwood, & Light, 1990; Hastrup & Light, 1984). Maixner and Humphrey (1993) have also found that males and females differ in their cardiovascular responses to noxious forearm ischemia. Interestingly, while males showed greater increases in

arterial blood pressure in response to the ischemic pain task, females reported greater pain. Since elevations in arterial blood pressure may stimulate endogenous pain inhibitory processes, the authors argue that females may be less able to engage intrinsic pain modulatory systems. This would suggest that hypertension-related hypoalgesia may be more easily demonstrated in males than females.

Another gender-related issue concerns the possible confounding effects of cyclic hormonal influences on physiological reactivity and pain sensitivity. In the two studies which produced the most ambiguous results, pain sensitivity was assessed during (Study 1) and immediately following (Study 3) menstruation. It is possible that hormonal changes across the menstrual cycle may interact with risk for hypertension in a manner such that differences in pain sensitivity are more easily evident in later stages of the menstrual cycle. Recent evidence that differences in physiological reactivity between females with and without a parental history of hypertension may be restricted to the luteal phase (Miller & Sita, 1994) suggests that possible cycle effects on hypertension-related hypoalgesia warrants further investigation.

Findings with respect to coping style and pain reports failed to support the hypothesis that a repressive coping style is related to elevated pain thresholds in hypertension-related hypoalgesia. In general, repressive

coping could not account for pain ratings in these studies. Also, no evidence was found to suggest that female offspring of hypertensives were more likely to employ repressive coping strategies than other female subjects. Previous longitudinal research (Kahn et al., 1972; McClelland, 1979) relating a repressive coping style to the development of hypertension focused on male subjects, so the lack of significant findings in these studies may suggest a gender difference in the link between personality factors and hypertension. Another difference between earlier studies and those presented here is the method of assessing repressive coping style. Previous work associating repressive coping with increased pain tolerance used single scales such as the L-scale of the Eysenck Personality Inventory (Jamner & Schwartz, 1986) or the Repression-Sensitization Scale (Davidson & Bobey, 1970), while studies linking hypertension with repressive coping have used non-standardized checklists of personal concerns (Cumes, 1983; Kahn et al., 1972) to identify repressors. However, these methodologies have been criticized as failing to distinguish between repressors and truly low anxious individuals (Weinberger et al., 1979). The combination of Marlowe-Crowne and Trait Anxiety scores has been suggested as a more appropriate means of differentiating these two groups (Bruehl, Carlson, Baxter, & Curran, 1992; Weinberger et al., 1979). However, using this recommended method, this

research failed to support the hypothesis that repressive coping style would be associated with greater pain tolerance. This suggests that earlier reports concerning a relationship between repressive coping style, hypertension, and hypoalgesia may have been confounded by failing to account for anxiety levels, and that some of the lower pain ratings of "repressors" may be more a product of low anxiety.

In contrast, results concerning the effects of anxiety as a moderator of pain reports were largely consistent with the existing literature. Previous research has indicated that, in general, elevated levels of anxiety are associated with an increased perception of acute noxious events as painful (e.g., Craig, 1989; Merskey, 1980; Sternbach, 1968, 1974). In these studies, elevated levels of trait anxiety were associated with higher pain ratings at various points throughout the venipuncture procedure in Study 2, as well as with several of the pain measures for the laboratory tasks in Study 3. It is important to note, however, that there was no evidence of group differences in trait anxiety, so the hypoalgesia demonstrated by offspring of hypertensives in Study 2 and Study 3 could not be accounted for by lower anxiety levels. An additional finding was that state anxiety was also related to pain ratings in Study 2 and Study 3. One possibility is that the experience of the painful stimulus increased the subjects' level of anxiety.

However, since subjective anxiety ratings at various time points during the study protocols were highly correlated with pain ratings, it suggests that anxiety contributed to higher pain ratings. It is also worth noting that differences in pain ratings could not be accounted for by other psychological variables such as a tendency to respond in a socially desirable manner or to a general tendency to report physical symptoms or pain.

Two additional possible mechanisms which were addressed primarily in Study 3 were baroreflex activity (stimulation and sensitivity) and stress-induced analgesia. Although it has been speculated that baroreflex sensitivity may be diminished in hypertensive-prone individuals and that this may reflect alterations in endogenous opiate activity (de Visser, 1994; Ditto & France, 1990; Petty & Reid, 1981), this study failed to provide support for such a hypothesis. There was also no strong evidence that baroreflex sensitivity was related to pain sensitivity for these tasks. Similarly, there was only minimal evidence that baroreceptor stimulation, inferred from blood pressure response, was related to pain sensitivity. Resting mean arterial pressure was not related to pain sensitivity for either cold pressor or shock. While stress-induced changes in mean arterial pressure were related to pain sensitivity for the shock task among offspring of hypertensives who were above the median on change in mean arterial pressure, this effect was also

seen on the doodling day, when no stimulus to elicit a large blood pressure response was present.

One final consideration regarding the role of the baroreflexes is worth note. The methods used in Study 3 to infer baroreflex activity primarily reflect activity of the high pressure baroreceptors. Results from the animal literature suggest that both the sinoaortic and the low pressure cardiopulmonary baroreflexes are involved in nociception, and that activation of either type of baroreceptor may inhibit pain to only certain types of noxious stimulation (Randich & Maixner, 1984). This may be why a recent study involving sodium loading (Ditto et al., 1993), which presumably had an effect on blood volume but not blood pressure per se, observed a significant reduction of sensitivity to the cold pressor test. Thus, despite the null findings in Study 3, it remains possible that the baroreceptors play an important role in reduced sensitivity to pain in offspring of hypertensives. Further study of this possibility is needed in the human literature.

Although previous studies have found that purely psychological stressors are capable of producing stress-induced analgesia (Bandura et al., 1988; Ditto et al., 1993), this effect was not seen when comparing pain sensitivity on the video game day versus the doodling task day in Study 3. While it is possible that the video game task was not perceived as stressful by the subjects, the

physiological data suggest otherwise. Alternatively, a psychological stressor may require certain qualities in order to elicit stress-induced analgesia. One dimension which has been postulated to be important is the issue of stressor controllability. Maier (1986) found opiate-mediated stress-induced analgesia in rats following inescapable stress but not in response to escapable stress. It is conceivable that subjects in this study felt that they had some degree of control over the stressful video game task, making it unlikely that stress-induced analgesia would occur. Unfortunately, subjects' perception of stressor controllability were not assessed, so this explanation is only speculative. It is interesting to note that when subjects were divided into reactors versus non-reactors on the basis of blood pressure response to the video game task, what might appear to be an effect of stress-induced analgesia was observed among those females at-risk for hypertension who were high reactors to the task. However, these same subjects were found to report less pain on the doodling day as well, which makes this finding seem more a reflection of risk for hypertension.

In sum, although the findings of reduced sensitivity to pain in female offspring of hypertensives are interesting, there are a variety of issues which require further study before firm conclusions regarding hypoalgesia in hypertensive-prone women can be drawn. First, given that

hypertension-related hypoalgesia was not seen across all the pain stimuli which were examined, future studies need to replicate these findings and confirm whether this effect can be seen in response to other pain stimuli. The use of other types of laboratory pain tasks which appear to be opiate-mediated, such as an ischemic pain task (Frid, Singer, Oei, & Rana, 1981; Schull et al., 1981), as well as modifying procedures for tasks such as the cold pressor to enhance the likelihood of opiate release (Buchsbaum, Davis, & Bunney, 1977) may help clarify this issue. With respect to naturalistic pain, other types of situations such as medical or dental procedures may provide the opportunity to test for this effect under circumstances where the release of endogenous opiates would be expected.

It may also be helpful to find ways to select subjects who maximize the potential risk for developing hypertension. This could include recruiting subjects who meet various criteria believed to be associated with genetic risk for hypertension. Rather than selecting subjects only on the basis of parental history of hypertension, subjects could be screened for a multigenerational family history of the disorder or for the presence of high blood pressure in both rather than one biological parent (Hunt, Williams, & Barlow, 1986). Another possibility is to select subjects using joint risk factors, such as parental history of hypertension in conjunction with elevated resting blood pressure levels

or elevated blood pressure reactivity in response to stress or a sodium-loading challenge (Everson, Lovallo, Sausen, & Wilson, 1992).

Directly assessing whether an endogenous opiate response is necessary for this hypoalgesia to occur is another important task which requires further study in humans. This may be tested by assessing pain sensitivity with and without naloxone blockade of endogenous opiate action. McCubbin and Bruehl (1994) reported that opiate blockade did not eliminate the relationship between resting blood pressure and pain ratings for the cold pressor test in their sample of male normotensives. However, further study of the effect of opiate blockade on subjects at risk for hypertension using a variety of pain stimuli is necessary to gain a better understanding of the potential mechanisms involved in hypertension-related hypoalgesia.

Finally, gender issues remain an important question in this area. In order to directly assess potential gender differences in hypertension-related hypoalgesia, hypertensive-prone males and females should be tested using the same pain tasks. Females should also be assessed at various points throughout the menstrual cycle to examine whether this hypoalgesia varies as a function of hormonal cycle.

Investigation of pain reactions among individuals at risk for hypertension may provide valuable information

regarding the etiology of hypertension, as well as contribute to the understanding of the means by which the pain and cardiovascular systems interact in general.

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LIST OF APPENDICES

PERSONAL AND FAMILY HEALTH QUESTIONNAIRE

GENERAL INFORMATION

Name: _____ _____
Last Name First Name

Date of Birth: _____ / _____ / _____
month day year

Height: _____ _____
feet inches

Weight: _____
pounds

Phone Number: _____

PERSONAL HEALTH

Has your doctor ever told you that you have:

a. High blood pressure? _____ yes _____ no

b. Some other significant circulatory problem? _____ yes _____ no
(if yes, please describe _____
_____)

c. Some other significant health problem? _____ yes _____ no
(if yes, please describe _____
_____)

Are you currently taking any prescription or non-prescription medication? (please include any birth control medication) _____ yes _____ no
(if yes, please describe _____
_____)

On what date did your last menstrual cycle end? (i.e., the last day of menstruation): _____

Are you a smoker? _____ yes _____ no
(if yes, how many cigarettes per day? _____)

PARENTAL HEALTH

The following questions refer to your BIOLOGICAL PARENTS.

Has your FATHER ever suffered from any of the following conditions?

a. angina or heart pain?	yes	no	don't know
b. heart attack?	yes	no	don't know
c. stroke?	yes	no	don't know
d. high blood pressure?	yes	no	don't know
e. diabetes?	yes	no	don't know
f. kidney disease?	yes	no	don't know

Has your MOTHER ever suffered from any of the following conditions?

a. angina or heart pain?	yes	no	don't know
b. heart attack?	yes	no	don't know
c. stroke?	yes	no	don't know
d. high blood pressure?	yes	no	don't know
e. diabetes?	yes	no	don't know
f. kidney disease?	yes	no	don't know

Because most people are not certain about their parents' actual blood pressure levels, it is most important that we contact each parent in order to confirm the blood pressure information that you have provided. Therefore we would appreciate it if you would give us your permission to contact your parents in order to inquire about their blood pressure status.

Father's Name	Mother's Name
street apt.	street apt.
city state zip	city state zip
( ) phone number	( ) phone number

Subject # _____

DAILY MONITORING INSTRUCTIONS

This package contains several forms for you to fill out on a daily basis. The items refer to different types of physical symptoms which you may or may not notice. Please fill out one form at the **end of each day** before you go to bed.

REMEMBER! You should fill out the first form **2 days before your period starts** and then continue to fill out one form each day **until your period is over.** Each form will take you only a few moments, but it is very important that you take the time to respond accurately and to complete one form each day. Also, make sure that you fill in the information at the top of the form on each day.

If you have any questions, please feel free to contact me at 593-1060.

When you have completed the forms, they can be dropped off at **Porter Hall, room 7F** on **Monday to Friday** from **9 a.m. until noon** (ask for **Janis**). Make sure you bring your card with you so that you can receive proof of your experimental points.

Daily Symptom Monitoring

Date (day/month/year): _____

Is today the first day of your menstrual period? YES NO

For each of the items below, please circle the letter that matches **how often you noticed that symptom TODAY**, using the following scale:

(a) not at all
(b) rarely
(c) sometimes
(d) often
(e) continuously

a b c d e 1. Felt irritable, easily agitated, and/or impatient
a b c d e 2. Had cramps
a b c d e 3. Felt depressed
a b c d e 4. Had abdominal pain or discomfort
a b c d e 5. Felt exhausted, lethargic, or tired
a b c d e 6. Felt weak and dizzy
a b c d e 7. Felt tense and nervous
a b c d e 8. Had diarrhea
a b c d e 9. Had a backache
a b c d e 10. Breasts felt tender and sore
a b c d e 11. Lower back, abdomen, and inner sides of thighs hurt or were tender
a b c d e 12. Felt like curling up in bed, using a hot water bottle on abdomen, or taking a hot bath
a b c d e 13. Felt constipated
a b c d e 14. Had pains which diminished or disappeared for several minutes and then reappeared
a b c d e 15. Had a continuous dull aching pain
a b c d e 16. Felt bloated
a b c d e 17. Felt nauseous
a b c d e 18. Had a headache

Medication use today:	Type (e.g., aspirin)	Amount (e.g., 2 tablets)
	_____	_____
	_____	_____
	_____	_____
	_____	_____

Parental History of Hypertension Survey - Father's Form

Since this study is concerned with the effects of a genetic history of hypertension, this form should be completed by the biological father only.

High blood pressure (hypertension) is commonly defined as having a systolic blood pressure over 140 mmHg and/or a diastolic blood pressure over 90 mmHg.

1. Has your physician ever told you that you have high blood pressure?

   Please circle your answer: Yes No

2. Do you presently have high blood pressure:

   Please circle your answer: Yes No

3. Are you currently taking any high blood pressure medication?

   Please circle your answer: Yes No
   If yes, please indicate the name of the medication:
   _____

4. Do you have diabetes?

   Please circle your answer: Yes No

5. Do you suffer from any kidney ailments?

   Please circle your answer: Yes No
   If yes, please describe:_____

6. Does/did your mother have high blood pressure?

   Please circle your answer: Yes No

7. Does/did your father have high blood pressure?

   Please circle your answer: Yes No

Subject # _____

PRE-DONATION QUESTIONNAIRE

1. Name (please print): _____

2. Age: _____

3. Height: _____ feet and _____ inches (or _____ cm)

4. Weight: _____ lbs (or _____ kg)

5. Ethnicity: _____

6. Do you have high blood pressure? NO YES

7. Are you currently suffering from any illnesses? NO YES
   If yes, what? _____

8. Are you on any prescription or non-prescription medication? NO YES
   If yes, what? _____

9. Have you had any alcohol in the past 6 hours? NO YES
   If yes, how many ounces of alcohol? _____
   If yes, how many bottles of beer? _____

10. Have you had any cigarettes in the past 6 hours? NO YES
    If yes, how many? _____

11. Have you had any caffeine in the past 6 hours? NO YES
    If yes, how many cups of coffee? _____
    If yes, how many cans of caffeinated soft drink? _____

12. Are you hungry right now? NO YES

13. Does your father have high blood pressure? NO YES

14. Does your mother have high blood pressure? NO YES

15. How many times have you given blood in the past? _____

16. How would you describe your mood right now?
    (a) not at all anxious or nervous
    (b) a little anxious or nervous
    (c) moderately anxious or nervous
    (d) quite a bit anxious or nervous
    (e) extremely anxious or nervous