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# Decreased pain perception and risk for hypertension: Considering a common physiological mechanism

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## Abstract

For almost two decades, researchers have demonstrated that hypertension is reliably associated with decreased perception of pain. More recently, a growing body of evidence has begun to suggest that hypoalgesia is not a consequence of high blood pressure, as the phenomenon precedes the onset of hypertension in individuals at risk for the disorder. This article provides a review of empirical evidence of decreased pain perception in normotensive persons with a family history of hypertension, elevated resting blood pressure, or exaggerated cardiovascular reactivity to stress. Based on the existing evidence, hypoalgesia is argued to be a correlate of dysregulation of central nervous system structures involved in both pain control and cardiovascular regulation in individuals who are genetically predisposed to develop high blood pressure. As such, hypoalgesia may serve as a valuable method of identifying individuals at greatest risk for hypertension.

**Descriptors:** Pain, Hypoalgesia, Risk for hypertension

Hypertension is often referred to as a “silent” killer because it is typically believed that individuals with high blood pressure rarely experience subjective symptoms of their disorder. In fact, two decades of research has demonstrated convincingly that hypertension is reliably associated with at least one subjective symptom—hypoalgesia, or decreased perception of pain. The following article will briefly review the existing literature on the association between hypoalgesia and high blood pressure, and will present evidence to suggest that this relationship may have important clinical and theoretical implications. In particular, evidence of hypoalgesia in normotensive individuals at increased risk for hypertension will be offered in support of the notion that hypertension and decreased pain perception may result from a common physiological dysfunction. Specifically, central opioid hyposensitivity is hypothesized as a mechanism of both hypoalgesia and exaggerated autonomic and neuroendocrine responses to stress in individuals at risk for hypertension. Finally, it will be argued that if hypoalgesia and hypertension share a common pathophysiology, then decreased pain

perception might serve as a behavioral marker of risk for hypertension long before the onset of high blood pressure levels.

## Hypertension and Decreased Pain Perception

### *Animal Findings*

A preponderance of the research on the relationship between blood pressure and antinociception has been conducted using animal models of hypertension (Ghione, 1996; Randich & Maixner, 1984; Zamir & Maixner, 1986). Most of these studies have examined nociception in the spontaneously hypertensive rat (SHR). The SHR strain has been bred for its genetic predisposition to hypertension. At 4 weeks of age, SHR have systolic blood pressure levels less than 120 mmHg, similar to control animals. By 12 weeks of age, SHR typically exhibit systolic blood pressure levels of 200 mmHg or more. An increased nociceptive threshold has been demonstrated in SHR using a number of noxious paradigms including tail-flick, hot-plate, and flinch-jump paradigms (Maixner, Touw, Brody, Gebhart, & Long, 1982; Randich, 1982, 1986; Saavedra, 1981; Sitsen & de Jong, 1983, 1984; Tsai & Lin, 1987; Wendel & Bennett, 1981).

### *Human Findings*

A significant relationship between hypertension and decreased pain sensitivity has also been observed in humans (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Ghione et al., 1985; Guasti et al., 1995a, 1995b, 1996; Rosa & Ghione, 1990; Rosa, Ghione, Panattoni, & Mezzasalma, 1986; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Sheps et al., 1992; Zamir & Shuber, 1980). In the first reported study (Zamir & Shuber, 1980), average pain threshold for electrical tooth pulp stimulation was significantly higher in

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individuals with hypertension than in normotensive controls. Subsequent investigations confirmed and extended these findings, demonstrating that hypertensive humans also report decreased pain in response to noxious thermal, electrocutaneous, and mechanical stimulation. Although a comprehensive review of the hypertension-related hypoalgesia literature is beyond the scope of this article, the interested reader is referred to an excellent review published by Ghione (1996).

### Clinical Implications of Hypertensive Hypoalgesia

Evidence of hypoalgesia has also been observed outside of the laboratory. France and Katz (1999) reported that men with high blood pressure experience significantly less pain during recovery from radical prostatectomy surgery. In this study, correlational analyses indicated that higher preoperative resting systolic blood pressure was associated with significantly lower pain ratings at 24 and 48 hr postsurgery. The inverse relationship between blood pressure and pain ratings was maintained even after controlling for individual differences in age, length of surgery, and postsurgical self-administration of morphine. These findings provide unique evidence of hypoalgesia in the context of actual tissue damage.

Although dampening of acute postsurgical pain can be viewed as beneficial insofar as individuals with hypertension may experience less suffering and disability, pain often serves a crucial biological function by signaling a physiological threat that may require an adaptive response to prevent harm or injury. In this respect, there is emerging evidence that hypertensive hypoalgesia may complicate accurate and early detection of cardiac disease. Data from the Framingham Heart Study indicate that men and women with hypertension are almost twice as likely to suffer an unrecognized myocardial infarction (Kannel, Dannenberg, & Abbott, 1985). Based on routine biennial electrocardiograms, 45% of women and 35% of men with hypertension were shown to have experienced a heart attack but could not recall any symptoms (e.g., angina) that may have been caused by the coronary event. One possible explanation for these findings is that high blood pressure is associated with a suppression of chest pain during episodes of myocardial ischemia. Such an effect has been observed during clinical exercise testing, as individuals with elevated resting systolic blood pressure show a delayed onset of angina during episodes of exercise-induced myocardial ischemia (Krittayaphong & Sheps, 1996; Sheps et al., 1989). A higher prevalence of silent myocardial ischemia has also been observed in the 24-hr Holter monitoring recordings of men with high blood pressure (Siegel, Cheitlin, Seeley, Black, & Hulley, 1992). In sum, hypertension may be associated with a significant attenuation of clinical pain perception, which may lead to serious adverse health consequences.

### Theoretical Implications of Hypertensive Hypoalgesia

Although the clinical implications of hypertensive hypoalgesia are only beginning to be explored, the theoretical implications of this relationship have attracted considerably more attention. Hypoalgesia has been described by different authors as a consequence, a cause, and a correlate of hypertension. According to a simple causal model, decreased pain perception can be viewed as a direct consequence of elevated blood pressure levels. This perspective was supported by many of the early human and laboratory animal studies that demonstrated that chronic and acute manipulation of blood pressure levels elicited significant decreases in pain percep-

tion. Although there are a number of mechanisms that may account for this effect, considerable evidence suggests that stimulation of carotid or sinoaortic baroreflex arcs attenuates pain perception in both humans and laboratory animals. Thus, pressor-mediated increases in baroreflex stimulation are frequently offered as a mechanism of hypertensive hypoalgesia (Dworkin, 1988; Ghione, 1996; Maixner, 1991). Endogenous opioids have also been implicated in this effect, as a number of laboratory animal studies have shown that hypertensive hypoalgesia is reversed by administration of opiate antagonists (Delbarre, Casset-Senon, Delbarre, Sestillange, & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1983, 1984; Wendel & Bennett, 1981).

Other authors have suggested that the arrow of causation is reversed such that, in some cases, hypertension is a consequence of hypoalgesia. As early as 1979, Dworkin and colleagues proposed that blood pressure increases are negatively reinforced by baroreflex-mediated dampening of central nervous system responses to aversive events (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979). This idea was later expanded into a model of hypertension development (Dworkin, 1988), which states that individuals who are exposed to chronic, aversive social or environmental stimulation *and* who exhibit a strong baroreflex-mediated dampening of central nervous system activity in response to this stimulation (including reduced pain and anxiety) may experience an instrumentally conditioned increase in blood pressure. In effect, hypertension is a learned coping response. Several lines of evidence suggest that increased blood pressure can be learned in this manner. First, there is considerable evidence that the physiological consequences of baroreceptor stimulation are not confined to cardiovascular regulation, but have widespread inhibitory influence on CNS activity including pain perception, emotional arousal, and sleep (Dworkin et al., 1994). Second, previous evidence has shown that laboratory animals and humans with spinal injuries can learn to regulate their blood pressure to bring about desired environmental outcomes (Dworkin, 1988). Third, individual differences in baroreflex dampening of pain perception have been used to predict longitudinal increases in resting blood pressure, and this effect is most pronounced in subjects with high ratings of daily life stress (Elbert et al., 1994).

Hypertension and hypoalgesia have also been described as correlated phenomena, possibly sharing a common underlying physiological dysfunction that may result in both decreased pain perception and increased blood pressure. Consistent with this model, some of the earliest laboratory animal studies of the relationship between hypertension and hypoalgesia indicated that decreased pain perception is not dependent upon high blood pressure. For example, SHR exhibit elevated nociceptive thresholds as early as 4 weeks of age, when their blood pressure levels are not yet significantly different from age-matched controls (Maixner et al., 1982; Sitsen & de Jong, 1983; Wendel & Bennett, 1981). Further, acute administration of the opiate antagonist naloxone can reverse hypoalgesia in SHR without affecting resting blood pressure (Maixner et al., 1982). Finally, the elevated nociceptive threshold observed in SHR is unaffected by antihypertensive treatments that attenuate blood pressure increases (Sitsen & de Jong, 1984). The latter finding was also supported in a study of human hypertensives (Ghione et al., 1988), in which a combination of antihypertensive medication and lifestyle change resulted in significant reductions in blood pressure but had no significant effect on pain threshold. In sum, results from both human and animal studies indicate that hypoalgesia is *not* dependent on elevated blood pressure levels. An alternative explanation is that decreased sensitivity

to noxious stimuli may reflect pathophysiological processes that are associated with a genetic predisposition to hypertension rather than a secondary consequence of chronic high blood pressure.

### Risk for Hypertension and Pain Perception

In the past few years, the correlational model of hypertensive hypoalgesia has motivated a number of investigators to ask whether risk for hypertension is associated with decreased pain perception in humans. Using a variety of indices of risk for hypertension (e.g., parental history of the hypertension, elevated resting blood pressure, enhanced cardiovascular reactivity to stress), these studies combine to provide strong support for the notion that hypoalgesia precedes the development of high blood pressure.

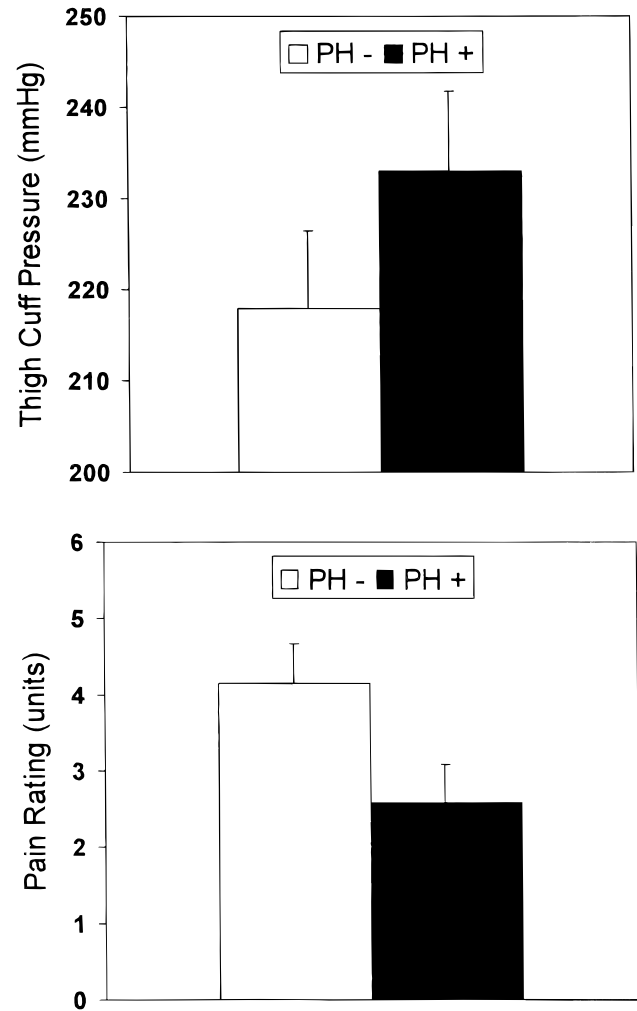
### Parental History of Hypertension and Pain Perception

Offspring of hypertensives are two to four times more likely to develop high blood pressure than those without a parental history of the disorder (Hunt, Williams, & Barlow, 1986). This risk ratio increases directly as a function of the number of first degree relatives affected, and inversely with the age of onset of hypertension in the affected relatives. Because hypertension generally does not develop until middle-to-late adulthood, assessment of pain perception in normotensive young adults with a parental history of the disorder is in some respects analogous to assessing nociception in very young SHR. Hence, normotensive offspring of hypertensive parents would be expected to exhibit decreased pain perception as compared to offspring of normotensive parents.

In the first published study designed specifically to assess pain sensitivity in individuals at genetic risk for hypertension (France, Ditto, & Adler, 1991), sensitivity to a constrictive thigh cuff was compared in young normotensive men with and without a parental history of hypertension. In this study, a thigh cuff was inflated until the participant first reported pain, at which point the cuff was deflated and a subjective pain rating was obtained. As illustrated in Figure 1, offspring of hypertensive subjects tolerated significantly higher inflation of the thigh cuff before they reported pain. Moreover, despite allowing significantly higher cuff inflation pressures, offspring of hypertensive individuals also rated the maximum cuff pressure as significantly less painful than offspring of normotensive individuals. As shown in Table 1, these findings were later confirmed and extended in subsequent investigations, which revealed that hypoalgesia in offspring of hypertensive persons is present in both men and women, is obtained using a variety of pain assessment strategies, and can be observed across diverse noxious stimuli such as cold pressor applied to the hand (Al' Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France & Stewart, 1995; Stewart & France, 1996), heat applied to the forearm (Bragdon, Light, Girdler, & Maixner, 1997), venipuncture for blood donation (France, Adler, France, & Ditto, 1994), mechanical finger pressure (D'Antono et al., 1999; Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998), forearm ischemia (France & Stewart, 1995; Stewart & France, 1996), and electrocutaneous stimulation to the forearm (Ditto, France, & France, 1997) and leg (Page & France, 1997). In fact, only one published study has failed to observe a significant effect of family history of hypertension on pain perception (Ghione et al., 1988).

### Resting Blood Pressure and Pain Perception

Normotensives with elevated resting systolic blood pressure are also at increased risk for developing hypertension (Jamerson & Julius, 1991; Julius & Schork, 1978; Yong, Kuller, Rutan, & Bun-



**Figure 1.** Mean (SEM) thigh cuff pressure at pain threshold and associated subjective pain rating as a function of a positive/negative parental history of hypertension (PH+/PH-).

ker, 1993). Therefore, a continuous relationship between resting systolic blood pressure levels and pain perception would provide additional evidence that hypoalgesia is related to risk for hypertension rather than hypertension per se. As can be seen in Table 2, more than a dozen studies have confirmed this relationship. Although some of these studies include participants with "borderline hypertension," who may meet current diagnostic criteria for hypertension (i.e., resting blood pressure levels  $\geq 140/90$  mmHg), as a whole the research indicates that there is a continuous relationship between resting blood pressure and hypoalgesia that extends into the normotensive range. This work also confirms that this relationship is present in both men and women, exists across a variety of pain paradigms and measures, and can be observed as early as adolescence.

Family history of hypertension and resting blood pressure are both predictors of hypertension, yet most offspring of hypertensive persons and individuals with mildly elevated blood pressure *do not* go on to develop hypertension (Hunt et al., 1986; Jamerson & Julius, 1991; Julius & Schork, 1978). Thus, studies that rely exclusively on a single index of risk may lead to negative findings due to an inadequate concentration of participants who actually go on to develop the disorder. This may account for the failure to

**Table 1.** Evidence of Decreased Pain Perception in Offspring of Hypertensives

Reference	Pain stimulus (location)	Significant pain measures	Nonsignificant pain measures
Ghione et al., 1988	Electrical (tooth)		Pain Threshold
France et al., 1991	Mechanical (thigh)	Pain threshold Pain Intensity Scale	—
France et al., 1994	Venipuncture (arm)	Pain Intensity Scale	
France & Stewart, 1995	Cold (hand) Ischemia (arm)	Pain Intensity Scale Pain Intensity Scale McGill Pain Questionnaire	McGill Pain Questionnaire —
Al' Absi et al., 1996	Cold (hand)	Pain Intensity Scale McGill Pain Questionnaire	—
Stewart & France, 1996	Cold (hand) Ischemia (arm)	McGill Pain Questionnaire Pain Intensity Scale Pain Unpleasantness Scale McGill Pain Questionnaire	Pain Intensity Scale Pain Unpleasantness Scale —
Bragdon et al., 1997	Heat (arm)	Pain Threshold Pain Tolerance <sup>a</sup>	—
Ditto et al., 1997	Electrocutaneous (arm) Cold (hand)	Pain Intensity Scale —	McGill Pain Questionnaire Pain Intensity Scale McGill Pain Questionnaire
Page & France, 1997	Electrocutaneous (ankle)	Pain threshold Flexion reflex threshold	McGill Pain Questionnaire
Ditto et al., 1998	Mechanical (finger)	Pain Intensity Scale <sup>b</sup>	—
D'Antono et al., 1999	Cold (hand) Mechanical (finger)	Pain Unpleasantness Scale <sup>b</sup> McGill Pain Questionnaire Pain Unpleasantness Scale <sup>b</sup> McGill Pain Questionnaire	Pain Intensity Scale Pain threshold Pain Intensity Scale Pain threshold

<sup>a</sup>Significant interaction effect (lowest pain tolerance observed in female offspring of normotensives with low resting blood pressure). <sup>b</sup>Significant interaction effect (lowest pain ratings observed in offspring of hypertensives with high resting blood pressure).

observe significant effects of resting blood pressure on pain perception in a number of the studies listed in Table 2. A more powerful test of the relationship between risk for hypertension and hypoalgesia involves the simultaneous assessment of multiple risk factors. Page and France (1997) examined pain thresholds as a function of both family history of hypertension and resting systolic blood pressure. This study assessed pain threshold using the nociceptive flexion reflex, which has been proposed as a naturally occurring, objective physiological correlate of nociception in humans (Chan & Tsang, 1985; Willer, 1977). In this paradigm, electrocutaneous stimulation of the sural nerve of sufficient intensity to stimulate small diameter nociceptive fibers invokes a reflex contraction of the biceps femoris muscle of the upper leg (Kugelberg, Eklund, & Grimby, 1969). This polysynaptic spinal reflex subserves withdrawal from noxious stimuli to avoid tissue injury. As seen in Figure 2, analyses of the intensity of electrical stimulation required to reach the thresholds for nociceptive withdrawal and subjective pain revealed a pattern of hypoalgesia in individuals at risk for hypertension. First, significantly higher intensities of electrocutaneous stimulation were required to elicit the nociceptive flexion reflex in offspring of hypertensive versus normotensive individuals. Second, offspring of hypertensive persons endured significantly more intense stimulation before reporting pain. Third, both parental history of hypertension and resting systolic blood pressure were significant independent predictors of electrical stimulation intensity required to elicit nociceptive withdrawal and to reach subjective pain threshold. Although Page and France (1997) observed significant independent effects for both risk factors, in other studies significant differences in pain perception were ob-

served only when resting blood pressure and family history of hypertension were used in combination to define high versus low risk participants (Bragdon et al., 1997; D'Antono et al. 1999; Ditto et al., 1998). In either case, a combination of risk factors appears to provide the most reliable evidence of significant differences in pain perception.

#### **Cardiovascular Reactivity and Pain Perception**

Cardiovascular reactivity to physical and psychological stress has been shown to contribute significantly to the prediction of future resting blood pressure levels, even after controlling for such standard risk factors as age, body mass index, resting blood pressure, and family history of hypertension (Light, Dolan, Davis, & Sherwood, 1992; Matthews, Woodall, & Allen, 1993; Menkes et al., 1989). Therefore, according to the correlational model of hypertensive hypoalgesia, one might also expect an inverse relationship between cardiovascular reactivity to stress and pain perception. As seen in Table 3, only a few investigators have addressed this question. Nonetheless, four of the five studies published to date confirmed that increased reactivity to a variety of stressors (i.e., cold pressor, video game, or a brief speech about an angering incident) is associated with hypoalgesia to a diversity of painful stimuli (i.e., dental pain, forearm ischemia, forearm shock, forearm heat). Although the data from these studies are not straightforward, often involving significant results for some measures of reactivity but not others, an important finding that emerges from several studies is that cardiovascular reactivity effects may combine with other hypertensive risk factors. For example, France and Stewart (1995) observed that forearm ischemic pain ratings were best explained

**Table 2.** Evidence of Decreased Pain Perception in Individuals With High Normal Resting Blood Pressure

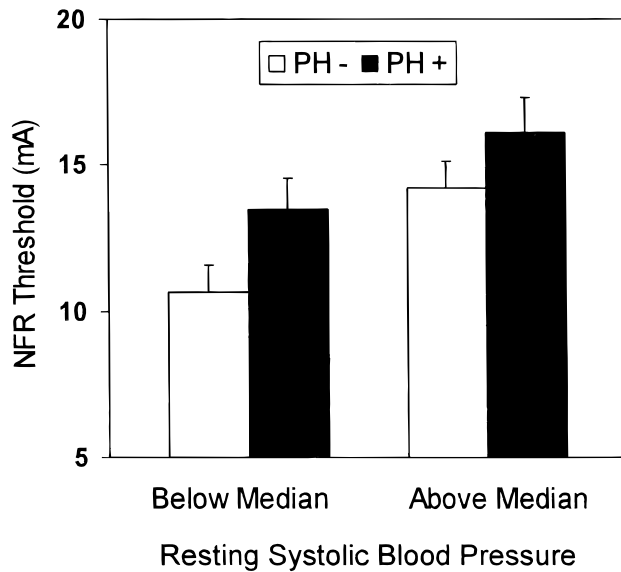
Reference	Pain stimulus (location)	Significant pain measures	Nonsignificant pain measures
Rosa et al., 1986	Electrical (tooth)	Pain threshold	—
Elbert et al. 1988	Electrocutaneous (arm)	Pain threshold	—
Ghione et al., 1988	Electrical (tooth)	Pain threshold	—
Bruehl et al., 1992	Mechanical (finger)	Pain Intensity Scale	—
McCubbin & Bruehl, 1994	Cold (hand)	Pain Intensity Scale	McGill Pain Questionnaire
Rau et al., 1994	Heat (hand)	Pain threshold	—
	Mechanical (finger)	—	Pain threshold
Guasti et al., 1995a	Electrical (tooth)	Pain threshold & tolerance	—
Al' Absi et al., 1996	Cold (hand)	—	Pain Intensity Scale McGill Pain Questionnaire
Fillingim & Maixner, 1996	Heat (arm)	Pain threshold & tolerance	—
	Ischemia (arm)	Pain tolerance	Pain threshold
Schobel et al., 1996	Mechanical (skin folds)	Pain Intensity Scale	—
Stewart & France, 1996	Cold (hand)	—	Pain Intensity Scale Pain Unpleasantness Scale McGill Pain Questionnaire Pain Intensity Scale Pain Unpleasantness Scale McGill Pain Questionnaire
	Ischemia (arm)	—	
Bragdon et al., 1997	Heat (arm)	Pain threshold Pain tolerance <sup>a</sup>	—
Maixner et al., 1997	Heat (arm)	Pain threshold	Pain tolerance
	Ischemia (arm)	Pain tolerance	Pain threshold
Page & France, 1997	Electrocutaneous (ankle)	Pain threshold Flexion reflex threshold	—
Sheffield et al., 1997	Heat (arm)	Pain Intensity Scale Pain Unpleasantness Scale	—
Ditto et al., 1998	Mechanical (finger)	Pain Intensity Scale <sup>b</sup>	—
Fillingim et al., 1998	Heat (arm)	Pain Unpleasantness Scale	Pain threshold & tolerance Pain Intensity Scale Pain threshold & tolerance Pain Intensity Scale Pain Unpleasantness Scale
	Heat (face)	—	
Schobel et al., 1998	Mechanical (skin folds)	Pain Intensity Scale	—
D'Antono et al., 1999	Cold (hand)	Pain threshold Pain Unpleasantness Scale <sup>b</sup>	Pain Intensity Scale McGill Pain Questionnaire
	Mechanical (finger)	Pain threshold Pain Intensity Scale Pain Unpleasantness Scale	McGill Pain Questionnaire
France & Suchowiecki, 1999	Electrocutaneous (ankle)	—	Flexion reflex threshold

<sup>a</sup>Significant interaction effect (lowest pain tolerance observed in female offspring of normotensives with low resting blood pressure). <sup>b</sup>Significant interaction effect (lowest pain ratings observed in offspring of hypertensives with high resting blood pressure).

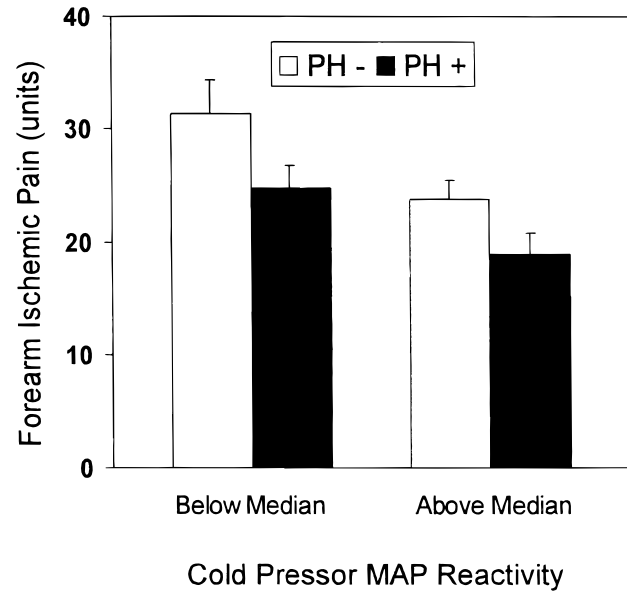
by a combination of cardiovascular responsivity to the cold pressor test (hand immersion in ice water) and parental history of hypertension. Based on the results of previous longitudinal studies, increased blood pressure responsivity to the cold pressor test was identified as a significant predictor of risk for hypertension. As illustrated in Figure 3, France and Stewart (1995) observed the lowest forearm ischemic pain ratings in participants with both a parental history of hypertension and elevated mean arterial responsivity to cold pressor, whereas the highest pain ratings were reported by participants with neither risk factor. Similarly, Ditto et al. (1997) reported decreased sensitivity to forearm shock in women with a parental history of hypertension and high blood pressure reactivity to a video game stressor. Finally, Bragdon and

colleagues (1997) reported greater thermal pain tolerance levels in women identified as having increased cardiovascular reactivity to stress or elevated resting blood pressure levels. Further, the lowest thermal pain tolerance levels were observed in women with low resting mean arterial pressure and a negative parental history of hypertension.

In sum, hypertension risk factors have been shown to combine both additively and interactively to determine pain perception (Bragdon et al., 1997; Ditto et al., 1997; D'Antono et al., 1999; France & Stewart, 1995; Page & France, 1997). However, because risk factors are commonly dichotomized for methodological and statistical convenience, the actual manner in which these risk factors combine is unclear. Participants are often assigned to high or low



**Figure 2.** Mean (*SEM*) level of electrical stimulation required to elicit a nociceptive withdrawal reflex as a function of a positive/negative parental history of hypertension (PH+/PH-) and resting systolic blood pressure.



**Figure 3.** Mean (*SEM*) forearm ischemic pain rating index scores on the McGill Pain Questionnaire as a function of a positive/negative parental history of hypertension (PH+/PH-) and mean arterial pressure (MAP) reactivity to cold pressor.

resting blood pressure groups despite the fact that blood pressure is related to risk for hypertension in a continuous fashion. Similarly, genetic history of hypertension is commonly defined on the basis of parental history in lieu of a more complicated assessment of the number of first degree relatives with hypertension and the age of onset of their disorder. Given this limitation, it is not possible to conclude whether these hypertensive risk factors combine in an additive or interactive manner to determine pain perception. Hence a conservative interpretation of the data would be that individuals with multiple risk factors are more likely to exhibit hypoalgesia.

### Mechanisms of Hypoalgesia in Individuals at Risk for Hypertension

Evidence of decreased pain perception in normotensive individuals at elevated risk for hypertension provides strong support for the

notion that hypoalgesia precedes the onset of high blood pressure. These findings also suggest the possibility of a common underlying mechanism(s) for both hypoalgesia and hypertension.

France and Ditto (1996) proposed that the paraventricular nucleus (PVN) of the hypothalamus plays an important role in mediating decreased pain perception in individuals at risk for hypertension. The hypothalamus is part of a central autonomic network that is responsible for integrating autonomic, neuroendocrine, and behavioral responses to stress (Benarroch, 1993). This reciprocally interconnected network includes areas of the forebrain (insular and medial prefrontal cortices, amygdala, hypothalamus), midbrain (periaqueductal gray, pons), and brain stem (nucleus of the solitary tract, ventrolateral medulla). Within this network, the PVN of the hypothalamus serves the crucial function of integrating responses to both painful and nonpainful stressors through its innervations of autonomic relay centers, production of corticotrophin releasing factor (CRF), and neuronal projections to various

**Table 3.** Evidence of Decreased Pain Perception in Normotensives with Enhanced Cardiovascular Reactivity to Stress

Reference	Pain Stimulus (location)	Stressor	Significant Pain Measures	Nonsignificant pain measures
Rosa et al., 1988	Electrical (tooth)	Cold pressor	Pain threshold	—
France & Stewart, 1995	Ischemia (arm)	Cold pressor	Pain Intensity Scale McGill Pain Questionnaire	—
Bragdon et al., 1997	Heat (arm)	Speech	Pain tolerance	Pain threshold
Caceres & Burns, 1997	Cold (hand)	Arithmetic	—	Pain threshold & tolerance
Ditto et al., 1997	Electrocutaneous (arm) Cold (hand)	Video game	Pain Intensity Scale <sup>a</sup> —	McGill Pain Questionnaire Pain Intensity Scale McGill Pain Questionnaire

<sup>a</sup>Significant interaction effect (lowest pain ratings observed in high reactors with a parental history of hypertension).

areas of the central nervous system involved in pain modulation (Benarroch, 1993; Cechetto & Saper, 1988; Sawchenko & Swanson, 1982; Swanson & Kuypers, 1980).

McCubbin (1991) proposed that the PVN of the hypothalamus fails to respond normally to endogenous opioids in individuals at risk for hypertension. In a series of investigations, McCubbin and colleagues demonstrated that administration of the opiate antagonist naloxone to individuals with below average resting blood pressure resulted in exaggerated blood pressure, epinephrine, adrenocorticotrophic hormone (ACTH), cortisol, and beta-endorphin responses to stress (McCubbin, 1991). Naloxone had no such effect on individuals with above average resting blood pressure, suggesting that individuals at risk for hypertension fail to exhibit a normal dampening of sympatho-adreno-medullary (SAM) and hypothalamo-pituitary-adrenocortical (HPA) activity in response to endogenous opioids. McCubbin interpreted his findings as evidence that exaggerated SAM and HPA responsivity to stress may be due to a deficiency of direct or indirect (e.g., via limbic, brain stem, and other central nervous system structures) opioid inhibitory input to the PVN. In line with a central tenet of this model, previous research demonstrated opioid innervation of CRF neurons in the PVN as well as endogenous opioid inhibition of CRF release (Almeida, Hassan, & Holsboer, 1993).

France and Ditto (1996) proposed an extension of McCubbin's (1991) model to explain decreased pain perception in individuals at risk for hypertension. As illustrated in Figure 4, the central opioid hyposensitivity model of hypoalgesia asserts that attenuation of inhibitory opioid input to the PVN may have important consequences for pain modulation. As described in detail below, these consequences include (1) greater activation of baroreceptor reflex arcs, (2) enhanced release of endogenous opioids during stress, and (3) increased stimulation of descending pain modulation pathways.

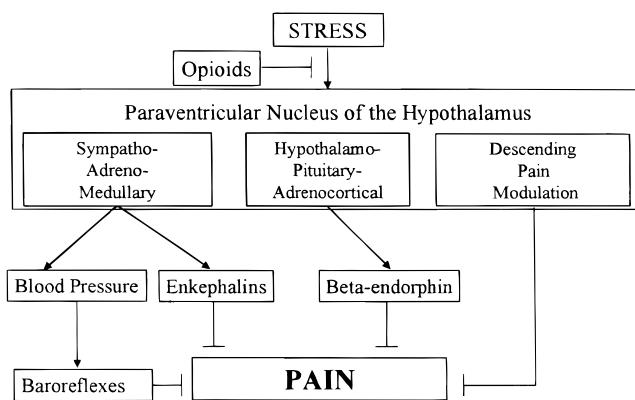
#### Baroreceptor Reflex Arc Stimulation

As noted above, activation of baroreflex arcs has been shown to increase pain thresholds for noxious electrical, mechanical, and thermal stimulation. According to the central opioid hyposensitivity model of hypoalgesia, individuals at risk for hypertension would be expected to exhibit exaggerated blood pressure responsivity to stress due to exaggerated autonomic arousal. Increased blood pres-

sure responsivity would, in turn, elicit enhanced activation of baroreflex pain dampening mechanisms. Consistent with this hypothesis, enhanced blood pressure reactivity to physiological and psychological stress has been demonstrated in individuals at risk for hypertension (Ditto, 1986; Widgren, Wikstrand, Berglund, & Andersson, 1992). There is also evidence that baroreflex-mediated dampening of pain perception is enhanced in individuals at increased risk for hypertension (Elbert et al., 1988). Therefore, enhanced stimulation of baroreflex arcs may be one mechanism of hypoalgesia in individuals prone to hypertension. However, because some studies have failed to observe an effect of baroreflex stimulation on pain perception in individuals at risk for hypertension (France et al., 1991; Schobel et al., 1996), or have shown this effect with some pain stimuli but not others (Rau et al., 1994), enhanced baroreflex stimulation is unlikely to be a complete explanation.

#### Endogenous Opioid Responsivity

A second prediction of the central opioid hyposensitivity model of hypoalgesia is that individuals at risk for hypertension may exhibit increased endogenous opioid responsivity to stress. First, release of peripheral opioids is stimulated during both SAM and HPA activation (Viveros, Diliberto, Hazum, & Chang, 1979), hence attenuation of inhibitory opioid inputs to the PVN could enhance stress-related release of beta-endorphins from the pituitary and enkephalins from the adrenal medulla. Second, neurons within the PVN synthesize a variety of neuropeptides (e.g., enkephalins, dynorphin, vasopressin) that have analgesic effects (Benarroch, 1993; Khachaturian, Lewis, Schafer, & Watson, 1985; Rossier et al., 1979; Watson et al., 1982), suggesting that hypertensive-prone individuals may experience enhanced peripheral and central opioid levels during stress. In fact, studies of humans subjects have shown that stressors elicit larger increases in blood levels of met-enkephalin in normotensive individuals with versus those without a family history of hypertension (Fontana et al., 1994), and greater increases in plasma beta-endorphin in hypertensive versus normotensive persons (McNeilly & Zeichner, 1989). Further, elevated endogenous opioid levels have been observed in blood plasma in hypertensive humans (Guasti et al., 1996; Sheps et al., 1992) and in the pituitary, hypothalamus, and spinal cord of hypertensive-prone rats (Zamir, Simantov, & Segal, 1980). Finally, hypoalgesia is reversed in the SHR following administration of opiate antagonists (Delbarre et al., 1982; Saavedra, 1981; Sitsen & de Jong, 1983, 1984; Wendel & Bennett, 1981). Nonetheless, the role of endogenous opioids as mediators of hypoalgesia in humans at increased risk for hypertension remains controversial. McCubbin and Bruehl (1994) observed that opioid blockade with naloxone attenuated the inverse relationship between resting blood pressure and cold pressor pain ratings (from  $r = -.54$  to  $-.11$ ), although the change in correlation failed to reach statistical significance in their small sample of 16 participants. Schobel and colleagues (1998) also reported that naloxone failed to significantly alter the inverse relationship between resting blood pressure and pain ratings in response to noxious mechanical stimulation (skin fold pinch) in a small sample of borderline hypertensive ( $n = 12$ ) and normotensive ( $n = 9$ ) men. Although normotensive subjects reported significantly higher pain ratings following naloxone administration, there was no significant change in pain sensitivity for the borderline hypertensive subjects. In sum, additional research is required to more adequately address the role of endogenous opioids as potential mediators of hypoalgesia in hypertensive and hypertension-prone humans.



**Figure 4.** The central opioid hyposensitivity model of hypoalgesia in individuals at risk for hypertension. Lines ending with arrows represent activation, whereas flat terminals represent inhibition.

### Descending Pain Modulation

Neurons within the PVN project to various areas of the central nervous system involved in pain modulation such as the periaqueductal gray, nucleus raphe magnus, nucleus of the solitary tract, and substantia gelatinosa of the spinal cord (Benarroch, 1993; Cechetti & Saper, 1988; Sawchenko & Swanson, 1982; Swanson & Kuypers, 1980). Therefore, hypertensive-prone individuals may also demonstrate hypoalgesia due to a deficient inhibition of descending central pain modulation pathways. Specifically, hypothalamic input to descending pain modulation systems may initially be stimulated in a normal fashion by either painful or nonpainful stressors. However, an exaggerated or prolonged dampening of pain signals may be observed in individuals at risk for hypertension because of a reduced response to the endogenous opioids that normally inhibit hypothalamic activity and, in turn, activity of descending pathways for modulating pain.

We provided preliminary evidence of enhanced activity of central descending pain modulating systems in offspring of hypertensives using both the exteroceptive suppression (France et al., 1996) and nociceptive flexion reflex (Page & France, 1997) paradigms. In the exteroceptive suppression paradigm, electrocutaneous stimulation of the trigeminal nerve during voluntary contraction of the jaw is used to elicit brief suppressions of activity in jaw closing muscles (e.g., temporalis, masseter). Previous research has demonstrated that the second exteroceptive suppression period, known as ES2, is mediated by inhibitory brainstem interneurons that receive input from limbic pathways involved in pain modulation (Godaux & Desmedt, 1975). Further, patients with a variety of chronic and recurrent pain disorders exhibit a shortened ES2 (Wallasch & Gobel, 1993), indicating that this response may provide a noninvasive index of the integrity of central pain modulation systems in humans. Results of our study indicated that individuals with a parental history of hypertension exhibited a protracted ES2 as compared with offspring of normotensive persons (France et al., 1996), suggesting an enhancement of central pain modulation activity in people at risk for hypertension. Similarly, as noted above and illustrated in Figure 2, offspring of hypertensive persons exhibit an elevated nociceptive flexion reflex threshold compared with offspring of normotensive individuals (Page & France, 1997). Because the nociceptive flexion reflex can be elevated by stimulation of descending pain modulation systems (De Broucker, Ce-

saro, Willer, & Le Bars, 1990; Roby-Brami, Bussel, Willer, & Le Bars, 1987; Willer, Boureau, & Albe-Fessard, 1979; Willer, Roby, & Le Bars, 1984), our findings provide additional support for the notion of enhanced activation of central pain modulation systems in individuals at risk for hypertension.

Although evidence exists to support baroreflex, opioid, and descending pain modulation mechanisms as possible mediators of hypoalgesia, it must be emphasized that there is considerable interaction among supraspinal structures involved in pain modulation and cardiovascular control. Therefore it is perhaps most likely that hypoalgesia results from a complex physiological interaction between these mechanisms. Further, the predominant mechanism of influence may vary with the nature of the stressful stimulus. For example, hypoalgesia in the context of acute pain may be mediated primarily by descending pain modulation pathways, whereas hypoalgesia during prolonged exposure to noxious stimulation may be mediated primarily by endogenous opiate mechanisms.

### Future Directions

This review suggests that hypoalgesia in normotensive individuals at risk for hypertension may reflect dysregulation at central nervous system structures involved in both pain control and cardiovascular regulation. From a theoretical perspective, attempts to understand the biological basis of hypoalgesia may lead to new insights into pathophysiological mechanisms of hypertension. From a practical perspective, hypoalgesia may serve as a valuable method of identifying those at greatest risk for clinically significant blood pressure elevations among otherwise heterogeneous groups of offspring of hypertensive or normotensive individuals with mildly elevated blood pressure. In fact, individual differences in pain perception during baroreflex stimulation have been used to predict increases in blood pressure up to 20 months later (Brody & Rau, 1994; Elbert et al., 1994). Evidence from these short-term follow-up studies argue for additional assessment of the ability of hypoalgesia to predict long-term changes in blood pressure among individuals at risk for hypertension. Ultimately, decreased pain perception may serve as a behavioral marker of hypertensive risk that could be used to promote early and efficient identification of strong candidates for pharmacological and nonpharmacological prevention efforts.

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