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Review

Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain

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Abstract

Endogenous pain regulatory system dysfunction appears to play a role in the maintenance of chronic pain. An important component of the pain regulatory process is the functional interaction between the cardiovascular and pain regulatory systems, which results in an association between elevated resting blood pressure (BP) and diminished acute pain sensitivity. This BP/pain sensitivity relationship is proposed to reflect a homeostatic feedback loop helping restore arousal levels in the presence of painful stimuli. Evidence is emerging that this normally adaptive BP/pain sensitivity relationship is significantly altered in chronic pain conditions, affecting responsiveness to both acute and chronic pain stimuli. Several mechanisms that may underlie this adaptive relationship in healthy individuals are overviewed, including endogenous opioid, noradrenergic, and baroreceptor-related mechanisms. Theoretical models are presented regarding how chronic pain-related alterations in the mechanisms above and increased pain facilatory system activity (central sensitization) may contribute to altered BP/pain sensitivity interactions in chronic pain. Clinical implications are discussed.

Keywords: Pain; Acute pain; Chronic pain; Blood pressure; Cardiovascular; Endogenous opioid; Noradrenergic; Alpha-2 adrenergic; Dysfunction

Contents

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1. Introduction

The ability to adapt effectively to both acute and persistent pain stimuli is an important contributor to quality of life. Adaptation to pain is determined by a complex endogenous pain regulatory system composed of both descending inhibitory and descending facilatory pathways [1]. Activity within this system is dependent on duration of pain stimuli, and functions to maximize survival [1,2]. The initial response to nociceptive stimuli engages descending inhibitory mechanisms that allow the organism to escape the injury-causing event (e.g. attack) without experiencing intense pain sensations that might interfere with immediate survival [1,2]. After the acute danger has passed, the pain regulatory system shifts to a relative predominance of descending facilitation, making pain more salient as a signal to avoid additional injury and to allow healing [1,2]. If pain persists beyond this initial healing period, descending inhibitory pathways display progressively increased activity to facilitate resumption of normal activities required for survival [1].

While the above process is adaptive, the development of chronically painful conditions is clearly maladaptive. Numerous authors have proposed that chronic pain develops when ongoing nociceptive stimulation results in failure of descending pain inhibitory mechanisms [1–6]. In such circumstances, continued activation of descending pain facilatory mechanisms that sensitize the spinal nociceptive processing pathways may overwhelm the exhausted inhibitory system, leading to a chronic dysfunctional pain state [1,7].

This review will focus on one important component of the pain regulatory process: the functional interaction between the cardiovascular and pain regulatory systems (see Ref. [8], for a general review). This functional interaction is reflected in the relationship between elevated resting blood pressure (BP) levels and diminished acute pain sensitivity that is reliably observed in normotensive humans (e.g. Refs. [9–16]). It has been proposed that this adaptive cardiovascular/pain regulatory relationship reflects a homeostatic feedback loop that helps restore arousal levels in the presence of painful stimuli [4,8,17].

Nearly all published studies of the relationship between resting BP and acute pain sensitivity have used brief experimental pain stimuli in healthy or hypertensive subjects. However, until recently, the important question of whether these adaptive cardiovascular/pain regulatory interactions function normally in the context of chronically painful conditions had been largely neglected. As will be detailed below, recent work regarding this issue suggests that there may be substantial alterations in the BP/pain sensitivity relationship in chronic pain sufferers [18–20]. Identifying the source of these changes will provide important clues for understanding the processes contributing to pain regulatory dysfunction in chronic pain.

2. The relationship between blood pressure and acute pain sensitivity

Research initially focused on understanding the hypoalgesia associated with hypertension [21–24] has highlighted the importance of interrelationships between the cardiovascular and pain regulatory systems. Even in the absence of clinical hypertension, familial risk for hypertension in healthy individuals appears to be associated with diminished responsiveness to acute pain apart from the influence of actual BP levels [25–31]. There is suggestive evidence that these effects are mediated in part by elevated central descending pain inhibitory activity (e.g. Refs. [28,29]). Although these studies might suggest that BP-related hypoalgesia is specifically associated with

central mechanisms contributing to hypertension risk, other studies have demonstrated that regardless of hypertension status, elevated resting BP levels are associated with decreased pain sensitivity in healthy normotensive individuals [9–16]. Correlational analyses further indicate that this relationship is linear across the normotensive BP range [9,11]. The BP/pain sensitivity relationship does appear to be of clinical relevance, given that presurgical resting systolic BP is inversely associated with acute postsurgical pain intensity [32].

Although the data are not yet entirely clear, it appears that while the exaggerated hypoalgesia associated with hypertension risk may be a marker for central pathophysiological mechanisms contributing to hypertension development, the BP/pain sensitivity relationship in healthy normotensives appears to serve an adaptive homeostatic function. The mechanisms underlying this adaptive BP/pain sensitivity relationship appear complex. The following review will focus on three possible mechanisms: baroreceptor-mediated processes, endogenous opioid activity, and noradrenergic activity. While the first two of these mechanisms have been evaluated in both animals and humans, this latter noradrenergic mechanism has received no previous test in humans. Because this latter mechanism has received relatively less research attention, this review will focus particularly on issues regarding possible noradrenergic mediation of the BP/pain sensitivity relationship.

3. Mechanisms underlying the relationship between blood pressure and acute pain sensitivity

3.1. Structural interactions

The relationship between resting BP and pain sensitivity arises from what has been described as a central autonomic network, reflecting integrated brain regions that coordinate responses to environmental stimuli [8]. The brain regions underlying control of the cardiovascular system are known to overlap substantially with those contributing to antinociception [17]. Fig. 1 summarizes the current literature with regard to brain pathways that may underlie the BP/pain sensitivity relationship. Given the particular focus of the current review on noradrenergic mechanisms, areas with known alpha-2 adrenergic receptors and/or norepinephrine-containing neurons are noted.

Of particular interest is the nucleus tractus solitarius (NTS), which serves as the interface between autonomic and sensory systems, and is the location of the first synapse in the baroreceptor reflex pathway [17]. The NTS plays an important role in the processing of visceral information, receiving major afferent input from both the vagus nerve (subserving the baroreflex) and spinal laminae involved in nociceptive processing [17]. Participation of the NTS in pain regulatory pathways is evidenced by the fact that stimulation of the NTS induces antinociception [33]. Antinociception elicited by activation of the NTS may derive in part from its direct and indirect efferent projections

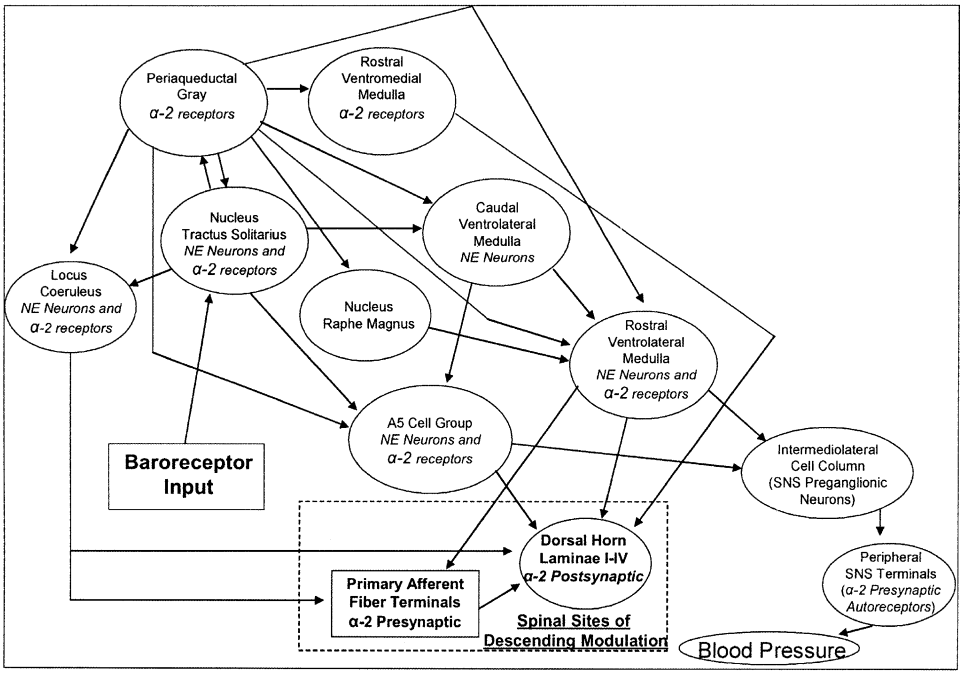

Fig. 1. Schematic representation of brain pathways known to be involved in descending pain modulation and blood pressure control. Arrows indicate direction of neuronal circuits. Sites with known alpha-2 (α-2) adrenergic receptors or norepinephrine (NE) neurons involved in pain and/or cardiovascular modulation are marked. SNS, sympathetic nervous system.

to the periaqueductal gray (PAG) and other brain structures such as the nucleus raphe magnus (NRM) and rostral ventrolateral medulla (RVM) that are known to be involved in modulation of pain pathways [1,17,34–37]. In addition to the brain regions above, efferent projections from the NTS to the A5 nuclei and A6 nuclei (locus coeruleus, LC) of the medulla may be important contributors to BP-related antinociception, given that direct stimulation of these regions elicits analgesia [38–40]. Interconnections between the NTS and the LC may be particularly important in mediating nonopioid analgesia, given that the LC is a primary source of noradrenergic neurons in the neuraxis [17]. Pathways from the NTS to spinal cord nuclei modulating cardiovascular tone, including sympathetic (intermediolateral cell column) and parasympathetic preganglionic nuclei, also interact with descending pain modulation pathways and may be important to consider [1,41,42]. Thus, through a baroreceptor feedback loop, descending pain inhibitory pathways may be able to self-regulate their activity through actions in autonomic centers of the spinal cord modulating cardiovascular function [1].

3.2. Role of baroreceptors

A functional model of the BP/pain sensitivity relationship has been proposed in which: (1) pain, through a somatosensory reflex, increases sympathetic arousal producing increased BP, (2) increased BP leads to increased baroreceptor stimulation, which (3) triggers descending pain inhibitory activity, thereby helping to return arousal levels to a state of homeostasis [8,43]. This functional model presumes a significant role for baroreceptor activation in the relationship between resting BP and acute pain sensitivity [17,22,44].

In addition to the structural links described above between baroreceptor and antinociceptive pathways, numerous experimental studies support a role for baroreceptors in the observed relationships between BP and pain sensitivity. This support derives from several lines of evidence. First, direct electrical stimulation of baroreceptor (vagal) afferents induces antinociception [45,46], as does pharmacologic stimulation of baroreceptor afferents [17]. In addition, surgical denervation of baroreceptor afferents eliminates the hypoalgesia induced by pharmacological pressor agents [47], eliminates the hypoalgesia displayed by spontaneously hypertensive and experimentally hypertensive rats [22,48], and produces hyperalgesia in normotensive animals [22]. A second line of evidence comes from animal studies indicating that increases in baroreceptor stimulation resulting from experimental hypertension induced by social isolation [49] or renal clip application [23,24] result in significant hypoalgesia. Finally, experimental data in normotensive humans also support a role for baroreceptors in mediating the relationship between resting BP and acute pain sensitivity. In a naturalistic methodology, spontaneous BP increases during stressful tasks resulting in elevated natural baroreceptor stimulation produce diminished pain sensitivity [50,51]. Furthermore, direct stimulation of baroreceptors using experimental methodology (e.g. application of phase-related external suction to carotid artery) produces diminished acute pain sensitivity [52–58]. It should be noted that the effects of baroreceptor stimulation on pain responsiveness are likely to impact on both the sensory and affective components of pain. Experimental stimulation of baroreceptors results not only in decreased sensory acute pain intensity, but also diminished sympathetic nervous system reactivity [56], one indicator of affective pain intensity [59].

The issue of baroreceptor resetting must be addressed in discussions of this potential mechanism. Persistent baroreceptor stimulation related to BP elevations lasting from a few minutes to a few days may result in a resetting of baroreceptors [60,61]. It is believed that the BP set point around which the baroreflex is centered is increased, and the BP threshold required to trigger baroreceptor activation is therefore increased [63]. It should be noted that while much evidence exists that such resetting occurs, support for this concept remains somewhat mixed. For example, recent work in dogs indicated that chronic activation of carotid baroreceptors over seven days produced prolonged sympathetic inhibition and diminished BP throughout this period [62]. If baroreceptors do not, in fact, reset after sustained BP elevations, this issue would not appear to impact significantly on understanding the relationship between resting BP and pain sensitivity. However, to the extent that baroreceptor resetting *does* occur after prolonged BP elevations, this might raise questions as to how presumably stable resting BPs would be associated with diminished pain sensitivity if baroreceptor mechanisms were involved. Recent work suggests the possibility that the key issue may not be the degree of *tonic* baroreceptor stimulation, but rather, the degree of *phasic* baroreceptor stimulation related to the cardiac cycle. Edwards et al. [64,65] found that sensitivity to very brief electrical pain stimuli among normotensive humans covaried with the cardiac cycle, with subjects displaying the lowest pain sensitivity during systole and the greatest pain sensitivity during diastole. In light of the fact that baroreceptors may not be tonically stimulated at normotensive systolic pressures and therefore would not reset [67], natural phasic baroreceptor stimulation occurring with systole may account for the observed inverse relationship between resting BP and pain sensitivity. Thus, in normotensives, higher systolic pressure elevations might produce greater baroreceptor activation, and thus greater antinociceptive activity, with little effect of diastolic pressure levels. Consistent with this proposal, numerous studies have reported a greater effect size for systolic BP on pain sensitivity than is observed for diastolic BP (e.g. Refs. [9–11,16,26,30,32,67–69]). Taken together,

the data above would support baroreceptor activity as a likely contributor to the resting BP/pain sensitivity relationship in normotensives. A role for baroreceptors in this relationship supports the concept that this relationship reflects a homeostatic feedback system, at least in healthy normotensive individuals.

3.3. Endogenous opioid mechanisms

One important neurochemical substrate of descending pain inhibitory pathways is endogenous opioid activity [1,4]. A role for endogenous opioids in expression of the BP/pain sensitivity relationship has been shown in numerous animal studies. For example, decreased pain sensitivity associated with hypertension [22–24,49,70–72] is reversible with pharmacological opioid blockade. These animal studies, all of which addressed presence/absence of hypertension rather than resting BP levels in normotensive animals, are consistent with the idea that endogenous opioid activity may be necessary for full expression of the inverse relationship between BP and pain sensitivity.

Human studies, in contrast, provide weaker support for opioid mechanisms. Several studies have reported that elevated BP was associated with both lower levels of pain sensitivity and increased plasma levels of beta-endorphin, a potent endogenous opioid analgesic [73–75]. However, it is unclear whether these elevated levels of beta-endorphin mediated the BP/pain sensitivity relationship, given evidence that beta-endorphin levels were not significantly associated with degree of pain responsiveness [74]. More recent work in normotensives examining plasma levels of beta-endorphin also failed to support opioid mediation of the BP/acute pain relationship [19]. In summary, findings of studies assaying plasma levels of opioids are mixed regarding opioid mediation of the BP/pain association in humans. Presence of clinical hypertension could be an importance consideration in interpreting these studies, given that two of the three studies showing elevated circulating endogenous opioid levels in association with both elevated BP and diminished pain responsiveness were obtained using designs comparing hypertensive to normotensive subjects [73,74]. This interpretation would be consistent with support for opioid mechanisms derived from numerous animal studies comparing hypertensive to normotensive animals.

Work using opioid blockade methodology in humans has consistently failed to support a significant role for endogenous opioids in mediating the BP/pain relationship. Among both normotensive [11,76] and borderline hypertensive males [76], naloxone failed to alter significantly the inverse association between resting BP and pain sensitivity to cold pressor or electrical pain stimuli. More recent results from our lab further indicate that opioid blockade with naloxone does not significantly alter the inverse relationship between resting BP and both ischemic and pressure pain sensitivity in pain-free normotensive males or females [10]. It should be noted, however, that none of these blockade studies were conducted in clinically hypertensive samples.

In light of the strong animal evidence for opioid mechanisms using opioid blockade methodology, this failure to support opioid mechanisms in humans is somewhat surprising. McCubbin and Bruehl [11] found that the simple correlation between resting systolic BP and pain sensitivity was reduced by naloxone from -0.54 to -0.11, suggesting initially at least partial opioid mediation. However, examination of the simple correlations between BP and pain ratings across placebo/naloxone conditions may be somewhat misleading. When multiple regression was conducted controlling for main effects of BP and drug, there was no significant drug X BP interaction on pain. A similar nonsignificant interaction was noted in our recent work [10]. Interaction effect sizes for these nonsignificant findings are small, with a hypothetical tripling in sample size still not being sufficient to produce a significant opioid-mediation effect [10]. In light of similar negative findings in the only other relevant opioid blockade study [76], the evidence suggests that the BP/pain sensitivity relationship *can* occur independently of opioid-mediated mechanisms in normotensives. Despite the negative results of blockade studies conducted to date, the strength of the animal literature supporting opioid mechanisms and the relative paucity of human studies addressing this issue would suggest that the role of endogenous opioids in the BP/pain sensitivity relationship may best be considered an open question. The human data above would suggest that a role for endogenous opioids should be further investigated particularly with regard to hypertensive populations.

In summary, while animal studies suggest that endogenous opioid mechanisms are important, results of human studies suggest that the BP/pain sensitivity relationship *can* occur in normotensives even in the absence of functionally active endogenous opioid systems. This pattern of findings highlights the potential importance of examining nonopioid mechanisms that could contribute to this adaptive relationship in normotensive humans.

3.4. Noradrenergic mechanisms

A primary nonopioid mechanism to consider is noradrenergic activity. Central noradrenergic pathways, particularly those mediated by alpha-2 adrenoceptors, are a crucial component of the descending pain inhibitory system [1,77,78]. Complex interactions between several of the brain regions described above may lead to adrenergically mediated antinociception [79] (see Fig. 1). For example, it is believed that nociceptive stimulation directly activates the RVM, triggering excitatory neurotransmitters that increase norepinephrine release from the LC, thus activating descending noradrenergic pathways leading to antinociception mediated by spinal

alpha-2 inhibitory adrenergic receptors [79]. The specific role of alpha-2 adrenergic activity in descending nociceptive inhibition is evidenced experimentally by: (1) clinical use of alpha-2 agonists as analgesics [80,81]; (2) ability of such agents to produce analgesia through supraspinal mechanisms [82,83]; (3) the effects of several analgesic agents can be eliminated by selective alpha-2 adrenergic receptor blockade [82–86], and (4) acute pain responses are increased following selective alpha-2 adrenergic blockade [87–89]. Limited human data also supports the role of alpha-2 adrenergic mechanisms in endogenous pain modulation. Intravenous yohimbine, a selective alpha-2 adrenergic antagonist, resulted in significant increases in self-reported pain in response to an experimental rectal distension pain stimulus [90,91]. Pilot data in a small sample of healthy subjects examined in our lab further support these findings, indicating that intravenous yohimbine resulted in a significant 18% increase in mean pain intensity ratings obtained during an ischemic laboratory pain task (unpublished data). The composite yohimbine effect size across all pain rating measures obtained and across ischemic and finger pressure pain tasks was $r=0.42$, indicating a moderate-sized hyperalgesic effects of yohimbine in humans (unpublished data). These data support an important role for noradrenergic mechanisms in human endogenous pain regulatory systems.

Central noradrenergic pathways are also known to be important in cardiovascular regulation [92,93]. For example, noradrenergic projections from the LC to the NTS have been shown to be involved in baroreceptor-mediated neurotransmission [93,94]. In particular, activity at alpha-2 adrenergic receptors appears to be an important modulator of the baroreceptor reflex, as evidenced by altered baroreflex responses following selective alpha-2 blockade [93,95–97].

Overlap in noradrenergic pathways underlying both cardiovascular regulation and pain transmission is apparent. Given the important role of the NTS as an interface for cardiovascular and pain regulation [17], it is notable that significant populations of alpha-2 adrenergic receptors are located within the NTS [98]. Other areas described above as being structurally important in cardiovascular/pain regulatory relationships, such as the NRM, PAG, the RVM, and the LC are all sources of noradrenergic influences on descending pain modulation, particularly through alpha-2 adrenoceptor activity [1,8,17,38,40,99–102]. Thus, the interlinked brain structures underlying both cardiovascular regulation and descending pain inhibition have large populations of noradrenergic fibers and alpha-2 adrenergic receptors that impact on both BP and antinociception.

Based on these findings, alpha-adrenergic activity has been proposed to be a contributor to the functional relationship between BP and acute pain sensitivity [17]. Animal studies provide support for this hypothesis. Analgesia resulting from activation of baroreceptors can be eliminated by blockade of alpha adrenergic receptors [17]. Moreover, hypertension is associated with antinociception reversible with adrenergic receptor blockade [48,70]. Chemical lesioning of the brainstem noradrenergic system has also been shown to eliminate the hypoalgesia associated with spontaneous hypertension [103]. These latter findings suggest an important role for supraspinal alpha-2 adrenergic descending pathways in mediating BP-related analgesia. Other evidence for adrenergic involvement in baroreceptor-mediated analgesia comes from work indicating that pharmacological blockade of adrenergic receptors significantly attenuates the hypoalgesia resulting from direct stimulation of vagal baroreceptor afferents [104]. In humans, a possible role for alpha-2 adrenergic mechanisms in the BP/pain sensitivity relationship is indirectly suggested by work indicating that normotensive subjects with higher BP exhibited both increased electrical pain tolerance and elevated circulating levels of norepinephrine (an endogenous alpha-2 agonist), although mediation was not directly tested [75]. Work suggesting that noradrenergic mechanisms contribute significantly to baroreceptor-mediated analgesia is likely to account for the failure of opioid blockade to eliminate the hypoalgesia resulting from experimental stimulation of baroreceptor pathways [105], and its failure to significantly attenuate the relationship between resting BP and pain sensitivity in normotensive humans [10,11,76].

In summary, there is much direct and indirect evidence from animal research that alpha-2 adrenergic mechanisms may contribute to the relationship between BP and pain sensitivity. Although the lack of human data on this issue makes direct evaluation of the relative merits of opioid versus alpha-2 adrenergic hypotheses difficult, both theory and animal work would suggest that examination of alpha-2 adrenergic mechanisms in humans may represent a fruitful line of inquiry. This review will now turn to the issue of chronic pain-related alterations in the adaptive relationship between BP and acute pain sensitivity, and will highlight several possible mechanisms that may underlie these alterations.

4. Alterations in the blood pressure/pain sensitivity relationship associated with persistent pain

4.1. Effects of prolonged acute pain

Nearly all studies of the BP/pain sensitivity relationship, animal and human, have used brief experimental acute pain stimuli (typically <5 min in duration). The importance of pain duration as a potential moderator of this relationship is suggested by three animal studies that have examined the BP/pain sensitivity relationship in the context of more prolonged acute pain stimuli. Injection of formalin into rat paws was used to produce prolonged (90 min) inflammatory

pain [103,106,107]. While hypertensive rats as expected exhibited lower pain sensitivity relative to normotensive rats to brief acute pain tests (e.g. hotplate test, paw pressure), hypertensives displayed *greater* pain sensitivity to the more prolonged formalin pain task relative to normotensives [103,106,107]. These results would be consistent with an inverse relationship between resting BP levels and sensitivity to brief acute pain stimuli as has been found in numerous other studies, but a significant positive relationship between resting BP and pain sensitivity to more prolonged acute pain stimuli. The multiphasic pain regulatory response described above [1] might lead one to predict alterations in the pattern of the BP/pain relationship dependent upon pain duration like those observed in the studies above. For example, elevated BP might be associated with enhanced activation of pain inhibitory pathways in the context of brief pain, but might also be associated with greater activation of pain facilatory pathways in response to more prolonged pain. Although comparable human data are not available, these results do suggest that it may be important to consider BP/pain sensitivity interactions not as an invariant phenomenon, but rather, part of a plastic, adaptive process that may change with ongoing nociceptive input. Studies in clinical chronic pain conditions highlight the importance of this latter consideration.

4.2. Effects of clinical chronic pain on blood pressure/pain interactions

Limited work in human chronic pain samples suggests that chronic pain is associated with significant alterations in the relationship between resting BP and acute pain sensitivity. In contrast to the significant inverse relationship observed in pain-free individuals, Maixner et al. [20] reported that resting BP was unrelated to responsiveness to ischemic or thermal acute pain stimuli among orofacial pain patients. More recent work suggests not simply a dissociation of BP and acute pain sensitivity, but rather, a reversal of this normally adaptive relationship in chronic pain. For example, Bragdon et al. [19] reported a reversal in direction of the relationship between resting BP and sensitivity to ischemic and thermal pain stimuli in chronic orofacial pain sufferers compared to pain-free controls [19]. Previous work in our lab also indicated that the expected inverse relationship between resting BP and ischemic pain sensitivity among pain-free controls was significantly reversed (i.e. positive) among chronic low back pain sufferers [10]. This effect is best exemplified by ischemic pain threshold data that are summarized in Fig. 2 below. Although this figure suggests a possible nonlinear relationship in the chronic back pain group, data in this figure reflect post hoc tertile splits on resting systolic BP levels conducted solely for display purposes. General linear model analyses confirmed a linear trend for the relationship between BP levels and pain threshold that was in opposite

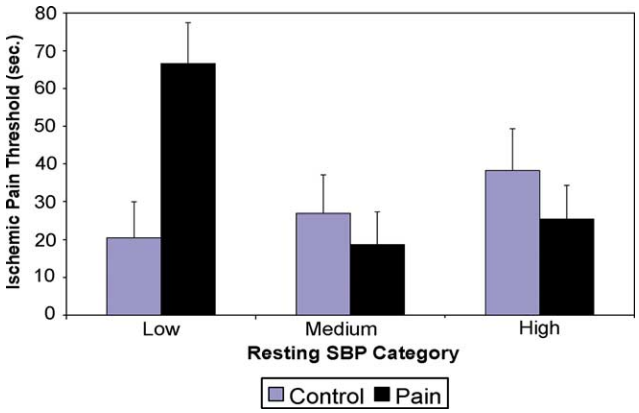

Fig. 2. Relationship between resting systolic BP and ischemic pain threshold across chronic pain/pain-free groups. *Note*: Control, Pain-free healthy normotensive controls; Pain, Chronic low back pain.

directions across pain-free control and chronic back pain groups. The likelihood that cardiovascular/pain regulatory system interactions are altered in individuals with chronic pain is further underscored by findings that chronic back pain patients responded to experimental stimulation of carotid baroreceptors with *increased* sensitivity to electrical pain rather than the diminished pain responsiveness typically reported in pain-free individuals [108].

The positive relationship between resting BP and acute pain sensitivity in chronic pain patients may reflect generalized dysfunction in pain inhibitory systems, given that these effects extend beyond acute pain responsiveness. Our work in a low back pain patient sample also indicated a significant positive relationship between resting BP and ratings of clinical chronic pain intensity [10]. Other work in a chronic pain sample displaying diverse pain etiologies similarly reported resting BP to be positively correlated with clinical pain intensity [18]. Interestingly, this latter study suggested that the pain regulatory dysfunction apparently reflected in this positive BP/chronic pain relationship was progressive, as might be expected if it were due to gradual exhaustion of pain inhibitory systems or gradual changes in baroreceptor function. A statistically significant interaction was detected between pain duration and resting systolic BP in predicting ratings of clinical pain. For chronic pain of 6–14 months duration, the correlation between BP and chronic pain intensity was $r = -0.18$ ($p > 0.10$); for 15–28 month duration, $r = 0.14$ ($p > 0.10$); and for pain of more than 28 months duration, $r = 0.50$ ($p < 0.001$). Thus, while a small inverse correlation between resting BP and chronic pain intensity was detected in patients with the shortest chronic pain syndromes, consistent with the adaptive inverse BP/acute pain relationship noted in healthy individuals, this relationship becomes positive and increasingly strong with greater pain duration.

Overall, available data suggest that the normally inverse relationship between resting BP and acute pain sensitivity may be altered in chronic pain conditions, with consequences for the experience of clinical pain as well.

The observed alterations in the BP/pain sensitivity relationship are likely to reflect broader alterations in endogenous pain regulatory systems related to chronic pain. As described previously, the pain regulatory system is composed of both pain inhibitory and pain facilatory pathways. There is evidence suggesting that activity in both of these pathways is altered in chronic pain conditions. Chronic pain-related alterations in both of these pathways could contribute to the observed alterations in the functional relationship between BP and pain sensitivity. Changes in baroreceptor pathways related to chronic pain may also contribute to altered relationships between BP and pain sensitivity. Evidence for chronic pain-related changes in each of these areas will now be overviewed, and the potential relevance of such changes for cardiovascular/pain regulatory interactions will be described.

5. Possible contributors to chronic pain-related alterations in the blood pressure/pain sensitivity relationship

5.1. Impaired descending inhibitory mechanisms

Descending pain inhibitory pathways appear to display progressively increased activity if nociceptive stimulation persists [1,7]. It has been suggested that persistent and excessive antinociceptive demands may eventually exhaust these descending inhibitory systems, thereby contributing to development or maintenance of chronic pain [1,3,4]. Evidence supporting this antinociceptive dysfunction hypothesis comes from several sources. Studies in patients with diverse chronic pain conditions indicate that chronic pain is often associated with increased experimental acute pain sensitivity relative to pain-free controls as assessed by both objective (i.e. brain evoked potentials) and subjective measures [5,109–114]. Furthermore, chronic pain patients do not display the progressive adaptation to repeated pain stimuli observed in pain-free controls [112,113]. These findings suggest that pain perception may be enhanced, and pain inhibitory processes impaired, in chronic pain sufferers.

There is evidence indicating that these changes are due at least in part to alterations in descending pain inhibitory pathways. One experimental indicator of descending pain inhibitory activity is activation of diffuse noxious inhibitory controls (DNIC) by heterotopic conditioning stimulation [115]. In pain-free individuals, an intense pain stimulus applied to one body location results in diminished responsiveness to pain stimuli applied to multiple other body regions, presumably reflecting DNIC activation [5,115]. In patients with chronic osteoarthritis or fibromyalgia, heterotopic conditioning stimulation fails to activate DNIC whereas pain-free control subjects exhibit evidence of DNIC activation [5,6,116]. Interestingly, one study indicates that surgical correction of the source of chronic nociceptive input (i.e. hip replacement in osteoarthritis patients) restored a normal DNIC response [6]. Taken together, these results suggest that ability to activate descending pain modulation pathways is impaired in chronic pain patients, and that dysfunction in these descending inhibitory pathways is both a consequence of and a contributor to the chronic pain state [6].

Neural mediators of these chronic pain-related changes in descending inhibitory mechanisms are likely to include endogenous opioid as well as nonopioid mechanisms. Endogenous opioids play an important functional role as inhibitory neurotransmitters in the antinociceptive system [1]. It is therefore notable that patients with chronic pain of a variety of etiologies display lower plasma and CSF levels of endogenous opioids than do pain-free normals (see Ref. [4], for a review). This pattern would be consistent with impairment in opioid-mediated pain inhibitory pathways in chronic pain sufferers [4]. Opioid blockade studies indicate that opioid-mediated antinociception to acute pain may be functionally impaired at least in a subset of chronic pain patients, and this impairment may also impact on chronic pain intensity. Work in our lab indicates that failure to elicit opioid analgesia to acute pain stimuli (as reflected in lack of response to opioid blockade) was associated with greater clinical pain in chronic low back pain patients with higher disability levels [117]. In other words, endogenous opioid antinociceptive impairment may contribute to elevated acute *and* chronic pain sensitivity, at least among more disabled chronic pain patients.

Central noradrenergic mechanisms also appear to be crucial for descending pain inhibitory pathways [1,87–89]. Although widely studied in the context of acute pain, changes in descending noradrenergic inhibitory pathways associated with chronic pain have been less widely examined. Animal models indicate decreased dorsal horn alpha-2 adrenergic receptor density following chronic pain, a finding consistent with chronic pain-related attenuation of noradrenergic descending inhibitory capabilities [118]. Consonant with receptor changes mediating impaired descending alpha-2 pain inhibition, decreased analgesic responsiveness to alpha-2 agonists is observed in animal chronic pain models compared to pain-free animals, indicating possible alpha-2 receptor deficits [119]. In addition to reduced adrenergic receptor density, animal chronic pain models suggest that up-regulated norepinephrine turnover in the dorsal horn should also be considered, given that this process might contribute to eventual exhaustion of noradrenergic pathways [120]. Human studies provide indirect support for impairments in descending noradrenergic inhibitory pathways in chronic pain. Diminished release of beta-endorphin in response to alpha-adrenergic stimulation has been described in chronic headache patients relative to pain-free controls [121], a finding consistent with the receptor changes noted above [118]. Likely impairments in noradrenergic inhibitory

pathways in human chronic pain are also suggested by the efficacy of pharmacological agents that enhance descending noradrenergic activity (e.g. tricyclic antidepressants) for decreasing chronic pain intensity [122,123]. A conceptual argument could also be made. While descending opioid and alpha-2 adrenergic pain inhibitory systems are not conceptually identical, there are obvious parallels in the factors that might underlie their dysfunction in chronic pain (i.e. exhaustion through chronic activation; [1]). In the absence of data indicating otherwise, there are strong theoretical reasons to believe that chronic pain-related dysfunction in alpha-2 adrenergic systems would likely parallel those reported in endogenous opioid systems.

As described previously, increased BP/baroreceptor activity is associated with activation of descending pain inhibitory pathways mediated in part by endogenous opioid and alpha-2 adrenergic mechanisms. Therefore, chronic pain-related impairments in either of these pathways might have an impact on expression of the BP/pain sensitivity relationship. Our recent work suggests that endogenous opioid mechanisms do not account for chronic pain-related changes in the BP/pain sensitivity relationship in normotensives [10]. Specifically, opioid blockade did not exert a significant interaction effect on differences in the resting BP/acute pain sensitivity relationship across chronic pain and pain-free groups [10]. Given the potential importance of noradrenergic mechanisms in expression of this relationship in humans, impairments in noradrenergic inhibitory pathways may be of particular relevance for understanding chronic pain-related alterations in the BP/pain sensitivity relationship.

5.2. Increased descending facilatory mechanisms

Both nociceptive and neuropathic pain trigger increased excitability in spinal cord nociceptive neurons [124]. This central sensitization is an important pathophysiological mechanism contributing to persistent pain. The clinical consequences of central sensitization include hyperalgesia and increased wind-up [125,126]. Wind-up is observed when nociceptive C-fibers are repeatedly stimulated at a frequency similar to their natural firing rate (every 2–3 s), causing a slow temporal summation of this nociceptive firing [127]. With repeated stimulation of C-fibers at this rate, even at sub-pain threshold levels, the responses of nociceptive dorsal horn neurons undergo a progressive increase [126,127]. As a result, levels of stimulation initially described as nonpainful are reported to be painful as temporal summation/wind-up occurs. Central sensitization processes may be relevant to understanding the BP/pain sensitivity relationship, given recent evidence that the hypoalgesia associated with increased hypertension risk may be mediated in part by diminished triggering of temporal summation [28]. Given the focus of this review, it is notable that temporal summation is exaggerated in individuals experiencing chronic pain, due to the process of central sensitization [114,125,127–129]. The impact of chronic pain-related central sensitization on the BP/pain sensitivity relationship is not known, although the physiological interconnections described below suggest that it may be an important factor to consider.

Central sensitization is not purely a local phenomenon occurring at primary afferent fibers [1], but rather, results in part from descending pain facilatory mechanisms [130]. Brain regions involved in descending pain facilitation appear to include the PAG [131], the NRM [132], the NTS [132], and the RVM [133]. For example, lesions in the NTS and NRM can substantially block development of central sensitization [132]. While there are multiple peptides and neurotransmitters mediating the development of central sensitization, one important factor is substance P, a peptide acting at the NK1 receptor [134–137]. Pharmacological blockade of NK1 receptors or use of genetic ‘knockout’ mice lacking NK1 receptors results in significant reductions in wind-up phenomena [134–136]. There is evidence that substance P is involved in central sensitization through descending facilatory pathways arising from the brain regions above as well as local release at primary afferent fibers [138,139].

Given the emphasis of this review, it is noteworthy that baroreceptor activation may trigger not only pain inhibitory activity but descending pain facilatory activity as well, possibly through substance P-mediated pathways [1,3,140,141]. Brain structures believed to be involved in central sensitization and known to contain substance P fibers, particularly the NTS and NRM, are also extensively involved in cardiovascular regulation through baroreceptor pathways, and appear to be important sites underlying the BP/pain sensitivity relationship [17,42,132]. Experimental studies indicate that the substance P present in these baroreceptor pathways is functionally involved in cardiovascular regulation [142–145].

In summary, reduced temporal summation could contribute to BP-related antinociception. Chronic pain activates descending pain facilatory pathways, mediated in part by substance P, resulting in central sensitization and increased temporal summation. Substance P pathways and the brain structures underlying the BP/pain sensitivity relationship appear to overlap, and substance P has effects on both pain regulation and baroreflex control of cardiovascular function. Taken together, these findings suggest a possible mechanism by which chronic pain-related activation of pain facilatory pathways might contribute to alterations in the functional relationship between BP and pain sensitivity.

5.3. Alterations in baroreceptor sensitivity

Maixner et al. [3] have hypothesized that changes in baroreceptor sensitivity may contribute to alterations in pain regulatory processes associated with chronic pain. Changes in baroreceptor sensitivity may occur due to

altered threshold for baroreceptor firing or altered central nervous system gain associated with this firing [17]. The functional consequences of diminished baroreceptor sensitivity include impaired inhibition of sympathetic nervous system arousal responses and impaired activation of parasympathetic nervous system inhibitory responses in the face of stressful stimuli [17]. To date, the baroreceptor sensitivity hypothesis has not been subjected to adequate experimental evaluation. Only one published study has examined baroreceptor-issues in chronic pain sufferers [108]. Activation of carotid baroreceptors using phase-related external suction was found to produce increased sensitivity to electrical pain stimuli in chronic low back pain patients [108]. This finding is in contrast to the numerous studies indicating that similar baroreceptor manipulation produces analgesia in pain-free normotensives (see Ref. [53], for a review).

That baroreceptor sensitivity might be altered in chronic pain would not be unexpected, given that it may be altered in other disease states and in response to stress. For example, baroreceptor sensitivity appears to be reduced in chronic hypertension [146–148]. Decreases in baroreceptor sensitivity are also associated with increased anxiety levels [149]. This latter finding highlights the importance of the proposed concept of central baroreflex clamping, in which some circumstance (such as increased sympathetic activation due to fear or anxiety) result in baroreceptor input being overridden at the limbic or hypothalamic levels [17]. Consistent with this concept, a number of human studies suggest that baroreceptor sensitivity may be decreased in response to acute experimental stress [150–154]. Moreover, chronic stress in animals appears to be associated with decreased baroreceptor sensitivity [155,156]. There is some evidence that central noradrenergic changes may account for the reduced baroreceptor sensitivity associated with chronic stress [155,157]. Taken together, these data indicate that baroreceptor sensitivity may be diminished in response to both acute and chronic stress, and therefore, the stress associated with chronic pain might be expected to lead to similar diminished baroreceptor sensitivity. To the extent that baroreceptor stimulation is necessary for expression of the BP/pain sensitivity relationship, chronic pain-related reductions in baroreceptor sensitivity might help explain chronic pain-related alterations in this relationship. Possible interactive effects of substance P and alpha-2 adrenergic activity in baroreceptor-mediated cardiovascular regulation, combined with chronic pain-related changes in pathways mediated by these neurochemicals, might also suggest a role for baroreceptor changes in the altered BP/pain sensitivity relationship in chronic pain.

One potential limitation to the arguments above should be noted. While the relationship between stress-related reductions in baroreceptor sensitivity and alterations in pain sensitivity has not been examined, there exists a clear paradox with regards to hypertension. Specifically, there is good evidence that clinical hypertension is associated with diminished baroreceptor sensitivity [146–148], yet hypertension is also clearly associated with diminished pain sensitivity despite this decreased baroreceptor sensitivity. Reconciling this fact with other evidence, primarily in normotensives, that experimental baroreceptor activation produces analgesia (and the converse) is difficult, although the possibility is raised that multiple potential pathways (baroreceptor, opioid, norepinephrine, and others) could lead to the inverse BP/pain sensitivity relationship under different conditions. Resolution of such issues must await future work.

5.4. Summary

The studies reviewed above indicate that: (1) the functional relationship between BP and pain sensitivity is an important part of the pain regulatory process, (2) baroreceptor-mediated pathways and alpha-2 adrenergic activity may contribute to expression of this relationship in normotensives, (3) the BP/pain sensitivity relationship is significantly altered in normotensive chronic pain sufferers, and (4) endogenous opioid mechanisms are not required to account for these alterations. Based on brain structural studies, experimental animal work, and theoretical considerations, it is proposed that chronic pain-related alterations in the BP/pain sensitivity relationship could be due to changes in baroreceptor sensitivity, impairments in descending noradrenergic pain inhibitory pathways, and/or activation of pain facilatory pathways. Several possible theoretical models detailing how these mechanisms could lead to a positive relationship between resting BP and both acute and chronic pain responsiveness will now be described.

6. Possible theoretical models

Several theoretical models (not mutually exclusive) could help explain the alterations in the BP/acute pain sensitivity relationship observed in chronic pain patients. Model 1 is based on the finding that nociceptive input triggers a direct somatosympathetic reflex elevation in BP [36,158]. If persistent nociceptive input leads to failure of descending alpha-2 adrenergic inhibitory systems contributing to the inverse BP/pain sensitivity relationship, direct SNS-mediated BP increases may predominate in chronic pain. In the presence of inhibitory failure, resting BP would be expected to increase as clinical pain intensity (and related SNS arousal) increased. Thus, chronic pain would lead concurrently to failure of descending pain inhibitory systems and direct SNS-mediated BP increases. This pattern would result in a positive relationship between resting BP and both acute pain sensitivity and chronic pain intensity in chronic pain patients, a finding we have reported previously [10,18].

In addition, Model 1 would predict relatively greater SNS arousal in chronic pain patients.

Evidence to support elevated SNS arousal in chronic pain patients comes from several sources. Of greatest relevance to this review are cardiovascular indices that reflect SNS arousal, including BP and heart rate [159–161]. Chronic pain patients with myofascial pain, orofacial pain, and arthritic pain all display greater resting heart rates than do pain-free healthy controls [3,162]. Given the focus of the current review, the strongest indirect support for Model 1 would derive from studies indicating elevated BP in chronic pain patients. Although data from prior work in our lab cannot be used to address this issue because samples were preselected for normotensive status [10,18], work of other investigators in nonpreselected samples does suggest elevated resting BPs in persistent pain sufferers. In a well-designed laboratory study, chronic low back pain patients were found to display significantly higher mean diastolic BP (79 mm Hg) than did pain-free controls (71 mm Hg) [108]. Work in the primary care setting has also indicated that patients suffering from widespread chronic pain display higher resting systolic BP levels (133 mm Hg) than do pain-free patient controls (120 mm Hg) [163]. Also relevant is work indicating that retail cashiers experiencing persistent shoulder pain displayed higher mean resting systolic and diastolic BP levels than age-matched cashiers not experiencing pain [164]. Not only do resting cardiovascular parameters appear to be elevated in chronic pain sufferers, but so does cardiovascular reactivity. Carlson et al. [165] reported that chronic orofacial pain patients displayed significantly greater systolic BP and heart rate levels during a mental stressor than did pain-free age and sex-matched controls. Maixner et al. [3] reported similarly elevated heart rate reactivity to stress in chronic orofacial pain patients relative to pain-free controls.

Another possible index of excessive SNS activity in chronic pain patients may be the presence of clinical hypertension. There is substantial evidence that hypertension is associated with elevated SNS arousal [166–171]. Recent clinical research may therefore be relevant regarding this issue [172]. We compared the prevalence of clinical hypertension and use of antihypertensives in randomly selected samples of 300 tertiary care chronic pain patients and 300 nonpain internal medicine patients. Results indicated that 39% of the chronic pain sample was diagnosed with clinical hypertension compared to only 21% of the internal medicine sample, with parallel results regarding antihypertensive use (p's < 0.001). In light of the work cited above, these findings would be consistent with chronic pain patients experiencing chronically elevated SNS activity and would support Model 1.

Cardiovascular parameters are not the only indices suggesting elevated SNS activity in chronic pain patients. Previous work indicates that chronic low back pain patients and chronic arthritic pain patients display a significantly higher baseline electrodermal response and greater electrodermal reactivity to laboratory stressors than is observed in pain-free controls [162,173,174]. This increased electrodermal response indicates elevated sympathetic (sudomotor) arousal [175–176]. Based on tests of autonomically mediated pupillary light reflexes, Perry et al. [162] have also reported evidence for elevated central sympathetic drive in chronic myofascial pain patients relative to pain-free controls. Finally, work examining overnight urinary catecholamines indicates elevated levels in chronic myofascial pain patients relative to pain-free controls [177], also supporting elevated sympathetic/adrenergic activity in these patients.

In summary, a number of studies using different indices of sympathetic arousal are consistent with the presence of elevated SNS activity in chronic pain patients. The limited controlled work in humans addressing BP levels in chronic pain patients and pain-free controls is consistent with the predictions of Model 1 that chronic pain is associated with increased SNS drive and consequently elevated resting BP.

The mechanism described in Model 1 also implies some degree of cardiovascular baroreflex failure; otherwise, direct SNS-mediated increases in BP would trigger baroreflex mechanisms that would restore pressures to lower levels (and lead to an inverse BP/pain relationship). In fact, some work suggests that stress produces an opposing interaction between direct SNS-mediated pressor responses and baroreflex-mediated depressor responses, with the balance of these two processes determining BP levels [178]. It may therefore be important to consider baroreceptor sensitivity if chronic pain-related alterations in the BP/pain sensitivity relationship are to be fully understood (Model 2). For example, in the absence of functioning baroreflex mechanisms (due to baroreceptor deafferentation), increasing stress results in increased SNS activity and increased BP [179]. To the extent that baroreceptor activation accounts for the BP/pain sensitivity relationship, significantly diminished baroreceptor sensitivity among chronic pain patients might eliminate the normally observed relationship between BP and pain sensitivity. Therefore, in the absence of baroreceptor-mediated pain inhibition and presumably impaired baroreflex-mediated cardiovascular depressor responses, the direct pressor effect of pain on BP (through somatosympathetic reflex activation) may predominate, and lead to the positive BP/pain correlation observed in chronic pain patients. Given the role of alpha-2 adrenergic mechanisms in the baroreflex loop [180], the adrenergic dysfunction described above would likely be involved in these baroreceptor changes. If the mechanisms in Model 2 are operative, experimental studies should demonstrate that the degree of alteration in the BP/pain sensitivity relationship across chronic pain/pain-free subjects is accounted for by the degree

of reduction in baroreceptor sensitivity associated with chronic pain. To date, this hypothesis has not been directly tested.

A third mechanism may be important as well. Animal work by Taylor et al. [103] found that elevated BP was associated with increased noradrenergically mediated antinociception in response to brief acute pain, but impaired noradrenergic antinociception in response to more prolonged acute pain. Consistent with these changes in the BP/pain sensitivity relationship as a function of pain duration, the only human study addressing baroreceptor issues in persistent pain states indicated that direct stimulation of baroreceptors resulted in relative increases in pain sensitivity among chronic pain patients, in contrast to the decreased pain sensitivity typically observed in pain-free subjects [108]. These findings may be explained by the fact that while inhibitory processes may predominate in response to brief acute pain, pain facilatory process may predominate with more prolonged pain stimuli [1]. This possibility may be important to consider given that baroreceptor activation may trigger not only descending pain inhibitory activity, but pain facilatory activity as well, possibly mediated by substance P [1,3,140,141]. It is therefore possible that chronic pain-related increases in BP might activate baroreceptors, triggering pain facilatory activity without adequate opposing inhibitory activity due to chronic pain-related failure of these latter systems (Model 3). This process would result in a positive association between acute pain sensitivity and resting BP occurring in the context of *normal or increased* baroreceptor sensitivity. If these mechanisms are operative, experimental studies should demonstrate that the degree of alteration in the BP/pain sensitivity relationship across chronic pain/pain-free subjects is accounted for by the degree of increased temporal summation associated with chronic pain. This possibility has also not been directly tested.

A final, albeit indirect, mechanism could also account for the positive relationship between resting BP and acute pain sensitivity in chronic pain patients. That there would be a positive link between *chronic* pain intensity and BP levels is not unexpected, given the direct effects of nociceptive stimulation on SNS arousal and BP [36,37,158]. Chronic pain is associated not only with elevated BP [10,18,108, 163–165], but is also generally associated with elevated negative affect (e.g. anxiety, depression; [10,181,182]). Moreover, negative affect is often (but not always) associated with increased acute pain sensitivity [183–186]. Given the pattern above, there might be indirect links between increased BP and increased acute pain sensitivity mediated by chronic pain-related negative affect (Model 4). It would be important in future studies to rule out this latter indirect mechanism as a potential explanation for the alterations in the BP/pain sensitivity relationship in chronic pain patients.

7. Methodological and interpretive issues in use of alpha-2 adrenergic blockade methodology

The role of endogenous opioid mechanisms that may contribute to the BP/acute pain sensitivity relationship has been examined in several human studies using opioid blockade. Although comparable alpha-2 adrenergic blockade methodologies are available to examine this possible mediator of the BP/pain sensitivity relationship in humans (e.g. yohimbine is an FDA-approved selective alpha-2 antagonist), no studies to date have yet employed this methodology. Many of the animal data implicating alpha-2 adrenergic mechanisms in descending pain regulation in general, and in mediating the analgesic effects of elevated BP in particular, derive from studies using pharmacological alpha-2 adrenoceptor blockade. Future human studies of possible noradrenergic mechanisms will require use of alpha-2 adrenergic blockade methodologies as well. Therefore, several interpretive issues regarding use of this potentially important methodology may bear consideration, particularly given that this methodology is used less frequently than the more common opioid blockade methodology.

Noradrenergic mechanisms in the LC interconnected with other limbic structures underlie not only pain responses, but emotional responses as well, particularly anxiety [187]. Because of this, systemic pharmacologic blockade of alpha-2 adrenergic inhibitory mechanisms, which help modulate emotional regulatory brain structures, results in increased negative affect even as it blocks antinociceptive pathways. The animal studies described previously have not addressed whether alpha adrenergic blockade increases pain responsiveness directly through deactivation of noradrenergic pain inhibitory pathways (that may overlap with cardiovascular modulatory pathways), or indirectly through increased anxiety, which is typically associated with increased pain responsiveness [184–186]. Limited human work indicates that while yohimbine-induced increases in anxiety do impact on human experimental pain responses, statistical control of this anxiety does not eliminate yohimbine's hyperalgesic effects [90]. While these results suggest that blockade-induced emotional changes do not account for the hyperalgesic effects of alpha-2 blockade, this potential confound is important to address in interpreting results of such blockade studies.

It is also important to recognize that designs employing alpha-2 adrenergic antagonists will result in blockade of both central and peripheral alpha-2 adrenoceptors at both presynaptic and postsynaptic sites. Interpretation of the effects of alpha-2 antagonists with regard to implied functioning of descending adrenergically mediated pain modulatory pathways in the intact state therefore requires careful consideration. It is helpful to consider the relevant adrenergic pathways involved in descending pain

modulation and their overlap with brain structures involved in BP control (see Fig. 1 above).

Alpha-2 antagonists such as yohimbine may result in several relevant effects, including: (1) blockade of central alpha-2 adrenoceptors in the brain structures noted above involved in descending adrenergically mediated pain inhibition [188–192], (2) blockade of presynaptic alpha-2 adrenergic pain inhibitory receptors on terminals of primary afferent fibers synapsing at the spinal cord dorsal horn [100,193–196], (3) blockade of postsynaptic alpha-2 adrenergic pain inhibitory receptors in the spinal cord dorsal horn [197–202], (4) blockade of inhibitory alpha-2 adrenergic input into SNS preganglionic neurons (intermediolateral cell column) resulting in increased central sympathetic outflow [203–206], and (5) blockade of presynaptic alpha-2 modulatory autoreceptors on terminals of sympathetic fibers, resulting in increased norepinephrine release from these terminals [203,207, 208]. Blockade effects as described in numbers 1–3 above reflect blockade of the descending noradrenergic pain pathways hypothesized to underlie the association between resting BP and pain sensitivity. Blockade effects described in 4–5 will result in acute increases in SNS activity, and as a result, will produce acutely increased BP in response to the blockade agent. If increased sympathetic outflow or peripheral norepinephrine release were themselves either hyperalgesic or analgesic, this could undermine the ability to draw firm conclusions about mediators of the relationship between BP and descending pain regulatory mechanisms based on responses to alpha-2 adrenergic antagonists.

Elevated SNS activity appears to be hyperalgesic only in a subset of pathological pain conditions involving sympathetically maintained pain mechanisms, such as Complex Regional Pain Syndrome Types I and II (aka RSD and Causalgia; [209]). This effect is due to sprouting of adrenergic receptors on afferent nociceptive fiber terminals in these conditions, resulting in ability of circulating catecholamines and norepinephrine released from SNS nerve terminals to directly increase nociceptive firing [210,211]. In healthy individuals and chronic pain sufferers without prominent catecholamine-sensitive pain mechanisms (e.g. low back pain and many other chronic pains), expected hyperalgesic effects of alpha-2 blockade [89,90] can be assumed to derive from direct blockade of central descending noradrenergic pain inhibitory pathways.

Elevated SNS activity resulting from yohimbine administration could also in theory be analgesic, although this action would be through indirect mechanisms. Activation of the sympatho-adrenamedullary axis can result in release of circulating opioid peptides from the pituitary and adrenal medulla [212]. In principle, these circulating opioids could have analgesic effects [212]. However, the importance of systemically circulating opioids in producing analgesia remains unclear. For example, although several studies report an inverse association between plasma endogenous opioid levels and pain levels [19,72,213,214], other work indicates no relationship [73,215–219] or even a positive relationship in some situations [220]. If increases in SNS activity associated with alpha-2 blockade did produce analgesia, the hyperalgesia noted previously in response to alpha-2 adrenergic blockade would represent the net effect of SNS-mediated analgesia and direct centrally mediated hyperalgesia. Available human studies [90,91] (unpublished data) clearly indicate that yohimbine is hyperalgesic rather than analgesic, despite prominent effects on increasing SNS outflow, and this would argue for the effects of alpha-2 adrenergic blockade on central pain regulatory pathways far outweighing any analgesic effects deriving through SNS mechanisms. In vitro work indicates that yohimbine specifically decreases the firing of neurons in the NRM that are involved in both descending pain inhibition and the BP/pain sensitivity relationship, a finding also suggesting the relative importance of yohimbine's effects on descending pain inhibitory pathways in determining its' hyperalgesic effects [221].

The relative importance of SNS-related effects of alpha-2 adrenergic blockade as opposed to its effects on descending pain inhibitory pathways can be determined using statistical methods. BP and norepinephrine (NE) increases due to disinhibition of SNS activity are a primary sign of alpha-2 blockade effects on SNS outflow [222]. Therefore, analyses of alpha-2 blockade effects on the resting BP/pain sensitivity link controlling for blockade effects on BP and plasma NE would permit a test of whether blockade effects on SNS outflow confound such analyses. If alpha-2 blockade eliminates the relationship between BP and pain sensitivity in healthy individuals even after blockade effects on BP and NE are statistically removed, this would argue that the SNS-related effects of blockade do not account for the apparent alpha-2 adrenergic mediation of this relationship. In this case, the most parsimonious interpretation would be that the hyperalgesic effects of alpha-2 adrenergic blockade derive from blockade of central alpha-2 adrenergic pain inhibitory pathways overlapping with cardiovascular modulatory pathways. Use of such analytic strategies is recommended in future studies using alpha-2 adrenergic blockade to test mediators of the BP/acute pain sensitivity relationship.

We should note that although acutely elevated BP (such as occurs with alpha-2 blockade) may be associated with diminished pain sensitivity [51], such drug-induced BP increases do not necessarily confound interpretation of potential blockade studies regarding noradrenergic mechanisms underlying the BP/pain sensitivity relationship. For example, significant yohimbine-related BP increases do not eliminate hyperalgesia resulting from this drug's administration [90,91] (unpublished data). Conceptually, this finding is likely due to the drug's blocking the theorized noradrenergic pathway by which BP is associated with analgesia. Thus, even as alpha-2 adrenergic blockade

increases BP, it may block the pathway by which these BP increases would alter pain responses.

Another interpretive issue is whether the hyperalgesic effects of alpha-2 adrenergic blockade specifically in descending pain modulatory pathways are due to presynaptic or postsynaptic effects (exclusive of presynaptic effects on SNS autoreceptors above). Alpha-2 adrenergic mechanisms appear to mediate endogenous analgesia in part through presynaptic actions at the terminals of primary afferent fibers [100,193–196]. However, alpha-2 adrenergic pain modulation also derives from postsynaptic effects in the spinal dorsal horn itself [197–199,202,223–225]. Thus, both presynaptic and postsynaptic sites of action appear to be involved in descending noradrenergic pain modulation. It is impossible using alpha-2 adrenoceptor blockade methodology (or any other in vivo methodology that is not extremely invasive to the spinal cord) to isolate whether the hyperalgesic effects of alpha-2 blockade on descending pathways derive from presynaptic or postsynaptic sites of action. Given that there are no known adrenergic fibers originating in the spinal cord itself [226], descending norepinephrine outflow from brain areas such as the LC and A5 regions appears necessary for BP-related spinal pain modulatory effects, whether pre- or postsynaptic in nature. This conclusion is bolstered by evidence that chemical lesioning of these areas eliminates BP-related analgesia in rats [103]. Regardless of whether the hyperalgesic effects of alpha-2 adrenergic blockade are occurring locally in the brain (e.g. LC, RVM, A5) by inhibiting descending norepinephrine outflow, or postsynaptically in the dorsal horn or presynaptically at primary afferent fiber terminals to block the effects of descending norepinephrine activity, all of these effects ultimately derive from the same descending noradrenergic pain inhibitory pathways that overlap with BP regulation.

In summary, pharmacological alpha-2 adrenergic blockade is a necessary methodology for investigating noradrenergic mechanisms that may contribute to expression of the BP/acute pain sensitivity link. Interpretation of such studies may be complex. Consideration of the issues above in the design and interpretation of future blockade studies may be helpful.

8. Clinical implications

The review above has been generally focused on understanding the basic mechanisms underlying important aspects of the pain regulatory process, and how these may be altered in chronically painful conditions. However, the theoretical models presented may have clinical ramifications as well. As described above, we have previously reported a positive relationship not only between resting BP and acute pain sensitivity, but between resting BP and chronic pain intensity [10,18]. This latter relationship may be intuitively obvious to chronic pain practitioners, given the known pressor effects of clinical pain. However, considering that there are parallel effects on acute *and* chronic pain responsiveness, the theoretical models described above would suggest that this positive relationship reflects a failure of overlapping endogenous inhibitory systems that would normally moderate both BP and pain sensitivity in the context of painful stimuli. It is surprising therefore that little research attention has been devoted to the implications of chronic pain for cardiovascular disease risk. The limited studies described previously indicate that resting BP levels may be elevated in patients with persistent pain [108,163–165], although only one published study has directly examined the issue of hypertension as it relates to chronic pain [172]. We hypothesized that if chronic pain-related alterations in functional interactions between the cardiovascular and pain regulatory systems reflect failure of overlapping systems modulating both pain and BP, there would be an increased prevalence of clinical hypertension in the chronic pain population. A retrospective review was conducted on the records of 300 randomly selected chronic pain patients (Pain) evaluated at a tertiary care pain management center and 300 randomly selected nonpain internal medicine (Medicine) patients seen at the same institution. Results revealed that over 39% of the Pain group was diagnosed with clinical hypertension, compared to only 21% of the Medicine group ($p<0.001$). Analyses by gender revealed similar group differences in males ($p<0.05$) and females ($p<0.001$). While hypertension prevalence in the Medicine group was comparable to national population values (p's>0.10), prevalence in the pain group was significantly higher for both genders (p's<0.005). Similar results were obtained for antihypertensive use (p's <0.001). Stepwise logistic regression in the Pain group revealed that chronic pain intensity was a significant predictor of hypertensive status independent of the effects of age, race/ethnicity, and parental hypertension (p's<0.05). These results suggested the possibility that chronic pain may be associated with increased risk of hypertension. Future work will have to address whether this apparent relationship is causal, and if so, determine the direction of causality.

9. Conclusions

Functional interactions between the cardiovascular and pain regulatory systems appear to be an important part of the pain regulatory process. In healthy normotensive humans, there is much evidence that baroreceptor-mediated mechanisms are an important determinant of the adaptive BP/pain sensitivity relationship. There is weak evidence for partial mediation by endogenous opioids, with opioid mechanisms possibly more important in clinically hypertensive populations. Animal work suggests that

noradrenergic mechanisms mediated by alpha-2 adrenergic receptors may also be important to consider, although there is no human work directly testing this hypothesis. The adaptive relationship between BP and acute pain sensitivity appears to be significantly altered in chronic pain conditions, most likely reflecting chronic pain-related dysfunction in the pathways mediating this relationship. There is no evidence that these dysfunctional pathways are opioid-mediated. In the absence of opioid mechanisms, conceptual arguments and indirect data would suggest that chronic pain-related changes in baroreceptor sensitivity, alpha-2 adrenergic pain inhibitory pathways, or pain facilatory pathways may contribute to the observed changes in the BP/pain sensitivity relationship. Preliminary clinical research suggests that these chronic pain-related changes could contribute to increased hypertension risk in chronic pain sufferers.

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