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Sensory disturbances in complex regional pain syndrome:
clinical observations, autonomic interactions and possible mechanisms

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Abstract

Objective. To review mechanisms that might contribute to sensory disturbances and sympathetically-maintained pain in complex regional pain syndrome (CRPS).

Background. CRPS is associated with a range of sensory and autonomic abnormalities. In a subpopulation of patients, sympathetic nervous system arousal and intradermal injection of adrenergic agonists intensify pain.

Results. Mechanisms responsible for sensory abnormalities in CRPS include sensitization of primary afferent nociceptors and spinothalamic tract neurons, disinhibition of central nociceptive neurons, and reorganization of thalamo-cortical somatosensory maps. Proposed mechanisms of sympathetically-maintained pain include adrenergic excitation of sensitized nociceptors in the CRPS-affected limb, and interaction between processes within the central nervous system that modulate nociception and emotional responses. Central mechanisms could involve adrenergic facilitation of nociceptive transmission in the dorsal horn or thalamus, and/or depletion of bulbo-spinal opioids or tolerance to their effects.

Conclusions. Sympathetic neural activity might contribute to pain and sensory disturbances in CRPS by feeding into nociceptive circuits at the site of injury or elsewhere in the CRPS-affected limb, within the dorsal horn, or via thalamo-cortical projections.

Key words: complex regional pain syndrome; hyperalgesia; allodynia; sympathetic nervous system

Introduction

In complex regional pain syndrome (CRPS), pain and other sensory disturbances may spread from the initial site of injury to other parts of the limb and body. Patients typically describe a burning sensation that is aggravated by movement, the limb being touched, changes in ambient temperature, emotional arousal, and sometimes even loud or unexpected noises. The pain and other symptoms are often so severe that they lead to profound disability.

One of the most intriguing aspects of CRPS is the association between emotional reactions and pain. In fact, in the first descriptions of this syndrome in soldiers with gunshot wounds sustained during the American Civil War, Mitchell [1] noted that “every strong moral emotion made him worse – anger or disappointment expressing themselves cruelly in the aching limb” (page 201). Conversely, “Under such torments the temper changes, the most amiable grow irritable, the soldier becomes a coward, and the strongest man is scarcely less nervous than the most hysterical girl” (page 196). In such circumstances, reciprocal interactions between pain and emotional distress might set up a vicious circle that aggravates CRPS. In the review that follows, sensory disturbances in CRPS are described, and mechanisms that might account for the impact of emotional reactions on pain are discussed.

Sensory disturbances in CRPS

Positive and negative symptoms

In a neurological study of 145 patients with CRPS, Birklein et al. [2] identified hyperalgesia to pinprick in the affected limb of 37% of patients and brush-evoked allodynia in 30% of patients. Conversely, sensory loss to touch was detected in 53% of cases and to pinprick in 45% of cases. Sensitivity to cold-pain was greater in

CRPS-affected than unaffected limbs whereas heat-pain sensations were symmetrical. Similar findings were reported for patients studied shortly after diagnosis of CRPS [3]. Sethna et al. [4] investigated thermal and mechanical sensations in 42 children and adolescents with CRPS in a lower limb, and compared the findings with normative values in 101 healthy children. They detected hyperalgesia in the CRPS-affected limb to cold (33% of cases), heat (17% of cases) and pinprick (69% of cases), and allodynia to brushing (67% of cases). In addition, heat pain thresholds were lower in the contralateral unaffected limb of CRPS patients than controls. Hugel et al. [5] noted that hyperalgesia to heat was present bilaterally in CRPS of less than 12 months duration when compared with findings in age- and sex-matched controls, and hyperalgesia to cold was present bilaterally in acute and chronic CRPS. However, both in the acute and chronic stages, CRPS patients were less sensitive to small changes in warmth and coolness than controls. Thus, CRPS seems to be characterized by a mixture of noxious sensations (“positive symptoms”) and sensory loss (“negative symptoms”).

We investigated sensory disturbances in 61 patients with CRPS [6]. The normal range of variation for heat pain thresholds, light touch and static mechanical pressure was determined by comparing thresholds at two sites in the unaffected limb. The standard deviation (SD) of the difference between these sites was calculated over the whole group of patients, and the normal range for individual patients was defined as the mean value in their unaffected limb ± 2 SD. A value in the CRPS-affected limb that fell outside this range was considered abnormal. The prevalence of symptoms is shown in Table 1, and mechanisms that might account for these symptoms are listed in Table 2. CRPS pain intensity was greatest in patients with positive symptoms (particularly cold allodynia and thermal hyperalgesia) but was unrelated to negative

symptoms (loss of heat-pain or touch sensations). In extreme circumstances, negative symptoms might ultimately result in a neglect-like syndrome where the CRPS-affected limb feels disconnected from the rest of the body [14].

Cortical mechanisms in CRPS

At least some of the positive symptoms of CRPS are associated with heightened activity in cortical nociceptive networks. For example, Maihöfner et al. [15] reported that gently brushing the CRPS-affected hand evoked pain and abnormal activity in the contralateral primary somatosensory cortex, parietal association cortex, anterior cingulate cortex, and bilateral secondary somatosensory and insular cortices. Similar regions were activated during pinprick hyperalgesia in CRPS patients [16] and during brush allodynia in children with CRPS [17].

Paradoxically, heightened activity in cortical nociceptive networks may also mediate the negative symptoms of CRPS. For example, Pleger et al. [18] investigated two-point discrimination thresholds in CRPS-affected and non-affected limbs, and compared them with values in healthy controls. The two-point discrimination threshold was greater in the affected than non-affected limb of CRPS patients, particularly in patients with high levels of spontaneous pain, and was greater than in healthy controls. Tactile impairment was associated with *shrinkage* of representation of the CRPS-affected hand in the contralateral somatosensory cortex when mapped in response to painless stimulation of the hand. Importantly, decreases in pain following treatment were associated with an improvement in tactile discrimination and enlargement of representation of the CRPS-affected hand in the contralateral somatosensory cortex [19]. Thus, pain-induced cortical reorganization of receptive fields may suppress normal tactile processing in CRPS, possibly because the barrage

of nociceptive activity heightens central inhibitory drive both to noxious and innocuous sensations [17].

Referred sensations and spread of pain in CRPS

Reorganization of cortical somatosensory maps in CRPS may also account for mislocalization of sensations to tactile stimulation of the CRPS-affected limb. For example, McCabe et al. [20] reported that light touch or pinprick sensations were referred from the hand to the face or from the foot to the knee (adjacent areas in the cortical somatosensory map) in five of 16 CRPS patients when examined with their eyes closed. Referred sensations disappeared when vision was permitted, implying that cortical processes mediated the referred sensations. The location of the referred sites was consistent with distortion of the cortical somatosensory map, suggesting that excessive nociceptive activity in the cortical area representing the painful limb encroached on adjacent cortical regions. In a similar study, tactile stimulation of the first and fifth fingers evoked sensations elsewhere in the CRPS-affected hand in 33% of cases, particularly in those with pinprick hyperalgesia [21], again consistent with pain-evoked reorganization of cortical somatosensory maps.

Sensory disturbances and pain sometimes spread beyond the site of injury to include the entire limb in CRPS. Furthermore, sensory disturbances often extend to the face and trunk on the side of injury and occasionally to other limbs, implying the involvement of supraspinal circuits rather than a purely local or spinal mechanism [22]. Loss of light tactile sensations on the painful side of the body [23-25] suggests that abnormal sensory input from the painful area inhibits innocuous sensations from the remaining half of the body. Conversely, hyperalgesia to blunt pressure extends from the affected limb to the ipsilateral forehead in the majority of patients with CRPS [26]. We found that loss of light tactile sensations in the CRPS-affected limb

was associated not only with diminished sensitivity to cold, pinprick and heat-pain in the ipsilateral forehead (consistent with pain-evoked suppression of ipsilateral sensations) but also with hyperalgesia to blunt pressure, implying a rostral spread of central sensitization (Table 3). The mechanism of central sensitization is not completely understood, but may involve disinhibition of spinal and trigeminal nociceptive neurons or facilitation of nociceptive activity by excitatory neurons that project from the rostroventral medulla [27]. This sensitizing process appears to distort or suppress non-noxious sensations. Loss of an inhibitory influence of normal cutaneous sensations in the CRPS-affected limb may enhance the excitability of thalamo-cortical nociceptive networks, thereby establishing a vicious circle [12,13,17,18,26].

McCabe et al. [28] investigated the idea that disruption of central sensory processing contributes to the pain of CRPS. In patients with pain for less than two years, function improved and pain decreased while watching movements of the unaffected limb in a mirror, thus creating the illusion of normal movements in the affected limb. The absence of a waitlist control group weakens the impact of these findings; nevertheless, the immediate analgesic effect of mirror image feedback in patients with acute CRPS suggests that conflict between motor intention and sensory feedback generates intractable pain and functional disturbances. These findings have since been replicated and extended [29].

Adrenergic involvement in CRPS

Mechanism of autonomic disturbances

Autonomic disturbances in the symptomatic limb of patients with CRPS range from signs of sympathetic deficit (warmth and loss of vasoconstrictor reflexes) to sympathetic overactivity (sweating and coldness). In a cross-sectional

study of 25 CRPS patients, Wasner et al. [30] found that whole-body cooling and warming provoked three distinct vascular patterns: increased skin blood flow and warmth in the symptomatic limb irrespective of body temperature; decreased flow and coolness in the symptomatic limb irrespective of body temperature; and an intermediate type where the symptomatic limb was warmer or cooler than the contralateral limb at different body temperatures. In contrast, changes in limb temperature and blood flow during body heating and cooling were symmetrical in healthy subjects and in patients with limb pain not associated with features of CRPS. The cold pattern was most common in CRPS patients with the longest duration of pain, thus supporting the notion that the warm dry limb of CRPS can evolve into a cool moist limb as the condition progresses [2]. This would be consistent with the development of adrenoceptor supersensitivity in the later stages of CRPS.

Depletion of sympathetic neurotransmitters. In the majority of patients with CRPS, the venous concentrations of sympathetic neurotransmitters such as noradrenaline and neuropeptide Y are lower in the affected than unaffected limb, irrespective of the duration of the condition or whether the limb is warm or cool [30-34]. For example, plasma DHPG (the intracellular metabolite of noradrenaline) was lower in the painful than contralateral limb of 26 patients with features of CRPS [31]. In addition, levels of noradrenaline and neuropeptide Y were lower in the affected than the unaffected limb if the limb was abnormally sweaty or if light touch provoked pain [31-32]. Harden et al. [33] and Wasner et al. [30] noted a similar depletion of noradrenaline levels in the affected limb of CRPS patients, and Goldstein et al. [34] reported that adrenergic markers were noticeably lower on the symptomatic side in several patients with CRPS. Taken together, these findings

suggest that sympathetic neurotransmission is compromised in the affected limb of at least some patients.

Central involvement in autonomic disturbances. Surprisingly, the sympathetic deficit in CRPS may be reversible. In an intriguing case report described by Wasner et al. [35], features of CRPS (swelling of the hand, a feeling of heat, and burning pain in the right forearm and hand) developed ten days after a woman fractured her right distal radius. When examined two weeks later, vasoconstrictor reflexes were absent in the patient's right hand but were normal in the left hand. In addition, skin temperature was high and venous levels of noradrenaline were lower in the affected limb than contralaterally. After five weeks of intensive treatment involving sympathetic blocks, corticosteroid treatment, nonsteroidal anti-inflammatory drugs and physiotherapy, spontaneous pain subsided and signs of sympathetic activity returned. Thus a central process, presumably linked with the mechanism of pain, apparently inhibited sympathetic outflow in the affected limb. Curiously, limb pain evokes ipsilateral increases in blood flow through scalp vessels [36]. The response is inhibited by pre-treatment with guanethidine, an agent that displaces noradrenaline from sympathetic nerve terminals (Fig. 1), consistent with the notion that limb pain inhibits ipsilateral sympathetic vasoconstrictor tone [37].

Autonomic disturbances spread beyond the CRPS-affected limb [38] and are reversible [35], implying a central disturbance in regulation of autonomic activity. Birklein et al. [39] studied vasoconstrictor responses to various sympathetically-arousing tasks (the veno-arteriolar reflex, inspiratory gasp, cold pressor test and mental arithmetic) in 20 patients with clinical features of CRPS. Most patients were studied in the acute stage of the disease (median duration 8.5 weeks). Vasoconstrictor

responses were impaired in the affected limb to stressful mental arithmetic but not to the other tests, consistent with disruption of central sympathetic control but not of spinal or postganglionic reflexes. In contrast, Ide et al. [40] reported that vasoconstrictor responses to an inspiratory gasp (presumably a spinal reflex) were enhanced on the affected side in patients with chronic CRPS, possibly due to the development of adrenergic supersensitivity as the condition progressed.

Thermoregulatory sweating appears to be greater in the affected than unaffected limb both in acute and chronic CRPS [39], implying that central thermoregulatory processes are compromised.

Adrenergic supersensitivity in CRPS. Animal models of neuropathic pain provide strong support for the concept of a chemically mediated sympathetic–sensory neural coupling that underpins a sympathetic component of pain; moreover, supersensitivity to adrenergic agents may increase the prominence of this nociceptive mechanism [41–42]. Human studies endorse this view. For example, Arnold et al. [38] reported that dorsal hand veins in the affected limb of CRPS patients constricted to lower doses of noradrenaline than veins in the unaffected limb or those of control subjects. In a small-scale study of five CRPS patients and seven controls, the relative density of α_1 -adrenoceptors labeled by the selective radioligand [125 I]-HEAT was investigated in skin biopsies taken from CRPS-affected and unaffected limbs [43]. The density of specific binding was significantly greater in samples from the affected skin of patients than in control samples, consistent with a greater representation of α_1 -adrenoceptors in affected skin. Chemali et al. [44] reported that axon-reflex sweating induced by iontophoresis of the α_1 -adrenergic agonist phenylephrine was greater in the affected than unaffected limb of patients with CRPS, and was greater than in control subjects and patients with resolved CRPS. In addition, Jorum et al. [45]

recently provided electrophysiological evidence that nociceptive fibres in a patient with CRPS were activated by endogenous sympathetic activity and by intradermal injection of noradrenaline. Thus, an adrenergic supersensitivity that develops in response to persistent sympathetic deficit may evoke autonomic disturbances and augment pain in the CRPS-affected limb.

Adrenergic agonists evoke pain in a subgroup of CRPS patients

Wallin, Torebjork and Hallin [46] were the first to report that intradermal injection or iontophoresis of noradrenaline provoked pain in the affected skin of patients with CRPS. Importantly, noradrenaline rekindled pain that had subsided after sympathectomy of the affected limb, indicating that the sympathectomy suppressed but did not abolish the mechanism responsible for pain. In normal circumstances, sympathetic neural discharge does not trigger activity in primary sensory afferents. However, in animal experiments stimulation of the sympathetic chain and administration of noradrenaline increased activity in surviving sensory nerve fibres after peripheral nerve transection and neuroma formation [47], partial destruction of a peripheral nerve [48-49], and intradermal injection of inflammatory substances [50-52]. Similar findings have been reported in humans [41-42]. Thus, an adrenergic sensitivity appears to develop in primary sensory afferents after nerve injury and inflammation, possibly because of direct expression of adrenergic receptors on sensory nerves or because of adrenergic release of an intermediary substance (e.g., prostaglandins, bradykinin or nerve growth factor) that excites sensory nerves.

The traditional treatment for CRPS involves anaesthetizing or destroying sympathetic neurons that supply the affected limb. These procedures are effective in only a subgroup of patients, said to have “sympathetically maintained pain”. In such patients, intradermal injection of noradrenaline in the affected limb is more likely to

evoke pain than in patients who do not benefit from sympathetic blockade [53-54], thus bolstering the concept of sympathetically maintained pain.

Sympathetic arousal evokes pain in CRPS patients

Seventy years after Mitchell [1] first described the nociceptive consequences of arousal in soldiers with gunshot wounds, Kirklin et al. [55] documented similar effects in soldiers who were injured in the Second World War. We recently confirmed that pain increased in the majority of CRPS patients after they were startled with a loud noise or when their forehead was cooled (both strong stimuli for evoking sympathetic nervous system activity) [6]. In contrast, pain evoked by heat *decreased* during and after these tasks and during various other forms of sympathetic stimulation in healthy subjects whose skin had been sensitized to heat with topically-applied capsaicin (the hot component of chilli peppers; at low concentrations capsaicin evokes hyperalgesia by increasing the excitability of polymodal nociceptive C-fibres whereas higher concentrations induce hypoalgesia via desensitization and conduction blockade).

Baron et al. [56] investigated the effect of warming and cooling the body on pain and hyperalgesia in 13 patients with CRPS. In seven cases, a decrease in pain after regional sympathetic blockade suggested that sympathetic neural discharge contributed to pain. In this subgroup, spontaneous pain and mechanical hyperalgesia increased during whole-body cooling, indicating an association between nociceptive discharge and heightened sympathetic vasoconstrictor activity. In contrast, body cooling had no effect on pain or hyperalgesia in six patients whose pain remained unchanged after sympathetic blockade.

Drummond and Finch [57] investigated whether sympathetic blockade selectively alleviated pain in patients who reported that pain increased during

sympathetic arousal. The painful effect of a startle stimulus disappeared in patients who experienced pain relief after sympathetic blockade, consistent with a reduction in adrenergic excitation of nociceptors in the affected limb. Nonetheless, the startle stimulus still evoked pain in a few patients whose pain remained unchanged after sympathetic blockade; moreover, sympathetic blockade failed to inhibit the nociceptive effect of forehead cooling in 50% of patients. It has generally been assumed that sympathetic neural discharge during arousal provokes pain in CRPS by aggravating inflammation or by exciting adrenergic receptors on sensory nerves in the affected limb. However, these findings suggest that arousing stimuli might also act on a central process to intensify pain in some patients.

Central mechanisms that might intensify pain to arousing stimuli in CRPS

Several sites within the central nervous system that modulate nociceptive information are also involved in arousal responses and sympathetic control. The amygdala and anterior cingulate cortex regulate the unpleasant and distressing aspects of pain, and modulate anticipatory responses and attention to pain. These centres communicate with the midbrain periaqueductal gray which, in turn, projects downstream to the raphe nuclei and brainstem adrenergic nuclei [58]. The periaqueductal gray also links indirectly with the locus coeruleus via the nucleus paragigantocellularis, itself an important integrating center for autonomic control [59]. One major role of the periaqueductal gray is to activate the cardiovascular system and to trigger non-opioid analgesia in the fight-flight response. A second major role is to initiate opioid analgesia and to inhibit cardiovascular activity, locomotion and responsiveness to the environment during periods of inescapable pain and stress (the “defeat” response) [60]. Inhibitory pain control pathways descend from the raphe nuclei and from brainstem adrenergic nuclei to the trigeminal nucleus caudalis and

dorsal horn of the spinal cord [58,61]. Apart from their role in pain modulation, brainstem adrenergic nuclei are involved in central autonomic control, affective behaviour, cortical arousal, selective attention and vigilance [59].

Intense pain and fear strongly activate these pain modulation circuits, resulting in pain- or stress-induced analgesia. However, less intense stimulation and negative affect appear to increase pain [62-63], possibly due to an increase in activity in facilitatory circuits that descend from the midbrain and brain stem to the dorsal horn of the spinal cord [27,64]. In CRPS, an imbalance between inhibitory and facilitatory influences might enhance nociceptive transmission to stimuli that heighten arousal. Possible mechanisms are reviewed below.

Injury to primary sensory afferents. CRPS type II (causalgia) develops after injury to a peripheral nerve trunk. In rats subjected to dorsal rhizotomy, the normal inhibitory influence of locus coeruleus activation on spinal nociceptive neuronal discharge is transformed into a facilitatory influence [65]. That is, destruction of the spinal projections of primary sensory afferents apparently removes a necessary link in the inhibitory bulbo-spinal circuit, and appears to unmask a facilitatory influence of locus coeruleus activation on spinal nociceptive neurons. Hence, activation of the locus coeruleus or nearby brainstem adrenergic nuclei during heightened states of arousal may enhance rather than inhibit nociceptive transmission in the dorsal horn of patients with CRPS type II.

Facilitation of nociceptive transmission in the thalamus. An attentional focus on pain may be crucial for survival after a life-threatening injury and may help to prevent further injury during recuperation. Thus, it might be adaptive that projections from brainstem adrenergic nuclei, which mediate cortical arousal and that sharpen attention, also facilitate nociceptive transmission in the thalamus (and presumably also

the somatosensory cortex) [66]. Therefore, if pain modulation processes are overwhelmed or fail, activation of brainstem adrenergic nuclei during emotional reactions, heightened states of arousal or sympathetic thermoregulatory control could intensify thalamic nociceptive discharge.

Depletion of endogenous opioids or tolerance to their effects. Endogenous opioids are involved in descending pain control [61]. Persistent activation of inhibitory pain modulation circuits in chronic pain patients might result in tolerance to opioids or deplete opioid reserves [67]. In addition, tolerance to opioids could be compounded by opiate medication. Consequently, facilitatory influences on spinal nociceptive discharge could outweigh inhibitory endogenous opioid influences in chronic pain states such as CRPS. An inhibitory opioid influence in the locus coeruleus mediates passive coping behaviours to inescapable stress and pain [68]. The fatigue of this inhibitory influence might potentiate arousal responses and nociceptive transmission in the thalamus.

Persistent inhibition of central sympathetic activity. The periaqueductal gray “defeat” response inhibits peripheral sympathetic vasoconstrictor discharge [60]. In the early stages of CRPS, sympathetic vasoconstrictor tone is often diminished in the affected limb [30,39]. Inescapable pain and stress evokes the periaqueductal gray “defeat” response which might inhibit sympathetic activity regionally in the painful limb and, to a lesser extent, in other limbs. Sympathetic vasoconstrictor inhibition could secondarily contribute to spontaneous pain and pain evoked by arousal by encouraging the development of adrenergic supersensitivity at nociceptive foci in the CRPS-affected limb.

Conclusions

Mechanisms that might contribute to sensory disturbances in CRPS are summarized in Figure 2. Sympathetic neural activity might feed into nociceptive circuits at various places: the site of injury or distally in the CRPS-affected limb; the dorsal horn; or thalamo-cortical projections. Interactions such as these may explain the association between emotional reactions and pain described so evocatively by Mitchell [1] in soldiers with gunshot wounds. If so, they may represent new therapeutic targets in this debilitating and often intractable condition.

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Table 1
Sensory disturbances in 61 CRPS patients

<u>Positive Symptoms</u>	
Hyperalgesia to heat-pain (to a heat ramp)	25%
Punctate allodynia (to von Frey hairs)	33%
Cold allodynia (to 2°C)	34%
Allodynia to brushing	56%
Hyperalgesia to pressure (algometer)	54%
<u>Negative Symptoms</u>	
Loss of touch sensations (to von Frey hairs)	20%
Loss of sensitivity to heat-pain (heat ramp)	29%
Loss of sensitivity to pressure (algometer)	3%

Data taken from Drummond et al. [6]. Heat pain: Before the heat pain threshold was measured, skin temperature was brought to at least 32°C with the servo-controlled radiant heat lamp and maintained at that temperature for 10 to 15 seconds. To assess the heat pain threshold, skin temperature increased at 0.5°C per second until the patient signaled pain or to a maximum of 49°C. Punctate allodynia was considered to be present if stimulation of the symptomatic limb with von Frey hairs provoked paresthesia or pain. Cold allodynia: The circular end of a cylindrical copper bar (10 cm long, 1.3 cm wide, 2°C) was applied to each site on the patient's hands or feet. Because pain was never reported during stimulation of the nonsymptomatic limb, cold allodynia was considered to be present if local cooling provoked paresthesia or pain. Allodynia to brushing: A soft brush was moved slowly over each site on the patient's hands or feet. Allodynia was considered to be present if brushing provoked paresthesia, a rough or sharp sensation, or pain. Hyperalgesia to pressure: Force was applied to each site with a spring-loaded algometer. The hemispheric tip (1 cm diameter) of the algometer's plunger was applied in 250-g increments to a maximum of 2.5 kg or until pain was reported. The force was applied for a few seconds while the patient was questioned about pain, then the force was released and applied at a higher level.

Table 2

Potential mechanisms of hyperalgesia in CRPS

Heat and chemical mediators	Sensitization of heat-specific, cold-sensitive or polymodal C-nociceptors [7,8]
Deep pressure	Sensitization of mechano-insensitive (silent) C-nociceptors [9]
Cold	Dysfunction of cold-specific A- δ fibres disinhibits central nociceptive neurons [10]
Pinprick and brushing	Nociceptive input sensitizes spinal nociceptive and wide dynamic range neurons to input from A- δ and A- β fibres (perhaps in association with fatigue of descending inhibitory influences or recruitment of descending facilitatory influences) [11]
Hyperpathia	<ol style="list-style-type: none"> 1. Dysfunction of cutaneous low-threshold mechanoreceptors disinhibits central nociceptive neurons (Gate-Control effect; also in post-stroke pain) [12,13] 2. Sensitization of central nociceptive neurons inhibits processing of tactile sensations [17,18]

Table 3

Correspondence between diminished touch in the CRPS-affected limb
and sensations in ipsilateral forehead

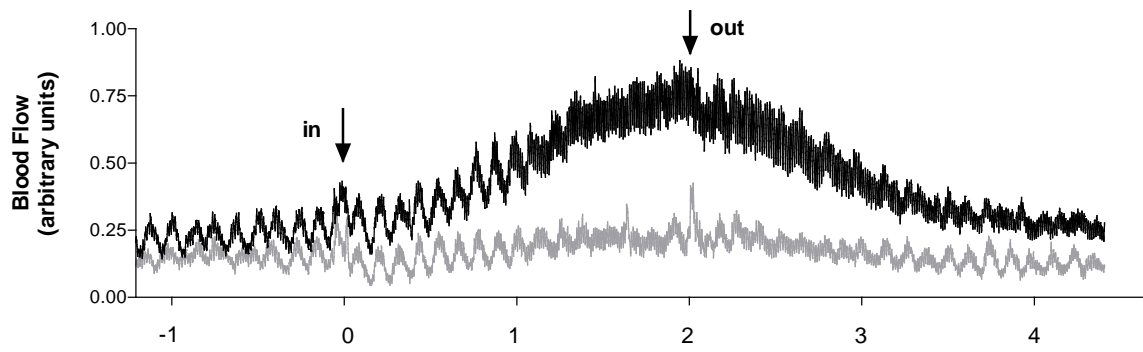
	Sensations in the ipsilateral forehead			
	Diminished cold	Diminished sharpness	Diminished heat-pain	Pressure hyperalgesia
Diminished touch in the affected limb	++	+	+	+

Data from Drummond and Finch [26]. Correlation significant ++ $p < 0.01$; + $p < 0.05$.

Figure legends

Figure 1. Effect of immersing the right hand in 2 °C water for 2 minutes on blood flow in the right temple (black waveform) and left temple (grey waveform) after bilateral saline pre-treatment (A), and after guanethidine pre-treatment to the right temple and saline pre-treatment to the left temple (B). The hand was immersed in the water at the arrow marked “in”, and removed from the water at the arrow marked “out”. The cold-pain-induced increase in blood flow in the right temple after saline pre-treatment was inhibited by guanethidine pre-treatment. Pulse amplitude (indicated by the thickness of the blood flow signal) also increased in the right temple after saline pre-treatment, and this response was inhibited by guanethidine pre-treatment. Reprinted with permission from Drummond [37].

Figure 2. Mechanisms that might contribute to sensory disturbances in CRPS. Inflammation associated with nerve or tissue injury may sensitize primary afferent nociceptors in the CRPS-affected limb which, in turn, sensitize spinal nociceptive neurons. Bulbospinal facilitatory influences contribute to central sensitization, which could be further augmented by fatigue of inhibitory pain modulation mechanisms. Pain-induced reorganization of receptive fields in the thalamus and somatosensory cortex may suppress normal tactile processing in CRPS and maintain pain. Sympathetic neural discharge could enhance pain in CRPS by aggravating inflammation or by exciting adrenergic receptors on nociceptive afferents in the CRPS-affected limb. In addition, a facilitatory influence of locus coeruleus activation on nociceptive neurons in the dorsal horn or thalamus might increase pain during heightened states of arousal. Furthermore, pain-induced suppression of sympathetic activity could increase sensitivity to adrenergic agents, thereby exacerbating the adrenergic component of nociception.

A. Saline Pre-treatment**B. Guanethidine Pre-treatment**