COMPLEX REGIONAL PAIN SYNDROME: WHY DOES PAIN SPREAD FROM THE INJURED LIMB TO THE FACE?

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Declaration

This thesis contains no material which has been accepted for the award of any other degree in any other university and, to the best of my knowledge or belief, contains no material previously published or written by another person, except when due reference is made in text.

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Abstract

In patients with complex regional pain syndrome (CRPS), sensory disturbances commonly spread outside the affected limb, in particular hemilaterally. Hyperalgesia to pressure-pain was, for instance, documented in the forehead ipsilateral to the affected limb [7]. The aim of this thesis was to investigate potential mechanisms involved in this spread. Firstly, the effect of experimental limb pain (the cold pressor test) on sensory changes to pressure-pain and sharpness outside the immersed limb was investigated on each side of the forehead in samples of 45 and 32 healthy volunteers. Prior to pain induction, differences in pressure-pain or sharpness sensitivity between the left and right side of the forehead were generally small or non-existent. The induction of severe limb pain in healthy volunteers produced a bilateral reduction in forehead sensations to pressure-pain and sharpness with greater analgesia to pressure in the ipsilateral forehead. Central inhibitory pain control mechanisms may have mediated this effect.

The second study attempted to disrupt inhibitory pain control prior to cold-induced limb pain (cold pressor test) in 85 healthy volunteers and investigated the effect of these procedures on sensitivity to pressure-pain and sharpness on each side of the forehead. Optokinetic stimulation was employed to disrupt inhibitory pain control as increased forehead sensitivity was reported following this form of motion sickness-producing stimulation [4; 6]. Sensitivity to pressure-pain and sharpness increased in the forehead after optokinetic stimulation. However, during the subsequent cold pressor test, forehead sensitivity to these stimuli decreased in the most pain sensitive participants, suggesting that inhibitory pain control mechanisms remained intact.

The finding of a previous study that unilateral carageenan-induced hindpaw inflammation in the rat produces thermal hyperalgesia both in the inflamed hindpaw and

the non-inflamed forepaw, but not in the contralateral paws [16] prompted us to investigate a link between limb inflammation and hemilateral hyperalgesia. Pressure-pain and sharpness sensations were assessed on each side of the forehead in 17 healthy volunteers during 48 hours of topical treatment of the forearm with the inflammatory agent, capsaicin. Capsaicin-treatment evoked a bilateral reduction in forehead sensitivity to sharpness and an ipsilateral reduction in forehead sensitivity to pressure-pain. Differences in the tissue affected (muscle in the rat study and skin in the human study) may explain the differing results from the rat study.

The issue of inflammation-induced hemilateral sensory disturbances was explored further in patients with CRPS. NMDA-receptors are up-regulated in inflamed human skin [15] and appear to be involved in sensitizing primary afferent nociceptors during inflammation and tissue injury [2; 8; 10]. In a double-blind placebo-controlled trial, the NMDA antagonist, topical ketamine, was applied to the affected or unaffected limb of 20 patients with CRPS and the effect on sensitivity to a range of sensory stimuli (touch, pinprick, thermal, pressure, brushing) was investigated in the affected and unaffected limb and on each side of the forehead. Hyperalgesia to sharpness, pressure, cold and heat, and allodynia to brushing, were detected in the ipsilateral forehead before treatment. This was generally associated with heightened sensitivity in the affected limb. The topical application of ketamine reduced allodynia and sharpness hyperalgesia in the affected limb. As allodynia to brushing the skin and sharpness hyperalgesia are mediated by sensitized spinal nociceptive and wide dynamic range neurons that receive input from nociceptive A-delta fibers and non-nociceptive A-beta fibers [12; 13], peripheral NMDA-receptors may play a role in the sensitization of central neurons in CRPS. In some patients with allodynia in the forehead, forehead allodynia was reduced following treatment of the affected limb

with ketamine, suggesting that a similar mechanism may contribute to the heightened sensitivity in the forehead.

Prior to this thesis, a small number of studies suggested that central inhibitory pain control is disrupted in patients with CRPS [3; 5; 14]. The laterality of such mechanisms, and their potential contribution to hemilateral hyperalgesia, was explored. CRPS pain increases during startle with a loud tone [3; 5]. Whether this increase in pain to acoustic startle differs between startle in the ipsilateral and contralateral ear was investigated in 28 CRPS patients. Acoustic startle in the ear ipsilateral to the affected limb induced greater limb pain than startle in the contralateral ear. In addition, auditory discomfort was greater to ipsilateral than contralateral ear stimulation and in patients with increased pain to startle than in a small group of non-responders, suggesting not only that inhibitory pain control is disrupted in CRPS but that central neurons both in the somatosensory and auditory systems are facilitated, in particular to stimulation on the ipsilateral side of the body.

The laterality of a dysfunction in inhibitory pain control was explored further by investigating pressure-pain and sharpness sensations on each side of the forehead in 22 CRPS patients during noxious cold stimulation of the affected limb versus noxious cold stimulation of the contralateral unaffected limb. Cold water immersion of the healthy limb decreased forehead sensitivity to pressure-pain bilaterally and decreased clinical pain in the affected limb. In contrast, immersion of the symptomatic limb increased pressure-pain sensitivity on both sides of the forehead. Sharpness ratings in the forehead remained unchanged to immersion of either limb. Nociceptive afferent input from the CRPS affected limb may thus either fail to evoke inhibitory processes or simultaneously evoke a pain facilitatory mechanism that masks inhibitory influences.

Finally, pressure-pain and sharpness sensations were investigated on each side of the forehead in 35 chronic pain patients without CRPS (neuropathic or nociceptive limb pain, back pain or acute herpes zoster/postherpetic neuralgia) and were compared to similar measurements obtained in 34 patients with CRPS. Ipsilateral forehead hyperalgesia to pressure-pain was more common in CRPS patients (59%) than patients without CRPS (14%). Non-CRPS patients mainly reported symmetrical (within normal range) forehead sensations. Ipsilateral forehead hyperalgesia to sharpness occurred in 38% of CRPS patients which was similar to that in patients without CRPS. Nonetheless, symmetrical sharpness sensations dominated in both groups. In general, heightened sensitivity to pressure and sharpness in the ipsilateral forehead was present in patients with greater pain, sharpness hyperalgesia and swelling at the pain site.

In sum, the results of this thesis indicate that ipsilateral forehead hyperalgesia, in particular to pressure-pain, may be specific to CRPS. Nociceptive input from the inflamed CRPS limb may sensitize neurons in the dorsal horn and neurons at supraspinal sites that receive input from the affected limb such as the contralateral thalamus. Hyperexcitability in thalamic nuclei contralateral to the affected limb which receive convergent input from hemilateral body sites could not only explain the presence of hemilateral hyperalgesia but could also explain heightened sensitivity to other forms of sensory input (e.g., auditory input). Failure of inhibitory pain control, in particular to stimulation on the symptomatic side of the body, or a shift toward facilitatory control in mechanisms with a bidirectional role in pain modulation such as the noradrenergic actions from the locus coeruleus, the serotonergic actions from the raphe nuclei or diffuse noxious facilitatory versus inhibitory controls [1; 9; 11; 17; 18] may further promote the transfer of nociceptive messages to

higher brain sites. The ipsilateral noradrenergic actions from the locus coeruleus is a particular candidate for the hemilateral facilitation of nociception in CRPS.

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Publications

Refereed articles

Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. Pain In Press.

Knudsen L, Drummond PD. Cold-induced limb pain decreases sensitivity to pressure-pain sensations in the ipsilateral forehead. Eur J Pain 2009, doi:10.1016/j.ejpain.2008.12.005.

Submitted articles

Knudsen L, Drummond PD. Limb inflammation produces analgesia to pressure-pain in the ipsilateral forehead of healthy volunteers. Eur J Pain.

Knudsen L, Finch PM, Drummond PD. Ipsilateral auditory startle enhances hyperacusis and limb pain in complex regional pain syndrome. Pain.

Knudsen L, Finch PM, Drummond PD. Failure of inhibitory pain modulation to noxious stimulation of the symptomatic limb, but not the healthy limb, in complex regional pain syndrome. Pain.

Knudsen L, Finch PM, Drummond PD. Hemilateral pressure hyperalgesia: a specific sign in complex regional pain syndrome? Pain.

These articles are reproduced in the thesis in their full, original state. This accounts for a certain degree of repetition and inconsistencies in reference style.

Author contributions

In keeping with doctorate research regulations, this is a statement of my part in the research work of this thesis. The study design and ideas for Study one, two, three, six and seven were developed in cooperation with Professor Peter Drummond who was my supervisor throughout my PhD. He also provided valuable consultation throughout the studies. I conducted the testing, analysed the results and wrote the first draft of the papers for these studies and was thus assigned first author. Dr Philip Finch was involved in the recruitment and selection process of patients in Study six and seven and together with Peter Drummond provided editorial comment on the papers.

The ideas for Study four and five were brought forward by Philip Finch who was also involved in the recruitment and selection process of patients for these studies. However, I planned the more detailed practical design in cooperation with Peter Drummond. I carried out the assessments of the patients in both studies and analysed the data for Study five. I was also involved in the data analysis of Study four. Parts of the paper for Study four was written by me, and I wrote the first draft of the paper for Study five. Both Peter Drummond and Philip Finch provided input on intellectual and editorial content throughout this process, and both contributed to writing parts of Study four.

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noxious inhibitory controls or serotonergic projections from raphe nuclei may explain findings of generalized sensory disturbances in CRPS patients. For clarity, descending influences from the LC are presented schematically.