UNDERSTANDING PAIN: HOW IS PAIN PROCESSED IN HEALTHY HUMANS?

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Declaration

This thesis is my own account of my research and contains as its main content work that has not previously been submitted for a degree at any tertiary education institution.

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Abstract

The aim of this thesis was to examine the effects of experimentally-induced limb pain on pain in other remote body sites in a pain-free healthy population. In Study one, we compared the effects of limb-pain induced by high-frequency electrical stimulation (HFS) and ultraviolet B (UVB) on sensitivity to heat, and to sharpness and pressure-pain on the conditioned forearm site, the contralateral control site, and on each side of the forehead in samples of 30 (HFS) and 16 (UVB) healthy participants. Prior to pain induction, sensitivity to heat, sharpness and pressure-pain was similar at the conditioned site and the control site, and between the two sides of the forehead. UVB triggered more intense signs of primary hyperalgesia at the conditioned site than HFS. Secondary hyperalgesia developed after HFS but not UVB, indicating that HFS evoked signs of central sensitisation. Pressure-pain sensitivity decreased on both sides of the forehead with a greater reduction on the ipsilateral side after HFS, but not UVB. Furthermore, electrically-evoked pain at the HFS-conditioned site decreased significantly more during ipsilateral temple cooling than contralateral cooling, whereas pain reduction at the UVB-conditioned site was similar irrespective of the side of forehead that was cooled. Thus, central sensitisation evoked by HFS might also have triggered ipsilateral pain-inhibitory modulation processes in healthy humans.

In Study two, to further delineate pain modulation processes evoked by HFS, we examined sensory changes in the forearm and forehead, and nociceptive blink reflexes elicited by supraorbital electrical stimulation with and without counter-irritation (electrically-evoked pain at the HFS-conditioned site) in 20 healthy

participants before and after HFS conditioning. In line with Study one, secondary hyperalgesia and bilateral and ipsilateral forehead analgesia to pressure-pain developed after HFS conditioning. In general, counter-irritation of the forearm and HFS suppressed pain perception, and inhibited the amplitude of nociceptive blink reflex to supraorbital stimuli. However, in the absence of forearm counter-irritation, HFS facilitated the ipsilateral blink reflex amplitude to supraorbital stimuli delivered ipsilateral to the HFS-conditioned site. Thus, HFS might have triggered hemilateral pain-inhibitory and pain-facilitatory mechanisms simultaneously.

In Study three [53], to determine whether central sensitisation is necessary for triggering this sign of ipsilateral inhibitory pain modulation, we compared the effects of HFS and low frequency electrical stimulation (LFS) in the forearm on sensitivity to pressure-pain in the ipsilateral forehead in samples of 50 (HFS) and 18 (LFS) healthy individuals. LFS was chosen as it triggers only minor sign of central sensitisation. Before conditioning, sensitivity to heat, sharpness, and pressure-pain were similar at the conditioned and the control sites, and between the two sides of the forehead. Pain perception was higher after HFS than LFS, and central sensitisation developed after HFS but not LFS. Nevertheless, pressure-pain sensitivity decreased in the ipsilateral forehead after both forms of electrical stimulation. This decrease was associated with a heightened sensitivity to pressure-pain at the conditioned forearm site, but with a reduced sensitivity to heat in skin surrounding the electrically-conditioned site. Thus, the ipsilateral pain-inhibitory process might have suppressed sensitivity to pressure-pain in the ipsilateral forehead and secondary hyperalgesia to heat.

Evidence from rat studies indicates adrenergic influences descending from the locus coeruleus (LC) in mediating ipsilateral inhibitory pain control via the activation

of inhibitory α_2-adrenoreceptors.Therefore, in the final study (Study four), to determine whether ipsilateral forehead analgesia to HFS is mediated by α_2-adrenoreceptors, we attempted to block their effects with oral administration of yohimbine, an α_2-adrenoreceptor antagonist, in a double-blind placebo-controlled crossover design in a sample of 22 healthy individuals. Sensitivity to heat, sharpness, and pressure-pain at and adjacent to the conditioned and control sites, and on each side of the forehead was assessed at baseline, following drug administration, and after HFS conditioning. Blood pressure, heart rate and electrodermal activity were also measured across these three stages. Nociceptive blink reflexes to supraorbital stimulation were also investigated following drug administration and after HFS conditioning. In addition, the effects of ipsilateral versus contralateral temple cooling on electrically-evoked pain at the HFS-conditioned site were compared. Prior to drug administration, sensitivity to heat, sharpness, and pressure-pain were similar at the conditioned and the control site, and between the two sides of the forehead. In line with our previous studies, in the placebo condition, HFS evoked primary and secondary hyperalgesia in the forearm, ipsilateral forehead analgesia to pressure-pain, and a reduction of electrically-evoked forearm pain during ipsilateral temple cooling. As expected, yohimbine increased blood pressure and electrodermal activity compared to placebo. Yohimbine also enhanced the excitability of the ipsilateral nociceptive blink reflex compared with placebo, consistent with yohimbine facilitating pro-nociceptive effects. Unexpectedly, the development of ipsilateral forehead analgesia to pressure-pain following yohimbine, and a greater reduction of electrically-evoked forearm pain during ipsilateral temple cooling following yohimbine compared to placebo, suggests that yohimbine might have enhanced

analgesia. Thus, non-noradrenergic mechanisms may also be involved in mediating these analgesic effects, in addition to adrenergic influences.

Together, these findings indicate that in healthy humans noxious stimulation with HFS may trigger ipsilateral inhibitory modulation processes, which could be mediated both by noradrenergic and non-adrenergic mechanisms. Further investigation of ipsilateral inhibitory modulation processes is important, as this process may be disrupted in conditions such as complex regional pain syndrome.

Publications

Refereed Articles

Vo, L., Drummond, P.D. (2013). High frequency electrical stimulation concurrently induces central sensitization and ipsilateral inhibitory pain modulation. *Eur J Pain* 17, 357-368.

Vo, L., Drummond, P.D (2014). Coexistence of ipsilateral pain-inhibitory and facilitatory processes after high-frequency electrical stimulation. *Eur J Pain* 18, 376-385.

Vo L, Drummond P. D. (2014): Analgesia to pressure-pain develops in the ipsilateral forehead after high- and low-frequency electrical stimulation of the forearm.*Exp Brain Res* 232,685-693.

Submitted Articles

Vo L, Drummond PD: Involvement of α_2-adrenoceptors in inhibitory and facilitatory pain modulation processes.

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.

For my parents

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Table of Contents

List of Tables

Tables from Study Three

Tables from Study Four

List of Figures

Figures from Study One

Figures from Study Two

Figures from Study Three

Figures from Study Four

site during the recovery period after the ipsilateral temple was cooled (* $p < .01$). In the placebo session, decreases were greater at the test site during ipsilateral than contralateral temple cooling (* $p < .05$). 224