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PERSPECTIVES

Descending controls: how to harness for the relief of pain?

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Descending control of spinal nociception, which originates in many brain regions, is a major determinant of the pain experience. Descending control is dynamic and can either depress or enhance spinal nociceptive signalling depending on where it originates or what triggers it (Heinricher *et al.* 2009). A major challenge for therapeutic utility, whether that be engaged by physical or chemical means, is to harness the beneficial aspects of descending control.

Descending inhibitory and facilitatory controls are widely reported to be activated by noxious stimulation of spino-bulbo-spinal circuits (Ossipov *et al.* 2014). Inhibitory control mediates anti-nociception and descending facilitation is pronociceptive. There is evidence to support the view that descending facilitation is engaged at lower nociceptive stimulus intensities than that required to trigger descending inhibition (You *et al.* 2010). Wherein lies the problem: how to engage the beneficial inhibitory controls alone. Nociceptive stimuli are conveyed to the spinal cord in A- and C-fibre afferents. An often overlooked issue with respect to descending control of spinal nociception is that C-fibre afferents also convey information about thermal stimuli and a significant unknown, which is addressed in the paper from Hao-Jun You's laboratory in this issue of *The Journal of Physiology*, is the extent to which non-noxious thermal stimulation, conveyed in C-fibres, may activate descending pain control systems (You *et al.* 2014).

Moxibustion is a therapeutic strategy that has been used in oriental medicine for more than 2000 years. It is the practice of applying non-noxious thermal stimuli for the treatment of a number of disorders including pain (Bonica, 1974). In contrast to diffuse noxious inhibitory controls (DNIC; Le Bars *et al.* 1979), this paper provides novel experimental evidence to explain how non-noxious heat stimuli may harness potentially therapeutic mechanisms for the relief of pain.

The paper also extends previous work from this laboratory (You *et al.* 2013) that relates to the role of different thalamic nuclei (mediodorsal and ventromedial nuclei) in the control of spinal nociception. Important advances of potential therapeutic relevance are twofold: (i) inhibitory control from the thalamic ventromedial nuclei is activated by both noxious (46°C) and non-noxious stimuli (43°C) whereas facilitatory control from the thalamic mediodorsal nucleus is activated by noxious stimulation alone, and (ii) these two thalamic nuclei are chemically distinct with respect to their opioid sensitivity; descending inhibition from the thalamic ventromedial nucleus elicited by non-noxious heat stimuli (43°C) is selectively δ-opioid receptor dependent, unlike nociceptive-evoked controls from the thalamic ventromedial nucleus which are μ-, δ-, and κ—opioid sensitive. Descending facilitation from the thalamic mediodorsal nucleus is μ-opioid receptor dependent, providing a new context in which to interpret μ-opioid-mediated analgesia followed by hyperalgesia.

As such, these findings provide novel insights into pain control mechanisms that are of potential therapeutic relevance.

References

Bonica JJ (1974). Therapeutic acupuncture in the People's Republic of China. Implications for American medicine. *JAMA* **228**, 1544–1551.

Heinricher MM, Tavares I, Leith JL & Lumb BM (2009). Descending control of nociception: specificity, recruitment and plasticity. *Brain Res Rev* **60**, 214–225.

Le Bars D, Dickenson AH & Besson JM (1979). Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain* **6**, 305–327.

Ossipov MH, Morimura K & Porreca F (2014). Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care* **8**, 143–151.

You HJ, Lei J, Niu N, Yang L, Fan XL, Tjølsen A & Li Q (2013). Specific thalamic nuclei function as novel 'nociceptive discriminators' in the endogenous control of nociception in rats. *Neuroscience* **232**, 53–63.

You HJ, Lei J, Ye G, Fan XL & Li Q (2014). Influence of intramuscular heat stimulation on modulation of nociception: complex role of central opioid receptors in descending facilitation and inhibition. *J Physiol* **592**, 4365–4380.

You HJ, Lei J, Sui MY, Huang L, Tan YX, Tjølsen A & Arendt-Nielsen L (2010). Endogenous descending modulation: spatiotemporal effect of dynamic imbalance between descending facilitation and inhibition of nociception. *J Physiol* **588**, 4177–4188.

Additional information

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