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PERSPECTIVES

Mechanical allodynia generated by stimulation of unmyelinated afferent nerve fibres

Wilfrid Jänig
Department of Physiology, Christian-Albrechts-Universität zu Kiel, Kiel, Germany

Email: w.janig@physiologie.uni-kiel.de

Allodynia is defined as a pain sensation generated by physiological stimulation of low-threshold mechano- or thermosensitive afferent nerve fibres (e.g. mechanical or cold allodynia). Pain generated by physiological stimulation of sensitized nociceptors is called hyperalgesia. Thus allodynia is due to changes of central processing of impulse activity in low-threshold primary afferent neurons which feed into central nociceptive pathways, leading to allodynia. This is most impressively demonstrated by the following experiment (Torebjörk *et al.* 1992). Repetitive electrical intraneural microstimulation of large diameter myelinated afferent nerve fibres innervating Meissner's touch corpuscles or Merkel cells in the skin of the foot or hand in humans leads to a tactile sensation projected to a small skin area (which is identical or located close to the receptive fields of the stimulated afferent nerve fibres). Continuous stimulation of cutaneous nociceptors by intradermal injection of the TRPV1-agonist capsaicin leads to ongoing pain, heat hyperalgesia generated by heat stimulation of the sensitized nociceptors and mechanical allodynia generated by stimulation of low-threshold mechanoreceptors in the zone of secondary hyperalgesia/allodynia surrounding the area of primary hyperalgesia. The underlying mechanism of this secondary allodynia is sensitization of spinal lamina I neurons by the continuous capsaicin-induced nociceptive input. Using this capsaicin model Torebjörk and co-workers showed that intraneural microstimulation of large diameter mechanosensitive afferents which had their sensory projected fields in the zone of secondary hyperalgesia now elicits pain, in addition to a tactile sensation. One to two hours after capsaicin injection when the zone of secondary hyperalgesia had retracted and did not any longer overlap with the sensory projected field, the intraneural microstimulation generated only a tactile sensation but not pain. The pain produced by intraneural microstimulation of large diameter myelinated afferents exhibits a somatotopic organisation, arguing that the central sensitization (generated by the capsaicin-induced activity of nociceptive afferents) is limited to spinal interneurons representing the cutaneous territory of the secondary hyperalgesia. It also shows spatial and temporal summation of the synaptic inputs from the large-diameter mechanosensitive afferents to the sensitized interneurons. Based on the experiment described by Torebjörk *et al.* (1992) and other experiments (Campbell *et al.* 1988; references in Meyer *et al.* 2006; Baron 2009; Nagi *et al.* 2011), it is believed that mechanical allodynia elicited in the skin under experimental or pathophysiological conditions is elicited by stimulation of mechanosensitive large diameter myelinated afferents. However, whether this also applies to pain projected into the deep somatic or visceral body domain or to various chronic pains is unknown.

In a recent issue of *The Journal of Physiology*, Nagi and co-workers (2011) show in healthy human subjects that ongoing deep somatic pain generated by infusion of hypertonic saline solution into the anterior tibial muscle is enhanced by neutral touch (vibration) stimuli applied to the skin overlying this muscle. This pain is a form of mechanical allodynia generated by stimulation of low-threshold cutaneous mechanoreceptors during continuous excitation of muscle nociceptors. Interestingly this mechanical allodynia: (1) was not attenuated during conduction block of the myelinated fibres of the hindlimb by compression; (2) was abolished during conduction block of unmyelinated cutaneous nerve fibres generated by a local anaesthetic injected into the skin stimulated while conduction of the myelinated fibres was either blocked or not; and (3) was generated by gentle brushing the skin while the myelinated afferents were conducting or not. These results unambiguously show that this mechanical allodynia is mediated by the activation of low-threshold mechanosensitive cutaneous unmyelinated afferent nerve fibres.

The cutaneous afferent nerve fibres mediating this mechanical allodynia are suggested to be touch-sensitive unmyelinated nerve fibres (C-tactile fibres). These afferent nerve fibres innervate hairy skin (but not glabrous skin) and are adequately activated by tactile moving (shearing) stimuli (Vallbo *et al.* 1999; Olausson *et al.* 2010). The responsiveness of the C-tactile fibres to sinusoidal vibration stimuli as used by Nagi *et al.* (2011) remains to be tested. They are suggested to belong to the large group of afferent C-fibres that monitor the metabolic, mechanical, thermal and inflammatory states of the body tissues. Their activity is encoded in the activity of a functional type of lamina I neurons of the spinal dorsal horn that project to several brainstem centres and above all to the ventromedial posterior thalamic nucleus (VMpo), which in turn projects to the dorsal posterior insular cortex (dpINS) sometimes called limbic or interoceptive sensory cortex (Craig 2003) but not or very little to the primary and secondary somatosensory cortices. This lamina I-VMpo-dpINS system represents the interoception of the body which includes nociception and pain, an idea that was first propagated by Bud Craig (Craig 2003).

The paper by Nagi and co-workers is important for understanding the pathophysiology underlying various types of chronic pain. The C-tactile fibres innervating hairy skin in humans may well be involved in mechanical allodynia observed in many patients with neuropathic pain (Baron, 2009), in patients with chronic complex regional pain syndrome type I (Jänig, 2009, Jänig & Baron, 2003) and in the cutaneous referred zones of patients with chronic deep somatic or visceral pain (Giamberardino, 2009).

In conclusion, this is the first study showing that stimulation of cutaneous C-tactile afferent fibres, which are suggested to mediate the feeling of emotional touch, evokes mechanical allodynia during concurrent activation of muscle nociceptive afferents. This experimental finding will turn out to be important for understanding the mechanisms of protective body behaviour during injury of deep somatic

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and visceral body tissues and of chronic pain behaviour related to these deep somatic body domains.

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