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SCIENTIFIC COMMENTARIES

Translating synaptic plasticity into sensation

This scientific commentary refers to 'Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans', by Henrich *et al.* (doi:10.1093/brain/awv108).

The nociceptive system is endowed with powerful mechanisms to modify its own responsiveness to noxious stimuli, ranging from complete analgesia, e.g. in stressful fight or flight situations (Willer *et al.*, 1981) to pronounced hyperalgesia, e.g. to better protect inflamed or injured tissue (Sandkühler, 2013). Changes in synaptic strength are a versatile and powerful means to modulate nociception on demand (Sandkühler, 2009). Opioids, for example, temporarily depress synaptic strength in nociceptive pathways while injuries, trauma and inflammation may lead to synaptic long-term potentiation (LTP) (Ikeda *et al.*, 2006) that amplifies pain. Human studies are the gold standard for assessing one of the most important endpoints of nociception, the perception of pain (Treede *et al.*, 1999). However, in human studies it is, in striking contrast to *in vitro* or animal studies, notoriously difficult to identify the cellular elements that induce and/or express neuronal plasticity. In this issue of *Brain*, Rolf-Detlef Treede and his colleagues use a spectrum of experimental tools to selectively block or activate subgroups of primary afferent nerve fibres in healthy volunteers to elegantly pinpoint the neuronal elements that either trigger or mediate LTP-like amplification of pain perception (Henrich *et al.*, 2015).

An array of needle contact electrodes was used on one forearm for selective electrical stimulation of the most superficial nerve endings in the skin, which are from fine unmyelinated C- and myelinated Aδ-fibre nociceptors. Topical application of capsaicin was used to temporarily desensitize a subgroup of cutaneous C-fibre terminals that express the TRPV1 receptor, and which mediate heat-pain (Cavanaugh *et al.*, 2009). Finally, a well-controlled local compression of the radial nerve in one hand was used to reversibly block the myelinated A-fibres that mediate tactile- and cold perception. With these tools at hand the authors were able to study the relative importance of the various fibre types for LTP-like pain amplification after conditioning high-frequency electrical stimulation of fine cutaneous afferents. The conditioning stimulation protocol was adapted from *in vitro* and animal experiments in which synaptic LTP was studied in nociceptive pathways. This experimental congruence invites conclusions about potential synaptic mechanisms that may underlie changes in pain perception.

Conditioning high-frequency electrical stimulation immediately and temporarily induced a pain sensation at the stimulation site. Furthermore, conditioning stimulation also triggered a long-lasting amplification of the pain intensity elicited by single electrical test stimuli applied via the same array of electrodes. This lasting effect was labelled 'homotopic pain-LTP' as it was induced at the site of conditioning stimulation and considerably outlasted the period of conditioning. Interestingly, in the surrounding area of skin outside the array of stimulation electrodes, pain sensitivity to mechanical pinprick stimuli also increased for prolonged periods of time (heterotopic pain-LTP). When light stroking stimuli were applied to the skin adjacent to the electrode array on the forearm, the volunteers reported slightly painful sensations before conditioning stimulation. After conditioning, the same stroking stimuli were perceived as significantly stronger. This indicates that dynamic mechanical allodynia was induced by conditioning high-frequency stimulation of cutaneous C-fibre afferents.

The key experiments were then conducted by evaluating the impact of two different types of nerve blocks. The experimental data suggest that all types of nociceptive nerve fibres, i.e. TRPV1-positive and TRPV1-negative C- and A-fibres, contribute to the pain sensation elicited by conditioning electrical high-frequency stimulation. This is, of course, to be expected from a non-selective electrical stimulus. Interestingly however, the various afferent fibre types differentially contributed to the induction of homo- versus heterotopic pain-LTP. For homotopic pain-LTP at the site of conditioning stimulation, the evidence suggests that only C-fibres—either TRPV1-positive or TRPV1-negative—but not A-fibres contributed

Glossary

A-fibres: These fibres are all myelinated but vary in axonal diameter. Most of the thick primary afferent A-fibres, the Aß-fibres, have low stimulation thresholds for mechanical stimuli and thus sense touch or vibration. Most of the thin A-fibres, the Aδ-fibres, have higher mechanical thresholds and sense mechanical pain or can be excited by cold or heat stimuli.

Allodynia: Pain triggered by a stimulus that under normal, physiological conditions does not evoke the sensation of pain.

C-fibres: These fibres are thin, unmyelinated fibres. Most primary afferent C-fibres have high stimulation thresholds for mechanical or heat stimuli or can be activated by protons or a range of molecules including inflammatory mediators. Some C-fibres are, however, activated by mechanical stimuli of low intensity, e.g. by pleasant touch.

Long-term potentiation (LTP): If not stated otherwise LTP usually refers to an increase in synaptic strength, i.e. the long-lasting increase in post-synaptic currents that are elicited by a single presynaptic action potential. Here the authors used the phrase 'pain-LTP' to refer to a long-lasting increase in the perceived intensity of pain. LTP, e.g. at the first synapse in nociceptive pathways, likely underlies the presently described form of 'pain-LTP', but other mechanisms must not be excluded.

Nociceptor: Free, peripheral nerve endings of primary afferent, high-threshold nerve fibres that sense noxious stimuli.

Nociception: Refers to the encoding of noxious stimuli in the peripheral and the central nervous system. A large number of recent studies indicate that in the CNS not only neurons but also non-neuronal cells such as glial cells, vascular cells, mast cells and T cells may contribute to nociception causing the state of neurogenic neuroinflammation (Xanthos and Sandkühler, 2014). The current definition by the International Association for the Study of Pain (IASP) limiting nociception to 'the neural process of encoding noxious stimuli' is thus no longer all-embracing. Nociception may lead to a large number of distinct effects that do not necessarily emerge all at the same time. Endpoints of nociception include, but are not limited to, the perception of pain, withdrawal reflexes and vegetative responses such as a rise in blood pressure and heart rate.

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (definition by the International Association for the Study of Pain, IASP).

Transient receptor potential vanilloid type 1 (TRPV1) receptor channel: This ligand-gated cation channel belongs to the group of TRP ion channels that are mostly expressed on the plasma membrane of diverse cells types. On primary afferent Aδ- or C-fibres, TRPV1 receptors sense heat stimuli and can be activated quickly; they become desensitized upon prolonged exposure to capsaicin.

to its induction. In contrast, for the induction of heterotopic LTP in the area surrounding the site of conditioning stimulation, only the TRPV1-positive C- and A-fibres appeared to be essential.

The present study has a number of important implications. First, the data support the conclusion that fundamental neuronal mechanisms that have been identified and characterized *in vitro* and in animal studies (Sandkühler, 2013) may have counterparts in human subjects (Klein *et al*., 2005). Second, the differential contribution of distinct primary afferent fibre types to the induction of either homo- or heterotopic pain-LTP suggests that the mechanisms of LTP induction and perhaps expression are also different. This should stimulate the appropriate *in vitro* studies to test this hypothesis. Third, the data further suggest that hyperalgesia at the site of conditioning stimulation (i.e. primary hyperalgesia) and in the non-stimulated, surrounding area (secondary hyperalgesia) both have CNS components that are triggered by activity in partially distinct primary afferent fibre types (neurogenic hyperalgesia) (LaMotte *et al*., 1991).

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