


**WHY DOES AN INFLAMMATION IN THE JOINT HURT?**

PAIN is one of the major symptoms of inflammation, and it is the one that affects patients most. In healthy joints, pain is only evoked by high-intensity stimuli, such as twisting of the joint or strong pressure. By contrast, in inflamed joints, pain may be present in the absence of intentional stimulation (resting pain), or it may be elicited by normally non-painful mechanical stimuli such as movements in the working range of the joint or gentle pressure applied to the joint. Research into the mechanisms of nociception under inflammatory conditions attempts to gain insights into the neuronal events involved.

In general, the neurobiological response to noxious or painful stimuli is more complex than previously thought. Recent research has revealed that under clinically relevant conditions such as inflammation, the nervous system does not simply react to noxious stimuli; it undergoes changes that modify the neuronal processing of nociceptive stimuli (functional neuroplasticity) [1–4]. In a state of inflammation-evoked neuroplasticity, sensory stimuli such as the application of pressure to a joint may evoke much larger responses in the nervous system than under normal conditions. Functional neuroplasticity is thought to be of major importance for the generation of clinically relevant pain [1–4].

The sensitization (increase in excitability) of afferent nociceptive fibres (nociceptors or 'pain fibres') to mechanical, thermal and chemical stimuli is a major component of the generation of inflammatory pain. Articular nociceptors in a healthy joint respond only to noxious (painful) stimuli such as twisting of the joint or intense pressure applied to the joint. During inflammation, nociceptors are sensitized. Then they are activated by normally non-painful stimuli such as light pressure onto the joint or movements in the working range of the joint. Hence, the message 'noxious stimulus' is signalled to the spinal cord by innocuous stimuli which are usually not painful. Another group of articular nociceptors does not even respond to noxious mechanical stimulation of the normal joint. A high proportion of these initially mechanoinsensitive (silent) nociceptors are also sensitized during inflammation and start to respond to mechanical stimuli. The sensitization of joint nociceptors is induced by inflammatory mediators such as prostaglandins, bradykinin and others (for details, see [4]).

Recently, the functional neuroplasticity in the spinal cord has been a major focus of research [1–4]. Spinal cord neurons can be sensitized as well. During an experimental inflammation in the knee joint, spinal cord neurons with input from the knee exhibit an increased sensitivity towards the afferent inputs from the inflamed joint [4, 5]. This can be expected from the increased afferent input in sensitized nociceptors [4]. However, these neurons also exhibit enhanced responses to afferent inputs from non-injured regions of the leg which are adjacent to or even remote from the inflamed site [4, 5]. This suggests that the spinal cord neurons are not just excited by the enlarged afferent input from the inflamed joint, but that they are rendered hyperexcitable. This 'central sensitization' leads to an amplification of the spinal nociceptive processing [1–5].

The cellular mechanisms involved in the generation and maintenance of spinal cord hyperexcitability are currently being investigated. The development of hyperexcitability is dependent on the release of
excitatory amino acids such as glutamate [6] and of neuropeptides from afferent fibres and/or spinal cord interneurons, and their postsynaptic effects [1–4, 6, 7]. Glutamate activates N-methyl-D-aspartate (NMDA) receptors, non-NMDA receptors and metabotropic glutamate receptors [5, 8]. The development of inflammation-evoked hyperexcitability was blocked when antagonists at either of the glutamate receptors were administered ionophoretically close to the neurons during the induction of inflammation [5, 8]. The development of hyperexcitability was significantly attenuated when antagonists at either the neurokinin-1 receptor (activated by substance P), the neurokinin-2 receptors (activated by neurokinin A) or the CGRP1 receptor (activated by calcitonin gene-related peptide) were administered close to the neurons [9–11]. Thus, the generation of inflammation-evoked hyperexcitability seems to depend on the combined action of excitatory amino acids and neuropeptides in the spinal cord. These receptors are also involved in the maintenance of the hyperexcitability, since the administration of either of these antagonists reduced the responses of the hyperexcitable neurons [5, 8, 9–11].

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REFERENCES