



- **FACT SHEET No. 16**

Joint Neurophysiology and Pathophysiology: Nerves, Receptive Fields, Sensitization

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Joint diseases are important sources of acute and chronic pain. The most frequent causes are osteoarthritis, rheumatoid arthritis, gout, and other forms of arthritis, as well as sport injuries. Typically, patients suffer from pain during walking, but at advanced stages pain at rest may occur (Philipps and Clauw 2013; Schaible 2012).

Joints are innervated by thick myelinated A β -fibers (equipped with corpuscular endings), thin myelinated A δ -fibers, unmyelinated sensory C-fibers, and sympathetic postganglionic C-fibers. The vast majority of A β -fibers and about half of the A δ -fibers are non-nociceptive because they show significant responses to innocuous stimuli such as movements in the working range. By contrast, the other A δ -fibers and most of the C-fibers are nociceptive because they preferentially or exclusively encode noxious stimuli to the joint.

In addition, a proportion of sensory C-fibers are silent nociceptors not responding to any stimulus applied to the normal joint. Sensory endings of nociceptive fibers are located in all structures of the joint except the cartilage, which is not innervated (Schaible 2013).

During diseases of the joint such as arthritis, nociceptors of the joint are sensitized to mechanical stimuli. Their excitation threshold is lowered into the innocuous range, and their responses to suprathreshold stimuli are significantly increased. In addition, silent nociceptors also become mechanosensitive (Schaible 2013). The process of sensitization is generated by inflammatory mediators,



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which act on membrane receptors in nociceptive endings, thereby activating second messengers that render ion channels of stimulus transduction and voltage-gated ion channels more excitable.

Inflammatory mediators such as bradykinin and prostaglandin E₂ cause a short-lasting sensitization at a latency of few minutes. Proinflammatory cytokines such as TNF- α , interleukin-6, and interleukin-17 evoke a slowly developing but persistent sensitization to mechanical stimuli (Schaible 2013, 2014). Another mediator with long-lasting hyperalgesic effects in the joint is nerve growth factor (NGF) (Ashraf et al. 2014). Joint nociceptors also express receptors for mediators that are inhibitory (e.g., receptors for opioids and somatostatin) (Schaible 2013).

Joint nociceptors activate synaptically spinal cord neurons. Typically, spinal cord neurons with joint input show convergent inputs from the joint and adjacent muscles, and many of them receive cutaneous input as well. The convergence is the basis for referred pain into areas beyond joints upon noxious stimulation of the joint (Arendt-Nielsen et al. 2014). Importantly, the increased input from the joint after peripheral sensitization triggers a process of central sensitization in which the spinal cord neurons with input from the inflamed joint become hyperexcitable. At this stage the neurons show decreased excitation thresholds for mechanical stimuli applied to the joint, stronger responses to suprathreshold stimuli, and often exhibit an expansion of the receptive fields (Schaible 2013). Spinal sensitization depends on NMDA and other receptors, and glial cells may be involved (Ogbonna et al. 2013). The spinal sensitization causes an expansion of the hyperalgesic areas in the leg, a typical phenomenon upon significant joint pain in patients (Arendt-Nielsen et al. 2014).

Ascending spinal cord neurons with joint input activate the cortical pain matrix, thus evoking the conscious pain sensation (Kulkarni et al. 2009). In addition, they activate the amygdala, which is involved in the processing of fear (Neugebauer et al. 2004). Ascending nociceptive tracts and the cortical processing augment the activity of descending pathways mediating descending inhibition. While descending inhibition is increased at acute stages of arthritis, some forms of descending inhibition, the diffuse noxious inhibitory control, becomes inefficient during chronic joint pain (Arendt-Nielsen et al. 2014, Kosek and Ordeberg 2000). Thus, in addition to peripheral and central sensitization, reduced descending inhibition contributes to the sensitized state that many patients with joint diseases are exhibiting.

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