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Pain

Mechanisms underlying joint pain

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Joint pain is associated with injury, inflammation of the joint and severe remodeling of the subchondrial bone. The leading reason of articular pain is osteo- and rheumatoid arthritis. The most important component of joint pain is sensitization of high threshold nociceptors, which release neuropeptides, express excitatory receptors and ion channels. Ongoing hyperexcitability of nociceptors results in permanent CNS changes contributing to the maintenance of chronic pain.

Introduction

One of the most frequent chronic pain sensations people experience is associated with pathological conditions of the joints. Although injuries, infections and systemic diseases could produce short-term arthralgias, the most common reasons for joint pain are osteoarthritis (OA) and rheumatoid arthritis (RA). About 10% of the world's population over 60 suffer from OA, and about 1% are affected by RA. In contrast to acute pain caused by injury, pain associated with OA and RA does not promote restoration of function. Instead, it worsens the long-term functional outcome and quality of life. Current therapies for OA or RA are often inadequate and carry considerable adverse reactions. The development of new analgesics is hampered by the lack of understanding the complex pathways involved in the development and maintenance of these diseases.

Although, joint pain has both peripheral and central (spinal and brain) components [1,2], the present review concentrates on the peripheral mechanisms, because they are pivotal in the initiation and maintenance of pain in OA and RA.

Sensory innervation of joints

Fibers innervating joints generally respond to mechanical stimuli, but some are called 'silent' polymodal primary afferents, because they are activated only after sensitization by inflammatory agents. Specific nociceptors, which innervate the joint, belong to the class of thinly myelinated (Aδ) or to unmyelinated I fibers. They can be activated by noxious mechanical stimuli, such as overstretching the joint, but some of them form the class of polymodal sensory primary afferents, which in addition to mechanical stimuli responds to noxious thermal- and chemical stimuli. They express various types of receptors and ion channels, which are essential for neurotransduction. A subpopulation produces neuropeptides and other neurogenic substances, which are released both in the spinal cord and to the joint tissue. The central release couples nociceptors with spinal neurones, whereas the peripheral release induces neurogenic inflammation, such as plasma protein extravasation, vasodilation and accumulation of immune cells in the joint. The special group of silent fibers is not activated even by noxious stimuli under physiological conditions; however, they can be sensitized and start responding to non-noxious stimuli during inflammation [3,4].

The innervation of the joint is highly specific: (1) myelinated Aα-, Aβ-, thin myelinated Aδ- and the unmyelinated C-sensory

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fibers contribute to the sensory innervation of the capsule, ligaments, periosteum, subchondral bone and menisci; (2) only C-fibers innervate the synovial membrane and (3) the articular cartilage has no nerve supply [5,6]. It is estimated that about 80% of the total number of sensory fibers supplying the joints belongs to the unmyelinated C primary afferents [3,7,8]. About 15–35% of the small caliber fibers are peptidergic, containing substance P (SP) and calcitonin-gene related peptide (CGRP) [9,10,11].

In general, while Aα, Aβ and a proportion of Aδ fibers can be activated by innocuous light pressure and stretch, these fibers do not contribute to the generation of joint pain; their main function is 'proprioception'. Large proportion of the Aδ-fibers and virtually all C-fibers are solely responsive to noxious stimuli. The responsiveness of these fibers to mechanical, chemical and thermal stimuli can be enhanced by the induction of receptor and ion channel expression. Nerve Growth Factor (NGF) is one of the major factors that can produce such effects [12]. The increased responsiveness, called sensitization is evident both by reduced activation threshold to the level of innocuous stimuli and increased impulse generation of the fibers [4]. NGF, however, is only one factor that produces sensitization. Many inflammatory mediators, such as prostaglandins and bradykinin have similar effects. They can also stimulate increased neuropeptide production in the peptidergic fibers. The decreased threshold and the enhanced neuropeptide production cause hypersensitivity of the nociceptive system during inflammation.

The sensitization phenomenon is the most striking in silent fibers [13,14]. Silent fibers account at least for the third of the C-fiber population [3]. Although our knowledge about silent fibers innervating the joint is relatively limited, it is well established that cutaneous fibers with similar modalities play a strong role in neurogenic inflammation in humans [14,15].

Molecular characteristics of C-fibers innervating joints

C-fibers, including the peptidergic fibers express a series of membrane molecules that can be activated by various chemical and physical stimuli. The modality of pain experienced in joints affected by OA and RA is predominantly mechanical, it develops within the normal moving range of the joint and is generally described as throbbing or stabbing. The molecular characteristics of the joint fibers associated with the above sensations is not completely understood, however, recent studies suggest that a broad variety of receptor and channel proteins expressed on joint nociceptors can be the transducers. For direct activation by inflammatory mediators, bradykinin, B1 and B2 receptors, prostaglandin EP1 and EP2 and histamine receptors are expressed in joint nociceptors [16]. Primary afferents have large populations of neurotransmitter receptors, such as muscarinic, P2X, adrenergic, opioid [17], cannabinoid (CB1) and 5-HT, which provide plenty of opportunities for direct modulation of excitability. Most peptidergic nociceptors express receptors for neurokinins, such as substance P (NK-1 receptors), neuropeptide Y (NPY, Y1, Y2); [18], somatostatin (SOM-1,2,3,4) and calcitonin gene-related peptide (CGRP) [18a]. In general, opioids, somatostatin and cannabinoids act as inhibitors of nociceptor activation, however their up- or downregulation during inflammation defines their hyperalgesic potency. It has been shown recently, that all four SOM receptor subtypes are present in joint fibers and SOM-2 is downregulated in monoarthritis leading to reduction of inhibition of primary afferent activation [19].

Specific ion channels, such as members of the acid sensing ion channels (ASICs) and transient receptor potential (TRP) superfamily provide sites for pH and heat sensitization and activation. ASICs are expressed in C fibers, activated by acidic pH; however, recent studies revealed that they are also direct targets of some NSAIDs [20]. The TRPV1 receptor is activated by capsaicin, protons and noxious heat, whereas other members of the super family (TRPV2,3,4,8 and TRPA1) are likely to be involved only in thermal nociception [21]. TRPV8 is expressed in large and small caliber fibers, however TRPV1 expression is largely restricted to C fibers [22]. Interestingly, those fibers that express these two TRPs have also tyrosine kinase (trk) receptors, which are activated by NGF [23]. Both trk and cytokine receptor activation can modulate the phenotype of the fibers and contribute to the sensitization of silent fibers [12,24].

Other, voltage gated ion channels, such as K^+, Na^+ and Ca^{2+} channels also contribute to the activation of primary afferents. TTX-insensitive Na channels play a particularly prominent role in nociceptor function (see later).

Mechanisms involved in the development of joint pain

Joint pain in arthritis is characterized by spontaneous pain in addition to hyperalgesia and allodynia (pain sensation induced by non-noxious stimuli, such as touch), which are considered the consequences of both peripheral and central sensitization [1,3]. RA-affected joints and the surrounding tissues show increased sensitivity to noxious stimuli [25]. Activation of these sensitized fibers, through triggering a series of changes in the responsiveness of neurons in the central nervous system, results in pain sensation. Desensitization or degeneration of the sensitized fibers by capsaicin results in reduced pain [26,27]. This is one of many observations which supports our present knowledge, that pain associated with arthritis is largely due to sensitization of the primary afferents, in particular of nociceptors innervating the joint. As a consequence, the activation threshold of the polymodal nociceptors will be reduced and fibers will be activated by non-noxious stimuli, such as gentle move within the normal range of the joint or light touch (mechanical allodynia). Also, inflammatory mediators, pH changes and