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Osteoarthritis pain

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A B S T R A C T

Osteoarthritis (OA) represents one of the most frequently occurring painful conditions. Pain is the major OA symptom, involving both peripheral and central neurological mechanisms. OA pain is initiated from free axonal endings located in the synovium, periosteum bone, and tendons, but not in the cartilage. The nociceptive message involves not only neuromediators and regulating factors such as neuronal growth factor (NGF) but also central modifications of pain pathways. OA pain is a mixed phenomenon where nociceptive and neuropathic mechanisms are involved in both the local and central levels. OA pain perception is influenced by multiple environmental, psychological, or constitutional factors, and OA pain intensity is not correlated with joint degradation. OA pain may present with different clinical features: constant and intermittent pain, with or without a neuropathic component, and with or without central sensitization. Finally, OA pain should be considered as a complex and not unique pain condition, where precise clinical assessment may drive specific therapeutic approaches.

Introduction

In Europe, 20% of chronic pain is related to osteoarthritis (OA) [1] and pain is the main symptom in OA. Furthermore, pain related to OA is considered as the prototypical chronic nociceptive pain condition, and this is used as a major clinical model for the development of new analgesics dedicated to treating chronic pain.

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In 420 BC, Hippocrates described the "*rheuma* theory: joints are driven by the brain." This theory suggests that when the brain sends more liquid to the lower parts of the body pain is induced in the hip, which finally reaches all the joints (in Ref. [2]). This theory is now being revisited in the 21st century with neurosciences, describing all influences of the neurologic system in joint disorders.

Pain is a ubiquitous symptom in osteoarticular diseases [3], especially in OA [4], much more prevalent than stiffness and disability. OA frequency is increasing, mostly related to age and obesity. Paradoxically, compared to inflammation and immunity research, for many years, joint pain pathophysiology has not been extensively studied. OA pain has been considered as a prototypical nociceptive pain condition, and clinicians have expected that pain can be an alarm signal, correlating with the intensity of joint degradation [5]. In OA, most authors have focused their studies more on joint architecture and local degradation than on pain; however, the present study shows that it may have a neuropathic component, and it is not a stable and continuous symptom [6].

OA pain pathophysiology is a recent subject for researchers, and, as in other clinical pain conditions, OA pain pathophysiology includes four different processes:

- Transduction: conversion of energy induced by a painful stimulus (mechanical, thermal, and chemical) into electrical energy by specific receptors
- Transmission: from periphery to centers (spinal cord and brain), with specific pathways
- Perception in the brain cortical zones
- Modulation by brain and spinal structures, by inhibiting and facilitating ways, this phenomenon being crucial for reducing pain sensation

It can be seen that OA pain is a complex phenomenon, involving peripheral and central mechanisms, modulated by many factors, including psychological [7] and genetic factors [8]. Recent findings of neuroimaging have improved knowledge in these mechanisms, and new treatments may be proposed in the coming future for better management.

Experimental pain models: is there a model of OA pain?

In OA, as in any pain condition, animal models have tried to be as close as possible to the human condition in OA. In fact, experimental studies on OA pain have been mostly developed from inflammatory models, from arthritis, comparing data in arthritis and control animals. Several models of OA have been described, but most OA models have been initially developed to analyze structural joint changes rather than to analyze nociceptive sensations in animals. Recently, few models have also been developed to analyze nociceptive pain behavior, after cruciate ligament transection, meniscectomy, and monoiodoacetate injection [9,10]. However, the most frequent animal models of chronic joint pain are inflammatory models such as the models of Freund's adjuvant injection [11], carrageenan plantar injection, [12] or urate joint injection [13].

Experimental tests that can assess nociceptive behavior in animals are mostly represented by mechanical stimuli, such as the Randall and Selitto test [14], or thermal stimuli, for example, by immerging the hind paw in different temperatures. Other tests are based on observations of spontaneous behavior: motility, writhing, etc. As in all animal studies, the translation to the human context is limited, and many animal findings have not been confirmed in humans [15]. Some studies investigate nociception in animals, and others investigate pain only in humans.

Neuroanatomy of joint and peripheral mechanisms of OA pain

The origin of joint pain has been unknown for a long period of time. In 1945, Davies reported the first experimental joint pain and noted that synovium was insensitive to pressure but that needle puncture induced diffuse intra-articular pain. [16] In 1950, Kellgren and Samuel [17] studied pain induced by needles in the knee of healthy volunteers: the authors demonstrated that synovium was insensitive to needle punctures, but that the capsule and ligaments were sensitive to pain.