

Osteoarthritis pain goes central

For years osteoarthritis was the preserve of rheumatologists, with joint erosion assumed as the be-all and end-all of the disease. However, important findings in pain research are forcing a shake up in thinking, and osteoarthritis is now increasingly seen as a neurological disease with a powerful central input. At a Novartis Foundation meeting in London, UK (July 1, 2003) rheumatologists and neuroscientists came head-to-head to discuss the clinical implications of these emerging ideas.

The prevalence of osteoarthritis is on the rise. 13% of people aged over 55 years have the disorder, and the numbers are set to double in the next 17 years. This situation prompts fears of an "epidemic" driven by the two main risk factors: ageing and obesity.

"People come to us because they are in pain", says rheumatologist David Felson (Boston University School of Medicine, MA, USA). "Unfortunately treatments are limited, and preventing cartilage loss is not necessarily the solution." To develop better pain control it is crucial to understand what is generating osteoarthritic joint pain.

"The nervous system isn't a passive bystander; it is an important player in the persistence of joint pain", asserts Bruce Kidd (Bart's & The London School of Medicine, London, UK). Kidd, a rheumatologist, has pinned down one important difference between how people with arthritis and how healthy individuals process pain. He used a capsaicin-based test that elicits an intense, short-lived pain. Whereas controls soon recover, patients with arthritis develop a neurogenic flare with heightened sensitivity in areas surrounding the affected joints.

Kidd proposes that this hypersensitivity results from a complex interaction between the immune and nervous systems. Sensory fibres at the site of injury release neuropeptides, such as substance P and calcitonin-gene-related peptide (CGRP). These changes in sensory fibres not only trigger pain directly but also sensitise the peripheral and central nociceptive systems, which leads to a hypersensitive state. As a result, the person's pain threshold is lowered to the extent that even

movements within the normal range become painful. "We should consider using neuropeptide antagonists to act as modulators in the long term", says Kidd.

For Gunnar Ordeberg (Karolinska Institute, Stockholm, Sweden), an orthopaedic surgeon, sensitisation explains the baffling symptoms of this joint disease. "Osteoarthritis symptoms usually start with localised pain that responds to analgesics", he explains. "Eventually the response to pain killers is lost and the area with pain spreads, to the thigh and knee, then the leg, and often there is pain all over the body."



Osteoarthritis pain with central involvement

To test whether sensitisation is driving patients' spontaneous pain and hyperalgesia, Ordeberg applied a tourniquet in 15 patients with osteoarthritis and in 13 healthy controls while testing for pain. He found that although the tourniquet increases the pain threshold for healthy people—a sign of pain inhibition—there is no such effect in patients. This finding suggests that the chronic pain in inflamed joints disrupts central inhibitory controls, resulting in central hyperexcitability. "When patients complain of widespread pain it is often regarded as a sign of psychological distress", says Ordeberg, "but it appears that central sensitisation is driving these abnormal pain states."

This state of hyperexcitability is not confined to human beings. Hans-Georg Schaible (University of Jena, Germany) has used neuronal recordings from cat and rat spinal cords to show that a

painful message from the periphery may create a state of central sensitisation. "If you trigger inflammation in the joint, not only does the pain increase in the inflamed joint but there is an expansion of the neuronal receptive field leading to symptoms in healthy adjacent and even remote tissues", says Schaible.

How much noxious stimulus it takes for central sensitisation to kick in is not known. Schaible has found that, in addition to substance P, several mediators contribute to this inflammation-induced spinal hyperexcitability: glutamate, neurokinin A, CGRP, prostaglandins, and others may all serve as potential drug targets. "The CNS is not just a cable from a diseased joint to the brain. It is also modifying the whole pain story for the human being", explains Schaible.

David Blake (University of Bath, UK) pushes the case for CNS involvement even further. "Probably every pain becomes central if you know how to find it", he says. His assertion stems from clinical experience of the treatment of "inappropriate" pain. Puzzled as to why many people with a rheumatological disorders have pain that cannot be matched to physical findings, he thought that it may be a situation similar to phantom limb pain in amputees. Blake set out to test the hypothesis that a mismatch between motor intentions and sensory feedback underlies this type of pain.

With Candy McCabe, Blake has adapted Ramachandran's mirror experiments and tested them on people with complex regional pain syndrome. By practicing movements in the mirrors to correct the incongruent perception, pain and stiffness subsided. "In some people we can induce this in seconds", says Blake, who believes these findings may have important implications for the treatment of rheumatological pain.

As James Henry (University of Western Ontario, Canada) puts it: "arthritis should be seen as a disorder not only of the periphery but also of the CNS". The hope is that, by examining osteoarthritis in this new light, researchers will come up with a host of new, more effective therapies.

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