• **FACT SHEET No. 2**

Assessing Joint Pain Experimentally in Humans

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The clinical manifestation of joint pain does not allow detailed information about the various pain mechanisms involved. This information is important for targeting the treatment and for developing new and more efficient therapies. A number of human quantitative, mechanism-based pain-assessment techniques have been developed and applied in patients with joint pain, particularly osteoarthritis.

The pain associated with chronic joint pain is highly individual, and features from radiological imaging have not demonstrated robust associations with the pain manifestations. *It seems evident that other factors, such as sensitization mechanisms, are involved in enhancing the nociceptive drive from a damaged joint structure and hence causing more pain than can be accounted for by the damage per se.*

In recent years, a variety of mechanistic human quantitative pain-assessment tools (Quantitative Sensory Testing, QST) have been developed. These have provided new opportunities to profile patients and reach a greater understanding of the mechanisms involved in chronic joint pain. Because joint pain is a complex interaction between many different pain mechanisms, it is important to have tools available for profiling and providing the basis for the development of new drugs and for developing individualized surgical and nonsurgical pain-management regimes.

The psychophysical response (pain threshold or pain ratings) can be evoked by painful or non-painful stimuli (e.g., using a pressure algometer), thereby quantifying the degree of sensitization in joint pain patients as compared with controls.

As the assessment of pain needs to be multidimensional, the experimental quantification of sensitization should preferably be multidimensional by including various stimulus modalities—

mechanical (e.g., by pressure), chemical (e.g., by ischemia), electrical, etc.—and assessing different pain mechanisms (pain and tolerance thresholds, stimulus-response functions, spatial and temporal summation, and conditioned pain modulation (CPM)). Handheld pressure algometry (single location) is the most commonly applied modality when assessing periarticular sensitization in joint pain. In general, it is not clinically applicable to assess the intra-articular pain reactions to, for example, electrical stimulation or arthroscopically guided localized pressure stimulation. Hence, the quantitative pain-assessment techniques primarily probe some secondary reactions to joint nociception (e.g., ligaments, muscles).

Increased pain sensitivity or reduced pressure pain thresholds found locally at periarticular structures (ligament, muscles, tendons) reflect peripheral and central sensitization, while increased pain sensitivity distant from the affected joint may reflect more widespread general sensitization.

If a localized pressure stimulus is repeated (e.g., a train of five stimuli with an interval of two seconds), the pain intensity will gradually increase during the stimulus train. This is termed “temporal summation.” Temporal summation is a measure of central integrative mechanisms. In patients with chronic joint pain, this integrative mechanism is unregulated, resulting in facilitated temporal summation. The repeated stimuli can be applied to the periarticular structures around the painful joint or to non-affected extrasegmental locations (generalized facilitation of the central integration). Facilitated temporal summation can experimentally be inhibited by N-methyl-D-aspartate (NMDA) receptor antagonists but is difficult to block by most other drugs.

An important factor for the spreading of pain and hyperalgesia is the status of the descending pain control. Reducing the potency of the descending inhibitory pain control or increasing the descending pain facilitation will cause the entire neuroaxis to be more vulnerable to pain as a result of induced generalized widespread hyperalgesia. This balance between descending inhibition and descending facilitation can be assessed experimentally in chronic joint pain patients, and the general finding is that the pain inhibition is impaired. It has been suggested that the balance may be beneficially improved by, for example, serotonin-norepinephrine reuptake inhibitors.

In conclusion, many patients with chronic joint pain show signs and symptoms of localized as well as generalized widespread sensitization. Human mechanistic pain-assessment tools can be used for profiling pain mechanisms in patients with chronic joint pain and reveal new possibilities to understand some of the features driving the pain. Of specific importance is sub-grouping and stratification of specific joint pain patients, which require a more individualized management regime.

In general, the degree of enhanced responses to experimental pain stimulation and the attenuated specific pain mechanisms is associated with the intensity and duration of the joint pain.

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