

**54th Annual Meeting of the
Orthopaedic Research Society
March 2-5, 2008
Moscone West Convention Center
San Francisco, California**

WORKSHOP 8

Pain as a Critical Component to Understanding Musculoskeletal Disorders - TMJDs as a Model

Organizers:
Stephen L. Gordon, PhD

Speakers:
Peter Grigg, PhD
Ronald Dubner
William Maixner

Workshop Abstract:

Pain is the leading symptom on presentation for treatment of musculoskeletal conditions. The total economic impact of pain for all medical conditions exceeds \$100B. Scientists have uncovered new mechanistic understanding of pain receptors, signal modification, and brain interpretation of the pain sensation. Additionally, there is emerging information on the population and protein level influence of genetic predisposition for stronger than normal perceptions of pain. This workshop will provide a review of key aspects of the status of pain research and possibly stimulate interdisciplinary research related to pain.

Temporomandibular joint and muscle disorders (TMJDs) serve as a well-studied model system that is broadly representative of many joint structures in the body.

Joint Innervation by Nociceptors

Peter Grigg Ph.D.

Department of Physiology University of Massachusetts Medical School
55 Lake Avenue Worcester MA 01655

Pain is a sensory modality associated with activation of nociceptor neurons. The neurons of the nociceptor system have properties that are different in fundamental ways from neurons in other sensory systems. Unlike other sensory modalities, where the properties of neurons are invariant, neurons in the nociceptor system are remarkably plastic. Neurons at all levels of the nociceptor pathway are capable of changing their properties depending on local conditions relating to the local inflammatory state and the condition of cells of the immune system. A nociceptor neuron may be in any of three states of excitability: the naive, the primed, and the hyperalgesic state. When in the naïve state, nociceptors mediate 'physiological' pain. The hyperalgesic state is found in conditions of local inflammation, in which the excitability of nociceptor neurons is increased. Neuropathic pain refers to the state in which pain is sensed in the absence of explicit stimuli. Physiological pain is the most studied; neuropathic pain is the situation in most clinical cases of pain, and is the least well understood from a mechanistic point of view.


In this presentation I will briefly review the current understanding of physiological and inflammatory pain mechanisms, and of the factors that cause transition from one to the other. Our understanding of nociceptor mechanisms comes from a wide variety of experimental models ranging from studies in animals to ex vivo preparations to studies of cells grown in culture. What emerges from all these approaches is a story that broadly accounts for nociception. Findings made in cutaneous nociceptor systems appear to apply those from joints, and vice-versa. And the literature on joint nociceptors indicates a common story for all synovial joints. Hence while this workshop is focused on the TMJ, what I describe is derived from a variety of sources and applies to all synovial joints.

Physiological pain: Virtually every tissue has a sensory innervation by nociceptor neurons. When activated by noxious stimuli they generate action potentials that are conducted into the spinal cord along axonal processes. The noxious stimuli that excite nociceptors include intense mechanical and thermal stimuli in addition to numerous chemical signals in interstitial fluid. The chemical stimuli are those that result from tissue injury, from inflammatory processes, or that are released by immune cells. When activated, nociceptor neurons mediate a sensation of intense stimuli or pain. In addition to serving as sensors, nociceptor neurons have a second role as amplifiers of interstitial signals that are part of the pain sensing mechanism. How are they amplifiers? When activated,

they release pro-inflammatory compounds into the interstitial space. These compounds act on other nociceptors, and sensitize them. A nociceptor neuron is both an afferent and an efferent. Afferent, when suitable stimuli are present in the peripheral tissue, and the stimuli are transduced and an action potential is initiated, and that action potential is conducted into the CNS. Efferent, when action potentials are initiated in the nociceptor cell body in the dorsal root ganglion, or via dorsal root reflexes involving synaptic terminals in the spinal cord initiate spikes that are conducted antidromically from the spinal cord to the peripheral tissue, where they cause release of inflammatory mediator substances from the nociceptor ending.

Inflammatory Pain: Inflammatory processes have powerful effects on nociceptors. Chemical signals released by cells of the immune system alter the properties of virtually every component of the nociceptor system, so that thresholds are lowered and neuronal activation by stimuli (both noxious and non-noxious) is increased. Activity is recruited in nociceptor neurons that are silent except under conditions of inflammation. Activity in nociceptor neurons amplifies and extends the inflammatory process in a process known as neurogenic inflammation. Spinal cord neurons in the nociceptor pathway become sensitive to activity in non-nociceptor afferent neurons, resulting in allodynia. Injury causes the involvement of both nociceptors and immune cells. Nociceptors are activated by injury, and they release inflammatory mediators into the interstitial fluid. In response to injury, resident immune cells such as mast cells release cytokines and chemoattractants. As an inflammation develops, other immune cells such as neutrophils, macrophages, and T cells migrate to the site of the injury. All these cells release cytokines and other factors that act to both stimulate nociceptors and sensitize them. Thus pain accompanies and can be caused by inflammation.

References.

1. Ikeda H, Stark J, Fischer H, Wagner M, Drdla R, Jäger T, Sandkühler J.  Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science*. 2006 Jun 16;312(5780):1659-62.
2. Cummins TR, Sheets, PL, Waxman SG. The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain* 131 (2007) 2434 – 257.
3. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Rev*. 2006 Aug;51(2):240-64.

CENTRAL NERVOUS SYSTEM PLASTICITY AND PERSISTENT PAIN

RONALD DUBNER, D.D.S., PH.D.

DEPARTMENT OF BIOMEDICAL SCIENCES
UNIVERSITY OF MARYLAND DENTAL SCHOOL
BALTIMORE, MARYLAND, USA

Injury to peripheral tissues following trauma or surgery often results in hyperalgesia that is characterized by increased sensitivity to painful stimuli. Often innocuous stimuli such as light touch are perceived as painful. Until recently, it was thought that the increase in pain was due to changes at the site of injury. We now know that the increase in pain also involves central nervous system hyperexcitability leading to plasticity or long term changes in the nervous system.

After tissue injury, there is an increased sensitivity of nociceptors located in the injured zone. These changes in the periphery result in an increased neuronal barrage into the central nervous system and contribute to the increase in pain after injury.

The increased neuronal barrage into the central nervous system (CNS) leads to hyperexcitability of CNS neurons, particularly at the level of the spinal dorsal horn. The hyperexcitability or central sensitization involves activation of excitatory amino acid and neuropeptide neurotransmitters and their receptors. Initially, activation of G-protein coupled receptors such as the metabotropic glutamate receptor and the Substance P receptor lead to release of calcium from intracellular stores and the phosphorylation of subunits of the N-methyl-D-aspartate (NMDA) receptor by calcium-dependent protein kinases. Subsequent activation of the NMDA receptor leads to the influx of calcium into neurons and the further activation of protein kinases and phosphorylation of receptors. There are also changes in the gene expression of NMDA as well as other receptor subunits. The sum effect of these changes is an alteration in the sensitivity of receptors, increased excitability, and ultimately an amplification of pain. These changes are referred to as activity-dependent plasticity or central sensitization and appear to be most robust in response to deep tissue injury.

The transmission of information in the CNS related to persistent tissue injury is modulated by descending control systems in the brain. These descending pathways are also subject to changes in excitability due to the persistent neuronal barrage. A similar form of activity-dependent plasticity occurs in brain stem descending pathways to complement the plasticity found at the level of the spinal cord. Under usual conditions, the net effect of the descending projections from brain stem sites to the spinal cord is a balance between descending facilitation and inhibition with inhibition predominating after persistent tissue injury. Under some conditions, this balance shifts to a net excitatory effect in which descending modulation results in more

hyperexcitability and more pain after injury. In patients suffering from deep pain conditions, where central sensitization appears to be a prominent component, such as temporomandibular joint disorders, fibromyalgia and irritable bowel syndrome, the diffuse nature and amplification of pain, in part, may be due to this imbalance.

These findings have functional implications relevant to the survival of an organism in response to the threat and presence of tissue injury. The problem of persistent pain can now be attacked at sites of activity-dependent plasticity where it is initiated and maintained.

REFERENCES

- DeLeo JA, Yeziarski RP (2001) The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain* 90:1-6.
- Ren K, Dubner R (1999) Central nervous system plasticity and persistent pain. *J Orofac Pain* 13:155-1
- Ren K, Dubner R. Descending modulation in persistent pain: an update. *Pain* 2002;100:1-6.
- Woolf CJ, Salter MW (2000) Neuronal plasticity: increasing the gain in pain. *Science* 288:1765-1769

GENETICS, INTERMEDIATE PHENOTYPES, AND MUSCULOSKELETAL PAIN CONDITIONS: EMERGING INSIGHTS FROM PATIENTS WITH TEMPOROMANDIBULAR JOINT DISORDERS

William Maixner DDS, PhD
Director, Center for Neurosensory Disorders
School of Dentistry
University of North Carolina at Chapel Hill

Temporomandibular joint disorders (TMJD) are a heterogeneous family of musculoskeletal disorders that represent the most common orofacial pain conditions^{1,2}. Although there are several forms or subclasses of TMJD, the most common and debilitating forms are associated with persistent pain in the region of the temporomandibular joint, the periauricular region, and muscles of the head and neck^{1,2}. Worldwide epidemiological studies report the prevalence of TMJD to range from 5 to 50% with most studies reporting a prevalence rate of approximately 10%².

TMJD is associated with several co-morbid signs and symptoms - including, but not limited to, fatigue, sleep abnormalities, anxiety and fibromyalgia syndrome³. At present, we have a poor understanding of the pathophysiological mechanisms that mediate TMJD and related "idiopathic pain" conditions. However, several studies have provided evidence that idiopathic pain conditions like TMJD are multifactorial and are composed of a mosaic of intermediate phenotypes that manifest as enhanced sensitivity to painful events (i.e, a state of pain amplification), autonomic imbalances, and psychological distress. There is now considerable evidence that these intermediate phenotypes are influenced by multiple polymorphisms in genes that code for proteins which modulate pain processing, affect/mood, and autonomic function³⁻⁶.

Dr. Maixner will present findings from recently completed^{5,7} and ongoing (see www.oppera.org) cross sectional and prospective studies that examine the biopsychosocial and genetic factors contributing to the onset and maintenance TMJD and related conditions. (Supported by DE07509, NS45685, DE16558, NS41670, and DE017018).

References

1. Dworkin, S. F. *et al.* Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *Journal of Craniomandibular Disorders Facial Pain and Oral Pain* **6**, 302-355 (1992).
2. Okeson, J. P. *et al.* in *Orofacial Pain* (ed Okeson, J. P.) 113-184 (Quintessence, Chicago, 1996).
3. Diatchenko, L., Nackley, A. G., Slade, G. D., Fillingim, R. B. & Maixner, W. Idiopathic pain disorders--pathways of vulnerability. *Pain* **123**, 226-230 (2006).

4. Slade, G. D. *et al.* Influence of psychological factors on risk of temporomandibular disorders. *J. Dent. Res.* **86**, 1120-1125 (2007).
5. Diatchenko, L., Nackley, A. G., Tchivileva, I. E., Shabalina, S. A. & Maixner, W. Genetic architecture of human pain perception. *Trends Genet.* **23**, 605-613 (2007).
6. Nackley, A. G. *et al.* Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* **314**, 1930-1933 (2006).
7. Diatchenko, L. *et al.* Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum. Mol. Genet.* **14**, 135-143 (2005).