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Basic Science Issues Related to Improved Diagnoses for Chronic Orofacial Pain

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It is clear from the current literature on pain and from the Workshop papers presented elsewhere in this volume that pain is now conceptualized as a complex, multidimensional phenomenon embracing more than just a simple perceptual response to tissue pathology. As a result of this change in conceptualization, considerable advances have taken place in the last 20 years in our understanding of the mechanisms involved in pain and its control, particularly in regard to processes related to acute pain, and these advances have been coupled with improved knowledge and measures of how to assess pain and treat it. Nonetheless, there is widespread agreement that the differential diagnosis of chronic orofacial pain conditions is often frustratingly difficult. Clearly, knowledge about the fundamental mechanisms of chronic pain that underlie these clinical phenomena would lead to improved diagnosis and treatment; first, via a better understanding of their pathogenesis and second, via "spin-offs" from laboratory investigations that can lead to new or improved diagnostic tests.

Herein we concentrate on providing a summary of the gaps in our current knowledge, and of mechanisms underlying chronic pain and its pathogenesis. We will focus our report on recent advances in our knowledge about pain pathophysiology in the context of four broad categories of chronic orofacial pain: pain associated with inflammation, pain of vascular origin, musculoskeletal pain, and neuropathic pain.

It should be noted that in general, our understanding of pain is based on several decades of work that was strongly concentrated on acute cutaneous pain.[1–3] Many observations show that chronic pain, and especially chronic pain of noncutaneous origin, may be a very different phenomena. In addition, we deal here only with basic research in biology. Clearly, basic research in the physical sciences also has much to contribute as, for example, in the continued development of improved imaging techniques, and these issues are addressed in other papers in this volume.

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PAIN ASSOCIATED WITH INFLAMMATION

Inflamed tissue is a constant source of nociceptor input. The pain is largely due to inflammation-induced sensitization of nociceptor terminals and may be further increased by the tissue damage caused secondarily by inflammatory response. It has become clear in the last few years that the pain associated with inflammation is mediated by many substances from several sources. Inflammatory mediators originate from components of the damaged tissue itself (e.g., endothelium, mast cells), the terminals of nociceptive primary afferents, sympathetic efferent terminals, cells of the immune system, and are also delivered by the circulation (see articles by Levine and Hargreaves, this volume). All of these substances interact in a complex, coordinated pattern that is the organism's normal response to injury. This field of investigation holds great promise for the development of new ways to attack those parts of the inflammatory response that exacerbate pain.

Recent work has shown that inflammation is not only associated with an alteration in peripheral nervous system activity (i.e., primary afferent sensitization) but also has marked effects in the central nervous system. Both central and peripheral mechanisms contribute to the enhanced pain sensitivity that characterizes inflammation. These effects are evident at several levels of analysis. For example, even minor tissue damage results in the activation of the neuronal genome, e.g., the induction of the proto-oncogene. c-*fos*, in certain spinal cord neurons.[4] The significance of c-*fos* induction is not yet known. Tissue injury that evokes inflammation also activates the gene that encodes for the opioid neuropeptide, dynorphin. The dynorphin gene is activated within hours of inflammation and results in an enormous and sustained increase in the amount of the peptide in several populations of spinal neurons.[5] The functional significance of this effect is under

active investigation; it is possible that it represents the recruitment of endogenous pain-modulating systems. Injury and inflammation are also now known to have dramatic effects on the response properties of neurons in the medullary and spinal dorsal horns, and in the ventrobasal thalamus. Many of these neurons are believed to participate in the processing and transmission of pain signals that are sent to the brain. For example, lamina I of the dorsal horn contains a large population of neurons that normally respond only to noxious stimuli and that transmit their messages to the brainstem and thalamus. Within 5–6 hours of the induction of inflammation, these cells become hyperresponsive to stimulation of their peripheral receptive fields. This hyperresponsivity is characterized by an abnormal spontaneous discharge, by a very large increase in the size of their receptive fields, and by an increased sensitivity to low-intensity stimulation. These changes appear to be due mainly to an alteration in the central processing of peripheral input.[6–8] There is reason to believe that injury to muscle and other deep structures are especially potent in evoking this central hyperresponsivity.[9–11] With only a few notable exceptions, recent research on the effects of injury have investigated inflammation with durations of hours or days. The possibility of differences in truly chronic inflammation remains to be examined.

PAIN OF VASCULAR ORIGIN

Very important advances have been made in our understanding of the pathophysiology of vascular pain and headache. The nociceptive innervation of the cerebral vasculature has been characterized in detail and we are becoming increasingly familiar with the central connections of vascular afferents.[12] Detailed studies of the convergence of vascular and somatic afferents onto cells in the medullary/spinal dorsal horns and the actions of such cells on their targets in the ventrobasal thalamus are beginning to give a clear understanding of patterns of referred pain that are evoked by activation of cerebral vasculature nociceptors.[13,14] There are several key issues, however, where progress has been slow. We are still uncertain as to the stimulus (or stimuli) that normally excite vascular nociceptors. Headaches seem to have an unusually strong association with autonomic nervous system responses (nausea, fainting, etc.), but it is not clear why this is so. In addition, it is established that certain kinds of headache have a large genetic contribution, however, the details of this genetic relationship are unknown. Lastly, there have been few advances in headache pharmacology. Hopefully recent work on the neurochemistry of vascular afferents[12] will stimulate new research in this field.

PAIN OF MUSCULOSKELETAL ORIGIN

The significance of musculoskeletal nociception for chronic orofacial pain cannot be overestimated. Its pathophysiology is the key for understanding temporomandibular joint (TMJ) pain and myofascial pain. Moreover, it is also of key significance for pain conditions that are likely to be due to inadvertent damage to bone and ligaments during or following dental procedures. Musculoskeletal pain has become a very active field of research in the last few years, but it should be noted that most of the work has been done on the limb muscle and knee joint of cats and rats. We do not know whether there are any unique aspects to nociception in the human TMJ and orofacial musculature.

Muscles, tendons, and joints receive a rich innervation from both myelinated and unmyelinated nociceptors and these afferents respond to tissue damage, ischemia, and algesic chemicals.[7,15] As in the skin, these musculoskeletal afferents are also sensitized by injury and inflammation. For example, nociceptors that innervate the knee capsule normally respond only to joint movements that are injuriously extreme, but in the presence of inflammation they respond to the slightest movement.[7,16,17] This enhanced sensitivity is also reflected in the activity of central somatosensory neurons.[7,8] Another particularly noteworthy feature is the extensive convergence of musculoskeletal and cutaneous inputs onto neurons in the spinal and medullary dorsal horns.[7,11,18,19] It is very probable that these patterns of convergence are the neural basis of referred pain.

It is also especially noteworthy that several experiments have documented a difference between the central effects of input from deep versus cutaneous nociceptors.[9–11] This difference is potentially of the greatest importance for understanding chronic musculoskeletal pain. Electrically evoked volleys in cutaneous C-fibers produce a large increase in the excitability of the withdrawal reflex pathway and of the responsivity of pain-encoding neurons in the dorsal horn. Similar volleys in C-fibers from muscle nerves produce the same effect, but to a much greater degree and for a much longer time. Twenty seconds of activity in muscle C-fibers (20 volleys, 1 Hz) increases central excitability in the spinal and trigeminal somatosensory systems for nearly an hour. It is not difficult to imagine the profound effects that may occur when, for example, an inflamed TMJ generates days of continuous, deep C-fiber input.

There are two musculoskeletal pain phenomena that have yielded little to experimental analysis. First, we know practically nothing about the pathogenesis or functional significance of trigger points in muscle. Second, and perhaps relatedly, we know very little about the processes whereby musculoskeletal injuries evoke guarding reflexes.

It is common knowledge that neck injury (whip-lash) evokes guarding reflexes from the paravertebral muscles and that the resulting muscle contractions can themselves become very painful. Analogous guarding reflexes and secondary pain may be evoked by injury to the TMJ and muscles of mastication. For example, algesic chemical stimulation of the TMJ can reflexively induce sustained activity in the masticatory muscles.[20] It is of interest to consider the hypothesis that some chronic myofascial pains might be generated in this way.

NEUROPATHIC PAIN

We include under this heading the abnormal pain states that are known or suspected to arise when peripheral nerves are damaged by trauma or disease. Postherpetic neuralgia is undoubtedly the most common neuropathic pain of the orofacial region, and its incidence can be expected to rise as the average age of the general population continues to increase. Other neuropathic pain states in the orofacial region are relatively rare, but tic doloureux (trigeminal neuralgia) and other syndromes nevertheless are responsible for great suffering. The neural mechanisms that underlie neuropathic pain states are still very poorly understood, and this is at least partly responsible for our generally unsatisfactory therapeutic approaches to these disorders.

The last ten years have produced a tremendous increase in our understanding of the effects of nerve injury. It is now apparent that the primary afferent neurons in a damaged nerve undergo dramatic changes in their neurochemistry and their electrophysiological characteristics.[21,22] For example, damaged primary afferents acquire an abnormal spontaneous discharge that may be generated in the axon at the site of damage or in the neuron's cell body in the ganglion. Moreover, it is now clear that damage to a peripheral nerve evokes functional and structural changes in trigeminal brain stem neurons. Sugimoto et al.,[23] for example, have shown that damage to the inferior alveolar nerve can lead to the degeneration of neurons in the medullary dorsal horn and that this degeneration is likely to be a consequence of the abnormal discharge of the damaged primary afferents. In addition, Hu et al.,[24] have shown that tooth pulp deafferentation produces marked changes in the response properties of trigeminal neurons.

There appears to be a growing consensus that the various symptoms of neuropathic pain dysfunction (e.g., spontaneous burning pain, lancinating pain, allodynia, hyperalgesia, etc.) are caused by several different neural mechanisms. These different mechanisms may coexist in the same patient and, importantly, do not necessarily correspond in any simple way to our traditional diagnostic categories (e.g., two postherpetic neuralgia patients may have pain from different pathophysiological mechanisms). Differential diagnosis of these neural mechanisms promises to be of the greatest importance for proper therapy. For example, some patients with a continuous superficial burning pain have been suggested to have an abnormal sensitization of the peripheral terminals of C-fiber nociceptors.[25] The sensitization is abnormal in that it is divorced from its usual association with injury and inflammation. The identification of such a mechanism is of obvious value in directing a search for an effective therapy. A second and distinctly different mechanism has been proposed for the symptom of mechanical allodynia (touch-evoked pain). In at least some cases, this symptom appears to be due to abnormal central processing of input from A-beta low-threshold mechanoreceptors (touch fibers).[26] The nature of this central abnormality is not understood, but still, its proper identification suggests lines of therapeutic attack of a different sort than those of the preceding example.

ANIMAL MODELS OF CHRONIC PAIN

The experimental investigation of a disease is aided immeasurably when the clinical phenomenon can be produced in laboratory animals. Several animal models of particular relevance to chronic pain are in current use. An experimental polyarthritis can be produced by the systemic injection of Freund's adjuvant.[7] Joint inflammation also has been produced by injecting kaolin into the capsule,[27] and gout can be produced experimentally by injecting urate crystals into the joint space.[28] All of these models are useful for the analysis of pain arising from inflamed joints. An inflammation involving both the joint and soft tissues of a single extremity can be produced by a small subcutaneous injection of one of several irritants (Freund's adjuvant, yeast extract, phorbol ester, and carrageenan—a polysaccharide derived from seaweed). These substances produce a standardized and localized inflammation lasting for up to ten days.[29] To the best of our knowledge, no one has developed a model of chronic pain from muscle, fascia, ligaments, or tendons; the absence of such models is a notable deficiency. Similarly, laboratory analysis of pain arising from the vasculature is hampered by our inability to produce (or recognize?) these conditions in animals. Several models of neuropathic pain are in use. The pain syndrome associated with an amputation or complete nerve transection can be investigated in rodents.[30] A model of neuropathic pain arising from partial nerve injuries has been described recently and promises to increase our understanding of partial deafferentations arising from trauma and disease.[31] Diabetic neuropathy, another condition resulting in a partial deafferentation, can be detected in rodents with exper-

imental versions of diabetes.[32] Unfortunately, few new animal models have been developed specifically for pain conditions in the orofacial region; this should be an important focus for future research.

FUTURE DIRECTIONS IN BASIC SCIENCE PAIN RESEARCH

As we have noted, our knowledge of many aspects of chronic pain is seriously incomplete. Although pain research's emphasis on acute cutaneous (and tooth pulp) pain is definitely being supplemented by investigations of the consequences of injury and inflammation, there is still a tendency to concentrate on short-term responses rather than the consequences of chronic conditions.

Differential diagnosis is the surest path to successful therapy and prevention, but a correct diagnosis is often impossible without an extensive understanding of the fundamentals of the problem that confronts us. Thus, basic research in both the laboratory and the clinic, devoted to increasing our knowledge of the normal and abnormal neural mechanisms that generate chronic pain is of great importance. This research must be broadly based and include neuroanatomical, neurochemical, neurophysiological, and neuropharmacological methods. Although work on chronic pain in every region of the body is of clear value, work on the orofacial region must be given special attention.

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