REPORT OF A SCIENTIFIC MEETING

James C. Eisenach, M.D., Editor

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In the past 15 yr, there have been substantial advances in our understanding of the connectivity and pharmacology of systems that process nociceptive information. There has been a fundamental growth in the appreciation that afferent processing systems at every link are subject to alteration and modulation, either as a result of protracted afferent input or after nerve injury. One evolving concept is that, after a local tissue injury, events occur both at the central terminal and at the periphery, at the site of injury. These events may be considered in terms of those changes that occur at intervals of milliseconds or seconds (such as increased ion channel opening generated by transmitter/hormone activity), minutes or hours (such as facilitated transmitter release, changes in the terminal environment secondary to the appearance of inflammatory cells), and hours or days (such as upregulation of mRNA and an increase in receptor coupling or synthesis, appearance of ion channels). These fundamental insights have led us to the brink of a revolution in our ability to rationally define and explain a myriad of pain states hitherto seen as anomalies of the human observer. This perspective formed the focus of the satellite meeting of the Association of University Anesthesiologists held on May 19–21, 1995, in San Diego. Its focus was "New Horizons in Pain Research," with an emphasis on the postinjury pain state. To contribute to this ambitious topic, there were 11 primary speakers, 25 posters, and 73 attendees. The meeting was organized into three major sections: the pharmacology of the peripheral afferent terminal, persistent changes in afferent processing, and the pharmacology of the pain state.

The pharmacology of the peripheral terminal of the small primary afferent was reviewed by Andy Dray, Ph.D. (Sandoz, London). It is now emphasized that many of the afferent nociceptors are typically "silent" and gain sensitivity only in the presence of irritants or inflammatory mediators. Many of the inflammatory mediators in the "inflammatory soup"[1] exert their effect through specific receptors on the peripheral small afferent terminals. These receptors may be considered not only in terms of their respective ligands but in terms of how they couple to the processes of the membrane. These may be considered in terms of those that are (1) G-protein-coupled (bradykinin receptors), (2) ion channel-coupled (capsaicin), or (3) kinase-coupled (nerve growth factor). Notable examples of G-protein coupling with respect to afferents are the bradykinin receptors (BK1 and 2). Selective antagonists have been shown to be analgesic.[2] A specific receptor coupled to an ion channel is that with which capsaicin interacts. The development of specific agonists and antagonists at the capsaicin site clearly have shown that this is a specific receptor that increases terminal permeability to actions.[3] Kinase-coupled receptors located on the terminals of small primary afferents include those acted on by trophic agents, such as nerve growth factor (NGF).[4] It is clear now that this product, through a specific tyrosine kinase receptor (trkA), can influence regulation of terminal peptides and the syntheses of several important proteins, such as the capsaicin receptors and sodium channels. These factors provide mechanisms whereby the peripheral milieu can exert an acute (activation/sensitization) and prolonged effect on afferent transduction characteristics.

An important issue is the growing appreciation of the functional and structural complexity of the peripheral afferent terminal. Darrell Tanelian, M.D., Ph.D. (Department of Pain Management, University of Texas, Southwestern Medical Center), reviewed the structure and complexity of the so called free nerve ending. In an elegant model of the isolated cornea, the morphology of the peripheral terminals for identified Ad/C fibers was described. This model allows access to these structures and permits the characterization of events that transpire in and around the nerve terminal when there is local injury and the appearance of spontaneous activity after "distal" axotomy can be studied.[5] Changes in local ion permeability for calcium, potassium, and sodium are observed as a function of time after local axon injury. Over longer periods, these changes in ion permeability reflect on the formation of a neuroma and the evolution of spontaneous activity in this entity. On the other hand, local abrasion yields enhanced spontaneous activity that appears largely dependent on increased sodium conductance. Importantly, the ion channel properties of the axons show significant differences during degeneration and regeneration, and studies in the well defined cornea model will provide important insights into these changes.[6] Such information suggests a difference in the effects of distal injury to the terminal region of the nerve and the conducting axon and the role played by local channels in the electrophysiologic response to local tissue injury.

Gary Strichartz, Ph.D. (Department of Anesthesia, Harvard Medical School), reviewed the nature of the ion channels that define excitability in the axon and axon terminal. With regard to the afferent axon and the sodium channel, several points are evident. First, multiple sodium channels may be described in terms of their pharmacology and their gating kinetics. Second, it is appreciated that, after injury, there is an accumulation of channels in the sprouting membrane.[7] This change in density can account for alterations in spontaneous activity and the evolving mechanical sensitivity of the sprouting terminal. Third, despite its ubiquity, the sodium channel distribution is not uniform in the excitable membrane (*e.g.,* comparing dorsal root ganglion cells to axons to terminals regions). It appears likely that sodium channels with distinguishable properties may exist in different parts of the same axon (*e.g.,* terminal regions *vs.* the DRG). Moreover, the biophysics of the excitable membrane likely account for the complex transmission properties of afferent axons and the likelihood of differentially modulating transmission through axons mediating different sensory modalities.[8] Finally, even for the "analgesic" actions of sodium channel blockers, increasing evidence indicates these agents may exert multiple actions within the central nervous system to alter nociceptive transmission.[9]

Continuing with the consideration of the postinjury milieu, it can be appreciated that the effects of injury are mediated by a constellation of neural and nonneural elements that surround the peripheral terminal in the postinjury phase. Jon Levine, M.D., Ph.D. (Department of Medicine, University of California, San Francisco), reviewed the role for prostaglandins released from local cells and terminal systems (such as the sympathetic terminals) or circulating inflammatory cells as important intermediaries in the stimulatory and sensitizing effects of inflammatory mediators.[10] Importantly, after local injury, there are (1) phenotypic changes in the sensory neuron leading to, for example, an increase in afferent peptides[11] as well as opioid receptors in the peripheral terminals, and (2) an appearance of a variety of circulating immunocompetent cells. These cells have shown a surprising diversity in their ability to release a variety of products, such

as endogenous opioids. Such observations account for the peripheral antihyperalgesic action of opioids.

In the preceding discussions, the emphasis was on changes in the transduction properties of the intact systems exposed to nerve and tissue injuries. Jin-Mo Chung, Ph.D. (Marine Biomedical Institute, University of Texas, Galveston), considered the development of hyperpathic states that evolve after nerve injury. Several of these models have properties remarkably similar to those observed in humans, *e.g.,* sympathetically dependent.[12] Given the hyperpathia, mechanisms underlying the phenomena have been investigated. Importantly, such injuries have been shown to lead to changes in dorsal horn morphology, sprouting of large afferents into the substantia gelatinosa, and the appearance of sympathetic innervation in the dorsal root ganglia of injured nerves.[13] Importantly, at least some components of the allodynia may depend on ongoing input from the peripheral injury site.[14]

Within the nervous system, the first-order synapse has been a site of considerable study. Patrick Mantyh, Ph.D. (Molecular Neurobiology Laboratory, VA Medical Center, Minneapolis), discussed the nature of the receptor organization that occurs at the first-order synapse, with particular focus on the role of substance P. This peptide, released from small afferents, acts on dorsal horn, NK1 sites. The NK1 site is a G-protein-coupled receptor that undergoes phosphorylation and internalization. The reorganization is so significant that the morphology of the dendrites appears to change from columnar to beaded. Of further interest is the observation that afferent-derived sP may diffuse over a surprisingly considerable distance after release.[15] This redistribution raises considerations in defining how C fibers may interact with other spinal systems in the face of repetitive activation.

The advances in the organization of the encoding process have emphasized that protracted afferent input generates states of facilitated processing at the level of the spinal cord. Clifford Woolf, M.D., Ph.D. (Department of Anatomy and Developmental Biology, University College London), reviewed the current thinking on components of the changes in neuronal processing that are generated by this repetitive state of activation. Aside from the activation of specific receptor systems that leads to an enhancement of the stimulus-evoked response, these conditions also lead to prominent changes in the phenotype of the neuron, with upregulation of neuromodulators such as sP and CGRP, as well as modifying preterminal receptors (such as for opioids and GABA). Importantly, these changes may lead not only to an enhanced response of the cell to high-threshold input (*e.g.,* hyperalgesia) but to a state in which low-threshold afferent (*e.g.,* AB) fibers can induce an exaggerated response that correlates with a pain state (*e.g.,* allodynia).[16] These alterations provide important insights on the persistent changes that may be induced by the postinjury pain state in spinal organization.

Important advances have focused on the pharmacology of these systems, which are activated by afferent input. Jerry Collins, Ph.D. (Department of Anesthesiology, Yale University School of Medicine), discussed the effects of anesthetics on spinal function. In the operating theater, the patient, under volatile anesthetics, is strongly influenced by the presence of these powerful classes of agents, yet we know surprisingly little about their effects on the encoding of the message. Classic data have indicated that general anesthetics reduce spinal excitation. However, in the intact animal without anesthetics, it can be shown that anesthetics may serve to unmask excitation by blocking some inhibition.[17] These changes are in concert with studies that have shown that different anesthetics may serve to diminish the behavioral consequence of protracted input, whereas others are without effect.[18] These distinctions have not been well categorized in humans and may account for some components of the complexity that has been associated with the results of experiments focusing on "preemptive analgesia".[19]

Tony Yaksh, Ph.D. (Department of Anesthesiology, University of California, San Diego), reviewed current work that emphasized the complexity of dorsal horn systems that regulate the initiation of facilitated states of afferent processing. Based on the study of release and the spinal delivery of the appropriate antagonists, there seem to be strong data indicating that postinjury afferent input will yield a facilitated state, secondary to the release of glutamate and the activation of the respective glutamatergic receptors.[20] Of evolving interest is that this activation may yield a facilitated state secondary to the spinal action of prostanoids and nitric oxide.[21,22] Both families of agents have been shown to additionally facilitate the release of afferent peptides and excitatory amino acids.[23,24] The growing understanding of this facilitated processing has led to several key considerations: (1) Multiple forms of facilitation occur at the spinal level, some with time courses of seconds, such as those seen in C fiber-evoked windup, others lasting minutes to hours, as seen in the formalin test or the arthritic joint. (2) The facilitation evoked by C fiber input manifests itself in a progressive enhancement of the response to both low- and high-threshold afferent input. Thus, in the postinjury pain state, there is allodynia as well as hyperalgesia. (3) With post-nerve injury as well as post-tissue injury, there appears to be a sustained increase in spinal glutamate release that accounts for an important initiating circumstance in the facilitated processing observed under both conditions.

An obvious component of the message of the speakers was that there are pronounced organizational changes that may be described in the postinjury pain state. Given this thesis, it is important to query whether these changes reflect on the organization of the behavioral responses in clinical models. Srinivasa Raja, M.D. (Anesthesiology, Johns Hopkins), discussed the content of the afferent message in humans that is generated by peripheral injury. Classically, it has been the belief that the small afferents provide the important link for encoding a strong somatic stimulus, with frequency of firing and fiber type showing a strong correlation with the reported sensation. However, it is clear that, after tissue injury, there is prolonged bursting and relatively high-frequency discharge. Recent psychophysical studies with humans and animals have shown that there is a strong nonlinearity in the magnitude of the pain report and the stimulus in the face of injury or inflammation. Thus, there is a prominent rightward shift in the stimulus response curves for such observers, *e.g.,* a hyperalgesic state. Systematic observations have emphasized that, in such a condition, it is possible to define spatially associated changes referred to as primary (near the site of injury) and secondary (distal to the site of injury) hyperalgesia.[25]

The powerful role played by facilitation in the postinjury pain state in animal models and alluded to in the review by Raja suggests a potent role for the postinjury pain state being influenced by the presence of a protracted input. Donald Price, Ph.D. (Anesthesiology, Medical College of Virginia), reviewed the psychophysics of the human state after repetitive afferent input, using well defined electrical and thermal pulse stimuli. These studies emphasize that there is a significant central summation of the input generated by repetitive afferent input, and this central change in encoding leads to spatially extended regions of hyperpathia, *e.g.,* a secondary hyperalgesia. There is an increasing appreciation that the pharmacology of this secondary hyperalgesia is unique and may involve glutamate receptors of the

NMDA type. The relevance of the preclinical data showing a potent role for NMDA antagonists in facilitated pain states has been documented in humans. In well defined human psychophysical studies involving temporal and spatial summation of paired experimental stimuli, dextromethorphan showed a clear ability to suppress.[26] These studies strongly support the likelihood that, in some hyperpathic states, humans will respond well to NMDA receptor antagonism.

In addition to the primary speakers, a number of attendees were asked to present short summaries of drug classes under investigation, a brief highlight of their mechanism of action and at what stage they were in clinical development. Strichartz discussed new directions in channel blockers. He noted the likelihood of multiple sodium and potassium channels and the development of selective blockers for these channels. Scott Bowersox, Ph.D. (Neurex, Palo Alto), focused on the N-type calcium channels and the selective antagonists known as conopeptides, developed originally from lead molecules obtained from the conus snail.[28] He noted these agents had been demonstrated to be active in preclinical models of neuropathic pain,[29] and in ongoing work, they were found to be efficacious after spinal delivery in late-stage cancer pain. Considerable interest has been focused on the NMDA-glutamate receptor antagonist. Current work on the systemic actions of dextromethorphan and their potent synergic interaction with opioids were reviewed by Price.[26] Yaksh described the likelihood of spinal action of these agents and his group's current preclinical infusion work defining the safety of these agents for spinal delivery. John Cheronis, Ph.D. (Cortech, Denver), discussed the role played by the BK2 bradykinin receptor in the postinjury pain state and described dimeric agents that link a bradykinin antagonist and an opioid agonist, pharmacophores.[27] These agents likely have a dual effect on the peripheral terminal in the milieu of the injured tissue. John Hunter, Ph.D. (Syntex, Palo Alto), recounted the history of the κ receptor agonists as an analgesic class.[30] He emphasized the complexity of the role played by the κ receptor[31] and the likelihood of κ-selective compounds as agents with an improved side effect profile. Amy Veenhuizen, Ph.D. (Monsanto, St. Louis), reviewed the current trend regarding the role of inducible forms of cyclooxygenase (COX) and the synthesis of COX-selective inhibitors.[32] The possibility that some of the side effects typically associated with NSAIDs may be mediated by the constitutive COX, but not the inducible COX, suggests the possibility of improved side effect profiles. Thus, gastric side effects associated with NSAIDs may be mediated by a COX 1 inhibition. Dray reviewed the action of capsaicinoid agents and issues related to their development as therapeutic agents.[33] Frank Porreca, Ph.D. (University of Arizona, Tucson), and Hunter reviewed the mechanisms of CCK B antagonists in terms of their action as anxiolytics[34] and their ability to augment opioid action[35] and clinical trials in which such agents are being examined.

Perhaps most exciting about the 3-day gathering was the enthusiasm of the participants and the depth and breadth of the research. It is no exaggeration that the research focusing on spinal receptor regulation, second messenger coupling, transmitter release, and the role of growth factors, although relevant to pain processing, has a broad impact on the neurosciences in general. This sense of the horizon and the lure of the future was evident in the tenor of this meeting and the demeanor of its participants.

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ANNOUNCEMENT

The American Board of Anesthesiology will administer its written examination in PAIN MANAGEMENT on Saturday, September 7, 1996. Diplomates of the ABA who apply and are judged to be qualified by virtue of their additional training or experience in Pain Management will be accepted for examination. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 4101 Lake Boone Trail, Raleigh, North Carolina 27607-7506. The deadline for receipt of completed applications in the Board office is March 1, 1996.