The inaugural ASPET–Ray Fuller Symposium was held in Indianapolis, Indiana at the Omni Severin Hotel, on September 17–19, 1999. This was the first in a series of symposia sponsored by the American Society for Pharmacology and Experimental Therapeutics that are intended to bring together individuals from academia and industry in an interactive program. This first ASPET–Ray Fuller Symposium focused on three main themes: cellular mechanisms mediating pain sensitivity, central mechanisms of pain modulation, and novel therapeutic approaches for pain control. It is fitting the first symposium was held in Indianapolis, because Ray Fuller spent a substantial part of his career at Eli Lilly. Among his many contributions to pharmacology and therapeutics was the development of selective monoamine uptake inhibitors for the treatment of affective illness.

Attempting to ascertain the mechanisms of neuronal sensitization in the pain pathway continues to be critically important for understanding pain mechanisms and for developing new therapeutic strategies. Three major approaches for addressing this issue were discussed. The first is the use of techniques to reduce or eliminate specific proteins and/or transmitters indigenous to pain pathways followed by an examination of the consequences of these maneuvers on behavioral models of pain. Allan Basbaum (University of California, San Francisco) summarized the relative advantages and disadvantages of using transgenic mice to elucidate the cellular components important for chronic pain in laboratory animals. For example, there is a reduction in chronic pain-related behaviors in knock-out mice with a defect in Substance P/Neurokinin A or protein kinase C-γ. This reaffirms the importance of Substance P in the pain response and suggests that activation of specific transduction cascades in nociceptive neurons mediates sensitization.

Another approach for studying sensitization is to identify ion channels unique to sensory neurons that mediate excitability. John Wood (University College, London) discussed the use of DNA hybridization techniques to uncover novel gene products and emphasized recent studies on the importance of the ATP-gated ion channel, P2X3, and the proton-sensitive acid-sensing ion channels in acute and chronic pain. Michael Gold (University of Maryland) reviewed studies of voltage-gated sodium channels and their alteration following injury. It was reported that several voltage-gated sodium channels are present only, or predominantly, on small diameter sensory neurons typically associated with nociceptors and, therefore, are likely to contribute significantly to neuronal excitability. Grant Nicol (Indiana University) summarized work showing that voltage-gated potassium channels contribute to sensitization of peripheral sensory neurons. In general, the work demonstrates that both ligand- and voltage-gated channels in sensory neurons are modified in the presence of tissue injury and/or by activation of second messenger pathways and that this modification is an important component in the development and maintenance of chronic pain.

The third approach for examining mechanisms of nociceptor sensitization is to ascertain the potential involvement of novel inflammatory mediators in maintaining the activation of the pain pathway. As discussed by Lorne Mendell (SUNY-Stony Brook), nerve growth factor, which has both peripheral and central actions, augments nociceptive responses and enhances heat-induced and capsaicin-induced excitation of sensory neurons. At the level of the spinal cord, nerve growth factor appears to up-regulate brain-derived neurotrophic factor which, in turn, increases synaptic activity in the dorsal spinal cord. Thus, trophic factors may play a role in sensitizing pain pathways at various sites. Moreover, Linda Sorkin (University of California, San Diego) presented evidence indicating the importance of the immune system in mediating pain. Activation of the immune system, or administration of proinflammatory cytokines, augments neuronal excitability and produces nociceptive behaviors. These data, and work summarized by George Wilcox (University of Minnesota), support the notion that cytokines are mediators of chronic pain.

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pain during injury. The cellular mechanisms responsible for these actions of the cytokines remain to be determined.

The second session of the meeting focused on central mechanisms of pain modulation. Ronald Dubner (University of Maryland) discussed the ongoing search for a drug that would replace morphine as the prototypical analgesic. Whereas much emphasis has been placed on examining the importance of dorsal horn N-methyl-d-aspartate (NMDA) receptors as mediators of pain, less is known about the role of non-NMDA glutamate receptors. Work described by Tim Brennan (University of Iowa) suggests the role of glutamate receptor subtypes in the dorsal spinal cord is dependent on the type of injury. For instance, in models of postsurgical incision and controlled localized burn injury, NMDA receptor antagonists are not anti-hyperalgesic although they display this property in models of inflammatory hyperalgesia. Consequently, success in reducing nociceptive behaviors with excitatory amino acid receptor antagonists varies with the nociceptive stimulus and the behavioral endpoint. The emerging concept of descending facilitation was discussed by Jerry Gebhart (University of Iowa). Data suggest that pathways from the brainstem to the dorsal spinal cord augment activity in the dorsal horn of the spinal cord and may be involved in both the development and maintenance of secondary hyperalgesia.

Peter Isakson (G.D. Searle and Company) reviewed data suggesting prostaglandins produced by the inducible form of cyclooxygenase (COX-2) mediate swelling and pain during inflammation. Furthermore, inhibition of spinal cord COX-2 prevents hyperalgesia. These results indicate the importance of prostaglandins for neuronal sensitization in both the periphery and spinal cord during the inflammatory response and support the notion that COX-2 inhibitors work in the central nervous system. Frank Porreca (University of Arizona) discussed the use of antisense oligonucleotide administration to selectively eliminate a molecular target. He described studies demonstrating that “knock-down” of the tetrodotoxin-resistant sodium channel, SNS/PN3, by intrathecal injection of an antisense oligonucleotide reversibly attenuates pain produced by nerve or tissue injury. Pat Mantyh (University of Minnesota) led the discussion of the advantages and limitations of techniques for altering activity in the dorsal spinal cord, including local drug administration, antisense oligonucleotide-induced knockdown, transgenic (knockout) mice, and selective neurotoxicity.

The final session focused on novel therapeutic approaches for the control of pain. As pointed out by Andy Dray (AstraZeneca), drug development efforts center on identifying a target that is unique to the pain pathway, has been cloned, and is accessible. Many of the ion channels discussed in the earlier sessions are such targets, as are various neurotransmitter receptors. Dray reviewed data suggesting that selective δ-opioid receptor agonists may represent an important new class of analgesics, perhaps of lower efficacy than μ-receptor agonists but without many of the μ-agonist side effects. Ken Hargreaves (University of Texas Health, San Antonio) reviewed data on the potential importance of endogenous cannabinoids and drugs with agonist activity at cannabinoid receptors as antinociceptive agents. Cannabinoid receptors are expressed on sensory neurons, and the endogenous cannabinoid, anandamide, reduces peptide release from these cells. Moreover, cannabinoid receptor agonists reduce carrageenan-induced inflammation, whereas antagonists produce hyperalgesia. These data suggest that the endocannabinoid pathway may be tonically active in suppressing pain signals. As reviewed by Bob McCall (Pharmacia and Upjohn), the use of agonists for 5-hydroxytryptamine receptor subtypes has ushered in a new era in the treatment of migraine. Despite the effectiveness of sumatriptan and related agents, much work remains for developing effective therapy for migraine patients while minimizing side effects. McCall discussed basic and clinical studies of selective 5-HT1D and 5-HT1F receptor agonists, both of which display minimal vasoconstrictor effects while reducing migraine headaches in patients.

Glutamate receptor antagonists represent another class of potential analgesic agents. Although previous work revealed that NMDA receptor antagonists reduce nociceptive behaviors in animal models of chronic pain, the clinical utility of these agents is limited by toxicity. David Bleakman (Lilly Research Laboratories) discussed the therapeutic potential of drugs acting at (RS)-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors. Recent studies show that a mixed AMPA/kainate receptor antagonist prevents capsaicin-induced hyperalgesia and allodynia in humans, and that GluR5 antagonists block formalin-induced nociceptive responses in rats, suggesting these may be useful analgesics. Gabapentin, an antiepileptic, also displays efficacy in treating neuropathic pain, according to Donna Hammond (University of Chicago). She presented data showing that intrathecal administration of gabapentin decreases phase two of formalin-induced nociception and shifts the formalin stimulus-response curve.

As was clear from the outstanding presentations and lively discussions, there have been a number of novel discoveries that need to be actively pursued for developing new analgesics. This is an exciting time for pain research because of the significant promise that the integration of molecular and cellular techniques with physiological and pharmacological approaches will yield new treatments for the alleviation of pain.