Chronic Pain: Pathophysiology and Treatment Implications

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An examination of the current understanding of the processes and related therapies aimed at treatment of chronic pain in animals is presented. Discussion focuses on mechanisms involved in the neural pathways of chronic pain, differences between acute and chronic pain, and pharmacologic options for chronic pain as they relate to inflammatory, neoplastic, and neuropathic processes.

Keywords: chronic pain, inflammatory pain, cancer pain, neuropathic pain, analgesia, pain pathway

Management of animal pain has become a significant ethical as well as economic component in the modern practice of veterinary medicine. To this end, the incorporation of analgesic protocols in the perioperative period has garnered attention and expertise of the practicing veterinarian. Evidence to support specific anesthetic and analgesic protocols effective in the treatment of operative pain continues to increase. Similarly, specific details underlying the physiology and pathophysiology of chronic pain syndromes have advanced our knowledge and rationale for treatments. Chronic pain differs in fundamental aspects when compared with those of acute pain. This article will examine current understanding of the processes and related therapies aimed at treatment of chronic pain in animals.

What Is Chronic Pain?

Chronic pain has been defined as aberrant somatosensory processing in the peripheral or central nervous system (CNS) that is sustained beyond the normally expected time course relative to the stimulus. This definition, although helpful, provides only part of the story. Chronic pain is often insidious, vague, and difficult to pinpoint. Chronic pain may arise from a primary dysfunction within the nervous system. Chronic pain is difficult to diagnose by health care professionals, and its diagnosis may be especially elusive when the patient is nonverbal; obviously the situation veterinarians face every day. To appreciate the mechanistic differences in the physiology of chronic pain, it is useful to briefly review the pathway of normal (acute) or physiologic pain (see Lamont and coworkers[1]). Perception of pain is the culmination of transduction of spatially or temporally summated stimuli affecting peripheral nociceptors. Nociceptors may be specific for painful stimuli, or they may be generally responsive to a wide range of mechanical, thermal, chemical, or electrical stimuli. Nociceptive responses are transmitted from peripheral sites to the CNS via myelinated (type A-delta) or unmyelinated (type C) fibers. Neurotransmitters include substance P, neurokinin, neurotensin, glutamate, and N-methyl-D-aspartate (NMDA) among others. Synapses in the dorsal horn laminae of the spinal cord may be modulated through a variety of mechanisms before decussation and ascension to higher dermatones and ultimately to brainstem and midbrain centers. Additional processing passes the pain signal through the thalamus before projection to the cerebral cortex. Basic differences from this scheme that occur in the pathophysiology of chronic pain arise from the sensitization of neurons along the path.[2] Peripheral sensitization through chemical products of cell destruction (the "sensitizing soup") or CNS sensitization via activation of glutamate or NMDA receptor–mediated pathways creates the setting for development of a chronic pain syndrome, a phenomenon also known as windup. A second feature associated with the pathophysiology of chronic pain is related to the plasticity of the nervous system. With prolonged activation of pain pathways, augmented by sensitization, neural plasticity results in degeneration and remodeling of synapses and ganglia with collateral sprouting among nerve cells. Changes in neuronal function may thus occur, resulting in production of pain transmitter substances by cells that previously did not. For example, the nerve fibers that normally carry proprioceptive information (type A-beta) may be altered to begin producing substance P, effectively converting these previously innocuous signals to pain transmissions (Fig 1). Sectioned nerves have been associated with induction of cholecystokinin (CCK) production in afferent nerve fibers.[3] A direct antagonism of opioid-induced analgesia is mediated by CCK, potentially explaining the lack of opioid efficacy in some cases of neuropathic pain. These morphologic and functional changes in the nervous system can cause decreased pain threshold, exaggerated activation of the pain pathway, ectopic discharges, or loss of normal inhibitory processes. Chronic pain may elicit abnormal responses from the pain pathway that can be described as

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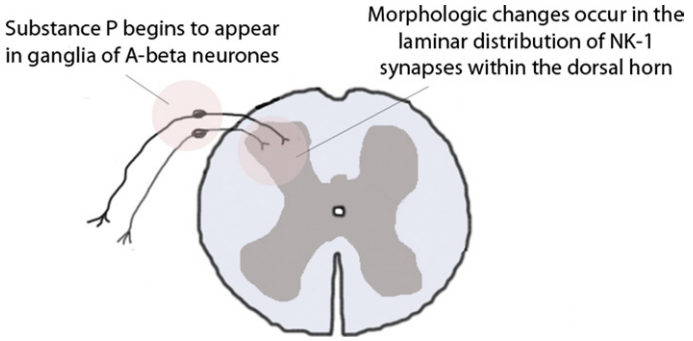

Figure 1. Morphologic changes in afferent fibers and the dorsal horn of the spinal cord typical of chronic pain syndromes. These changes are reflected by clinical symptoms of hyperalgesia or allodynia. (Color version of figure is available online.)

hyperalgesia (exaggerated response to a normally painful stimulus) or allodynia (pain from a normally nonpainful stimulus). Chronic pain syndromes often involve sensitization of the pain pathway through the NMDA receptor in the dorsal horn of the spinal cord.[4]

Therapeutic Implications

Better understanding of the pathophysiology associated with chronic pain will introduce the challenges to finding effective treatments and plant the seeds to nurture novel approaches in this quest. Drugs that are effective for acute pain may have little or no benefit when used for chronic pain syndromes. Conversely, drugs with little demonstrated benefit in treatment of operative pain may have significant efficacy in the treatment of chronic pain. The long-term therapies typically instituted for chronic pain syndromes may require unique routes of administration to achieve greater efficacy with fewer side effects. The use of oral, transdermal, and sustained-release formulations of analgesics has aided in the willingness of clients to comply with drug administration guidelines offered by the veterinarian. Species differences in absorption, metabolism, elimination, and therapeutic response dictate that the practitioner maintains vigilance in the

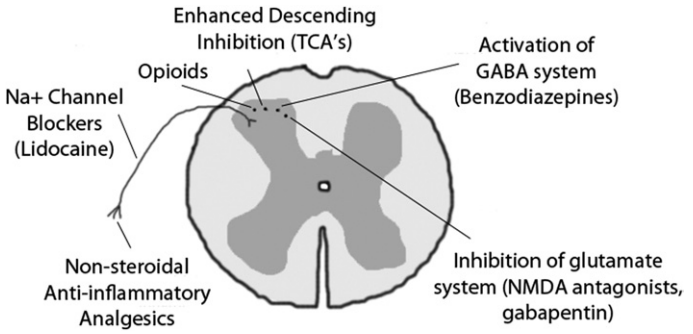

Figure 2. The pain pathway depicting sites of action for analgesics and adjuvants used in the treatment of chronic pain.

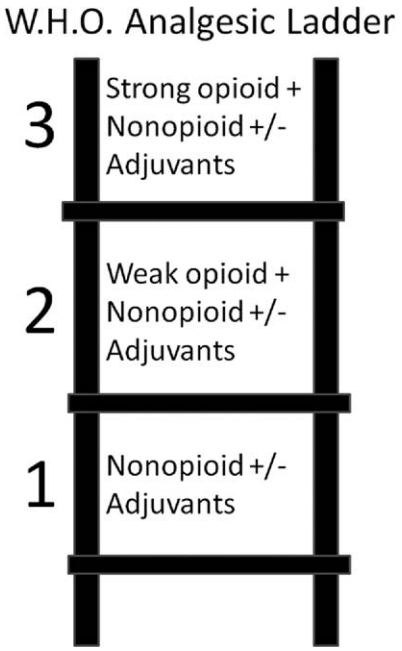

Figure 3. The World Health Organization (WHO) Analgesic Ladder: step one analgesics are used to control mild pain. When uncontrolled by step one analgesics (nonopioid analgesics ± an analgesic adjuvant such as gabapentin), step two analgesics are used. When step two pain is uncontrolled, step three analgesics are administered.

expanding database of biomedical literature, particularly when treating with off-label or novel agents. Combinations of analgesics may offer optimal therapeutic approaches by attacking pain through different mechanisms (Fig 2).

Recommendations for the treatment of chronic pain follow the established World Health Organization guidelines for pain management, sometimes referred to as the "WHO Ladder" (Fig 3). Pain of mild nature is initially treated with a nonopioid (e.g., nonsteroidal antiinflammatory analgesic). Nonsteroidal antiinflammatory analgesics available to the veterinarian include carprofen, etodolac, meloxicam, ketoprofen, deracoxib, tepoxalin, acetaminophen, and aspirin. Because of the differences in the spectrum of enzyme inhibition (e.g., cyclooxygenase [COX]-1 vs COX-2 vs lipoxygenase), efficacy may be variable among individuals, requiring the veterinarian to maintain stock of more than one agent. All are capable of side effects that include gastrointestinal ulceration and platelet dysfunction, so adherence to dosing guidelines is important. Appropriate washout periods for an initial treatment are suggested before beginning treatment with a different agent. Concurrent use of corticosteroids is not recommended beyond a single or short-term regimen. The nonsteroidal antiinflammatory analgesics have recently been implicated in the inhibition of nitric oxide radical generation and, rarely, in the promotion of immunosuppression.[5] Although currently the mainstay of chronic pain therapy, clearly there is still much to learn about the specific