Review Article

Chronic Pain and Decreased Opioid Efficacy: An Inflammatory Link

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Abstract:

Chronic pain is a devastating amalgam of symptoms that affects millions of Americans at tremendous cost to our healthcare system and, more importantly, to patients' quality of life. Literature and research demonstrate that neuroimmune cells called glia are not only responsible for initiating and maintaining part of the chronic pain disease process, but also release inflammatory molecules responsible for decreasing the efficacy of one of the most prominent treatments for pain, opioid analgesia. This article describes chronic pain as a disease process that has ineffective treatment modalities, explores the mechanisms of glial cell activation and inflammatory responses that lead to chronic pain and decreased opioid treatment efficacy, and hypothesizes novel chronic pain treatment modalities based on the glial cell inactivation and anti-inflammatory pathways.

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Chronic pain is a serious health concern of tremendous scope that spans socioeconomic boundaries; educational levels; and cultural, gender, and age demographics (Pleis, Ward & Lucas, 2009). An estimated 116 million Americans suffer from and are disabled by this chronic condition (Tsang et al., 2008), with a cost of $630 billion in lost work revenue, sick time, and healthcare costs (Gaskin & Richard, 2011); most importantly, chronic pain also has high costs in regards to patients' quality of life. Patients report not only a wide spectrum of painful symptoms and psychological effects, but also suffer from different types of pain in various anatomical locations. Current modalities utilized to treat these patients are limited in scope, and often ineffective for a large portion of the chronic pain population with a host of dangerous or self-limiting side effects. This raises the question of what more can be done for a patient population larger than all diabetic, coronary heart disease, stroke and cancer patients *combined* (Tsang et al., 2008).

For decades, pain research focused on neuronal opioid receptors as the primary target of pain physiology and management. Isolated from opium in the 1800s, morphine has become a mainstay of pain therapy (Ahlbeck, 2011; Mehendale, Goldman, Mehendale, & Rana, 2013), and clinicians eventually

developed an array of powerful synthetic opioids for pain relief. Yet, despite the useful addition of variably efficacious anti-depressive and anti-convulsant drugs, which decrease neuropathic pain symptomatology (Vranken, 2009), consistently effective treatment of chronic pain eludes the medical community. Fortunately, recent scientific discoveries have started to unmask various chronic pain neuroimmune pathways, which could lead to more effective treatment of this epidemic. One of the new directions for inquiry highlights central nervous system (CNS) inflammatory mechanisms that are believed to exacerbate and prolong neuropathic pain states via positive feedback mechanisms (Griffis, 2011). Recent pain literature suggests that the inflammatory mechanisms responsible for the initiation and prolongation of chronic pain are perpetuated by opioid therapy (Raghavendra, Rutkowski, & DeLeo, 2002; Tai et al., 2006). Given the widespread use of opioids in the anesthetic or pain management of patients with chronic pain, it is imperative for nursing and medical practitioners to understand the underlying mechanism of neuroimmune-mediated CNS inflammation, its hypothesized role in chronic pain, and the possibilities for novel pain management modalities if these inflammatory mechanisms are targeted.

ACUTE PAIN VERSES CHRONIC PAIN

Pain is an elegant physiologic mechanism that functions as a protective measure to preserve cellular function and life. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994, p. 213). However, there are instances when pain ceases to be protective and begins to be destructive. The neuroimmune-mediated CNS inflammatory mechanisms described here offer one possible way to differentiate between these two very different pain states.

Acute Pain

When pain pathways work as intended to detect tissue damage or trauma, pain-sensing receptors known as nociceptors detect chemical, mechanical, or thermal stimuli. Nociceptive detection is then converted and transduced as neural electrical impulses. Aδ and C primary afferent nerve fibers transmit these nociceptive signals to synapse at Rexed's Laminae II (located in the substantial gelatinosa) of the dorsal horn of the spinal cord (Todd, 2012). Via ascending spinothalamic tracts in the spinal cord, these nociceptive neural signals are transmitted to the thalamus, where the pain sensation is relayed to higher cortical regions for processing. The basal ganglia, anterior cingulate cortex, amygdala, periaqueductal grey region, hypothalamus, and prefrontal cortex are all areas of the higher cortex that process ascending nociception. As nociception proceeds, descending pain modulatory systems may be activated, resulting in increases and decreases in pain perception by the host. All of the higher cortical regions except the basal ganglia participate in descending pain modulation. Figure 1 depicts the acute pain process as described (Garland, 2012). Through a complex series of peripherally and centrally mediated neurocellular interactions, along with reflex and cognitive actions, sensing and responding to acute nociceptive pain helps the host remove itself from danger. Thus, pain, the proper perception of pain, and the proper withdrawal reaction to painful stimuli have aided in our species' survival.

Chronic Pain

Unfortunately, there are many conditions in which individuals' nociception and reaction to painful stimuli have developed into chronic pain states that provide no survival or protective benefit. Chronic pain, a term loosely and inconsistently defined in the literature, can be classified as any pain that endures beyond the expected healing phase following an injury or in the absence of injury, or pain that lasts longer than 3 months (Ruetsch et al., 2013). Common attributes of chronic pain include hyperalgesia, an increased sensitivity to painful stimuli, and allodynia, a sensation of pain in response to stimuli not normally producing pain. A barrage of sustained pain signaling via afferent pathways contributes to the maintenance of the chronic pain state and has been described in the literature as central sensitization (Mifflin & Kerr, 2013; Woolf, 2011). This paper will focus on the contributions of neuroinflammation to chronic pain syndromes as well as resistance to opioid analgesic therapy.

Glial Activation. Glia are neuroimmune cells located in the brain and spinal cord and comprise approximately 70% of all cells in the CNS. There are multiple glial cells responsible for the proposed inflammation-driven chronic pain pathways; in accordance with most of the experimental investigations of the phenomenon, this discussion will focus on two innate immune cell types known as microglia and astrocytes.

Historically, glia were thought to contribute exclusively to the structure and nourishment of neurons, until research using a rodent model of sciatic nerve injury identified a positive correlation between astrocyte activity and the level of hyperalgesia observed after an experimentally-induced nerve injury