

Narrative Review

Peripherally Acting Opioids and Clinical Implications for Pain Control

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Opioid receptors are widely expressed in the central and peripheral nervous system and in the non-neuronal tissues. Data from animal and human clinical studies support the involvement of peripheral opioid receptors in analgesia, especially in the presence of inflammation. Inflammation has been shown to increase the synthesis of opioid receptors in the dorsal root ganglion neurons and enhance transport and accumulation of opioid receptors in the peripheral terminals of sensory neurons. Under the influence of chemokines and adhesion molecules, opioid peptide-containing immune cells extravasate and accumulate in the injured tissues.

Stress, chemokines, cytokines, and other releasing factors in inflamed tissues stimulate these granulocytes to release opioid peptides. Once secreted, opioid peptides bind to and activate peripheral opioid receptors on sensory nerve fibers and produce analgesia by decreasing the excitability of sensory nerves and/or inhibiting release of pro-inflammatory neuropeptides.

Research has revealed that local application of exogenous opioid agonists produces a potent analgesic effect by activating peripheral opioid receptors in inflamed tissues. The analgesic activity occurs without activation of opioid receptors in the central nervous system (CNS), and therefore centrally mediated side effects, such as respiratory depression, mental clouding, altered consciousness, or addiction, are not associated with peripheral opioid activity. This discovery has stimulated research on developing peripherally restricted opioid agonists that lack CNS effects. In addition, it has been recognized that opioid receptors modulate inflammation, and that opioids have anti-inflammatory effects. The anti-inflammatory actions of opioids are not well known or understood. Conflicting reports on mu-opioids suggest both anti-inflammatory and pro-inflammatory effects. This article will present the basis for peripheral opioid analgesia and describe current research directed at developing novel treatments for pain with improved side effect profiles.

Key words: Opioids, opioid receptors, opioid agonists, peripheral nervous system, peripheral opioid receptors

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Opioids are potent analgesics that exert their pharmacological effects by binding and activating specific receptors in the nervous system. Three distinct membrane bound receptor subtypes with distinct behavioral characteristics are

described: mu (μ), delta (δ) and kappa (κ). These 3 classes of opioid receptors are widely distributed in the central nervous system (CNS). In addition to opioid receptors in CNS, peripheral neurons, neuroendocrine (pituitary, adrenals), immune, and ectodermal cells

(1) also express opioid receptors. These peripheral opioid receptors play a critical role in modulating pain and inflammation. Potent analgesia after peripheral administration of opioids has been reported in animal and human studies and new research is beginning to elucidate peripheral mechanisms of opioid analgesia. Russell et al (2) demonstrated that the peripheral analgesic effect of opioids is mediated by activation of opioid receptors in the peripheral nervous system (PNS) and other cells, especially in presence of inflammation. Opioid peptides such as β -endorphin and Met-enkephalin have been found in human synovium, mast cells, keratinocytes, and immune cells (3-9). Opioid peptide containing immune cells have been shown to migrate to sites of tissue inflammation (10-12), and release opioid peptides in response to stress, or release agents such as corticotrophin-releasing factor, chemokines, cytokines, and norepinephrine (13-17). Once secreted, opioid peptides bind to peripheral opioid receptors expressed on sensory nerve fiber terminal endings (18-20), activate and produce analgesia by inhibiting the excitability of sensory nerves, and /or inhibit the release of pro-inflammatory neuropeptides (substance P, calcitonin gene related peptide) (21,22). Clinically significant analgesia is obtained from this neuro-immune interaction without the accompanying side effects commonly associated with centrally mediated opioid analgesia, such as respiratory depression, nausea, cognitive disturbances, tolerance, and addiction (23). Endogenous immune cell derived opioids do not readily produce cross-tolerance to morphine, but rather prevent development of tolerance at peripheral opioid receptors (24-26). The evidence for therapeutically relevant opioid-induced analgesia at peripheral sites of inflammation is accumulating. Strategies and treatments that selectively attract opioid producing immune cells, increase expression of opioid receptors in damaged tissues in the periphery, and selectively activate peripheral opioid receptors appear to have immense therapeutic potential. Furthermore, opioids exert anti-inflammatory effects via changes in cellular activation and cytokine expression (27) and may have a role in the treatment of inflammatory arthropathy, inflammatory bowel disease, and other inflammatory skin disorders.

This article reviews current research on peripheral opioid receptors, opioid peptides, and opioid producing immune cells; modulation of pain and inflammation by opioids; and development of peripherally active opioid drugs.

PERIPHERAL OPIOID RECEPTORS

Three types of opioid receptors are described, mu (μ), delta (δ) and kappa (κ). All 3 receptors modulate pain and are expressed throughout the central nervous system (CNS). Animal studies have established presence of μ , δ and κ opioid receptors in nervous and non-nervous tissues outside the CNS. In 1987, Russell's group in Germany (2) demonstrated opioid receptors on nerve fibers in the knee joint of the cat and observed that locally administered opioid agonists decrease the frequency of spontaneous discharges in small diameter nerve fibers. It was suggested that opiates may exert a peripheral "analgesic" effect by binding to opiate receptors on primary afferent fibers in peripheral sites. Animal and human studies since then have demonstrated opioid receptors in fine cutaneous nerve fibers (28, 29), bone and joint tissue (30), keratinocytes (7,9), and immune cells (1). Opioid receptors are expressed in the small-, medium- and large-diameter dorsal root ganglion (DRG) neurons (28,31). Mu opioid receptors (MOR) are expressed in the enteric neurons in the gut (32) and play an important role in gut nociception, motility and secretion. MOR have also been described in epidermal and dermal layers of normal human skin and in nerve fibers of human dental pulp (9,33). In addition, μ , and κ receptors have been demonstrated in the capsule/synovium and periosteum (30).

Opioid receptors are synthesized in the DRG and transported centrally and peripherally to the nerve terminals. They belong to the family of G-protein-coupled receptors with 7 trans-membrane domains. Endorphins and locally administered opioids bind and activate the opioid receptors in the periphery. On activation, the receptors couple to inhibitory G-proteins (G_i/o) and inhibit cyclic AMP production and/or directly interact with K^+ , Ca^{2+} , and other ion channels in the membrane. Analgesia results from decreased nociceptor excitability, reduced action potential propagation, and decreased release of excitatory pro-inflammatory neuropeptides (substance P and calcitonin gene related peptide) at central and peripheral nerve terminals (21,26). Opioids injected locally into soft tissues or joints produce potent and receptor-specific analgesic effects that are mediated by peripheral opioid receptors, occur in the absence of central analgesic activity, and are naloxone reversible (34). Pain relief has been reported after knee arthroscopy on intra-articular injections of morphine (35-37) and after submucosal injection of morphine in patients undergoing dental surgery (38).

These and similar studies suggest a role for peripheral opioid receptors independent of centrally mediated analgesic activity (39).

The anti-nociceptive effects of opioids are markedly enhanced in the presence of inflammation and are mediated by peripheral opioid receptor-specific mechanisms (29,40,41). Although opioid receptor-mediated analgesia is enhanced, opioid receptor transcription in DRG is not enhanced in the early stages of inflammation (42). At later stages, however, the number of peripheral opioid receptors appears to increase and may enhance opioid efficacy. In animal studies, local administration of opiates into an inflamed paw produces dose-related, stereospecific analgesia restricted to the injected area (43). Peripheral analgesia mediated through the MOR has been demonstrated in a variety of clinical settings, with the preponderance of data generated with arthroscopic procedures. Morphine peripheral analgesia appears to depend on activation of the P13Kgamma/AKT/nNOS/NO/KATP signaling pathway (44). The MOR has also been shown to play a role in the control of gut inflammation (32 45). Schramm and Honda (46) showed that under normal conditions, δ -opioid receptor agonists enhance the effect of μ -opioid receptor agonists in the periphery, and local co-administration of δ - and μ -opioid receptor agonists may improve results of peripheral opioid therapy for the treatment of pain. A peripherally selective kappa agonist has been reported to be effective in relieving the pain associated with chronic pancreatitis (47). Furthermore, different regions of the body may exhibit different effects following the activation of peripheral opioid receptors. In the rat pain models of Sanchez et al (48), peripheral opioid receptors seem to participate in hypertonic saline (HS)-induced masseter pain, whereas only central opioid receptors reduced the nociception in the gastrocnemius and triceps. Their results suggest that the use of peripheral opioids may be more advantageous than central opioids for treatment of orofacial muscular pain (48).

OPIOID PEPTIDES AND INFLAMMATION

Inflammation not only increases expression, transport, and accumulation of peripheral opioid receptors on peripheral terminals of sensory nerves, but also triggers migration of opioid containing immunocytes (49). Immune cells containing opioid peptides migrate to the inflamed tissue and release endogenous opioid peptides that bind and activate peripheral opioid receptors to produce potent analgesic effect (49,50). The degree of endogenous pain inhibition is proportional to the

number of opioid-peptide producing cells.

Opioid peptide expressing leukocytes: Opioid peptide-containing leukocytes are T and B lymphocytes, granulocytes, and monocytes/macrophages (19). These leukocytes contribute to endogenous pain inhibition at different stages of inflammation. In early inflammation, granulocytes are the predominant opioid peptide-producing leukocytes, while in later stages opioid peptides are expressed mainly by monocytes or macrophages (51). Different types of opioid peptides are released from immune cells and include beta-endorphin (END), Met-enkephalin (ENK), and dynorphin-A (DYN), although the predominant opioid peptide involved in immune-cell mediated antinociception is thought to be END (52). These peptides are derived from distinct genes and respective precursors, i.e., pro-opiomelanocortin (POMC), pro-enkephalin, and pro-dynorphin (53). Leukocytes contain and process the precursors into functionally active opioid peptides. Studies have shown that both β endorphin and mRNA encoding its precursor pro-opiomelanocortin (POMC) are present in immune cells (14,53). Increased expression of POMC mRNA and β endorphin has been demonstrated in stimulated lymphocytes and lymphocytes of animals with inflammation (15). Labuz et al (54) showed that 30% to 40% of immune cells accumulating at injured nerves expressed opioid peptides such as beta-endorphin, Met-enkephalin, and dynorphin-A.

Recruitment of opioid peptide-containing immune cells: Opioid containing immunocytes migrate to inflamed tissue in a complex multistep process of recruitment, adhesion, and extravasation controlled by adhesion molecules that are up-regulated on vessel endothelia and co-expressed by opioid-containing immunocytes (19). The adhesion process consists of 3 main steps: tethering, triggering, and latching, and involves sequential interaction with separate classes of adhesion molecules (11,55). For instance, selectins mediate the rolling of leukocytes along the endothelial cell wall (56). Leukocytes are then activated by chemokines released from inflammatory cells and presented on the endothelium. Integrins and adhesion molecules mediate adhesion of leukocytes to endothelial cells and transmigration through the vessel wall into inflamed tissue (11,57). Neurokinins (e.g., substance P) contributes to leukocyte recruitment in inflammation by upregulating adhesion molecule expression through neurokinin-1 (NK1) receptors on endothelial cells; augmenting chemokine production; or chemotaxis through NK1 receptors on leukocytes

(58). Interference with the recruitment of opioid-containing immune cells into inflamed tissue by blockade of adhesion molecules or by intrathecal morphine injection reduces endogenous analgesia. For example, blocking selectins (cell surface glycoprotein) results in reduced numbers of β endorphin-containing cells, reduced quantity of β endorphin in inflamed tissues, and reduced stress and corticotrophin-releasing factor (CRF) induced peripheral analgesia (56,59). The migration of activated immune cells to inflamed tissues directed by chemokines and adhesion molecules may be hampered by treatment with anti-adhesion molecules and this may have implications in the treatment of pain in individuals with autoimmune disease on novel immunosuppressive drugs (11,19).

Secretion of opioid peptides by immunocytes: Infiltrating lymphocytes express, contain and release opioid peptides within inflamed tissues. Production of opioid peptides in immunocytes is inherently linked with activation of immune cells (13,14,56). Memory type T cells that contain opioids are present within inflamed tissues; naïve cells are not present in inflamed tissue and do not contain opioid peptides (14). Opioid peptide is released from the immune cells upon stimulation with CRF, noradrenaline (16), tumor necrosis factor alpha ($TNF\alpha$) (60), and interleukin 1beta (IL-1beta), and the corresponding receptors are present on opioid-expressing leukocytes (13,14,16,49,61,62). Multiple areas in the brain, inhibitory interneurons in the spinal cord dorsal horn, and immune cells in subcutaneous tissues, but not the peripheral sensory neurons, co-express CRF receptors and opioid peptides (63). Adrenergic α_1 , α_2 , and β_2 receptors are expressed on β -endorphin-containing inflammatory cells in close proximity to sympathetic nerve fibers in inflamed paws. The release of opioid peptides is calcium dependent and opioid receptor specific. Secretion requires intracellular calcium mobilization and activation of phosphoinositol-3-kinase and p38 mitogen activated kinase. The immune cells return to the local lymph node after opioid peptide is released and the cells are depleted of the peptide. Consistent with this model, systemic immunosuppression may lead to impaired endogenous analgesia as competent immune cells are essential to achieve release of endogenous opioid peptides within inflamed tissue. Complicating this further is the observation that exogenous opioids may impair immune cell function, although there is some evidence to suggest that endogenous opioid peptides do not share this immunosuppressive effect (62).

MODULATION OF PAIN AND INFLAMMATION

Tissue injury is associated with an inflammatory response, nociceptor activation, and pain. In early stages endogenous hyperalgesic mediators are produced, including cytokines, chemokines, nerve growth factor, bradykinin, prostaglandin, and ATP. Local inflammation also leads to simultaneous secretion of analgesic mediators such as opioid peptides, somatostatin, endocannabinoids, and certain cytokines. The immune system is a source of opioid peptides and plays an important role in control of inflammatory pain. Inflammatory pain can be effectively controlled by an interaction of opioid receptors on peripheral sensory nerve terminals with opioid peptides released from immune cells upon stressful stimuli. These mechanisms are based on the interaction between the immune and nervous systems. The initiation of pain and its control may be regarded as the body's response to prevent further injury, to support healing, and to return to normal function as quickly as possible.

Expression of peripheral opioid receptors: Peripheral inflammation upregulates opioid receptor mRNA (32,64); the synthesis of peripheral opioid receptors in DRG neurons and axonal transport is increased, and there is enhanced G-protein coupling at peripheral nerve terminals in the presence of tissue inflammation (65-67). The expression of receptors changes depending on receptor type and duration of inflammation. In case of MOR, there is an increase in both the number of neurons expressing MOR, and the number of MOR per neuron, while affinity of opioid agonists to MOR remains unchanged (67). The upregulation of sensory neuron MOR is governed by nerve growth factor (NGF) which is also implicated in inflammatory pain (68). In addition, the number of nociceptor nerve endings increase and the perineural barrier is disrupted, facilitating access of opioid agonists to their receptors, resulting in enhanced peripheral analgesic efficacy of opioids in inflammation (19,69). The effective number of peripheral opioid receptors does not increase during early stages of inflammation (42). At later stages, however, the number of peripheral MOR appears to increase and may enhance opioid efficacy (42,65).

Activation of peripheral opioid receptors: There appears to be an integral link between infiltrating immune cells and increased presence of opioid receptors on sensory nerves (14). Endogenous opioid peptides released from immune cells bind to opioid receptors on peripheral terminals of sensory nerves to evoke potent analgesic responses in animals with induced

inflammation (40,41). Inflammation-induced “activation” of the opioid receptors is of significance in the manifestation of peripheral opioid anti-nociception; in particular, receptor activation occurs in the early stages of inflammation when the infiltration of the tissue with immune-competent cells is just beginning (61). Machelska (70) showed that in early (within 6 hours) inflammation, leukocyte-derived beta-endorphin, Met-enkephalin, and dynorphin A activate peripheral mu-, delta- and kappa-receptors to inhibit nociception. In addition, central opioid mechanisms seem to contribute significantly to this effect. At later stages (4 days), antinociception is exclusively produced by leukocyte-derived beta-endorphin acting at peripheral mu- and delta- receptors (70). These findings indicate that peripheral opioid mechanisms of pain inhibition gain functional relevance and become more prevalent with duration and severity of inflammation (19). Corticotropin-releasing hormone (CRH) is an endogenous trigger of these effects at both stages. In a mouse model of neuropathy, selective stimulation of immune cells by local application of CRF led to opioid peptide mediated activation of opioid receptors in damaged nerves, and abolition of tactile allodynia suggesting that selective targeting of opioid-containing immune cells promotes endogenous pain control and offers novel opportunities for treating painful neuropathy (54). A study in a rat model showed that the majority of the C and C/A delta nociceptors innervating inflamed skin were opiate sensitive, and their excitability was attenuated by direct application of morphine to their receptive fields, lending support to the evidence that topical morphine acts through peripheral opioid receptors to inhibit activity of cutaneous nociceptors in inflamed tissues (29).

Inflammation and perineural barrier: The perineurium is a crucial determinant for peripheral opioid analgesia and is impervious in the absence of inflammation. Inflammation increases the permeability of the perineurium, thereby exposing the receptors at the sensory nerve terminals to endogenous and exogenous opioids. Peripheral opioid antinociception and perineural leakage occur simultaneously at a very early stage (within 12 hours) of the inflammatory reaction. Evidence supports the observation that the efficacy of locally applied hydrophilic or lipophilic neuromodulatory compounds can be improved dramatically by the concomitant modulation of perineural permeability (69).

Effect of central afferent blockade on peripheral endogenous analgesia: Central inhibition of pain de-

creases the efficacy of peripheral endogenous opioid analgesia. This was demonstrated by an experimental study in rats, where continuous intrathecal morphine infusion increased paw pressure threshold (indicating antinociception) without changing inflammation. The number of beta-endorphin-containing cells and cold water swim-stress induced endogenous analgesia were significantly reduced in intrathecal morphine-treated rats compared with controls suggesting interplay of central and peripheral mechanisms of pain control. An effective central inhibition of pain apparently signals a reduced need for recruitment of opioid containing immune cells to the injured site (71).

PERIPHERALLY ACTING OPIOIDS

Although currently there are no specific peripherally acting opioids available in the United States, investigators continue to work on developing novel potential agents. The novel D-amino acid tetrapeptide CR665, when injected intravenously in nanomolar range, elicited potent analgesia in the mouse writhing test without producing motor impairment (72). The peripherally restricted kappa-agonist FE200665, also known as CR665, has completed Phase I clinical trials and currently in Phase II (73). Arendt-Nielsen et al (74) compared the analgesic efficacy of the peripheral kappa-opioid receptor agonist CR665 to oxycodone in a multi-modal, multi-tissue experimental human pain model. CR665 had a selective effect on visceral pain. Oxycodone exhibited a generalized effect, elevating thresholds for cutaneous, deep somatic, and visceral pain stimulation (74).

6-amino acid-substituted derivatives of 14-O-methyloxymorphone were described as MOR agonists with restricted penetration to the central nervous system (75,76). Obara et al (77) assessed the antinociceptive effects of the 6-amino acid conjugates (glycine and phenylalanine), α - or β -orientated, 14-O-methyloxymorphone in rat models of inflammatory pain (induced by local intraplantar (IPL) formalin injection and neuropathic pain (produced by ligation of the sciatic nerve) after local IPL administration directly into the injured hindpaw and compared their antinociceptive effects to morphine. Local IPL administration of the new derivatives in rats with neuropathic pain induced by sciatic nerve ligation produced anti-allodynic and anti-hyperalgesic effects; however, the anti-nociceptive activity was lower than that observed in inflammatory pain (77). Moreover, the local opioid antinociceptive effects were significantly attenuated by naloxone methiodide,

a peripherally acting opioid receptor antagonist, demonstrating that the effect was mediated by peripheral opioid receptors (77). Obara et al (77) suggested their data indicate that the peripherally restricted 6-amino acid conjugates of 14-O-methyloxymorphone elicit anti-nociception after local administration, being more potent in inflammatory than in neuropathic pain.

Synthesis and opioid activity of fentanyl analogues including N-[1-phenylpyrazol-3-yl]-N-[1-(2-phenethyl)-4-piperidyl] propenamide (IQMF-4), showed an interesting anti-nociceptive activity. Intraperitoneally (IP) administered, it was as effective as fentanyl or morphine, being less potent than fentanyl, but more so than morphine (78). When IQMF-4 was administered IP, naloxone methiodide, a peripherally acting antagonist, was able to completely block its antinociceptive effect, whereas, after intracerebroventricular (i.c.v.) administration, the blockade was only partial. Although more assays are required, these results suggest that IQMF-4 appears to be a potent analgesic compound with an interesting peripheral component, with a reduced ability to induce dependence (78).

CLINICAL IMPLICATIONS

The inflammation-induced activation of opioid production and the release of endogenous opioids from immune cells may lead to novel approaches for the development of peripherally acting analgesics. In an animal model of inflamed knee joint, intra-articular injection of mu- and kappa- but not delta- opioid agonists, produced a dose dependent blockade of autonomic response to a noxious stimulus indicating that opioids, by an action at μ and κ receptors, can exert a direct anti-hyperalgesic action at the terminals of primary afferents projecting to a region of inflammation (34). A double blind, crossover study showed that morphine-6-beta-glucuronide (M6G) in doses that lack CNS effects, exerts anti-hyperalgesic effects in inflammatory pain through activation of peripheral opioid receptors. Since this occurs at concentrations that do not cause central opioid effects, M6G might be useful as a peripheral opioid analgesic (39). These observations offer strong support for a peripheral action of opioids in inflammation-induced hyperalgesia/pain. Opioid agonists have powerful anti-inflammatory properties and they exert their action in the periphery via opioid receptors found on immune cells and neural cells. The close spatial and functional association between nerves and immune cells suggests that modulation of neuro-immune interactions or neural pro-inflammatory path-

ways may contribute to the anti-inflammatory effect of these drugs. However the hypothalamic-pituitary-adrenal axis, a major point of neuro-immune convergence, is only partially involved in the anti-inflammatory actions of opioids.

Painful skin conditions: A topical route of analgesia might be extremely beneficial for children with painful skin lesions, including burns or post-surgical wounds, especially where acute inflammatory pain is a major symptom and effective analgesia is a major clinical problem. Topical morphine gel in 2 children with epidermolysis bullosa provided rapid reduction in pain scores without any reported adverse effects or tolerance. More studies are required to study the utility of peripheral opioid analgesia in children (79).

Neuropathic pain: Local application of mu-, delta- and kappa-opioid agonists produced anti-allodynic and anti-hyperalgesic effects in a dose dependent manner in animal models of neuropathic pain. The effective dose (ED) range of mu- and kappa-agonists required to induce analgesia in neuropathy was much higher than the ED for inflammation (50); delta-agonists were effective in the same dose range in both pain models supporting the use of opioid peptides, especially delta-agonists in treating chronic pain. These effects were mediated by peripheral opioid receptors localized at the site of tissue/nerve injury (80).

Inflammatory arthropathy: Kappa-opioids have a powerful anti-inflammatory effect and have been shown to attenuate arthritis in a dose dependent, stereoselective, antagonist-reversible manner, reducing disease severity by as much as 80% (27). Mu- and delta- opioid agonists, on the other hand, have therapeutic anti-inflammatory activity at near toxic doses. Kappa-opioids act at multiple sites in the inflammatory cascade, and exert their anti-inflammatory actions by reducing expression of the adhesion molecule, inhibiting cell trafficking, reducing release and expression of tumor necrosis factor (TNF), and altering expression of mRNA and levels of SP and CGRP protein in joint tissue (27). Neuropeptides (SP and CGRP) have been shown to play a role in the pathogenesis and maintenance of experimental arthritis and are strongly implicated in inflammation and arthritis. These neuropeptides are released at afferent nerve terminals in the synovial tissues. Kappa-opioids are therapeutic during disease onset and most likely alter cellular activation and cytokine expression. Kappa opioids have increased potency in females compared to males, which may be an advantage in the treatment of inflammatory arthritis. Peripherally

acting kappa opioids may prove to be a potent new treatment for rheumatoid arthritis and other inflammatory arthritis.

Inflammatory bowel disease: MOR have been shown to play a role in control of gut inflammation and MOR agonists may become novel treatments for inflammatory bowel disease (IBD). Subcutaneous administration of selective MOR agonists, such as DALDA and [D-Ala²,NMe-Phe⁴,Gly⁵-ol]enkephalin (DAMGO), significantly reduced inflammation in 2 experimental models of colitis in mice. The anti-inflammatory effect was completely abolished by naloxone. The mechanism underlying the anti-inflammatory effect of MOR in the colon is suggested to be mediated through regulation of cytokine production and T cell proliferation, both of which play a role in the development of colon inflammation in IBD in humans and mice (45).

SUMMARY

Experimental and clinical research has demonstrated that opioids can produce potent and receptor specific analgesic effects outside the central nervous system. Peripheral analgesia mediated through opioid receptors has been demonstrated in a variety of clinical settings. Receptor localization studies using human tissue have corroborated the presence of opioid receptors in the periphery and their endogenous ligands, opioid peptides, have been discovered in immune cells within inflamed tissue. Experimental and clinical research has shown that under conditions of inflammation, onset of peripherally mediated opioid analgesia is delayed, but once initiated, is of long duration. These findings open up the possibility of developing an entirely novel generation of peripherally active opioid analgesics that will selectively block pro-algesic mediators, or enhance the transport and release of immune-derived opioid peptides into injured tissue and stimulate the endogenous peripheral analgesic system to induce effective peripheral analgesia without central side effects. Clinical trials

with peripherally restricted mu, delta, and kappa agonists will be needed in the future to evaluate utility in neuropathic pain, cancer pain, and inflammatory painful disorders of gut, skin, etc. Finally, the mechanisms of endogenous pain inhibition by opioid peptide-producing immune cells may be important for understanding pain in immune compromised states such as cancer, diabetes, and acquired immunodeficiency syndrome (AIDS).

DISCLOSURES

Author Contributions: Dr. Sehgal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Sehgal, Smith and Manchikanti designed the study protocol. Dr. Sehgal managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All other authors provided revision for intellectual content and final approval of the manuscript.

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