MÆDICA - a Journal of Clinical Medicine

REVIEW

MAEDICA – a Journal of Clinical Medicine
2025; 20(1): 72-80
https://doi.org/10.26574/maedica.2025.20.1.72

Peripheral Opioid Receptors in the Modulation of Inflammatory Pain: a Narrative Review

Nader-Mugurel JAFAL[a, b], Smaranda STOLERU[a], Carmen ORBAN[a, b], Ion-Gigel FULGA[a]

[a]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[b]Department of Anesthesia and Intensive Care, University Emergency Hospital, Bucharest, Romania

ABSTRACT

Opioid receptors are key modulators of pain, with both central and peripheral subtypes contributing to analgesia. While central opioid receptors have been extensively studied, peripheral opioid receptors, located on sensory nerve terminals and immune cells, have gained attention for their ability to provide localized analgesia and anti-inflammatory effects without central side effects such as respiratory depression and sedation. This narrative review explores the classification, localization, and activation of peripheral opioid receptors, emphasizing their role in inflammatory pain modulation. These receptors are upregulated in inflamed tissues, enhancing analgesic efficacy. Their activation modulates nociceptive signaling through inhibition of excitatory neurotransmitter release, potassium channel activation, and immune regulation. Peripherally acting opioid receptor agonists offer targeted pain relief, while selective antagonists mitigate opioid-induced constipation without affecting central analgesia. Preclinical studies, including carrageenan-induced inflammation models, have reinforced the potential of peripheral opioid receptor targeting in pain therapy. Future research should focus on optimizing these agents for clinical use, improving drug delivery systems, and integrating them into multimodal pain management strategies.

Keywords: peripheral opioid receptors, inflammatory pain, analgesia, opioid modulation.

INTRODUCTION

Opioid receptors and their central actions have been extensively studied over the decades, being recognized as fundamental pillars in the regulation of pain, well-being and other essential functions of the central nervous system. This extensive research has unveiled the complex mechanisms by which opioid receptors, through interactions with endogenous peptides and exogenous substances, influence not only pain perception but also important aspects related to euphoria, addiction and alterations in respiratory functions. In the current context of developing analgesic therapies and efforts to reduce the adverse effects of opioid treatments, a thorough understanding of these receptors and their associated signaling represents a major area of interest for both neuroscientists

Address for correspondence:
Smaranda Stoleru
Email: smaranda.stoleru@umfcd.ro

Article received on the 3rd of February 2025 and accepted for publication on the 24th of February 2025

and clinicians (1). It is important to note that opioid receptors are not limited to the central nervous system but are also present in the peripheral system. This dual presence opens up new perspectives in pain modulation and other physiological functions, allowing for the development of analgesic therapies that specifically target peripheral receptors (2). Thus, activation of opioid receptors located on sensory nerve terminals and immune cells can help alleviate pain and reduce inflammation in affected areas, while simultaneously minimizing the adverse effects associated with central receptor activation, such as sedation and respiratory depression. This approach represents a major area of interest in modern research, with the potential to offer safer and better-tolerated therapeutic solutions (3). Peripheral opioid receptors have gained increasing attention in clinical practice due to their potential to provide analgesia and anti-inflammatory effects without causing most of the adverse effects associated with central receptor activation, such as profound sedation, respiratory depression, or dependency (4). The practical applicability in medicine is evident in the development of peripheral analgesics that selectively target these receptors, thereby facilitating the treatment of local pain and inflammation in patients with chronic conditions or postoperative pain. Such approaches allow the administration of drugs that remain confined to the peripheral system, reducing the risk of undesired systemic effects and offering a safer alternative for vulnerable patients or those requiring long-term treatment (5). Additionally, recent research suggests that activation of opioid receptors on immune cells and peripheral nerve terminals can not only alleviate symptoms but also positively modulate inflammatory responses, opening new perspectives for the treatment of inflammatory diseases. In conclusion, therapeutic strategies that exploit peripheral opioid receptors represent a major area of interest, with the potential to transform the management of pain and inflammation by providing effective treatment options with an improved safety profile (6).

Classification of opioids

Opioids represent one of the most longstanding and efficacious classes of pharmacological agents for the management of severe pain. Their clinical utilization dates back to 1806, when morphine was first isolated from the opium poppy (*Papaver somniferum*), marking a pivotal advancement in analgesic therapy. This progress was further facilitated by the advent of hypodermic needles in 1853, enabling more precise and effective administration (7).

Opioids can be broadly categorized into two principal groups: endogenous and exogenous compounds. Endogenous opioids, including enkephalins, endorphins, endomorphins, dynorphins and nociceptin/orphanin FQ, are naturally occurring peptides that bind to opioid receptors, playing a crucial role in the modulation of pain perception, reward mechanisms and various homeostatic processes. In contrast, exogenous opioids – such as morphine, heroin and fentanyl – are externally administered substances that exert their effects by interacting with the same receptor systems as their endogenous counterparts, thereby producing potent analgesic and psychoactive effects (8).

Opioids can be further classified based on the specific receptor subtypes through which they exert their pharmacological effects (9). Opioid receptors belong to the G-protein-coupled receptor (GPCR) superfamily and are categorized into three principal subtypes: mu (MOR), delta (DOR) and kappa (KOR) (10). The nomenclature of these receptors is historically derived from their initial ligand interactions: the mu receptor was named for its high affinity for morphine, the most well-characterized exogenous opioid ligand; the delta receptor was identified in the vas deferens, from which it derives its name; and the kappa receptor was so designated based on its binding affinity for ketocyclazocine, the first ligand recognized for this subtype (11). Opioid receptors are widely distributed throughout the central nervous system (CNS), where they play a pivotal role in modulating pain perception, emotional processing, and autonomic regulation. Within the brain, these receptors are prominently expressed in the limbic system, particularly in regions such as the amygdala and hippocampus, where they contribute to emotional regulation and reward mechanisms (12). Additionally, opioid receptors in the cerebral cortex and thalamus are integral to the modulation of sensory information, particularly nociceptive processing. In the spinal cord, they are highly concentrated in the dorsal horn, where they mediate analgesic effects by inhibiting the

transmission of nociceptive signals to higher-order brain centers. Beyond pain modulation, opioid receptors in the brainstem, particularly within the periaqueductal gray (PAG) region, play a critical role in descending pain inhibition pathways and the coordination of autonomic functions, including respiratory and cardiovascular regulation. Furthermore, opioid receptors are also expressed in peripheral tissues, where they contribute to inflammatory responses and modulate nociceptive signaling at the site of injury. The widespread distribution and functional diversity of opioid receptors underscore their significance in both physiological and pathophysiological processes, making them key targets for therapeutic intervention in pain management and other neurological disorders (13).

Localization and activation of peripheral opioid receptors

In addition to the well-characterized central opioid receptors, peripheral opioid receptors play a critical role in modulating pain and inflammatory responses outside the central nervous system (CNS). These receptors are widely distributed across various peripheral tissues, including immune cells, the gastrointestinal (GI) tract, and peripheral nerve terminals, where they contribute to diverse physiological and pathophysiological processes.

In immune cells, opioid receptors are involved in immunomodulation, influencing cytokine release and inflammatory signaling pathways. They have been implicated in the endogenous regulation of inflammation, with certain immune cells – such as macrophages and T lymphocytes – being capable of synthesizing and releasing endogenous opioid peptides (*e.g.*, enkephalins, endorphins, and dynorphins) in response to tissue injury. This localized opioid-mediated analgesia is particularly relevant in inflammatory conditions, where opioid peptides act on peripheral receptors to attenuate pain without engaging central mechanisms, thereby reducing the risk of central opioid-related side effects, such as sedation and respiratory depression (14). Within the gastrointestinal tract, opioid receptors are densely expressed in the enteric nervous system, where they regulate motility, secretion and visceral nociception. Activation of peripheral opioid receptors in the gut, particularly the mu-opioid receptor (MOR), is associated with decreased peristalsis and increased fluid absorption, which underlies the constipating effects commonly observed with opioid therapy. This has clinical implications in both pain management and the treatment of conditions such as diarrhea-predominant irritable bowel syndrome (IBS), where peripheral opioid receptor agonists can provide therapeutic benefit (15). At peripheral nerve terminals, opioid receptors modulate nociceptive signaling by inhibiting the excitability of sensory neurons. In the setting of inflammation or nerve injury, the expression and functional sensitivity of these receptors can be upregulated, enhancing the analgesic effects of both endogenous and exogenous opioids. This upregulation has been a focus of research in the development of peripherally acting opioid analgesics, which aim to maximize pain relief while minimizing central opioid-associated adverse effects (16). The presence and functional relevance of peripheral opioid receptors highlight their potential as therapeutic targets for pain management, inflammation and gastrointestinal disorders. Their selective activation represents a promising avenue for the development of novel analgesic strategies that circumvent the limitations associated with central opioid receptor activation (17). Peripheral opioid receptors are predominantly localized in sensory neurons, dorsal root ganglia and peripheral tissues affected by inflammation or injury. Under physiological conditions, their activity remains relatively low; however, in response to inflammatory processes or tissue damage, a series of adaptive mechanisms enhance their function (18). First, the expression of opioid receptors is upregulated in both sensory neurons and immune cells, increasing their availability for ligand binding. Additionally, leukocytes infiltrating inflamed tissues release endogenous opioid peptides – including endorphins, enkephalins and dynorphins – which contribute to local pain modulation. Furthermore, enhanced vascular permeability facilitates the diffusion of opioid peptides to nociceptive fibers, thereby augmenting their analgesic efficacy (19). Collectively, these mechanisms enable a localized, peripheral analgesic effect independent of central nervous system involvement, providing an effective strategy for pain relief while mitigating opioid-related systemic side effects (20).

Peripheral opioid receptor stimulation induces analgesic effects, contributing to inflammation reduction and constipation. Peripheral mu receptors primarily mediate analgesia and constipation, playing a significant role in reducing inflammation. Peripheral delta receptors are involved in analgesic mechanisms and contribute to constipation, while peripheral kappa receptors induce analgesia and exert an anti-inflammatory effect (21). Specific agonist ligands for peripheral opioid receptors, such as loperamide (for mu), UK-321,130 (for delta), or asimadoline (for kappa), can be used to control pain and inflammation without causing unwanted systemic effects, such as respiratory depression or euphoria. Antagonists like alvimopan or methylnaltrexone are used to counteract constipation-related adverse effects without affecting central analgesia (22).

In recent years, interest in peripheral opioid receptors has significantly increased, driven by efforts to find alternatives to classical opioids that provide effective analgesia without the well-known risks of respiratory depression, excessive sedation and dependence. Agonists and antagonists of these receptors represent promising directions in modern analgesia research, each with distinct mechanisms and therapeutic applications. Peripheral opioid receptor agonists selectively activate these receptors which are located outside the central nervous system, modulating pain and inflammation without interfering with cognitive functions or respiration. The most well-known example is loperamide, a selective MOR agonist, which has been used for decades as an effective treatment for diarrhea due to its ability to slow intestinal transit. Although it is an opioid, loperamide does not cross the blood-brain barrier under normal conditions, thus avoiding central effects (23). Beyond its role in treating diarrhea, peripheral opioid receptors have become important targets for pain management. One example is difelikefalin, a selective κ-opioid receptor (KOR) agonist investigated for the treatment of severe pruritus in patients with chronic kidney disease, as well as for postoperative analgesia (24). Unlike classical opioids that primarily act on μ-receptors in the central nervous system, KOR activation at the peripheral level appears to reduce pain without inducing euphoria or dependence (25). Another promising agonist is asimadoline, a peripheral κ-opioid receptor modulator that has shown efficacy in reducing visceral pain in patients with irritable bowel syndrome. Clinical studies have demonstrated that this class of compounds can benefit patients with painful gastrointestinal conditions without causing sedation or respiratory depression. While peripheral agonism can provide significant benefits in pain management, another important strategy is the selective blockade of opioid receptors in peripheral tissues to counteract the side effects of systemic opioids (26). Although opioids are among the most effective analgesic drugs, their use is often limited by side effects, particularly severe constipation caused by μ-opioid receptor activation in the gastrointestinal tract. In this context, peripherally acting opioid receptor antagonists have been developed to selectively block opioid effects at the intestinal level without interfering with central analgesia. One notable example is methylnaltrexone, a modified derivative of naltrexone that does not cross the blood-brain barrier. Administered to patients with opioid-induced constipation, methylnaltrexone restores normal bowel function without compromising pain relief (27). A similar mechanism is employed by alvimopan, a competitive μ-opioid receptor antagonist approved for the prevention of postoperative ileus, a common complication in abdominal surgery patients receiving opioids (28). More recently, naloxegol, a PEGylated form of naloxone, has emerged as an effective option for patients with chronic opioid-induced constipation. Due to its molecular properties, naloxegol acts exclusively in the intestines, offering a balance between the benefits of systemic opioids and the reduction of their unwanted side effects (29).

Intracellular mechanisms of peripheral opioid receptor-mediated analgesia

Upon activation, peripheral opioid receptors (PORs) initiate G-protein-mediated intracellular signaling cascades that effectively inhibit pain transmission at multiple levels of the peripheral nervous system. These mechanisms contribute to both direct neuronal inhibition and modulation of the inflammatory response, ultimately leading to reduced nociceptive signaling and pain perception (30). The binding of opioids to PORs on nociceptive afferent terminals leads to the inhibition of voltage-gated calcium (Ca^{2+}) channels, preventing calcium influx. This process

attenuates the release of key excitatory neurotransmitters, including glutamate and substance P, which are essential for nociceptive transmission. As a result, the propagation of pain signals from peripheral terminals to the central nervous system is significantly diminished (31). Opioid receptor activation also enhances potassium (K^+) channel conductance, leading to membrane hyperpolarization in postsynaptic neurons. This reduction in neuronal excitability lowers the likelihood of action potential generation, further suppressing pain signal transmission along peripheral nociceptive pathways (32). Beyond their direct effects on neuronal excitability, PORs exert potent anti-inflammatory actions by modulating immune cell activity. Opioid receptor activation in monocytes, macrophages, and lymphocytes leads to the suppression of pro-inflammatory mediator release, including prostaglandins, bradykinin and cytokines. This immunomodulatory effect not only attenuates peripheral sensitization but also prevents the amplification of pain signals in inflamed tissues (33).

The role of peripheral opioid receptors in inflammatory pain

Inflammation is a fundamental biological response of the immune system to harmful stimuli, including pathogens, cellular damage and irritants. Its primary function is to eliminate the underlying cause of injury, remove necrotic cells and initiate tissue repair. Based on its duration and pathological characteristics, inflammation is classified into acute and chronic forms (34). Acute inflammation is a rapid and self-limiting response characterized by vasodilation, increased vascular permeability and leukocyte infiltration, predominantly neutrophils. It serves as an immediate protective mechanism and typically resolves once the injurious agent is eliminated (34). In contrast, chronic inflammation persists over extended periods and is associated with sustained immune activation, macrophage and lymphocyte infiltration and progressive tissue remodeling or fibrosis. This prolonged inflammatory state can result from persistent infections, autoimmune disorders, or continuous exposure to harmful stimuli. While inflammation is essential for host defense and tissue homeostasis, its dysregulation is implicated in the pathogenesis of numerous chronic diseases, including rheumatoid arthritis, inflammatory bowel disease and atherosclerosis (35).

During inflammation, immune cells such as macrophages, lymphocytes and neutrophils upregulate the synthesis and release of opioid peptides, including endorphins, enkephalins and dynorphins. These endogenous opioids act on PORs located on primary afferent neurons, leading to localized analgesia. This mechanism allows for the control of inflammatory pain at the site of injury, effectively bypassing the central nervous system (36). Although traditionally considered resistant to opioids, neuropathic pain may be modulated by PORs, particularly when inflammation contributes to nerve injury. Emerging research suggests that targeted activation of PORs could provide relief in neuropathic conditions without significant central opioid side effects (37). Peripheral opioid receptors are also involved in postoperative and visceral pain modulation. Opioid agonists applied directly to surgical wounds or the peritoneal cavity can achieve effective analgesia by targeting PORs, minimizing systemic opioid exposure and reducing side effects (38, 39). Peripheral opioid receptors are not only involved in pain modulation but also in immune regulation. Opioid peptides influence cytokine release and immune cell function, contributing to both pro- and anti-inflammatory effects. This bidirectional relationship between POR activation and immune response suggests a potential role for opioids in inflammatory disease management (40). Endogenous opioid peptides, such as endorphins and enkephalins, interact with immune cells, leading to the suppression of pro-inflammatory cytokines (*e.g.*, IL-1β, TNF-α) and the promotion of anti-inflammatory mediators (*e.g.*, IL-10) (41). Activation of PORs modulates the activity of macrophages, T-cells, and dendritic cells, reducing excessive immune activation while preserving essential immune defense mechanisms (42).

Peripheral opioid analgesia is significantly enhanced under conditions of tissue injury, such as inflammation, neuropathy, or bone damage. One key mechanism involves an increased expression of peripheral opioid receptors. In neuronal cell cultures, MOR transcription is upregulated by interleukin-4 (IL-4) *via* STAT-6 transcription factor binding to the MOR gene promoter. Additionally, activator protein-1 (AP-1) plays a role in regulating this promoter (43). In dorsal root gan-

glia, peripheral tissue inflammation induces the synthesis and expression of opioid receptors, leading to an increased axonal transport of these receptors toward peripheral nerve terminals. This process is facilitated by IL-1β and enhances agonist efficacy. Moreover, the inflammatory microenvironment, characterized by low pH and increased prostanoid release, further augments opioid receptor activation by enhancing G-protein coupling and elevating cyclic adenosine monophosphate (cAMP) levels in neurons (44). Inflammation also contributes to nerve terminal sprouting and disrupts the perineural barrier, facilitating opioid agonist access to their receptors. Clinical studies suggest that perineural application of opioid agonists along uninjured nerves (such as the axillary plexus, interpleural, intercostal and mandibular nerves) does not consistently result in analgesia. This supports the hypothesis that inflammation is essential for opioid receptor accessibility and efficient coupling in primary afferent neurons. Furthermore, the release of endogenous opioid ligands within inflamed tissues may result in additive or synergistic effects, enhancing pain relief at peripheral opioid receptors (45).

In recent years, numerous studies have investigated the role of peripheral opioid receptors in inflammation-induced pain using carrageenan-induced inflammation models in animals. Carrageenan, a sulfated polysaccharide derived from red seaweed, is widely employed to induce acute inflammatory responses in rodents, serving as a well-established model for human inflammatory pain conditions (46). The injection of carrageenan triggers a localized inflammatory cascade, characterized by edema, leukocyte infiltration and the release of pro-inflammatory mediators such as prostaglandins, bradykinin and cytokines.

Recent research has demonstrated that carrageenan-induced inflammation leads to an upregulation of peripheral opioid receptors, particularly mu-opioid receptors (MORs), in inflamed tissues. This receptor upregulation enhances the analgesic efficacy of both endogenous opioid peptides and exogenous opioid agonists, facilitating localized pain relief while minimizing systemic opioid-related adverse effects (47). Studies have shown that carrageenan-induced inflammation increases MOR binding affinity and G-protein coupling in dorsal root ganglia neurons, thereby amplifying the analgesic response to MOR agonists. Furthermore, peripheral inflammation differentially regulates the expression of opioid receptors in sensory neurons, contributing to improved peripherally mediated opioid analgesia during inflammatory conditions (48).

Recent animal model research supports the local anti-inflammatory and analgesic effects of opioid receptor activation. In a carrageenan-induced inflammation model, intraplantar morphine reduced paw edema), while intraperitoneal morphine had no effect, suggesting a peripheral mechanism (49). Additional studies, including our previously published research, indicate that intraplantar morphine provides significant analgesia, with the strongest effects observed at three hours post-carrageenan administration coinciding with peak inflammatory mediator release (50).

Beyond pain modulation, the carrageenan-induced inflammation model provides valuable insights into the interplay between inflammation and opioid receptor function. Understanding the mechanisms underlying opioid receptor upregulation in inflamed tissues may pave the way for the development of novel peripheral opioid therapeutics that maximize analgesia while mitigating central opioid-related risks such as respiratory depression and dependence (51). This improved understanding of opioid receptor modulation in inflamed tissues is particularly relevant in the context of tissue injury, where peripheral opioid analgesia is significantly influenced by inflammatory and neuropathic processes. Tissue injury triggers a cascade of molecular and cellular events that further modulate opioid receptor expression and function, making it a key area of study in pain management research.

Peripheral opioids provide effective analgesia while minimizing central opioid-related side effects, making them valuable in postoperative pain management and chronic inflammatory conditions. Their targeted action reduces sedation, respiratory depression and dependency risks, enhancing safety. Compared to classical opioids, peripherally acting agents offer a more localized effect, reducing systemic exposure and the associated risks of cognitive impairment and respiratory suppression. In postoperative pain management, these agents can be used to con-

trol localized surgical pain while avoiding the central adverse effects of traditional opioids. Similarly, in chronic inflammatory pain, peripheral opioid agonists may provide sustained relief by acting at the site of inflammation without contributing to opioid dependence. However, prolonged opioid exposure, even at the peripheral level, has been associated with opioid-induced hyperalgesia, which may paradoxically increase pain sensitivity over time. Further research is needed to optimize their use, establish standardized clinical protocols and evaluate their long-term efficacy relative to conventional opioid treatments (52). Despite their benefits, peripheral opioids may interact with other analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetics, potentially altering efficacy. Additionally, their prolonged use requires careful monitoring to ensure safe clinical application and to develop strategies that maximize analgesic benefits while minimizing potential risks, including opioid-induced hyperalgesia (53). ❑

CONCLUSIONS

The study of opioid receptors, particularly their peripheral counterparts, has significantly expanded our understanding of pain modulation and inflammatory processes. While central opioid receptors remain crucial targets for analgesia, the increasing recognition of peripheral opioid receptors has paved the way for novel therapeutic strategies that mitigate the adverse effects associated with systemic opioid use, such as respiratory depression, sedation and dependence. The ability of peripheral opioid receptor agonists to provide localized pain relief while reducing systemic exposure holds great promise for the management of chronic pain, postoperative pain and inflammatory conditions.

Recent research has highlighted the dynamic regulation of peripheral opioid receptors in inflamed and injured tissues, demonstrating their upregulation in response to inflammatory mediators. This has provided valuable insights into their role in nociceptive processing, immune modulation and tissue repair. The development of peripherally acting opioid analgesics and antagonists has further refined pain management by addressing common opioid-related complications, such as opioid-induced constipation, without compromising analgesic efficacy.

Looking forward, continued exploration of opioid receptor signaling pathways and their interaction with inflammatory processes will be critical for developing safer and more effective opioid-based treatments. Advances in biotechnology and drug delivery systems may enable the design of targeted opioid therapies that selectively activate peripheral receptors, maximizing analgesic benefits while minimizing central side effects. Additionally, combination therapies involving opioid receptor modulators and non-opioid analgesics may offer a multimodal approach to pain relief, further enhancing patient safety and treatment outcomes.

As the opioid crisis continues to challenge healthcare systems worldwide, the refinement of opioid pharmacology through peripheral receptor targeting represents a crucial step toward safer and more sustainable pain management strategies. Future research should focus on translating these findings into clinical applications, optimizing dosage regimens, and exploring individualized patient responses to peripheral opioid therapy. By leveraging these advancements, the field of pain medicine can move toward a new era of opioid analgesia – one that prioritizes both efficacy and safety. ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. **David G. Lambert.** Opioids and opioid receptors; understanding pharmacological mechanisms as a key to therapeutic advances and mitigation of the misuse crisis. *BJA Open* 2023;6:100141. https://doi.org/10.1016/j.bjao.2023.100141.
2. **Li JX, Zhang Y.** Emerging drug targets for pain treatment. *Eur J Pharmacol* 2012;681:1-5. doi: 10.1016/j.ejphar.2012.01.017.
3. **Stein C.** Effects of pH on opioid receptor activation and implications for drug design. *Biophys* J 2024;123:4158-4166. doi: 10.1016/j.bpj.2024.07.007.
4. **Iwaszkiewicz KS, Schneider JJ, Hua S.** Targeting peripheral opioid receptors to promote analgesic and anti-inflammatory

actions.
Front Pharmacol 2013;4:132.
doi: 10.3389/fphar.2013.00132.

5. **Sehgal N, Smith HS, Manchikanti L.** Peripherally acting opioids and clinical implications for pain control.
Pain Physician 2011;14:249-258.
6. **Cunha TM, Roman-Campos D, Lotufo CM, et al.** Morphine peripheral analgesia depends on activation of the PI3Kgamma/AKT/nNOS/NO/KATP signaling pathway.
Proc Natl Acad Sci USA 2010;107:4442-4447.
https://doi.org/10.1073/pnas.0914733107.
7. **Toubia T, Khalife T.** The Endogenous Opioid System: Role and Dysfunction Caused by Opioid Therapy.
Clin Obstet Gynecol 2019;62:3-10.
doi: 10.1097/GRF.0000000000000409.
8. **Pathan H, Williams J.** Basic opioid pharmacology: an update.
Br J Pain 2012;6:11-6.
doi: 10.1177/2049463712438493.
9. **Dhawan BN, Cesselin F, Raghubir R, et al.** International Union of Pharmacology. XII. Classification of opioid receptors.
Pharmacol Rev 1996;48:567-592.
10. **Dietis N, Rowbotham DJ, Lambert DG.** Opioid receptor subtypes: fact or artifact?
Br J Anaesth 2011;107:8-18.
doi: 10.1093/bja/aer115.
11. **Kieffer BL, Evans CJ.** Opioid receptors: from binding sites to visible molecules *in vivo*.
Neuropharmacology 2009;56 Suppl 1(Suppl 1):205-212.
doi: 10.1016/j.neuropharm.2008.07.033.
12. **Fields HL.** How expectations influence pain.
Pain 2018;159 Suppl 1:S3-S10.
doi: 10.1097/j.pain.0000000000001272.
13. **Al-Hasani R, Bruchas MR.** Molecular mechanisms of opioid receptor-dependent signaling and behavior.
Anesthesiology 2011;115:1363-1381.
doi: 10.1097/ALN.0b013e318238bba6.
14. **Machelska H, Celik MÖ.** Opioid Receptors in Immune and Glial Cells—Implications for pain control.
Front Immunol 2020;11:300.
https://doi.org/10.3389/fimmu.2020.00300.
15. **Sobczak M, Sałaga M, Storr MA, Fichna J.** Physiology, signaling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future perspectives.
J Gastroenterol 2014;49:24-45.
doi: 10.1007/s00535-013-0753-x.
16. **Stein C.** Opioid Receptors on Peripheral Sensory Neurons. In: Madame Curie Bioscience Database (Internet).
Austin (TX): Landes Bioscience; 2000-2013.
17. **Machelska H.** Functional Evidence of Pain Control by the Immune System. In: *Madame Curie Bioscience Database* [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6447/
18. **Stein C, Machelska H, Schäfer M.** Peripheral analgesic and antiinflammatory effects of opioids.
Z Rheumatol 2001;60:416-424.
doi: 10.1007/s003930170004.
19. **Stein C, et al.** No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia.
J Clin Invest 1996;98:793-799.
20. **Zhou L, Zhang Q, Stein C, Schäfer M.** Contribution of opioid receptors on primary afferent versus sympathetic neurons to peripheral opioid analgesia.
J Pharmacol Exp Ther 1998;286:1000-1006.
21. **De Giorgio R, Zucco FM, Chiarioni G, et al.** Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel.
Adv Ther 2021;38:3589-3621.
doi: 10.1007/s12325-021-01766-y.
22. **Rodriguez RW.** Off-label uses of alvimopan and methylnaltrexone.
Am J Health Syst Pharm 2014;71:1450-1455.
doi: 10.2146/ajhp130632.
23. **Zoghbi SS, Liow JS, Yasuno F, et al.** 11C-loperamide and its N-desmethyl radiometabolite are avid substrates for brain permeability-glycoprotein efflux.
J Nucl Med 2008;49:649-656.
doi: 10.2967/jnumed.107.047308.
24. **Pilla JE, Patel P, Devulapally P.** Difelikefalin. (Updated 2024 Feb 28). In: *StatPearls* (Internet). Treasure Island (FL): StatPearls Publishing; 2025 Jan.
Available from: https://www.ncbi.nlm.nih.gov/books/NBK574566/
25. **Kim BS, Inan S, Ständer S, et al.** Role of kappa-opioid and mu-opioid receptors in pruritus: Peripheral and central itch circuits.
Exp Dermatol 2022;31:1900-1907.
doi: 10.1111/exd.14669.
26. **Mangel AW, Bornstein JD, Hamm LR, et al.** Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome.
Aliment Pharmacol Ther 2008;28:239-249.
doi: 10.1111/j.1365-2036.2008.03730.x.
27. **Thomas J, Karver S, Cooney GA, et al.** Methylnaltrexone for opioid-induced constipation in advanced illness.
N Engl J Med 2008;358:2332-2343.
doi: 10.1056/NEJMoa0707377.
28. **Feuchtbaum E, Wondra JP, Bumpass DB, et al.** Alvimopan for the reduction of postoperative ileus after long posterior spinal fusion: placebo-controlled double-blind randomized trial.
J Neurosurg Spine 2022;37:446-451.
doi: org/10.3171/2022.2.SPINE211551.
29. **Chey WD, Webster L, Sostek M, et al.** Naloxegol for opioid-induced constipation in patients with noncancer pain.
N Engl J Med 2014;370:2387-2396.
doi: 10.1056/NEJMoa1310246.
30. **Rogers TJ, Roy S.** Editorial: The Role of Opioid Receptors in Immune System Function.
Front Immunol 2022;12:832292.
doi: 10.3389/fimmu.2021.832292.
31. **Karcz M, Gharibo C.** Peripheral Nervous System Pain Modulation.
Curr Neuropharmacol 2024;22:65-71.
doi: 10.2174/1570159X21666230803100400.
32. **Kandasamy R, Hillhouse TM, Livingston KE, et al.** Positive allosteric modulation of the mu-opioid receptor produces analgesia with reduced side effects.
Proc Natl Acad Sci USA 2021;118:e2000017118.
https://doi.org/10.1073/pnas.2000017118.
33. **Cao B, Xu Q, Shi Y, et al.** Pathology of pain and its implications for therapeutic interventions.
Sig Transduct Target Ther 2024;9:155.
https:/
/doi.org/10.1038/s41392-024-01845-w.
34. **Scotece M, Conde-Aranda J.** Inflammation in Health and Disease: New Insights and Therapeutic Avenues.
Int J Mol Sci 2022;23:8392.
doi: 10.3390/ijms23158392.
35. **Cifuentes M, Verdejo HE, Castro PF, et al.** Low-grade chronic inflammation: a shared mechanism for chronic diseases.
Physiology (Bethesda) 2025:40:0.
doi: 10.1152/physiol.00021.2024.
36. **Stein C, Machelska H.** Modulation of peripheral sensory neurons by the immune system: implications for pain therapy.
Pharmacol Rev 2011;63:860-881.
doi: 10.1124/pr.110.003145.
37. **Gaveriaux-Ruff C, Kieffer BL.** Opioid receptor genes inactivated in mice: the highlights.
Neuropeptides 2011;45:119-125.
38. **Camilleri M.** Toward an effective peripheral visceral analgesic: responding to the national opioid crisis.
Am J Physiol Gastrointest Liver Physiol 2018;314:G637-G646.
doi: 10.1152/ajpgi.00013.2018.
39. **Rivière PJ.** Peripheral kappa-opioid agonists for visceral pain.
Br J Pharmacol 2004;141:1331-1334.
doi: 10.1038/sj.bjp.0705763.
40. **Bidlack JM.** Detection and function of opioid receptors on cells from the immune system.
Clin Diagn Lab Immunol 2000;7:719-723.
doi: 10.1128/CDLI.7.5.719-723.2000.
41. **McCarthy L, Wetzel M, Sliker JK, et al.** Opioids, opioid receptors, and the immune response.
Drug Alcohol Depend 2001;62:111-123.
doi: 10.1016/s0376-8716(00)00181-2.
42. **Sacerdote P.** Opioids and the immune system.

Palliat Med 2006;20 Suppl 1:s9-15.

43. **Hartrick CT.** Exploiting Injury-Induced Peripheral Opioid Receptor Changes in Novel Analgesic Development for Chronic Pain. *Front Pain Res* (Lausanne) 2022;3:883164. doi: 10.3389/fpain.2022.883164.
44. **Rodriguez-Gaztelumendi A, Spahn V, Labuz D, et al.** Analgesic effects of a novel pH-dependent μ-opioid receptor agonist in models of neuropathic and abdominal pain. *Pain* 2018;159:2277-2284. https://doi.org/10.1097/j.pain.0000000000001328.
45. **Wang X, Bao C, Li Z, et al.** Side Effects of Opioids Are Ameliorated by Regulating TRPV1 Receptors. *Int J Environ Res Public Health* 2022;19:2387. doi: 10.3390/ijerph19042387.
46. **Bileviciute-Ljungar I, Spetea M, Guo Y, et al.** Peripherally mediated antinociception of the mu-opioid receptor agonist 2-[(4,5alpha-epoxy-3-hydroxy-14beta-methoxy-17-methylmorphinan-6beta-yl)amino]acetic acid (HS-731) after subcutaneous and oral administration in rats with carrageenan-induced hindpaw inflammation. *J Pharmacol Exp Ther* 2006;317:220-227. doi: 10.1124/jpet.105.096032.
47. **Zollner C, Shaqura MA, Bopaiah CP, et al.** Painful inflammation-induced increase in mu-opioid receptor binding and G-protein coupling in primary afferent neurons. *Mol Pharmacol* 2003;64:202-210. doi: 10.1124/mol.64.2.202.
48. **Ji R, Zhang Q, Law P, et al.** Expression of mu-, delta-, and kappa-opioid receptor-like immunoreactivities in rat dorsal root ganglia after carrageenan-induced inflammation. *J Neurosci* 1995;15:8156-8166. doi: 10.1523/jneurosci.15-12-08156.1995.
49. **Nader-Mugurel Jafal, et al.** Anti-Inflammatory Effects Of Locally *Versus* Systemic Injected Morphine On Chemically Induced Inflammation: An Experimental Animal Study. *Farmacia* 2024;72:1209-1215. https://doi.org/10.31925/farmacia.2024.5.24.
50. **Jafal NM, Stoleru S, Zugravu A, et al.** The Analgesic Effect of Morphine on Peripheral Opioid Receptors: An Experimental Research. *J Crit Care Med* (Targu Mures) 2024;10:337-344. doi: 10.2478/jccm-2024-0042.
51. **Zhang Q, Schäffer M, Elde R, Stein C.** Effects of neurotoxins and hindpaw inflammation on opioid receptor immunoreactivities in dorsal root ganglia. *Neuroscience* 1998;85:281-291. doi: 10.1016/s0306-4522(97)00647-7.
52. **Stein C.** Opioid Receptors in the Periphery. *Curr Opin Pharmacol* 2018;40:109-113. doi: 10.1016/j.coph.2018.04.002.
53. **Hersh EV, Moore PA, Grosser T, et al.** Nonsteroidal Anti-Inflammatory Drugs and Opioids in Postsurgical Dental Pain. *J Dent Res* 2020;99:777-786. doi:10.1177/0022034520914254.