North Clin Istanb 2023;10(1):122–126
doi: 10.14744/nci.2022.92603

REVIEW PHARMACY

A possible alternative to Opiorphin and its stable analogues for treating fibromyalgia pain: A clinical hypothesis

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ABSTRACT

The work aimed to explore the clinical hypothesis on the possible alternative to Opiorphin and its stable analogues for treating fibromyalgia pain. Fibromyalgia is a condition characterized by chronic pain triggered by an interplay of biological and psychosocial variables, although the exact pathogenesis is still controversial. Standard therapy for low threshold tender point pain includes NSAIDs and opioid analgesics, both of which have serious adverse profiles after long-term exposure, highlighting the need for an intermediate compound capable of bridging the gap between NSAIDs and opioid analgesics. Opiorphin is an anti-nociceptive modulator which inhibits the enzyme responsible for the degradation of natural endogenous opioid neuropeptides. This paper hypothesizes and concludes that Opiorphin and its stable analogues (Sialorphine, STR-324) can be an alternative for the treatment of chronic long-standing low-threshold tender point pain associated with fibromyalgia.

Keywords: Analgesic; fibromyalgia; opioid; opiorphin; pain.

Cite this article as: *Roy D, Ahad HA, Chinthaginjala H, Kumar GA, Reddy GG, Teja AST. A possible alternative to Opiorphin and its stable analogues for treating fibromyalgia pain: A clinical hypothesis. North Clin Istanb 2023;10(1):122–126.*

Pain is a distressing experience that is associated with devastating and demoralizing effects. It results in potential changes in the sensory, emotional, cognitive, and social components of both patients and their caregivers [1]. Fibromyalgia is a chronic disorder that primarily affects the muscles and is accompanied by pain, stiffness, and tenderness of joints that are usually not involved with tissue inflammation [2]. Despite its intense body pain, the complications from tissue damage or deformity are minimal. Pain due to fibromyalgia is widespread, involving both sides of the body and generally affecting areas including the neck, buttock, shoulder, arm, upper back, and chest [3]. The use of newer and more effective treatments for fibromyalgia is of fundamental importance to minimize the adverse effects relating to the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics [4]. It can be overcome by substitution with a naturally occurring compound, Opiorphin, that may work as a bridge between the NSAIDs and narcotic analgesics [5].

OPIORPHIN: THE CAPABLE SUBSTITUTE

Enkephalin (ENK) is an opioid receptor agonist, predominantly (mu) and (delta) types. ENK plays a crucial role in the modulation of the pain pathway, specifically by inhibiting the release of neurotransmitters including substance P, vasopressin, dopamine, and calcium influx in neuronal cells [6]. *In vivo*, ENKs undergo rapid metabolism through neprilysin (NEP) and Aminopeptidase-N (APN) (two membrane-bound Zn metallopeptidases) [7]. Human Opiorphin is an endogenous QRFSR pentapeptide identified in human saliva that can be extracted

Received: July 26, 2022 *Accepted:* November 20, 2022 *Online:* February 20, 2023

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by the biochemical process. It consists of amino acids in two forms of its sequence (Gln-Arg-Phe-Arg and pGlu-Arg-Phe-Ser-Arg) [8], which came into public interest after the discovery of a similar analogue in mice as Sialorphin. Opiorphin is a dual inhibitor of human neutral exopeptidase NEP and human ecto-Aminopeptidase-N. These are two membrane-bound metallopeptidases responsible for the metabolism of ENK. In response [9], it inhibits acute and long-standing chemically stimulated pain. The analgesic capability of Opiorphin at a dose of 1 mg/kg is equivalent to 6 mg/kg of morphine (opioid analgesic) (human Opiorphin is a natural anti-nociceptive modulator). Opiorphin is being expressed in various biological fluids, including saliva (2.8–25.9 ng/ml), lacrimal fluid (2–183 ng/ml), human milk (3–23 ng/ml), semen (3–8.5 ng/ml), and urine (8.3–1.5 ng/ml) [10].

ENK: ITS DISTRIBUTION AND BINDING

In the central nervous system, ENK peptides are formed endogenously, which have been recorded to interact with the opioid receptors, namely, mu; delta; and κ (kappa) that are widely distributed in the brain regions, including the thalamus, periaqueductal gray, rostral ventromedial medulla, locus ceruleus, and dorsal horn region of the spinal cord (Laminae-I and II). In specific neurons, ENKs (Met and Leu) derived from pro-ENK are released through a Ca+2 dependent mechanisms and show their interaction with receptors leading to the regulation of pain [11]. Potent inhibition of ENK metabolizing peptidase can increase the extracellular concentration of ENK, which is released in response to a painful stimulus. Henceforth, increasing the bioavailability due to inhibition of its degradation is an effective alternative method to enhance its analgesic potency [12].

FIBROMYALGIA: THE PAIN PATHWAY

Patients who are suffering from fibromyalgia relay enhanced widespread stimuli of heat, cold, and mechanical stress [13, 14]. It produces pain in those whose pain threshold is much lower than normal. A low threshold induces the release of substance P and excitatory amino acids such as glutamate (neuropeptides), causing activation of the afferent pathway [15, 16]. In general, when the pain threshold is reached, the afferent fibers transmit the impulse to the pain-transmitting neurons (PTNs) through the synapse in the dorsal horn of the spinal cord. It occurs by the release of neuropeptides, particularly substance P and excitatory amino acids such as glutamate (Fig. 1) [17, 18].

Highlight key points

- In order to manage the pain associated with fibromyalgia, this study investigates the therapeutic hypothesis regarding a potential substitute for opium and its stable equivalents.
- Chronic pain that is brought on by the interaction of biological and psychological factors is a hallmark of the disorder known as fibromyalgia.
- NSAIDs and opioid analgesics are part of standard treatment for low-threshold tender point pain. Opiorphin is an anti-nociceptive modulator that blocks the enzyme that breaks down endogenous opioid neuropeptides in the body.

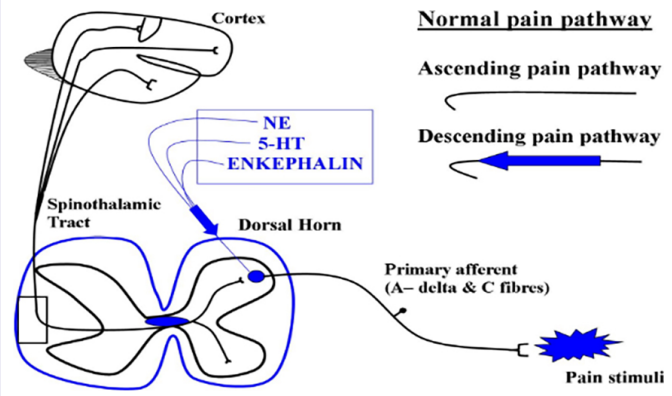

FIGURE 1. In a classic model of pain perception in acute pain, painful stimuli are transmitted from the periphery to the dorsal horn through the afferent fibers (A-delta and C nerve fiber) and from the dorsal horn to the brain through the spinothalamic tract. The perception of pain is modified or inhibited by activation of the descending inhibitory pathway (NE, 5-HT, Enkephalin) (NE: Norepinephrine; 5-HT: 5-Hydroxy Tryptamine).

They then predominantly bind to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and neurokinin-1 receptors at the postsynaptic neuron and cause the transmission of pain stimuli to various regions of the brain through the spinothalamic tract [19]. If the pain impulses of low threshold or prolonged or intense pain stimuli persist, it results in sensitization of PTNs. Over sensitization of PTNs is principally due to the release of nitric oxide (NO) in the postsynaptic region through the influx of Ca2+ due to activation of NMDA receptors [20]. Thus, the released NO then acts on both pre and postsynaptic neurons and further results in excessive release of neuropeptides from presynaptic neurons and hyperexcitability of PTNs [21]. In response, the glial cells get excited, and it further causes enhanced release of NO, leading to the perception of chronic pain (Fig. 2).

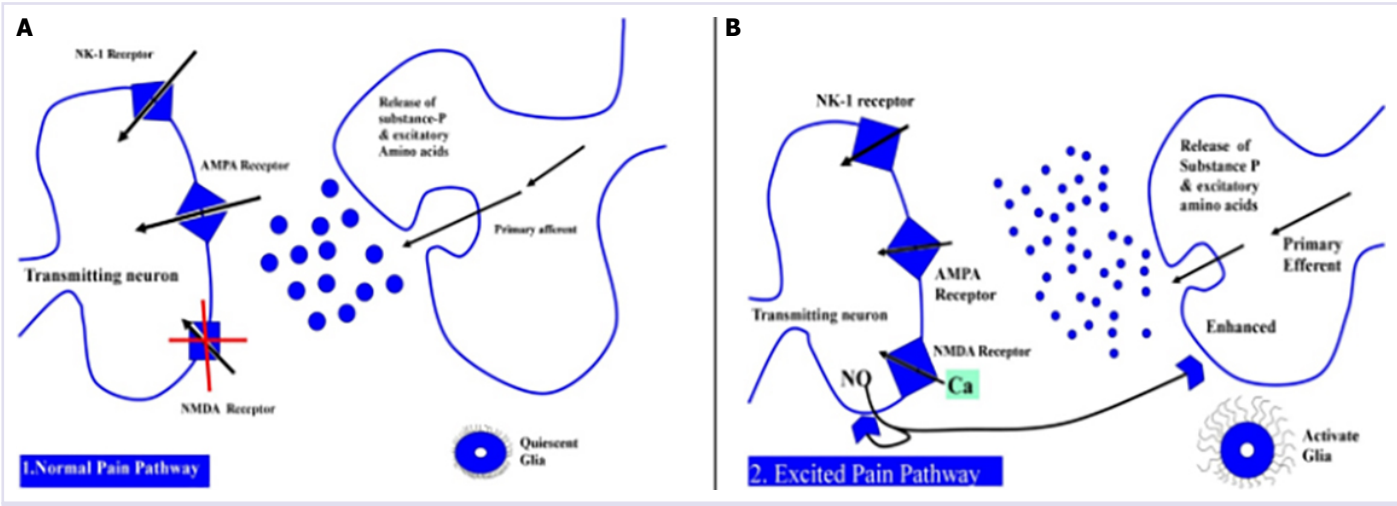

Figure 2. **(A)** In the dorsal horn, incoming afferent pain signals cause the release of substance P and excitatory amino acids, which bind to postsynaptic receptors on the pain transmitting neuron. Glial cells are in a quiescent stage **(B)**. With prolonged and intense exposure to painful stimuli, incoming afferent signals are increased, and presynaptic release of substance P and excitatory amino acids and influx of Ca^{2+} results in the production of nitric oxide (NO), which further causes hyper excitability with the release of excessive neuropeptides. AMPA is an abbreviation for amino-3hydroxy-5methyl-4-isoxazolepropionic acid; 5HT is an abbreviation for 5-Hydroxy Tryptamine; NMDA is an abbreviation for N-methyl-D-aspartic acid; NO is an abbreviation for nitric oxide; and NK-1 is an abbreviation for neurokinin-1.

THE DEGRADATION MECHANISM OF ENK AND THE ACTION OF OPIORPHIN AS A DUAL PEPTIDASE INHIBITOR

When the descending inhibitory pathway is activated, the precursor PROL1 gene produces proenkephalin, which leads to the production of ENK peptides in synaptic vesicles. It is then released and bound to the opioid receptors for analgesic like action. Despite this, it is rapidly degraded by two membrane-bound zinc metalloendopeptidases, NEP and aminopeptidase N (APN), resulting in analgesia inhibition in response to prolonged pain. When administered, opioid pain inhibits the metalloectopeptidases that are responsible for ENK's rapid degradation [22].

Thus, it enhances the availability of ENK for a more extended period at the synapse, causing analgesia. Unlike opioids, even after the long-term administration of high doses, Opiorphin failed consistently to show respiratory and hemodynamic adverse changes. Various approaches such as genetic, biochemical, molecular, and behavioral pharmacological methods such as conditional placed preference in mammals, a forced swim test, and *in vitro* analgesic activity were used to determine the presence of a dual inhibitor of membrane-bound zinc ectopeptidases such as NEP and APN (Fig. 3) [23].

THE PHARMACOLOGICAL PROPERTIES OF OPIORPHIN

In a study done by Philippe Sitbon et al. [24], they administered an intravenous infusion of titrated STR-324 (a cyclized form of N-terminal glutamine) in monkeys and observed that the opioid crossed the blood-brain barrier where the N-terminal glutamate of the opioid was converted to the pyroglutamate-1 peptide.

ANTIDEPRESSANT EFFECTS OF OPIORPHIN

In some preclinical studies, it was proved that, other than having analgesic action, it showed anti-depressant action when administered intravenously at a dose of 1–2 mg/kg body weight. This is due to the activation of Mu Opioid Receptor and Delta Opioid Receptor (DOR) when administered centrally, which activates DOR if administered peripherally. The dual activity of opioids as an analgesic and anti-depressant action through enhancing the level of ENK would pave the way for a novel therapeutic approach to the management of fibromyalgia. On administration of a single dose of morphine (6 mg/kg) through the intraperitoneal route, gastrointestinal motility was observed to decline in rats fed a normal diet. In contrast, under the same experimental condition, the an-

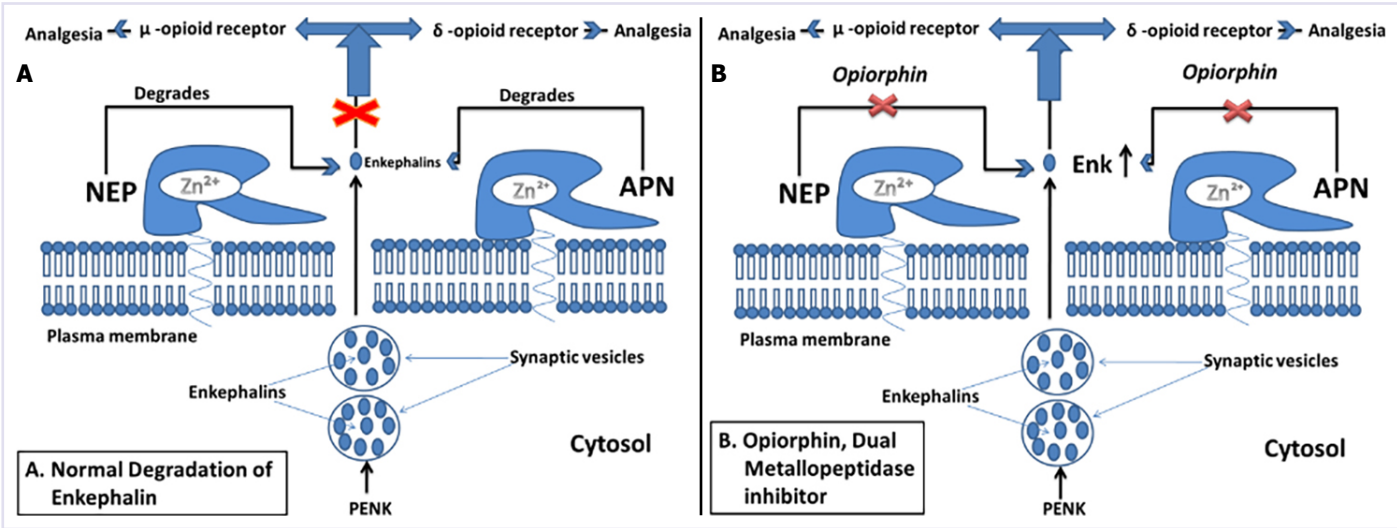

FIGURE 3. **(A)** Normal enkephalin degradation by the two membrane-bound zinc metalloectopeptidases neprilysin (NEP) and aminopeptidase N (APN) results in analgesia inhibition. **(B)** The mechanism of action of the bridging compound Opiorphin in inhibiting two membrane metalloectopeptidases for analgesia.

imals pre-treated with Opiorphin did not induce any inhibition of bowel motility function, even at a higher analgesic I.V bolus. This study showed evidence of minimal adverse effects due to Opiorphin administration. In a study on anaesthetized rats, intravenous administration of Opiorphin (200 g/kg) results in a rise in blood pressure (about 40 mmHg) and an increase in heart rate. It is mediated by the renin-angiotensin system, sympathetic ganglia, and the adrenal medulla. In addition, Opiorphin also causes colonic contraction in the gastrointestinal and urogenital tracts in a dose-dependent manner (from 106 to 104 M concentration) [25].

CONCLUSION

Chronic usage of NSAIDs and opioid analgesics has not shown promising clinical outcomes in patients diagnosed with fibromyalgia associated with severe tender point pain. Instead, it causes therapeutic failure due to the serious adverse effects associated with mood disturbances. Opiorphin, as a choice to opioids, seems to be the most promising naturally occurring drug that inhibits metalloectopeptidases, resulting in the maintenance of adequate synaptic ENK levels, ultimately leading to the cause of analgesia with minimal adverse effects. Despite its effectiveness, due to low stability and a short half-life, further studies must be done to enhance the half-life of Opiorphin. This would pave the way for a novel therapeutic agent for the effective management of pain due to fibromyalgia.

Acknowledgements: The authors are thankful to the college management for encouraging the research activities.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – DR; Design – HAA; Supervision – HAA; Fundings – HC; Materials – GAK; Data collection and/or processing – GGR; Analysis and/or interpretation – ASTT; Literature review – DR; Writing – DR; Critical review – HAA.

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