BETA-ENDORPHIN LEVELS IN OPIOID AND NON-OPIOID DRUGS

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Beta-endorphin (βEND) is a protein created in the anterior pituitary gland due to physiological stresses, such as pain. Opioids are commonly recognized for their ability to alleviate pain by binding to their opioid receptors and replacing βEND. Nevertheless, opioids pose a significant risk due to their numerous adverse effects, including drowsiness, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Moreover, prolonged administration of opioid analgesics such as morphine to individuals, particularly those suffering from chronic pain, can induce hyperalgesia. By augmenting the βEND levels, non-opioid medications can potentially provide an alternative to hazardous opioids. We did a comprehensive review article by searching the PubMed, Scopus, and Web of Science databases to investigate the potential of non-opioid medications in reducing postoperative pain without causing any harmful effects commonly associated with opioids. This study highlights the discovery that non-opioid pharmaceuticals that regulate βEND activity could be a feasible substitute for opioid treatments, which have intrinsic hazards.

Keywords: Beta-endorphin, Opioids, Non-opioid drugs, Pain management, Adverse effects

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INTRODUCTION

Postoperative pain management is a crucial element in the comprehensive treatment plan for surgical patients. Pain that is not relieved is unnatural, inhumane, and immunosuppressive (Chang et al., 2021). A study including 1490 surgical patients found 41% of patients felt pain on day 0, 30% on day 1, and 19%, 16%, and 14% on days 2, 3, and 4 (Sommer et al., 2008). According to a nationwide survey conducted in the United States, a total of 300 adults who had undergone surgical procedures within the past five years were included. The findings revealed that a significant majority, precisely 86% of the participants, reported experiencing post-surgical pain. Furthermore, among those who reported pain, approximately 75% described the severity of their pain during the immediate postoperative period as ranging from moderate to extreme (Gan et al., 2014). The occurrence of pain following a surgical procedure carries various implications, including adverse health outcomes, increased morbidity, the development of chronic postoperative pain, diminished physical functioning, delayed recovery, reduced quality of life, and extended reliance on opioids, leading to potential adverse events associated with their use. Furthermore, it is crucial to consider the implications for health economics (Gan, 2017).

Beta-endorphin (βEND) is a protein synthesized in the anterior pituitary gland. βEND is produced by responding to stressors such as pain, as in the postoperative period, osteoarthritis, and chronic low back pain (Ahn et al., 2019; Choi & Lee, 2019; Smyth, 2016). Opioids exert analgesic effects by engaging with μ-opioid receptors in the central nervous system (CNS) and peripheral nervous system (PNS) by different mechanisms (Pathan & Williams, 2012). Opioid medications operate by imitating the actions of endogenous endorphins (ENDs), thereby engaging in competition for receptor binding. In the acute condition, exogenous opiates impede the synthesis of endogenous opiates, whereas in the chronic condition, exogenous opiates hinder the synthesis of both endogenous opiates and μ-opioid receptors (Sprouse-Blum et al., 2010). Various risks, including the development of opioid-induced hyperalgesia, the development of tolerance, and the potential for addiction accompany chronic opiate use (Benyamin et al., 2008; Els et al., 2017). There is a limited amount of research available that examines the relationship between non-opioid medication and βEND. This review article discusses the differential effects of opioid and non-opioid drugs on βEND.

BETA-ENDORPHIN

Endogenous morphine, known as ENDs, are naturally occurring opioid neuropeptides in the body that primarily function as pain-blocking agents and are also present during pleasurable experiences (Shenoy & Lui, 2023). Prior to the discovery and comprehension of ENDs, morphine receptors were historically identified in the nervous system. This receptor indicated the potential presence and impact of ENDs, which was subsequently verified (Olson et al., 2017).

ENDs were found to serve as neurotransmitters in

the CNS and are released into the circulatory system by the pituitary gland as peptide hormones (Adeodu et al., 2018). Clinical studies have established a correlation between ENDs and various mental conditions, such as autism, depression, and depersonalization disorder. Additionally, ENDs have been associated with activities like laughter and intense aerobic exercise (Pilozzi et al., 2020).

Typically, the production of ENDs is known to be linked to the body's reaction to pain. The analgesic effect resulting from the secretion of ENDs has been found to surpass that of morphine. ENDs exhibit functional duality as they can be classified as either neurotransmitters or neuromodulators within the CNS and hormones within the pituitary gland (Giri & Hruby, 2014).

The mechanism of ENDs can be understood by examining their effects on both the PNS and the CNS. In the PNS, the sensation of pain alleviation occurs when βENDs attach to opioid receptors. β-endorphin, enkephalins, and dynorphins are often believed to be specific activators for the μ-, δ-, and κ-opioid receptors, respectively. The βENDs and the μ-receptors have the highest affinity for each other. M-receptors are distributed extensively in the PNS. Analgesic effects are achieved when βEND binds to μ-receptors on nerve terminals, either pre-synaptically or post-synaptically. The effects occur when the stated binding leads to the initiation of chemical reactions that inhibit the release of substance P, along with other tachykinins. The binding of βEND to μ-opioid receptors occurs in the PNS system and the CNS. However, the process activated by the binding works against releasing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) rather than substance P. The inhibition of GABA leads to an augmentation in the synthesis and function of dopamine, the neurotransmitter associated with pleasure and reward (Chaudry & Gossman, 2023; Fichna et al., 2007; Veening & Barendregt, 2015).

The immediate injection of exogenous opioids suppresses the formation of endogenous opiates like βEND—patients who receive general anesthesia experience a notable rise in βEND levels during surgery. The concurrent delivery of fentanyl successfully suppressed this rise (Cork et al., 1985; Dubois et al., 1982). Prior research has demonstrated that patients who underwent dental surgery and received just local anesthetic (lidocaine) experienced elevated levels of plasma βEND both during and after the surgical procedure. Nevertheless, the introduction of fentanyl resulted in a notable decrease in plasma βEND levels. Patients experienced significantly reduced pain levels during the surgical procedure when fentanyl was provided concurrently (Hargreaves et al., 1983, 1986).

The intensity of peri- and postoperative pain directly correlates with the concentration of βEND in their plasma. A study was conducted to analyze the levels of βEND prior to and following significant surgical procedures. The study found a positive connection between pre- and postoperative plasma βEND levels and the severity of postoperative pain (Matejec et al., 2003). A separate study revealed that the administration of local anesthetic drugs to patients following a cesarean delivery proved that the quadratus lumborum block successfully relieves pain and decreases the level of βEND (Seger et al., 2020).

OPIOID

Opioids are believed to exert their pain-relieving effects by acting on synapses in the CNS and PNS. Opioids are widely acknowledged to reduce the transmission of pain signals in the spinal cord. This is achieved through two mechanisms: inhibiting calcium channels and activating potassium channels, which occur at the pre- and postsynaptic levels. Opioids can enhance the functioning of the pain inhibitory systems that control the transmission of pain signals by suppressing the activity of γ-amino-butyric acid-ergic interneurons. Furthermore, opioids inhibit the experience of pain in the somatosensory cortex and modify the emotional aspect of pain by affecting the limbic regions. Nevertheless, when administered to patients over a prolonged period, opioid analgesics like morphine can induce a condition of heightened pain sensitivity, known as hyperalgesia, at least in certain circumstances. This could result in increased opioid dosages, which may carry the risk of serious problems (Vuong et al., 2010).

Morphine, thebaine, and papaverine, which are natural derivatives of opium, have been utilized for their analgesic properties for a considerable period (Kirby, 1967). Morphine and other opioids that are highly prone to misuse have a strong affinity for μ-opioid receptors. However, the extent to which these substances can activate opioid receptors and modify signaling ranges from partial to full agonists (Herz, 1998). Furthermore, morphine also attaches to δ- and κ-opioid receptors, although with a decreased level of affinity. The antinociceptive impact of morphine, as well as its rewarding and addictive properties, are predominantly mediated through the μ-opioid receptors (Matthes et al., 1996).

In both animals and humans, opioids often have the

effect of increasing growth hormone (GH) and prolactin (PRL) while decreasing luteinizing hormone (LH), testosterone, estradiol, and oxytocin (OT). However, the findings on the effects of opioids on arginine vasopressin (AVP) are contradictory. Animals experience a reduction in thyroid-stimulating hormone (TSH) when exposed to opioids, while humans experience an elevation in TSH when exposed to opioids. The impact of opioids on AVP and adrenocorticotropic hormone (ACTH) is uncertain. The activation of specific receptors and the precise timing of delivery are crucial factors in determining the impact of opioids on these endocrine hormones. Furthermore, opioids have many modes of action as they interact with receptors in the endocrine glands and also influence the expression of endogenous opioid peptide genes. Hypogonadism, specifically in males, is the primary disease that arises from opiate usage in humans. Individuals who engage in substance misuse should be conscious of both the widespread occurrence of this condition on their sexual performance, as well as the impact of opioids on the other hormones in their body, which can result in detrimental long-term consequences. Opioids can lead to the development of additional endocrine diseases, such as hyperprolactinemia and hyperthyroidism (Vuong et al., 2010).

NON-OPIOID

As a result of the harmful side effects of opioids, many medical professionals have chosen to avoid using these medications excessively. Instead, they are opting for non-opioid methods to control postoperative pain. These methods include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs)/cyclooxygenase-2 (COX-2) inhibitors, gabapentin, and various combinations of these non-opioid approaches. Several publications have covered the topic of alternative pain management techniques that do not include the use of opioids. The prevailing consensus endorses the utilization of these non-opioid options due to the potential adverse effects associated with opioids. Nevertheless, the practitioner must exercise caution in avoiding the tendency to apply a single method of pain management to all of their postoperative patients. The practitioner should also consider the possible negative consequences of these non-opioid analgesics and carefully evaluate the advantages and disadvantages for each patient.

Paracetamol is thought to block some kinds of cyclooxygenase, mainly in the CNS, to increase the pain threshold. Research has shown that patients who receive both paracetamol and morphine tend to use fewer opioids. However, existing literature generally fails to provide evidence of a reduced occurrence of negative consequences connected to opioid usage in these individuals. Multiple studies have been undertaken that illustrate the effectiveness of paracetamol for pain management. A meta-analysis revealed that administering a solitary prophylactic dosage of systemic paracetamol resulted in a considerable reduction in both postoperative opioid usage and postoperative occurrences of nausea and vomiting. Paracetamol has low harmful side effects when used per the Food and Drug Administration (FDA) recommendations. As a result, it has become a widely utilized method for managing postoperative pain. A study conducted on individuals with osteoarthritis revealed that paracetamol exhibited greater efficacy in reducing BEND within 1 and 3 months of medication when compared to rofecoxib, a COX-2 inhibitor (Sprott, 2005).

NSAIDs primarily function by reducing the activity of both cyclooxygenase-1 (COX-1) and COX-2, resulting in the suppression of prostaglandin synthesis. This mechanism leads to the production of analgesic, antipyretic, and anti-inflammatory effects. NSAIDs have demonstrated effectiveness and are linked to a notable reduction in opiate consumption among postoperative patients. However, a growing number of studies have revealed that NSAIDs have an analgesic effect not only in the periphery but also at the center. This indicates the presence of a central analgesic mechanism in addition to the peripheral mode of action of NSAIDs, with the primary mechanism likely involving βEND. Nevertheless, the precise mechanisms by which prostaglandin E2 or NSAIDs interact with βEND through signal transduction pathways remain rather ambiguous. Research has shown that administering flurbiprofen axetil as a preventive measure during the perioperative phase or 30 minutes before the completion of an operation can successfully increase the concentration of βEND in patients' plasma. In contrast, the control group had a significant fall in β-endorphin levels (Liu et al., 2011). A separate study discovered that administering lornoxicam before surgery could enhance the concentration of βEND in patients' plasma (Wang et al., 2005). In contrast, a prior investigation utilizing parecoxib sodium for analgesia following craniotomy demonstrated no significant rise in the concentration of βEND in the postoperative plasma (Li et al., 2012).

Gabapentin is a commonly prescribed medication for treating epilepsy that has demonstrated analgesic properties, potentially through its influence on the regulation of arachidonic acid, nitrergic, and serotonergic systems (Kilic et al., 2012). Most

literature indicates that dizziness and somnolence are the main adverse effects associated with its use (Inoue et al., 2012). A systematic review and statistical analysis of 12 randomized controlled trials concluded their research uncovered a significant decrease in the consumption of opiates in individuals who received dosages of gabapentin ranging from 300 to 1200 mg within one to two hours before the procedure. A study utilizing rats as subjects demonstrates that gabapentin enhances the expression of βEND (Ahmad et al., 2021).

Ketamine hydrochloride is a dissociative anesthetic not belonging to the barbiturate class. This compound is a derivative of cyclohexanone that exhibits quick onset and induces deep anesthesia and analgesia. Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) and glutamate receptors (Rosenbaum et al., 2023). The distinct ability of opiate μ-receptors to dissociate and partially activate allows for the execution of painful treatments while maintaining a stable level of sedation and ensuring patient comfort (Nichols & Paciullo, 2019). In addition, ketamine can also function as an antidepressant by acting as an NMDA antagonist. It has the ability to alleviate symptoms of sadness and reduce suicidal thoughts quickly (Jiang et al., 2021). Ketamine is commonly associated with adverse symptoms such as nausea, vomiting, dizziness, diplopia, sleepiness, dysphoria, and confusion. Emergence phenomena have been reported in around 6% to 12% of patients. Occasionally, patients may encounter hallucinations (Rosenbaum et al., 2023). Several studies have demonstrated that ketamine can increase the secretion of βEND by up to threefold (Jiang et al., 2021; YaDeau, 2003).

AUTHORS' CONTRIBUTION

MSS & CCSW: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to beaccountable for all aspects of the work. PSA & PL: Data acquisition, interpretation,drafting, final approval and agree to be accountable for all aspects of the work.

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