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Endogenous opioid system in pain management: Mechanisms, influences, and clinical implications

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Abstract

This manuscript discusses the role of the endogenous opioid system in pain management and its potential clinical applications. The endogenous opioid system is a network of naturally produced painkillers, known as opioid peptides, and the receptors to which they bind. The main components of this system are endorphins, enkephalins, and dynorphins. Opioid receptors (mu, delta, and kappa) interact with these peptides to regulate various physiological and psychological processes, such as analgesia, euphoria, and stress responses. The article provides detailed explanations of the biosynthesis, secretion, and receptor activation mechanisms of opioid peptides. Additionally, the effects of stress, exercise, and alternative treatment methods (acupuncture, meditation) on the endogenous opioid system are discussed. In clinical applications, dysfunction of the endogenous opioid system is noted to be associated with the risk of opioid misuse in chronic pain patients. The article also presents recommendations for future research to develop more effective pain management strategies.

Keywords: endogenous opioid system, pain management, opioid peptides

1. Introduction

1.1. The Importance of Pain Management

Pain is defined as a complex sensory and emotional experience that arises in response to tissue damage in the body and adversely affects an individual's quality of life (1). Its impact on public health is extensive; chronic pain can limit individuals' ability to perform daily activities, leading to a loss of workforce, social isolation, and psychological problems (2). Individuals suffering from chronic pain may require continuous medical treatment, imposing a significant economic burden on healthcare services (3). Moreover, pain, which significantly reduces the quality of life, can lead to additional health problems such as sleep disorders, depression, and anxiety (4). Therefore, developing effective pain management strategies is crucial for protecting public health and improving individuals' quality of life (5).

1.2. Definition of the Endogenous Opioid System

The endogenous opioid system is a complex network formed by opioid peptides, which are the body's naturally produced painkillers, and the receptors to which they bind. The primary components of this system include endorphins, enkephalins, and dynorphins. Endorphins are peptides that are particularly released in response to stress and pain and have effects similar to those of morphine (6). They are known to be released during intense exercise, painful stimuli, and stressful situations, creating a sense of well-being by alleviating pain. Enkephalins are short-chain peptides that play a role in pain modulation and neurotransmission, and they are particularly concentrated in the spinal cord. They are spread throughout the central nervous system and exhibit analgesic effects by inhibiting pain signals (7). Dynorphins are opioid peptides with high affinity and are particularly effective in chronic pain conditions. They play a significant role in the stress response and addiction mechanisms and can cause dysphoric effects by interacting with kappa opioid receptors (8). These components interact with opioid receptors to regulate various physiological and psychological processes such as analgesia, euphoria, and stress responses (9). Opioid receptors are distributed throughout the central and peripheral nervous systems and are crucial in modulating pain signals (10). The endogenous opioid system has been shown to play an important regulatory role in both acute and chronic pain management and in other psychological conditions such as addiction and stress (11).

1.3. Mechanisms of the Endogenous Opioid System

1.3.1. Opioid Receptors

Opioid receptors are G-protein-coupled receptors that play a critical role in pain modulation and many physiological

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functions. These receptors are classified into three main types: mu (μ), delta (δ), and kappa (κ) receptors. Mu receptors are associated with effects such as analgesia, euphoria, and respiratory depression, and they are widely distributed in the brain, spinal cord, and gastrointestinal (9). These receptors mediate the effects of morphine and similar opioid drugs(10). Delta receptors are linked to pain control and mood regulation and are typically concentrated in the brain and spinal cord (12). Activation of delta receptors is seen as a promising target in chronic pain treatment. Kappa receptors are associated with dysphoria, hallucinations, and some analgesic effects and are particularly found in the brain, spinal cord, and certain peripheral tissues. Activation of kappa receptors plays a significant role in stress and addiction mechanisms (8).

1.3.2. Synthesis and Secretion of Endogenous Opioid Peptides

The synthesis and secretion of endogenous opioid peptides are carried out through complex biochemical processes. The biosynthesis of these peptides begins with the gene expression of precursor proteins, which are then cleaved into active opioid peptides by proteolytic enzymes (13). For example, large precursor proteins such as proopiomelanocortin (POMC), proenkephalin, and prodynorphin are converted into active peptides like β-endorphin, enkephalin, and dynorphin, respectively. These peptides are stored in the vesicles of nerve cells and released into the synaptic cleft to function as neurotransmitters (14). The release process occurs via calcium-dependent exocytosis and is triggered by the electrical stimulation of the nerve cell (15). After secretion, opioid peptides bind to opioid receptors on target cells, activating intracellular signaling pathways (16). During the metabolism stage, these peptides are inactivated by enzymatic pathways and broken down into small peptides or amino acids, thus controlling the duration and intensity of the signal (17).

1.3.3. Activation of Opioid Receptors

The activation of opioid receptors triggers various physiological and pharmacological effects by activating cellular signaling pathways. Opioid receptors are G-protein-coupled receptors, and their activation causes the dissociation of G-proteins into α, β, and γ subunits (18). This dissociation leads to the inhibition of the adenylate cyclase enzyme, a decrease in cyclic AMP (cAMP) levels, and a reduction in protein kinase A (PKA) activity (19). Consequently, intracellular calcium levels decrease and potassium channels open, causing hyperpolarization of the cell membrane, reducing neuronal excitability, and inhibiting the transmission of pain signals (20). Additionally, opioid receptor activation can affect mitogen-activated protein kinase (MAPK) pathways, which regulate various cellular processes such as cell growth, differentiation, and apoptosis (21). Also, internalization and desensitization of receptors occur via beta-arrestin, playing an important role in tolerance and addiction mechanisms associated with long-term opioid use (22). These complex signaling pathways are crucial not only in pain control but also in regulating many systemic effects such as mood, respiration, and gastrointestinal motility (9).

1.4. Role of Endogenous Opioids in Pain Management

1.4.1. Effects of Endogenous Opioids on Pain Perception

Endogenous opioids are biochemical substances that modulate pain perception and provide analgesic effects. These opioids are naturally produced in the body and interact with mu, delta, and kappa receptors to alleviate pain. These interactions produce potent analgesic effects in pain management, guiding the development of more effective analgesics in clinical pain management (23). Additionally, endogenous opioids play a role in regulating cell growth and inflammation in various conditions, such as gastrointestinal and liver diseases (24). This versatile role of the endogenous opioid system allows it to have a broad range of effects in pain management.

1.4.2. Stress Response and Endogenous Opioids

Stress can trigger the activation of the endogenous opioid system, significantly impacting pain perception. For instance, during acute stress, the release of endogenous opioids like endorphins increases, helping the body cope with stress and reducing the sensation of pain. However, under chronic stress, the functioning of this system may be impaired, leading to an increased perception of pain. Furthermore, it has been found that stress can contribute to dysfunction in the opioid system, affecting emotional responses in chronic pain patients (25).

1.4.3. Exercise and the Endogenous Opioid System

Exercise is another crucial factor that increases the release of endogenous opioids, thereby producing analgesic effects. During physical activity, the release of endogenous opioids like beta-endorphin increases, reducing pain sensation post-exercise. Moreover, exercise therapy contributes to the modulation of endogenous opioids in managing post-stroke pain, supporting the analgesic effects of exercise (26).

1.5. Clinical Applications and Research

1.5.1. The Endogenous Opioid System and Pain Management

The endogenous opioid system plays a significant role in pain management. Opioids such as beta-endorphin and enkephalins bind to mu, delta, and kappa receptors, providing analgesia. These mechanisms guide research to develop more effective pain relief treatments in clinical applications (23). Clinical studies have shown that dysfunction of the endogenous opioid system is associated with the risk of opioid misuse in chronic pain patients (27). Additionally, long-term opioid treatment has been found to lead to a decrease in sex hormone levels and gonadal dysfunction in patients with cancer-related pain, correlated with opioid dosage and cortisol concentrations (28).

1.5.2. Placebo and the Endogenous Opioid System

The placebo effect is an important factor in pain management and

is largely modulated by the endogenous opioid system. When a placebo is administered, the body releases natural opioids like endorphins, reducing pain perception (29). This mechanism can enhance patients' responses to pain relief treatments and be used to increase treatment efficacy in clinical applications. The placebo effect works by triggering the release of endogenous opioids that bind to opioid receptors, explaining the strong analgesic effects of placebo.

1.5.3. Pharmacological Approaches

Opioid agonists and antagonists are pharmacological agents widely used in pain management. Opioid agonists provide pain relief by binding to endogenous opioid receptors. For example, morphine and similar drugs bind to mu-opioid receptors, providing potent analgesia (30). However, long-term use of opioid agonists can lead to tolerance, dependence, and other side effects. Therefore, opioid antagonists are used in opioid addiction and overdose treatment. These drugs bind to opioid receptors, blocking the effects of opioids, and thus can be lifesaving in treating opioid overdoses (31).

1.6. The Endogenous Opioid System and Alternative Treatment Methods

1.6.1. Acupuncture and the Endogenous Opioid System

Acupuncture is a treatment method that provides analgesic effects by activating the endogenous opioid system. This mechanism plays a significant role in explaining the effects of acupuncture on psychological conditions and behaviors (32). Acupuncture promotes the release of endogenous opioids in the brain, increasing T-lymphocyte transformation function and immune responses (33). Furthermore, the rapid effect of acupuncture in treating depression highlights the role of the endogenous opioid system in this treatment method (34). These findings support the effectiveness of acupuncture in the treatment of chronic pain.

1.6.2. Meditation and mindfulness

Meditation and mindfulness practices are effective alternative treatment methods for pain management. The analgesic effects of mindfulness meditation are provided through the endogenous opioid system. For example, the significant reduction in pain scores after mindfulness meditation indicates that this effect is related to endogenous opioid pathways (35). However, some studies have shown that the pain-relieving effects of mindfulness meditation are not dependent on the endogenous opioid system (36). These conflicting results suggest that more research is needed to better understand the complex mechanisms of meditation and mindfulness practices in pain management.

1.6.3. Nutrition and the Endogenous Opioid System

Nutrition can affect the activity of the endogenous opioid system. Endogenous opioid peptides play a crucial role in regulating feeding behavior. For example, opioid antagonists such as naloxone and naltrexone can reduce the intake of flavored water and food, while opioid agonists can increase the intake of certain foods (37). Additionally, nutrition can modulate the regulation of opioid receptors and peptides in the central and peripheral nervous systems, influencing pain relief and reward processing functions (38). These findings highlight the potential effects of nutrition on the endogenous opioid system and, consequently, its role in overall health.

1.7. Future Perspectives and Research Directions

1.7.1. New Treatment Methods

The endogenous opioid system stands out as a significant target in developing new treatment methods for pain management. The molecular and neuroanatomical features of this system form the basis for new pharmacological and non-pharmacological treatment methods. For example, pharmacological agents such as low-dose naltrexone (LDN) and opioid growth factor (OGF) hold promise in the treatment of various chronic diseases (39). Furthermore, the effects of genetic and epigenetic regulations on the opioid system contribute to the development of personalized treatment strategies (40). These new approaches have the potential to offer more effective and safer treatment methods for opioid addiction and other chronic pain conditions.

1.7.2. Combined Treatments

The integration of the endogenous opioid system with other pain management strategies can enhance the effectiveness of combined treatments. For example, the combination of transcranial direct current stimulation (tDCS) and placebo significantly activates the endogenous μ-opioid system, providing meaningful analgesic effects in pain management (41). Additionally, non-pharmacological approaches such as acupuncture can increase the release of endogenous opioid peptides, helping alleviate pain (42). These combined treatment strategies provide more effective pain management, especially in complex conditions such as chronic pain and neuropathic pain (30).

1.7.3. Genetic and Molecular Research

Research on the genetic and molecular level of the endogenous opioid system allows us to better understand its functioning and role in pain management. Genetic studies reveal the specific roles of opioid receptor genes in various physiopathological conditions. For example, genetic deletion of opioid receptors provides important insights into the role of the opioid system in chronic pain conditions (43). Additionally, modern gene editing technologies such as CRISPR/Cas9 help us understand the dynamics of endogenous μ-opioid receptors under continuous opioid stimulation, providing insights into cellular responses (44). These types of research contribute to identifying new treatment targets and developing personalized pain management strategies.

2. Conclusion

This article has examined the critical role of the endogenous opioid system in pain management and its potential clinical applications. Key findings include the biosynthesis and secretion of endorphins, enkephalins, and dynorphins, their interactions with opioid receptors, and how these processes play a role in analgesia and stress management. Additionally, the effects of stress, exercise, and alternative treatment methods on the endogenous opioid system were detailed.

Optimizing the endogenous opioid system in clinical applications for pain management is important. Specifically, targeting opioid receptors and regulating this system in chronic pain patients can reduce the risk of opioid misuse. Non-pharmacological approaches such as acupuncture and mindfulness can enhance the activation of this system, providing analgesic effects. It is recommended to update clinical protocols to include these approaches.

Future research should focus on better understanding the endogenous opioid system at the genetic and molecular levels. Using modern gene editing technologies such as CRISPR/Cas9, the dynamics of opioid receptors and their roles in chronic pain conditions should be examined. Additionally, the efficacy and safety of new pharmacological agents such as low-dose naltrexone and opioid growth factor should be investigated. These studies will contribute to developing personalized pain management strategies.

Conflict of interest

No conflict of interest to declare.

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Authors' contributions

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