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Insights into the Endogenous Opioid System: An Overview

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Abstract

Pain is a leading cause of medical complaints worldwide, underscoring the essential role of knowledge and use of opioids. Opioids are drugs that directly impact pain processing, immune functions, stress regulation, and more. They originate from opium, which is extracted from Papaver somniferum, a plant native to the Mediterranean region. Opioids are classified as either endogenous or exogenous. The former comprises β-endorphin peptides, enkephalins, dynorphins, and their G protein-coupled receptors, μ, δ, and κ. The group also includes the nocicepin Non-Opioid Receptor (NOP), formerly known as the type 1 opioid receptor. In contrast, exogenous opioids are not naturally present in the body and include drugs like morphine, heroin, and fentanyl, which target the same receptors as endogenous opioids. This study aims to review the essential concepts, applicability, distribution, mechanisms, and structures of the human endogenous opioid system.

Keywords: Opioids; Endogenous opioids; Opioid receptors; Nociception; Pain.

Introduction

Opioids are chemical substances that provide sedative and analgesic effects. The concept of opioids has evolved over time, with several interpretations, including their natural derivation. The original substance in the opioid group is opium, which is extracted from Papaver somniferum, a plant that evolved from wild species in Asia or from a species called P. setigerum, which grew around the Mediterranean [1]. The oldest historical evidence of poppy cultivation dates back 5,000 years and is described in an ideogram as a "plant of joy." In fact, remnants of opium use are found in ancient Greece and among the Egyptians in the 15th century BC. Later, at the beginning of the 19th century, Friedrich Sertürner discovered morphine and also warned of its risks [2].

Pain is one of the main reasons for medical complaints worldwide, and opioids are frequently associated with drug abuse, especially in developed countries. Excessive opioid consumption can result in hyperalgesia, tolerance, dependence, and overdose, which can lead to death [3].

Opioids can be classified into exogenous and endogenous groups, both of which activate the dopaminergic mesolimbic pathway or Reward Zone. This occurs through the μ- (MOR), κ- (KOR), and δ-Opioid Receptors (DOR), which reduces the release of neurotransmitters and breaks the transmission of information from the spinal cord to the brain [1]. Exogenous opioids, such as morphine, are obtained outside the body. In contrast, endogenous opioids, such as endorphins and enkephalins, are naturally produced by the body, regulating important mechanisms for survival [1]. Endogenous peptides act as neurotransmitters, targeting MOR receptors and closely linked to pleasure feelings and euphoria. The first evidence of endogenous opioids' existence dates back to 1975 when John Hughes and Hans Kosterlitz noted a molecule capable of inhibiting acetylcholine release from nerves in the guinea pig ileum [4]. Since then, en-

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dogenous opioids have been the subject of several studies and research [5]. This review will cover current knowledge on the concepts, classification, and mechanisms of endogenous opioids, as well as recent applications within opioids.

Classification of opioids

Opidoids are classified into three categories based on their strength: strong (morphine, pethidine, fentanyl, alfentanil, sufentanil), intermediate (pentazocine, butorphanol, nalbuphine, buprenorphine), and weak (codeine, dihydrocodeine) [1], presenting different actions in the organism. Opioids can also be categorized based on their origin: Natural, semi-synthetic, and synthetic.

Natural opioids are unmodified biomolecules. Opium, derived from the poppy milk of the P. somniferum plant [6], has been used for sedation and analgesia since prehistory. Morphine, a common natural opioid, binds to MOR in the CNS, inhibiting ascending pain pathways and causing generalized CNS depression [6]. Codeine also acts on MOR, and its effectiveness is based on its conversion to morphine in the liver. Papaverine and thebain are other examples of natural opioids [6].

Semi-synthetic opioids are derived from modified natural opioids, usually morphine. Oxycodone, for example, acts by opioid agonism, producing analgesic, anxiolytic, and sedative effects by acting on MOR, KOR, and DOR. Other examples include fentanyl, pethidine, levorphanol, methadone, dextropropoxyphene, and heroin. Originally referred to psychoactive compounds with numbing or paralyzing properties, they are also known as narcotics [6].

Synthetic opioids are fully synthesized in vitro and used therapeutically as potent analgesics. However, they have a greater amount of serious adverse effects when administered in high doses or with other drugs. Fentanyl is an example of a synthetic opioid that can be 50 to 100 times stronger than morphine and 30 to 50 times more potent than heroin, acting mainly on MOR. Other examples include pethidine, alfentanil, sufentanil, methadone, dextropropoxyphene, butorphanol, levorphanol, pentazocine, and benzylmorphine [6].

Opioids can be classified by their function, such as agonist-antagonist, partial agonist, or pure agonist [6]. Pure agonist opioids interact with a receptor to produce a maximal response, presenting high affinity and intrinsic activity at the cellular level. Examples of pure agonists include morphine, diamorphine, pethidine, and fentanyl [6].

Partial agonist opioids, such as buprenorphine and pentazocine, bind to opioid receptors and produce a submaximal effect compared to pure agonists, causing only a partial functional response [6].

Agonist-antagonist opioids trigger a reaction when a drug triggers it, called an agonist. However, if the interaction does not trigger any effect but prevents access to any agonist, it is called an antagonist. Pentazocine is an opioid agonist-antagonist with combined κ-agonist and μ-antagonist activity. Other examples include nalbuphine, nalorphine, levalorphan, butorphanol, and dezocine [7].

Pure antagonist opioids have affinity for receptors but lack intrinsic activity. They are sufficiently similar in structure to agonists to achieve combination with the recognized site, but without producing the biological effect. Naloxone, naltrexone, and nalmefene exhibit relatively high affinity for MOR opioid binding sites and have reduced affinity for other receptors. They can also reverse the effects of agonists at KOR and DOR sites [1].

The role of endogenous opioids

In the 1970s, the discovery of endogenous opioid peptides coincided with the initial growth of the International Narcotic Research Conference (INRC) and marked an important milestone in opioid research [8]. Several researchers gathered in Boston in 1974, at the Neuroscience Research Program, where the binding of opioid receptors was discussed and the first publications on endogenous opioids were launched [9]. The cloning of μ-, κ-, and δ-opioid receptors in 1990 was another significant landmark, allowing integration of previous pharmacological concepts with molecular aspects of the receptors [8]. Subsequently, the recognition of multiple endogenous opioids enabled researchers to advance knowledge of this system in physiology and its implications for understanding pain and opioid dependence [10].

Studies have shown that opioids not only have actions on CNS receptors but also on peripheral sensory neurons, elucidating the way opioids act outside brain receptors and spinal cord [11]. The discovery of opioid receptors in sensory neurons instigated research into tissue inflammatory processes to find endogenous binding peptides [12].

Endogenous opioid peptides that work like hormones are continuously secreted into the circulation by producing glands and conveyed to a variety of distant target tissues where they can induce a response [13]. The opioid system is present throughout the neuroaxis and particularly in pain pathways [14]. Emery and Akil (2020) noted that "The opioid system sits at the point of convergence between many systems, including addiction, stress, affect/mood, eating, sexual behavior, immune function, and others, and influences them all simultaneously" [15]. Thus, the opioid system plays a critical role in maintaining human well-being.

Currently, there are four families of endogenous opioid ligands: endorphins, enkephalins, dynorphins, and nociceptinorphanin FQ (N/OFQ) [14], with only the first three being better elucidated. The release of N/OFQ under stress, fear, or pain is still poorly understood, although it is known to be reduced in patients with severe and chronic pain. Therefore, it probably has a role in the development or maintenance of chronic pain, as well as in other affective disorders, although further research is still needed [16].

Each endogenous opioid family is encoded by a distinct gene, which initially allows the formation of a common precursor protein, such as pre-proopiomelanocortin, pre-proenkephalin, and pre-prodynorphin [17] (Figure 1). The precursors undergo a series of complex cleavage reactions by different enzymes, resulting in prohormones, such as pro-opiomelanocortin (POMC), pro-enkephalin, and pro-dynorphin. Prohormone convertases act, and several peptides are produced, some of which act as opioids [18].

POMC is the common precursor of both β-endorphin and non-opioid hormones, such as α-melanocyte-stimulating hormone and corticotropin-releasing hormone (ACTH) [19]. Each pro-enkephalin molecule contains four met- and one leu-enkephalin, one octa- and one heptapeptide [20]. Finally, pro-dynorphin contributes to the formation of dynorphin A, dynorphin B, and neoendorphin, which have amino acid chains with different lengths, such as dynorphin-A (1-8) and dynorphin-B (1-13).

Nociceptin, derived from pronociceptin, has a structural similarity to dynorphin A [19].

β-Endorphin is present in the anterior pituitary, which is the main site of POMC biosynthesis. However, it can also be found in the nuclei of the basal and medial hypothalamus, as well as in cells of the solitary tract nucleus. Pro-enkephalin and pro-dynorphin-derived peptides are widely distributed in the CNS. However, pro-enkephalin is also significantly distributed in peripheral systems, such as the adrenal medulla and the gastrointestinal tract [19].

There is a purported new family of endogenous peptides known as endomorphins, but its status as an endogenous peptide is not widely accepted. Although it has been reported in the brain, there is no evidence of its precursor, nor is it known whether this peptide is produced by the human body [21].

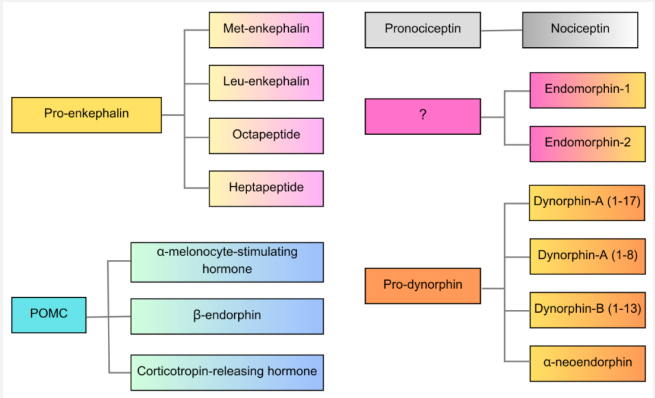

Figure 1: Endogenous opioid peptides derived from prohormones.

The precursor molecule, Pro-Opiomelanocortin (POMC), gives rise to several products, including β-endorphin, α-melanocyte-stimulating hormone, And Corticotropin-Releasing Hormone (ACTH). In addition, other prohormones, such as pro-enkephalin and pro-dynorphin, are also processed to generate distinct opioid peptides. The precursor for the endomorphins, denoted by "?", remains unknown.

The receptors of endogenous opioids

In the mid-twentieth century, the concept of cellular structures capable of recognizing molecules involved in various physiological processes, such as pain processing, immune functions, and stress regulation, was introduced. These structures, called receptors, exhibit high specificity for each molecule, whether endogenous or exogenous [22].

Opioids, which include compounds derived from opium and others that are chemically synthesized, act by binding to specific receptors to produce their characteristic effects. Scientists have long studied these receptors and their endogenous ligands [23].

Opioid receptors are involved in the sensory perception of sight, taste, and smell, as well as providing a response to neurotransmitters, hormones, and drugs. When an opioid drug stimulates the receptor, which is coupled to G protein, it inhibits the enzyme adenylate cyclase, which reduces the intracellular level of cAMP. As a result, calcium-dependent channels at synaptic endings close, leading to decreased neurotransmitter output and receptor activation. Potassium channels remain unaffected, resulting in neuron hyperpolarization and partial blockage of pain stimulus transmission [22]. In neuronal synapses, opioids can act either in inhibitory or excitatory ways through presynaptic or postsynaptic junctions [24].

The endogenous opioid system consists of peptides β-endorphins, enkephalins, dynorphins, and their G protein-coupled receptors, μ, δ, and κ (Table 1). The nociceptin Non-Opioid Receptor (NOR), formerly known as type 1 opioid receptor, is also included in this group [25]. Additionally, a subgroup of receptors represented by μ_1, μ_2, μ_3, κ_1, κ_2, κ_3, δ_1, and δ_2 has been described [24]. Genes encoding δ opioid receptors are located on chromosome 1, while those encoding κ receptors are on the long arm of chromosome 8, and those encoding μ receptors on chromosome 3 [22].

Table 1: Endogenous opioid system: Receptors, ligands, and role.

Receptor	Endogenous Ligand	Ligand Precursor	Action
μ	Endorphin and Endomorphin	Proopiomelanocortin	μ_1 for analgesia and dependence μ_2 for euphoria, dependence, respiratory depression, miosis, constipation μ_3 for vasodilation
κ	Dynorphin	Prodynorphin	Analgesia, diuresis and dysphoria
δ	Enkephalin	Proenkephalin	Analgesia and constipation
NOR	Nociceptin/Orphalin	Pre-pronociceptin	Analgesia and hyperalgesia (concentration dependent)
ζ	-	-	Development regulation in normal and tumor cells

Data obtained from [22].

MOR receptors are associated with endogenous ligands such as β-endorphin, endomorphin 1 or 2, and propiomelanocortin as its precursor. The μ_1 receptor, which has a sensitive binding site for naloxonazine, is related to analgesia and dependence [22]. The μ_2 receptor is selective for morphine and essential for euphoria, miosis, decreased motility/constipation of the digestive tract, respiratory depression, and dependence. The μ_3 receptor is responsible for vasodilation. The group of μ receptors can be found in laminae III and IV of the cerebral cortex, periaqueductal gray matter, gastrointestinal tract, substantia gelatinosa, and thalamus [22].

KOR receptors are associated with dynorphin A and B, with prodynorphin as a precursor. They play a primary role in analgesia and are involved in the control of diuresis and dysphoria. According to recent research, KOR receptors may also be associated with thermoregulation, nociception, and neuroendocrine secretion. They can be found in the hypothalamus, gelatinous substance in the spinal cord, periaqueductal gray matter, and peripheral sensory neurons [24].

DOR receptors, which are activated by enkephalins, having proenkephalin as a precursor [24], have a primary role in analgesia, and may also act in the reduction of gastric motility and

cognitive functions. They are located in the pontine nuclei, tonsils, olfactory bulb, deep cerebral cortex, and peripheral sensory neurons [22].

NOR receptor is associated with nociceptin/orphanin and has pre-pronociceptin as its precursor. It can promote either analgesic or hyperalgesic effects, depending on its concentration. In addition to NOR receptors, there are also reports of the existence of ζ receptors (ZOR), which are present in skin, cornea, and brain cells. ZOR receptors are related to regulatory situations such as developmental events in various tissues or cells, whether normal or tumorigenic [24].

The distribution of opioid receptors throughout the human body can be seen in Figure 2, including in the central and peripheral nervous systems and other organs.

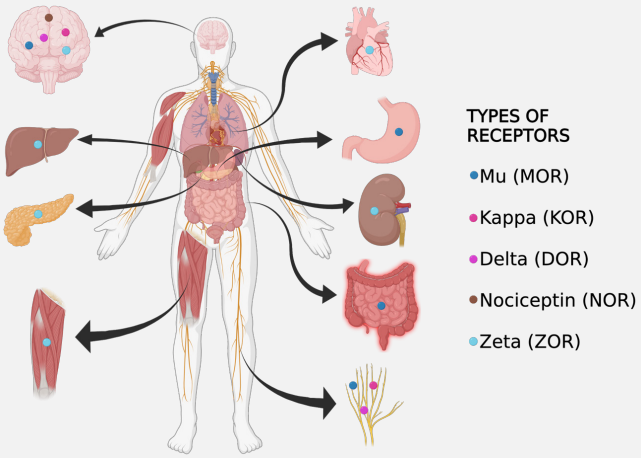

Figure 2: Distribution of Opioid Receptors in the Human Body.

This figure illustrates the distribution of opioid receptors in various parts of the human body. The colored balls represent the location of different opioid receptors, as follows: Dark blue: μ-receptor, found mainly in the central nervous system (CNS), gastrointestinal tract, and other organs such as the heart, lungs, and kidneys. Pink: κ-receptor, predominantly located in the CNS and in the gastrointestinal tract. Magenta: δ-receptor, primarily located in the CNS, including the spinal cord and brainstem. Brown: Nociceptin receptor, found in the CNS and in peripheral tissues such as the adrenal gland, gastrointestinal tract, and immune system. Light blue: ζ-receptor, recently discovered and not yet well characterized, but found in the brain and spinal cord. Figure created with BioRender.com.

The importance of endogenous opioids to modern medicine

Mechanism of action of opioids

Opioid receptor agonists are frequently used for moderate to severe acute pain management. The analgesic effect is mediated by the activation of μ receptor sites located in the brain, brainstem, spinal cord, and peripheral nerve endings, which are associated with pain perception [17].

Opioid receptors belong to the family of 7-transmembrane G-protein-coupled receptors composed of α, β and γ subunits. Upon agonist binding, adenylyl cyclase inhibition occurs, leading to decreased cyclic AMP levels, increased potassium conductance, neuron hyperpolarization, and decreased calcium conductance, ultimately reducing neurotransmitter release (Figure 3) [24].

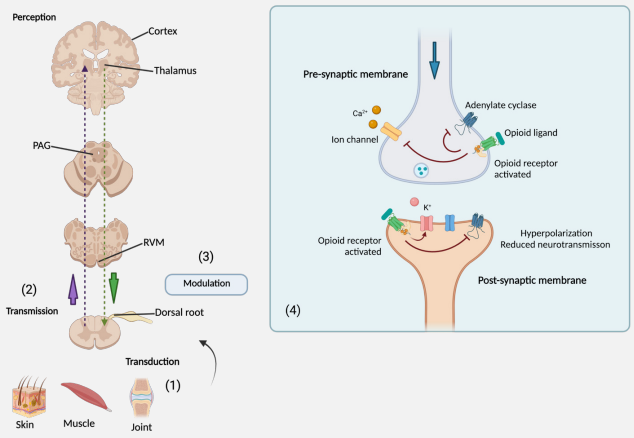

Figure 3: Mechanism of action of opioids.

The processes of pain start with the transduction, which is based on the reception of the nociceptive stimulus by the primary afferent neuron and can come from the skin, muscles, and other regions (1). After this process, transmission, modulation and then perception take place (2). The modulation (3) exerted by opioids can occur in the ascending pathway, through the presence of interneurons and acting on the presynaptic and postsynaptic membrane, and in the descending pathway, in which the endogenous opioid system acts in the midbrain in the Periaqueductal Gray (PAG) and generates activation of other regions such as neurons in the Rostral Ventromedial Medulla (RVM) and consequent release of neurotransmitters that stimulate enkephalin-containing interneurons connected with the dorsal horn and thus inhibit nociceptive transmission. Still, when the opioid receptors are activated by an agonist, they generate inhibition of adenylyl cyclase and consequent reduction in cyclic AMP levels and, thus, an increase in potassium conductance out of the cell, as a result of which there is hyperpolarization of neurons and decreased calcium conductance, so the neurotransmitter release is decreased, as well as neuronal firing (4). Figure created with BioRender.com.

Furthermore, opioids can interact with other molecules and generate processes such as allosteric modulation and biased signaling. In allosteric modulation, there are allosteric binding sites that are separate from the orthostatic site or specific binding region and can positively modulate receptor function and are part of the group of Positive Allosteric Modulators (PAMs) or can modulate in a negative form (group of negative allosteric modulators, NAMs). Thus, these sites are considered as possible therapeutic targets for modulating the activity of the opioid receptor to decrease the probability of developing tolerance or dependence. Different signaling by the same receptor can occur since G-protein-dependent or beta-arrestin-dependent signaling pathways can produce different effects [26].

Agonist binding causes conformational changes and recruitment of G proteins and arrestins, which mediate the inhibitory action of opioid signaling on neurotransmitter release and receptor internalization, respectively. The balance between these signals determines the analgesic and adverse effects of opioids [14].

The perception of pain is a complex physiological process that involves several stages. The initial stage is transduction, which occurs through the activation of primary afferent neurons by nociceptive stimuli. This is followed by transmission, where painful impulses propagate through fast or slow pathways and

end in the dorsal horn of the sensory nerve [27]. Fast pain is generated through stimulation of finely myelinated A-delta primary afferent fibers, while slow pain is generated through stimulation of unmyelinated C fibers. The release of glutamate and substance P is involved in both processes [20]. Transmission then occurs through second-order neurons to the central nervous system via the lateral spinothalamic tract or medial spinothalamic tract [27].

Opioids play a crucial role in the modulation of pain in both the ascending and descending pathways. In the ascending pathway, interneurons in the dorsal horn of the spinal cord inhibit afferent fibers through postsynaptic activation of opioid receptors, leading to hyperpolarization of ascending fibers and presynaptic inhibition of the release of glutamate and substance P. This reduces the upward transmission of pain [20]. In the descending pathway, the endogenous opioid system acts in the Periaqueductal Gray (PAG) in the midbrain, integrating information from cortical and subcortical areas to modulate pain-related behaviors and stimulate analgesia [28]. The inhibitory action of GABA and opioids on PAG neurons results in the activation of serotonergic neurons in the nucleus of the raphe magnus and noradrenergic neurons in the Rostral Ventromedial Medulla (RVM). The neurotransmitters released from this activation stimulate interneurons containing enkephalin in the dorsal horn of the spinal cord, leading to the inhibition of pain perception [20].

The central nucleus of the amygdala is also involved in the analgesia process, as electrical stimulation of this region and the action of opioids produce analgesia. In this scenario, the activity of neurons in the central nucleus of the amygdala that are projected to PAG is limited by the activation of their glutamatergic synaptic inputs and by the inhibition of GABAergic inputs. The activation of MOR receptors inhibits the release of GABA, leading to the disinhibition of neurons in this center and the activation of the descending pain pathway [28].

In addition to analgesia, the endogenous opioid system is also involved in the modulation of other functions such as stress and mood. The stress state is characterized by the sustained release of norepinephrine from the Locus Ceruleus (LC) due to Corticotropin-Releasing Hormone (CRH) from the Paraventricular Nucleus of the Hypothalamus (PVH). Thus, the activation of MOR generates inhibition of Norepinephrine (NE) secretion in the LC to attenuate the central stress response, improving the state. The limbic system, which contains high densities of MOR, is involved in the regulation of mood [24].

Clinical importance of endogenous opioids

The endogenous opioid system is crucial for various biological processes, but the use of exogenous opioids for pain relief is limited by their adverse effects, such as sedation, respiratory depression, and constipation. However, recent studies suggest that DOR receptors may not cause adverse gastrointestinal and respiratory consequences [20]. Exogenous opioids can induce analgesia by inhibiting the substantia gelatinosa in the dorsal horn of the spinal cord and peripheral afferent nerves [24].

It is important to note that endogenous opioids may facilitate pain and promote hyperalgesia, as non-nociceptive stress releases them. The indiscriminate use of opioids is a significant social problem that can lead to increased pain or hyperalgesia [29].

Nonetheless, it is premature to conclude that endogenous opioids facilitate pain, as stress also triggers the release of other peptides involved in pain mechanisms. Therefore, further studies are necessary to investigate the quantity, location, and conditions that affect the release of endogenous opioids [29].

The opioid system plays a vital role in modulating cardiac function, aging, and hypertension, as well as treating conditions such as diarrhea and mood disorders [20]. Still, the important role of the use of opioids in cancer pain, which can be divided into nociceptive pain and neuropathic pain, has been emphasized by recent guidelines such as the American Geriatrics Society, which considers its use effective and indispensable for the pain treatment in elderly patients [30].

Therefore, new generation therapies for chronic pain treatment should focus on neural brain circuits that underlie the negative effects of pain perception, instead of directly targeting the opioid system. This approach can prevent opioid activity in subcortical reward networks, reducing addiction and other side effects. This would have a dual benefit of reducing the suffering of patients with chronic pain and addressing the current opioid epidemic [31].

Adverse effects of opioid use

Opioids are known to produce a wide range of adverse effects that depend on the location of the receptors and the degree of their stimulation. Some of the most commonly reported adverse effects of opioids include respiratory depression, constipation, orthostatic hypotension, endocrine abnormalities, syndrome of inappropriate Antidiuretic Hormone (ADH) secretion, immune dysfunction, mood changes, sleep disturbances, addiction, and tolerance (Figure 4).

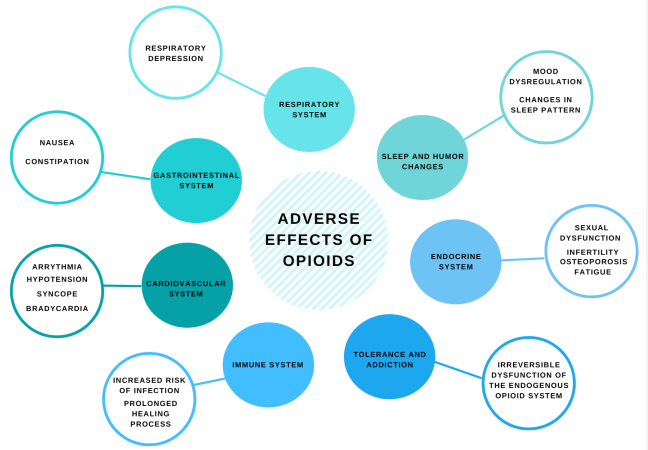

Figure 4: Adverse effects of opioids use.

Respiratory depression is a serious complication that can occur when opioids stimulate the abundant opioid receptors located in the respiratory center in the cerebral cortex, chemo and baroreceptors in the carotid and vagus bodies, and mechanoreceptors in the airways and lungs. This can lead to irregular and slow breathing, hypercapnia, and hypoxia [24]. Unfortunately, currently available opioids are unable to completely avoid the adverse effects related to respiratory depression [32].

Opioid receptors are also present in the autonomic nervous system, which can influence the functioning of the gastrointestinal system through the myenteric nervous system. Activation of these receptors by agonists results in the inhibition of the release of acetylcholine by myenteric neurons and a partial inhibition of the release of inhibitory mediators such as nitric oxide. This leads to a deceleration of intestinal propulsive motility and a decrease in chloride secretion by submucosal secretomotor

neurons. This reduction in movement of chloride-dependent water passage to the lumen ultimately leads to more hardened stools, causing constipation [33].

Cardiac tissue also contains opioid receptors, and their activation generates membrane hyperpolarization and vagus nerve activation, leading to bradycardia and peripheral vasodilation. These changes can result in orthostatic hypotension, syncope, and possible arrhythmias [32].

Long-term opioid therapy can lead to serious adverse effects in the endocrine system, which may be worsened by the presence of other comorbidities. Opioid receptor stimulation in the hypothalamus inhibits GnRH release, leading to decreased estrogen and testosterone secretion, and reduced activity of the hypothalamic-pituitary-adrenal axis, resulting in decreased cortisol levels. These changes can lead to sexual dysfunction, decreased libido, and fertility, and can be associated with conditions such as osteoporosis, osteopenia, hot flashes, menstrual cycle irregularity, mood disorders, and fatigue [32]. Opioid receptor stimulation in the hypothalamus may also be related to the development of Syndrome of Inappropriate Secretion of ADH (SIADH) [24].

Lastly, opioid receptor stimulation can result in immune dysfunction, as receptors are present in Natural Killer (NK) cells and phagocytes. Activation of these receptors can repress the activity of these cells, as well as the complement system, and affect the expression of immunoglobulin receptor and chemotaxis, ultimately impairing the immune system's activity and healing process [32].

Activation of opioid receptors in the middle pontine reticular formation can lead to sleep disturbances and changes in mood, as chronic stimulation of MOR affects neural activity in the hippocampus, leading to dysregulation of mood [24]. Additionally, the development of tolerance and addiction is a significant concern with the use of opioids, as chronic use can cause irreversible dysfunction of the endogenous opioid system, making individuals dependent on exogenous opioids and increasing the risk of hyperalgesia, dependence, and addiction. This process is mainly related to desensitization and uncoupling of MOR from downstream signaling pathways and ion channels, as well as downregulation, receptor internalization, and μ/δ-heterodimer formation [20]. β-arrestins play a role in this process, as they cause receptor internalization and are the targets of studies on morphine's ability to develop tolerance due to variable β-arrestin recruitment activity.

Moreover, chronic opioid use reduces endogenous opioid production, mainly in the locus ceruleus, leading to an increase in norepinephrine secretion, which can cause agitation and hyperexcitability, even after a stressful event [24]. Several ion channel mechanisms are involved in this process of tolerance development, as the acute action of opioids on calcium and potassium channels reduces neurotransmission in a short time, but chronic or abruptly interrupted signaling can generate excitatory synaptic plasticity [14].

Opioid use can have numerous adverse effects, with Opioid Use Disorder (OUD) being a particularly concerning issue. OUD is a recurring condition with a high global incidence and an increased risk of overdose. It is driven by the activation of brain reward neurocircuits and is characterized by a high level of dependence. While rehabilitation is possible, it requires appropriate treatment, and relapse rates are high. Research is ongoing on therapies involving long-term opioid antagonists such as methadone and buprenorphine. However, community-based preventive strategies, harm reduction interventions to minimize adverse consequences of prolonged use, and mutual help groups are also critical. Science can play a crucial role in guiding public policies and discovering information that will improve prevention and treatment techniques for OUD [34].

Final remarks

Endogenous opioids play a crucial role in human life, and numerous studies have been conducted to understand their functions. However, several gaps still exist, such as the need for further research on endogenous ligands such as nociceptin and endomorphin, whose precursors have not been fully elucidated. Additionally, the interaction between endogenous opioids and the immune system, which expresses high levels of opioid precursors and receptors, is poorly understood and requires more investigation. A better understanding of the endogenous opioid system is essential for fully comprehending the activities of exogenous opioids in all body tissues. This knowledge can be used to improve the manufacturing of opioid drugs for managing moderate to severe pain and to facilitate advances in modern medicine. Further research in this field is crucial for the development of safer and more effective opioid therapies that can improve the quality of life for patients.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

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