NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

The effects of morphine administration on the central nervous system (CNS): advantages and disadvantages

Arezou Mehrabi [1], Bahareh Lashtoo Aghaee [2], and Samaneh Farrokhfar [3]*

[1] School of Medicine, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
[2] Ramsar Campus, Mazandaran University of Medical Sciences, Ramsar, Iran
[3] Department of anatomical sciences, Faculty of Medicine, Ramsar Campus, Mazandaran University of Medical Sciences, Ramsar, Iran
* Correspondence: samanefarrokhfar@gmail.com; Tel.: +981155091125

Received: 7 March 2024; **Accepted:** 16 May 2024; **Published:** 26 June 2024
Edited by: Norshariza Nordin (Universiti Putra Malaysia, Malaysia)
Reviewed by: Muhammad Zulfadli Mehat (Universiti Putra Malaysia, Malaysia);
Mohamad Halim Mohamad Shariff (Universiti Teknologi MARA, Malaysia);
Jorge Estevez (Miguel Hernández University, Spain)
https://doi.org/10.31117/neuroscirn.v7i2.348

ABSTRACT: Morphine, a potent opioid analgesic, plays a critical role in pain management but elicits complex effects on the central nervous system (CNS), demonstrating both beneficial and detrimental outcomes. This paper reviews preclinical studies to examine morphine's interactions with the CNS, notably via binding to opioid receptors, leading to analgesia as well as a series of adverse effects, including addiction, tolerance, and neurological impairments. Acute exposure to morphine alters neurotransmitter activity, gene expression, and neuronal firing rates. In contrast, chronic use results in significant neuronal damage, altered memory functions, increased pain sensitivity, and neuroinflammation, highlighting the drug's impact on neurogenesis and neural cell viability. Additionally, morphine's protective properties against neurotoxic insults are discussed, alongside its potential to disrupt cellular and molecular pathways, culminating in neurotoxicity and cognitive deficits. Given the dual nature of morphine's impact on the CNS - protective vs. harmful, depending on specific conditions such as dosage, disease type, and administration frequency - this paper underscores the necessity for further research to untangle this complex interplay to leverage morphine's pain management benefits while minimizing its risks. A thorough evaluation of morphine administration practices can help reconcile these conflicting results.

Keywords: Morphine, CNS, Opioid, Pain management, Preclinical studies, Neurological impairments.

1.0 INTRODUCTION

Morphine, derived from the poppy plant, is a potent narcotic drug widely recognized for its efficacy in managing severe and acute pain (Gach et al., 2011). It has a chemical composition of 17 carbon atoms, 19 hydrogen atoms, one nitrogen atom, and three oxygen atoms, represented by the molecular formula $C_{17}H_{19}NO_3$, as illustrated in **Figure 1**. This intricate structure is essential for morphine's pharmacological actions, as it binds to specific receptors in the CNS to induce pain relief and sedation. The distinct configuration of atoms in morphine's chemical makeup

influences its effectiveness and potential benefits and drawbacks when utilized for medical purposes.

Morphine has been classified as a vital medication by the World Health Organization (WHO), highlighting its significance within the medical community. Extensive research has consistently demonstrated the drug's positive impact on pain reduction, making it a valuable treatment option for both musculoskeletal and neuropathic pain (Teasell et al., 2010). The beneficial effects of morphine on pain relief have been attributed to its interaction with the μ receptor (MOR), as indicated by several studies (Dominguez & Habib, 2013; Gach et al., 2011). This drug is commonly administered to alleviate pain in various scenarios, including post-cesarean section pain (Dominguez & Habib, 2013) pain associated with kidney diseases (Murphy, 2005), different forms of cancer (Roch & van Oorschot, 2020; Schuster et al., 2018), and bone-related issues like fractures (Jahanian et al., 2018).

Also, for many years, drugs such as morphine have been the primary choice for prescribing neurological problems like spinal cord injury. However, it has been downgraded to a less prominent role for several reasons. These include worries about drug safety, the potential for tolerance, dependence, and addiction with prolonged use, as well as the presence of side effects like nausea, headache, and breathing difficulties.

Furthermore, the use of morphine and other opioids has been linked to the opioid crisis, leading to increased caution and scrutiny of their prescription. Consequently, alternative treatments and medications have been explored and recommended for managing neurological problems, including spinal cord injury (Stampas et al., 2020). In a study, it was found that the consumption of elevated amounts of morphine during the early stages of spinal cord trauma can lead to addiction. Moreover, in the long-term, it can harm the recovery and restoration of functionality. However, another study has demonstrated that when used in analgesic doses, morphine does not exhibit addictive behaviors and effectively reduces pain (Stampas et al., 2020).

Studies have shown that persistent activation of dopamine neurons in the ventral tegmental area and decreased responsiveness of opioid receptors following morphine exposure may contribute to the development of addiction and diminished drug efficacy. This phenomenon is linked to the rapid development of tolerance to pain relief and the swift onset of addiction to morphine (Jahanian et al., 2018). Despite the significant and well-defined complications and effects of morphine, it continues to be a preferred drug among healthcare professionals. However, the current consensus among the medical community and most therapists is that the use of morphine should be limited to appropriate treatment settings. Typically, it is administered in a controlled manner within medical centers such as hospitals and clinics, primarily for pain management. This controlled administration may involve a single dose or repeated administration, particularly in cases of chronic diseases.

Today, the widespread use of morphine for pain reduction raises an important question regarding its potential side effects on other cells, particularly nerve tissue, even within the seemingly safe dosage range. This prompts us to inquire about the primary target audience for this drug and the nature of its effects. It is essential for therapists and patients who prescribe or consume morphine to be aware of its potential effects on the cellular levels of the nervous system. In this review study, the mechanism of action of morphine is explained, and the harmful and beneficial impacts of this medication on the CNS are compiled from a range of research studies. Also, the effects of morphine on cellular levels and in the nervous system of animals were considered. Therefore, the results of more than 115 preclinical articles from reliable scientific databases such as Scopus, ScienceDirect, Pubmed and Google Scholar were collected, and their data were analyzed and compared qualitatively.

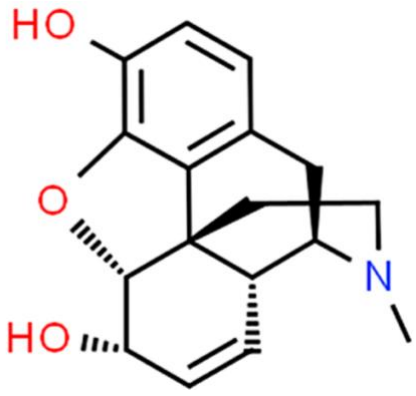

Figure 1: Chemical structure of morphine ($C_{17}H_{19}NO_3$)

1.1 How morphine works in the CNS

Morphine is an analgesic that directly affects the CNS by binding to μ, δ, and κ opioid receptors, effectively relieving pain. Opioid receptors are part of the G-protein coupled receptor group (Gach et al., 2011; Sargeant et

al., 2008; Schroeder & Lewis, 2006; Teasell et al., 2010; Zhang et al., 2019). Additionally, natural opioids like endorphins, endomorphins, and nociceptin exist in the human CNS and primarily participate in pain modulation (Teasell et al., 2010). The main effects of opioids involve the suppression of cAMP synthesis, blocking calcium ion flow, discharge of calcium from internal sources, and activation of potassium channels (Sargeant et al., 2008).

Figure 2 shows the opioid receptor signal transmission path. The use of drugs like morphine, which have both beneficial and adverse effects, can lead to various changes in neuronal activity and gene expression within the nuclei of neurons. These changes occur through intracellular signaling pathways (BOX1), ultimately resulting in altered neuronal function and manifesting in individual behavior (Zhang et al., 2019).

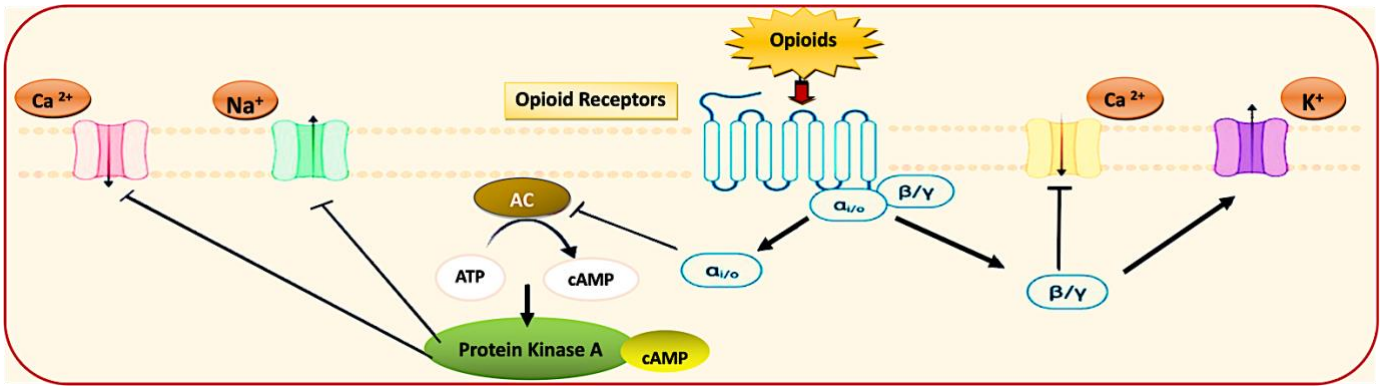

Figure 2: The signal transduction pathway of opioid receptor activation involves binding an agonist to the opioid receptor, which then couples with a heterotrimeric G protein. Subsequently, the G protein undergoes dissociation into its subunits, Gα and Gβγ, followed by the movement of subunit Gα, leading to the inhibition of adenylyl cyclase (AC) activity. The release of subunit Gβγ inhibits voltage-gated (VGCC, L and N-type) calcium (Ca^{2+}) channels and activates potassium (K^{+}) channels (Sakurada et al., 2005).

1.2 Morphine in analgesic pathways

The pathways that transmit pain signals begin with sensory neurons in the skin or other internal tissues. These pain receptors transmit impulses to the posterior region of the spinal cord, which then relay the information to the thalamus. Neurons in the thalamus subsequently transmit pain messages to the cerebral cortex, where they are combined and analyzed. In humans, most of the morphine is metabolized into morphine-6-glucuronide and morphine-3-glucuronide. These metabolites are responsible for their analgesic properties at lower concentrations, but they can induce pain at higher concentration (Sakurada et al., 2005).

At low concentrations (less than 50 mmol in mice and rats), morphine-6-glucuronide, produced from the metabolism of morphine in the body, binds to opioid receptors and induces analgesic properties through the spinal cord. However, at high doses (greater than 30 nanomoles in mice and greater than 100 nmol in rats), morphine instead causes hyperalgesia (increased sensitivity to stimuli) and allodynia (pain response to a normally non-painful stimulus). In this route, morphine-3-glucuronide triggers the discharge of substance P (SP) and glutamate at presynaptic locations, which then activate neurokinin-1 (NK1) and N-methyl-D-aspartate (NMDA) receptors on the postsynaptic membrane. The stimulation of NMDA receptors, facilitated by heightened calcium entry and calmodulin, increases nitric oxide (NO) production. This NO can then be released into presynaptic locations, subsequently triggering the discharge of substance P (SP) and glutamate. At high doses of morphine, contrary to its analgesic properties at low doses, morphine loses its ability to mediate pain through opioid receptors, and its analgesic effects diminish (**Figure 3**) (Gabel et al., 2022; Rueda-Ruzafa et al., 2020; Sakurada et al., 2005).

1.3 Pharmacodynamics of morphine

Morphine can be readily absorbed from all routes of administration except through the skin. The maximum plasma level is reached within 30-90 minutes after oral intake and 15-20 minutes after subcutaneous and intramuscular injection (Glare & Walsh, 1991). Oral administration of morphine leads to extensive first-pass hepatic metabolism. Therefore, subcutaneous or intravenous injections of morphine can achieve suitable blood levels without undergoing first-pass metabolism. Opioids exhibit differing degrees of attachment to plasma proteins before quickly exiting the circulation

and accumulating at high levels in well-vascularized tissues, incorporating the kidneys, brain, spleen, liver, and lungs. Conversely, the presence of the blood-brain barrier results in relatively low concentrations of opioids in the brain compared to other tissues.

Morphine undergoes rapid hepatic glucuronidation, forming two biologically active derivatives, morphine-3-glucuronide and morphine-6-glucuronide, which are subsequently excreted through renal pathways. Conjugated compounds with glucuronide are also present in bile, but due to hepatic enterohepatic circulation, only a limited amount of the drug is discharged through this route (Ofoegbu & Ettienne, 2021; Thigpen et al., 2019). In pharmacodynamics, various factors influence morphine's effects. For example, in a study on the metabolism of morphine in pediatric patients, it is observed that, in addition to body weight, OCT1 genotypes have a significant impact on the processing of morphine when administered intravenously. The higher prevalence of defective OCT1 alleles among Caucasians may lead to decreased elimination of morphine and potentially a greater likelihood of detrimental effects compared to African-American children (Fukuda et al., 2013).

2.0 DIVERSE EFFECTS OF MORPHINE ON CNS

2.1 Destructive role of morphine in the CNS

Morphine is a potent narcotic drug commonly used for pain relief. However, it can also harm the brain and spinal cord neurons. Morphine acts by attaching to opioid receptors located in the spinal cord and brain, which can lead to several adverse effects on neuronal cells. Morphine binds explicitly to a set of mu-opioid receptors (MORs) on the surface of brain and spinal cord neurons. This binding activates a signaling pathway that prevents the transmission of neurotransmitters such as glutamate and substance P, which are involved in pain perception and other physiological functions. One of the main ways in which morphine can be detrimental to neurons is through cell death (Li et al., 2023; Yang et al., 2018) Investigations have indicated that prolonged and continuous exposure to morphine can lead to apoptosis or programmed cell death in neurons. Research has revealed that morphine causes neuronal apoptosis in multiple brain regions, including the hippocampus, cerebellum, and cerebral cortex. This can impair brain function and cognitive disturbances (Asuni et al., 2021; Wang et al., 2020).

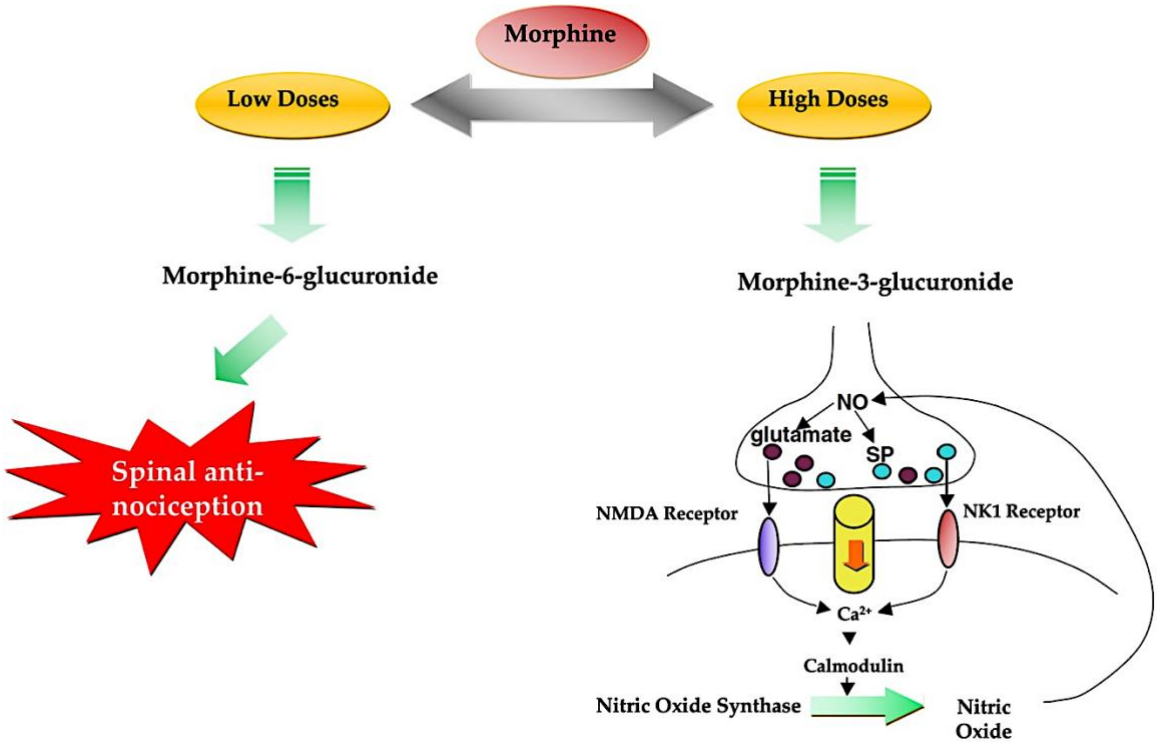

Figure 3: The analgesic pathways of morphine. Low doses of morphine are metabolized to morphine-6-glucuronide, which produces spinal analgesic properties. High doses of morphine are converted to morphine-3-glucuronide, leading to an increased release of glutamate and substance P (SP) in the presynaptic terminal. Glutamate and SP, acting on N-methyl-D-aspartate and NK1 receptors, respectively, in the postsynaptic site, increase calcium influx, producing nitric oxide. Nitric oxide is then released back into the presynaptic terminal, further enhancing the release of glutamate and SP.

The addition of morphine has been found to increase neurotoxicity in cultured human neuronal cells. The co-occurrence of morphine and human immunodeficiency virus (HIV) has been shown to lead to the apoptosis of neurons, astrocytes, and glial precursors in the striatum of mouse models. This highlights the need for further investigation into the neurological effects in individuals with morphine addiction and HIV infection. In experiments using mouse cortex neurons, researchers have observed that morphine induces an increase in lactate dehydrogenase release caused by beta-amyloid and activates caspases 2 and 3 (Harburg et al., 2007). The administration of morphine to mice at a dosage of 20 mg/kg for 12 days led to the initiation of apoptosis in the hippocampal neurons and the deterioration of their spatial memory (Lu et al., 2010). Additionally, rats that received morphine treatment at doses of 2.5, 5, and 7.5 mg/kg per day over 3 days displayed impaired spatial memory function and reduced neuronal distribution in the hippocampus (Jahanshahi et al., 2014). Morphine can also induce modifications in the morphology and activity of neurons. For instance, it can potentially modify the activity of particular genes and proteins that play a crucial role in signaling and neural communication. It has been shown that morphine can modulate gene expression in various regions of the brain, comprising the amygdala and nucleus accumbens, which may lead to changes in behavior and addiction (Khazali & Mahmoudi, 2019; Rouhani et al., 2019; Ucha et al., 2019).

Morphine can disrupt synaptic plasticity, which involves the capacity of synapses to modify their strength and connectivity in reaction to stimuli (Drastichova et al., 2021). It has been shown that morphine induces synaptic vulnerability in various areas of the brain, including the hippocampus and prefrontal cortex. This can lead to disruptions in neural networks and impairments in learning, memory, and other cognitive functions (Drastichova et al., 2021; Khani et al., 2022; Kupnicka et al., 2020). Morphine also has the potential to induce inflammation in neuronal cells. Inflammation is a natural response to injury or infection, but it can lead to damage and dysfunction when it occurs in neuronal cells. Neuroinflammation refers to inflammation in the brain mediated by immune cells called microglia and astrocytes. It has been found that morphine activates microglia and astrocytes, leading to neuroinflammation in various areas of the brain, including the spinal cord and cerebral cortex. This can result in chronic pain and other neurological symptoms such as depression and anxiety, as well as play a role in the onset of neurodegenerative conditions such as Alzheimer's and Parkinson's (Chen et al., 2020; Guan et al., 2021; Rahimi et al., 2021).

Another adverse effect of morphine on neuronal cells is its ability to alter the levels of neurotransmitters. Neurotransmitters are chemical substances that allow communication between nerve cells, and changes in their levels can disrupt normal brain function. Research has indicated that the use of morphine leads to a decrease in dopamine levels, a neurotransmitter that is essential for reward and motivation (Harburg et al., 2007). Studies have previously indicated that excessive morphine consumption can potentially cause damage to the nervous system in animals. It has also been reported that prolonged and continuous use of morphine induces cell death in diverse regions of the brain and spinal cord of a rat, including the cortical, frontal, striatal, posterior, entorhinal, perirhinal, and hippocampal areas.

In general, while morphine can be an effective analgesic, its detrimental effects on neurons highlight the importance of careful monitoring and management of its use. As a result, morphine has a destructive role on neuronal cells by inducing neuronal apoptosis, synaptic vulnerability, neuroinflammation, and gene expression changes. These effects can lead to cognitive impairment, chronic pain, neurological disorders, addiction, and other negative consequences.

2.2 The impact of single doses of morphine on the CNS

A study by Willner et al. (2014) showed that exposure to various morphine doses in a cell culture environment (as a single dose for 24 hours) reduced the proliferation of neural precursor cells. Additionally, in a clinical dose that induces addictive behaviors, the expression of active caspase-3, which is a factor in cell death, was increased. Furthermore, their research has demonstrated that morphine promotes the differentiation of neurons and glial cells while simultaneously reducing self-renewal in these cells, decreasing the number of nestin-expressing cells (Willner et al., 2014). Another study reported that different DNA methylation occurs in the administration of a single dose and chronic use of morphine in various regions of the rat brain (Barrow et al., 2017). Anghel et al. reported in a study that in the hypothalamus, short-term exposure to morphine led to an increase in the expression of 39 genes (at least 2-fold) and a decrease in the expression of 6 genes (Anghel et al., 2010). In research conducted by Ding et al. (2023), it was demonstrated that physical dependence on opioid substances like morphine occurs in non-human primates after exposure to analgesic doses of these substances in the short term.

Furthermore, in a study by Espinosa et al., they considered the downregulation of PC2, PC1/3 (a key regulator of many neurohormones), and P-CREB genes by morphine during short-term use as a signal against the increased expression of these genes in long-term morphine treatment, which could potentially shift drug use towards substance abuse (Espinosa et al., 2008). In research conducted by Cichewicz et al. (2001), the examination of Western blot data indicated a significant reduction in the levels of all three types of opioid receptor proteins (mu, kappa, delta receptors) in the midbrain of mice after short-term exposure to morphine. In 2021, Muchhala et al. conducted electrophysiological experiments that demonstrated exposure to 10 µM morphine for a duration of 15 to 18 hours in laboratory conditions resulted in the emergence of acute adaptation in wild-type neurons β-arrestin-2, without causing damage to the neurons themselves (Muchhala et al., 2021).

In a human study conducted by researchers, it has been shown that the administration of morphine during infancy does not have an impact on cognitive, neurological function or heat sensitivity in preterm infants without brain injury during early life. However, a substantial correlation (with coefficients ranging from 0.60 to 0.85) has been identified between gestational age, the frequency of procedures, morphine usage, and brain volume (Muchhala et al., 2021; Valkenburg et al., 2015). Moreover, in the report by Bian et al. (2022), research has shown that a solitary administration of morphine can induce behavioral sensitization in rats. This phenomenon shows a strong correlation with the dose of the drug and the withdrawal time. In Zhang et al.'s study, it was discovered that administering a one-time dose of morphine to rats has enduring impacts on dopamine neuron activity (Zhang et al., 2008). Ali et al.'s research also showed a one-time exposure to morphine that triggers a sustained and reduced reaction in the dopaminergic terminal areas of the rat's putamen (Ali et al., 2004).

Furthermore, Pirnik et al. (2001) discovered that a solitary dose of morphine affects plasma corticosterone levels and the primary gene of the NMDA in the adrenal gland but does not have an impact on the hippocampus. Another study also demonstrated that a single morphine administration leads to a decrease in c-Fos expression in the central amygdala of rats, persisting for 24 hours (Jin et al., 2004). Besides, Farhani and colleagues discovered that acute application of morphine reduces the firing rate of locus coeruleus neurons and alters action potential characteristics (Farahani et al., 2023). In the study by Nowycky et al. (1978), it was shown that a solitary dose of morphine usage results in a prolonged and diminished response to dopaminergic terminals within the putamen of rats. They also revealed that a single administration of morphine (20 mg/kg intraperitoneally) leads to a progressive and sustained rise in the firing rate of dopamine cells. This gradual increase is linked to a corresponding gradual buildup of the dopamine metabolite, dihydroxyphenylacetic acid (DOPAC) (Nowycky et al., 1978). As shown in **Table 1**, the effect of limited use of morphine on the CNS is summarized.

2.3 The effect of multiple doses of morphine on CNS

Occasionally, for therapeutic reasons, especially in chronic diseases, morphine consumption is common. A previous study on the brain of morphine-resistant rats showed that the addition of morphine inhibits calcium absorption stimulated by depolarization without affecting absorption under non-depolarization conditions. This study also demonstrated that adaptive changes in calcium uptake at synaptosomes exposed to morphine could play a role in the development of drug tolerance and addiction. However, the way morphine affects calcium absorption by synaptosomes separated from acute morphine tolerance is different from its effect in chronic morphine tolerance (Konno & Takayanagi, 1982).

In a similar experiment conducted on mice, Wang et al. (1989) examined the influence of morphine on calcium uptake in brain synaptosomes using two different methods: centrifugation and filtration. They observed that the presence of morphine decreased calcium uptake using both methods. However, after the animals developed tolerance and dependence due to morphine pellet implantation, an increase in synaptic calcium uptake was observed (Wang et al., 1989). Another study reported that in a 7-day consumption model in mice, morphine increases pain sensitivity and enhances microglial activity in the area of nerve injury (Li et al., 2019). Research indicates that in the nervous system, drugs such as morphine can alter the pathophysiology of spinal cord injury and lead to further loss of neural tissue, exacerbation of inflammatory responses, and increased macrophages at the site of injury (Aceves et al., 2019). It has been established that morphine use enhances the emergence of chronic pain, both in animal models and human studies (Woller et al., 2012). The protein that binds to the response element of cyclic-AMP, also known as CREB, and ΔFosB are two influential transcription factors in controlling the expression of genes in the nervous system.

Locus coeruleus is a model for studying some molecular-level changes that lead to the enhancement of the cAMP pathway. This upregulation in the brain is similar to the mechanism of action during drug dependence or withdrawal, in which CREB plays a central role. Repeated use of drugs increases the expression of CREB in the mentioned model, which is consistent with the repeated use of morphine. On the other hand, repeated drug use induces ΔFosB in the nucleus accumbens and posterior striatum, which can lead to molecular changes even long after drug cessation. Additionally, induction of ΔFosB expression also increases locomotor responses to morphine (Nestler, 2001).

Table 1: The effect of limited use of morphine on the CNS

Study Design	Key Results	References
In vitro	• Reduction in neural precursor cell proliferation. • Increase in caspase 3 activity. • Induction of neuronal and glial differentiation. • Decrease in autophagy.	Willner et al. (2014)
In vivo (Rat)	• Differential DNA methylation in different brain regions.	Barrow et al. (2017)
In vivo (Rat)	• Gene expression changes in the hypothalamus.	Anghel et al. (2010)
In vivo	• Emergence of physical dependence.	Ding et al. (2023)
In vivo (Rat)	• Downregulation of gene expression (P-CREB, PC2 and PC1/3).	Espinos et al. (2008)
In vivo (Mice)	• Decrease in opioid receptor proteins (mu, delta, kappa) in the midbrain.	Cichewicz et al. (2001)
In vitro & In vivo	• Induction of acute tolerance in wild-type neurons of β-arrestin-2.	Muchhala et al. (2021)
In vivo (Zebrafish)	• Development of behavioral sensitization.	Bian et al. (2022)
In vivo (Rat)	• Long-term effects on dopamine neuron activity.	Zhang et al. (2008)
In vivo (Rat)	• Reduced and prolonged response in dopaminergic terminal endings in the putamen.	Ali et al. (2004)
In vivo (Rat)	• No effect on the concentration of mRNAs encoding NMDAR1 within the hippocampus and anterior pituitary.	Pirnik et al. (2001)
In vivo (Rat)	• Inhibition of the c-Fos activity within the central amygdala.	Jin et al. (2004)
In vivo (Rat)	• Increase in action potential duration.	Farahani et al. (2023)
In vivo	• Increase in firing rate of dopamine cells.	Nowycky et al. (1978)

In numerous studies, it has been observed that repeated use of morphine in rats leads to memory impairment (Eisch et al., 2000). In research by Jiang et al. (2021), it was demonstrated that morphine synchronizes somatostatin and parvalbumin interneurons in the prefrontal cortex, inhibiting pyramidal neurons and increasing reward. The findings of Chahkandi et al. in 2015 showed that both acute and chronic morphine use increases blood glucose levels as the primary source of brain energy (Chahkandi et al., 2015). Furthermore, Soto-Montenegro et al. (2022) identified diverse patterns of brain glucose metabolism associated with morphine use in Lewis and Fischer 344 mice using neuroimaging. Lapierre et al. (2021) discovered that Beclin1 has a regulatory function in the release of inflammatory molecules in glial cells after being exposed to morphine and Tat (an HIV protein). They suggested that a decrease in glial-Beclin1 might offer protection for neurons under stressful conditions, such as exposure to morphine and Tat. In 2022, Chen et al. revealed that prenatal exposure to morphine leads to an elevation in gamma oscillations and enhanced theta coherence within the reward system of mice (Chen et al., 2022). In another study conducted on mice, it has been shown that prenatally administered morphine affects male offspring more than females, causing impairments in attention and task accuracy, which indicates the vulnerability of males to executive dysfunction in

response to prenatal opioid exposure, evidence for disrupted neuron-microglial signaling (Chen et al., 2022).

In contrast, Khani and colleagues demonstrated that giving morphine to adult rats leads to decreased spatial memory and synaptic plasticity in the dorsal hippocampus (Khani et al., 2022). Liu et al. discovered that morphine dependence in rats inhibits the production of new neural precursor cells in the granular layer of the hippocampus and decreases levels of cAMP, pCREB, and BDNF within the hippocampus (Liu et al., 2018). Research indicates that prolonged usage of morphine and heroin diminishes the formation of new neurons in the dentate gyrus of adult rats and suppresses this process in the hippocampus (Cao et al., 2002; Eisch et al., 2000). Moreover, Jimenez-Gonzalez et al. stated that morphine delays the differentiation of neural stem cells through excessive Nestin expression (Jimenez-Gonzalez et al., 2018). Nevertheless, in a separate investigation, it has been shown that the consumption of morphine by adult rats results in heightened neural stem cell differentiation and dendritic growth in the dentate gyrus. This research group attributed this effect to the increased activity of MOR receptors in these cells after being exposed to morphine (Zhang et al., 2019).

In a review article, it was mentioned that a common factor involved in neurogenesis in embryonic, postnatal, and adult neural structures is astrocytic lineage neural precursor cells, which are influenced by opioids in their proliferation (Sargeant et al., 2008). A study has shown that the activity of the three opioid receptors (mu, kappa, and delta) affects the behavioral maturation of cells (Hauser & Mangoura, 1998). Another study demonstrated that morphine administration considerably reduces the differentiation of neural cells in terms of phenotype and genotype in a culture medium (Dholakiya et al., 2016). It was also mentioned in the book "Neural Repair" that any drug, such as morphine, that increases adenosine monophosphate (AMP) expression hinders the repair process (Young, 2014).

While some researchers, such as Mandyam et al. (2004), have shown that chronic opioid treatment reduces proliferation and pre-mitotic phase in mice, others, like Holmes and Galea (2002), have reported that opioid exposure enhances the growth of precursor cells in the hippocampus. Exposing young rats to morphine has been discovered to diminish corticogenesis by lowering the density of somatosensory inputs, with no impact on cortical thickness (Sargeant et al., 2008). Zhang et al. (2016) demonstrated that morphine consumption in mice leads to a reduction in adult neurogenesis, accompanied by impaired maturation of neural stem cells. Research has indicated that morphine reduces the synthesis of DNA in cultured type 1 astrocytes derived from rat brains at an early stage of development (Sargeant et al., 2008). However, other studies have shown that the sensitivity of astrocytes to opioids depends on developmental age and the precise origin of the cells. The impact of morphine on proliferation and differentiation in complex live models is not inhibitory or stimulatory. Overall, this review article suggests that endogenous opioids are regulators of neurogenesis, which depends on the brain area and developmental age before and after birth (Sargeant et al., 2008).

Feizy et al. (2016) indicated that the survival of stem cells isolated from the telencephalon of rat embryos decreased in a morphine-treated culture medium. It has been observed that opioids have more inhibitory influences on cell proliferation in culture medium, and their effects on cell growth and production of DNA in the developing brain are dependent on age, duration of use, and the specific brain region under investigation (Eisch et al., 2000; Sargeant et al., 2008). Another study reported that morphine inhibits neurogenesis in adult mice and affects memory through a PKCε/Prox1 pathway (Fan et al., 2018). All addictive drugs, including narcotics, act on a common pathway involving the transmission of dopamine from the ventral tegmental zone to the nucleus accumbens. Additionally, these substances also share the effect of reducing neurogenic function in the hippocampus (Chambers, 2013).

Chen et al. stated that morphine inhibits glutamatergic input to dopaminergic neurons in the ventral tegmental area and stimulates dopamine neurons (Chen et al., 2020) . Additionally, apoptosis in this region is induced by increased lactate dehydrogenase release following morphine consumption (Nyberg, 2009). Assunção-Silva et al. (2015) also indicated that prolonged morphine administration in rats can abnormally hasten programmed cell death, leading to elevated expression of the proapoptotic Fas receptor protein and reduced expression of the antiapoptotic Bcl-2 oncoprotein in the cerebral cortex. In a similar study conducted in culture medium, prolonged use of morphine significantly and in a dose-dependent manner decreased the quantity of cultured neural cells obtained from embryonic mouse hippocampal cells (Nyberg, 2009). It has been observed that this drug inhibits cellular growth and induces apoptosis through the upregulation of proapoptotic Fas

receptor protein expression and downregulation of antiapoptotic Bcl-2 expression in human embryonic neurons and microglia (Nyberg, 2009). Several research teams also reported that long-term addiction to morphine results in reduced neurogenesis in the hippocampus, impaired memory function, altered emotional-cognitive responses, and increased anxiety levels in male rats (Eisch et al., 2000; Famitafreshi et al., 2015; Nestler, 2001). Another study, while highlighting the adverse impacts of morphine on neurogenesis in the hippocampal region of mice, suggests an inverse relationship between neurogenesis and the level of morphine dependence. It also indicates that proliferation in the subgranular zone decreases at higher levels of morphine dependence (Fischer et al., 2008).

Furthermore, it was revealed that repeated treatment with morphine considerably diminished cellular proliferation in the hippocampus of morphine-dependent rats, while also decreasing the expression of neural cell adhesion molecule for cell-cell interactions and altering the phenotype of glial cells (Kahn et al., 2005). All addictive drugs affect the function of dopaminergic synapses in the nucleus accumbens (Fürst et al., 2013). It has been suggested in a study that morphine, in addition to inhibiting growth and inducing apoptosis, can also hinder the repair of damaged nerve cells through its toxic effects (Nyberg, 2009). Exposure to morphine in adult rat neural stem cells can greatly accelerate the biosynthesis of dihydrotestosterone and estradiol (Feizy et al., 2016).

In the study by Farrokhfar et al. (2020), it was shown that the treatment of neural progenitor cells with morphine can hurt their morphology and gene expression, inducing a process of dedifferentiation. In another study by Zhaleh et al. (2020), it was observed that exposure of mesenchymal stem cells from bone marrow (BM-MSC) to morphine, in a time-dependent manner, increases cell death and reduces cell proliferation. However, they prevented the destructive process by changing the *in vitro* culture microenvironment (Zhaleh et al., 2020). It has been demonstrated in a study that simultaneous use of morphine with radiotherapy should be avoided in the treatment of certain cancers such as breast and cervical cancer, which may be a subject of discussion and contemplation for nervous system cancers (Naderi et al., 2019). Moreover, it was discovered that morphine disrupts the integrity of neural stem cells and reduces their ability to induce angiogenesis by inducing p53 and simultaneously increasing the activities of aromatase and 5-alpha reductase, particularly within the first 48 hours (Abdyazdani et al., 2017). Another study by Feizi et al. showed that in adult rat neural stem cells, when subjected to morphine, can greatly accelerate the biosynthesis of dihydrotestosterone and estradiol (Feizy et al., 2016).

Administering morphine shortly after a spinal cord injury increases the presence of microglia and macrophages in the injured area and changes the synthesis of neuropeptides by these cells, thus modifying the innate immune response (Terminel et al., 2022). Darvishi and Saadat mentioned in their research that prolonged morphine exposure leads to cellular aging in neural cells by reducing telomere length (Darvishi & Saadat, 2022). Besides, Zhang et al. reported in 2016 that morphine can reduce glutamate-induced apoptosis in astrocytes. They demonstrated that morphine reduces excitotoxic apoptosis mediated by glutamate in astrocytes by regulating calcium ion release and endoplasmic reticulum stress (Zhang et al., 2016). Additionally, Kashiwagi et al. showed that tolerance to morphine was developed after 7 days of intrathecal injection in rats. They reported a decrease in gamma coactivator-1alpha in dorsal horn neurons of the spinal cord and an increased delay in response to a hot plate in these animals (Kashiwagi et al., 2021).

In 2020, Osmanlıoğlu et al. (2020) reported that morphine elevates neuronal apoptosis, oxidative stress, lipid peroxidation, caspase-3 and caspase-9 levels, as well as neuroinflammatory cytokines (IL-1β, TNF-**α**, IL-6). They also stated that the adverse impacts of morphine-induced neurodegeneration occur via the activation of TRPM2 (a calcium-permeable cation channel) and excessive production of oxidative and nitric oxide stress. They suggested that inhibition of this channel may modulate morphine-induced neurodegeneration in the hippocampus (Osmanlıoğlu et al., 2020). In a different study, Feizy et al. (2016) investigated the corticotropin-releasing factor receptor (CRFr) and corticotropin-releasing factor (CRF) in the terminal bed nucleus of the stria terminalis (BSTal) in mice that were administered either saline or increasing doses of morphine for 14 days. There was no significant variance in the total number of axon terminals or the frequency of contact between these terminals and dendrites observed between the saline and morphine treatment groups. This suggests that morphine has no impact on the presence of CRF axons in the BSTal. These findings have significant consequences for the changes linked to drug abuse in the brain's stress response, potentially influencing the drive for ongoing substance consumption in addiction (Feizy et al., 2016; Jaferi et al., 2009).

In 2020, a study by Zhang & Zhai (2020) demonstrated that the administration of morphine led to enhanced expression levels of orexin1 receptor (OX1R) and c-FOS, as well as increased levels of proteins c-FOS and p/t-ERK/PKC through exogenous morphine administration. Besides, found that exposure to morphine led to a decrease in the nicotine-induced upregulation of nicotinic receptors and a reduction in voluntary nicotine consumption in a mouse model (Avelar et al., 2022). A study revealed that prolonged morphine consumption alters the expression and distribution of platelet-derived growth factor type B (PDGF-B) and platelet-derived growth factor beta (PDGFR-β) in the dorsal root ganglia and spinal cord of male rats (Cansız et al., 2022). The same study also reported that morphine reduces the neurotoxic effects of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the embryonic zebrafish by regulating the balance of oxidative/antioxidant and acetylcholinesterase activity (Cansız et al., 2022).

Furthermore, Doyle and colleagues reported that the development of tolerance to analgesia in mouse models is linked to the inactivation of mitochondrial superoxide dismutase (MnSOD) and the formation of peroxynitrite (PN) in relevant supraspinal sites. They also found that simultaneous administration of morphine with potent peroxynitrite scavengers based on manganese porphyrin reactivated the activity of the MnSOD enzyme, reduced nitroxidative stress derived from PN, and prevented the development of morphine-induced analgesic tolerance (Doyle et al., 2009). Lyu and Li's 2022 study reveals that prolonged administration of low-dose morphine can trigger endoplasmic reticulum stress and that inhibiting exosomal protein 4-PBA or TUDCA can improve the pain-relieving properties of morphine in cases of neuropathic pain (Lyu & Li, 2022).

Amini et al. reported in a study on pheochromocytoma-derived PC12 cells from the adrenal medulla of rats with neural crest origin that low concentration of morphine increases cell survival and suppresses cellular toxicity, cell death, and mitochondrial membrane potential formation compared to cells treated with nicotine, and also reduces intracellular and mitochondrial calcium levels (Amini et al., 2019). Reymond and colleagues investigated the impact of morphine at three varying concentrations (1, 10, and 100 µM) over 24 and 48 hours on human cerebral microvascular endothelial cells in their research. They discovered that the exposure to morphine resulted in the disturbance of the Nrf2 pathway and mitochondrial abnormalities in these cells, demonstrating a potential imbalance in redox status in human cerebral endothelial cells (Reymond et al., 2022).

Furthermore, Kong et al. (2019) showed in their study that morphine prevents the accumulation of PTEN-induced putative kinase1 resulting from mitochondrial damage in neurons. It hinders the entry of Parkin into impaired mitochondria and suppresses the catalysis of mitochondrial ubiquitin proteins by Parkin. Consequently, morphine hinders the identification of impaired mitochondria by autophagosomes via LC3 and sequestosome-1 (SQSTM1/p62), impeding autophagy and causing an increase in SQSTM1/p62. This ultimately prevents damaged mitochondria from reaching lysosomes for degradation, leading to the generation of potent ROS and the development of morphine tolerance (Kong et al., 2019). Another study also stated that cocaine, in addition to morphine, interferes with the activity of mitochondrial complex I in isolated brain and liver mitochondria, with a more pronounced impact on the liver (Cunha-Oliveira et al., 2013).

However, Nylander and colleagues stated that morphine does not affect mitochondrial morphology, unlike other opioid substances (Nylander et al., 2021). Some studies have also discussed the protective impacts of morphine on mitochondria. Feng et al. found that endomorphin 1/2 and morphine can shield brain mitochondria from oxidative stress induced by reoxygenation in experimental settings. This protective effect may significantly mitigate damage during ischemia-reperfusion injury and neurodegenerative diseases (Feng et al., 2008). Cansız and colleagues also stated that morphine reduces the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a neurotoxic intermediate in dopaminergic mitochondria by regulating the balance of oxidants/antioxidants and acetylcholinesterase activity in fetal guinea pigs (Cansız et al., 2022). **Table 2** provides a summary of the impact of repeated morphine use on the CNS.

2.4 The protective roles of morphine in the CNS

Numerous substances that are addictive can interfere with the regular operation of the brain. Since most neurons cannot regenerate, this can lead to long-lasting or permanent impairment of neurological function (Zhao et al., 2006). Misuse of addictive substances like morphine can lead to hyperexcitability in the CNS, as well as cognitive and behavioral impairments and potentially irreversible nerve damage (Parrott, 2018). The main mechanisms involved in these processes include imbalances in intracellular and extracellular ions, the generation of free radicals, toxicity, and inflammation, eventually leading to the death of cells (Arabian et al., 2018b).

Table 2: Summary of the impact of repeated morphine use on the CNS.

Study Design	Key results	References
In vivo (Rat)	• Stimulated calcium absorption inhibition. • Synaptosomal calcium uptake adaptive changes.	Konno and Takayanagi (1982)
In vivo (Mice)	• Decreased calcium absorption. • Increased synaptosomal calcium uptake.	Wang et al. (1989)
In vivo (Mice)	• Increased pain sensitivity. • Increased microglial activity at the site of injury to the tibial nerve.	Li et al. (2019)
In vivo (Rat)	• Increased loss of neural tissue • Exacerbation of inflammatory response • Increased macrophages at the site of injury	Aceves et al. (2019)
In vivo (Rat)	• Increased neuropathic pain	Woller et al. (2012)
In vivo (Rat)	• Increased expression of the transcription factor CREB. • Induction of the transcription factor ΔFosB • Increased locomotor responses	Nestler et al. (2001)
In vivo (Rat)	• Coordinated modulation of somatostatin and parvalbumin interneurons in the prelimbic cortex. • Suppression of pyramidal neurons • Increased reward response.	Jiang et al. (2021)
In vivo (Mice)	• Increased blood glucose levels	Chahkandi et al. (2015)
In vivo (Mice)	• Increased gamma oscillations and theta coherence in the reward system of prenatally exposed mice. • Greater vulnerability of males to executive function deficits.	Chen et al. (2022)
In vivo (Rat)	• Impairment of spatial memory. • Synaptic plasticity in the posterior hippocampus in mature individuals over time.	Khani et al. (2022)
In vivo (Rat)	• Reduction in the proliferation of neural precursor cells in the granular layer of the hippocampus. • Decrease in the levels of layers cAMP, pCREB, and BDNF in the hippocampus.	Liu et al. (2018)
In vitro (Mice & Human)	• Delayed differentiation of neural stem cells through excessive Nestin expression.	Jimenez-Gonzalez et al. (2018)
In vivo (Rat)	• Increased differentiation of neural stem cells. • Expansion of dendrites in the dentate gyrus. • Heightened MOR receptor expression.	Zhang et al. (2019)
In vitro	• Decreased differentiation of neuronal cells in terms of phenotype and genotype.	Dholakiya et al. (2016)
In vivo (Rat)	• As a result of corticogenesis, there is a decrease in the density of somatosensory neurons. • Reduction in DNA synthesis in cultured type 1 astrocytes.	Zhang et al. (2016)
In vitro	• Reduction in adult neurogenesis. • Hindered development of neural stem cells.	Young (2014)
In vitro	• Decreased survival of neural stem cells isolated from the subventricular zone of rat embryos. • Suppression of immunity through induction of apoptosis in T lymphocytes and macrophages.	Feizy et al. (2016)
In vivo (Mice)	• Inhibition of neurogenesis in adult mice. • Decreased neurogenic activity in the hippocampal region.	Fan et al. (2018)

Continued on the next page …

In vitro & In vivo	• Inhibition of dopaminergic neurons in the ventral tegmental area. • Activation of dopaminergic neurons. • Increased release of lactate dehydrogenase. • Apoptosis in the ventral tegmental area.	Chambers et al. (2013)
In vivo	• Acceleration of programmed cell death. • Increase in the protein production of proapoptotic Fas receptor. • Reduced expression of antiapoptotic Bcl-2 oncoprotein in cortical.	Nyberg (2009)
In vivo (Rat)	• An inverse relationship between neurogenesis and morphine dependence. • Decreased proliferation in the subgranular zone.	Famitafreshi et al. (2015)
In vivo (Rat)	• Severe reduction in cellular proliferation in the hippocampus. • Reduced expression of the molecule responsible for neural cell adhesion • Decreased phenotypic plasticity in the dentate gyrus. • Impact on dopaminergic synaptic function in the nucleus accumbens.	Kahn et al. (2005)
In vivo (Rat)	• Negative impact on morphology and gene expression of pseudo-neuronal cells. • Induction of undifferentiation process.	Farrokhfar et al. (2020)
In vitro	• Increase in cell death of BM-MSC. • Reduction in cellular proliferation. • Prevention of degenerative cellular processes.	Zhaleh et al. (2020)
In vitro	• Induction of p53. • Simultaneous increase in activities of aromatase and 5-alpha reductase. • Disturbance of the normal condition of neural stem cells. • Loss of angiogenic potential in cells.	Abdyazdani et al. (2017)
In vivo (Mice)	• Increase in microglia and macrophage immune cell population in the injury site. • Alteration in neuropeptide synthesis • Alteration in innate immune response.	Terminel et al. (2022)
In vitro	• Reduction in telomere length. • Cellular aging in neuronal cells.	Darvishi and Saadat (2021)
In vitro	• Increased expression levels of the orexin1 receptor (OX1R) and c-FOS, the p/t-ERK/PKC receptor. • Increased protein levels of the c-FOS and p/t-ERK/PKC	Zhang et al. (2020)
In vivo (Mice)	• Reduction of nicotine-induced upregulation of nicotinic receptors • Reduction of voluntary nicotine consumption	Avelar et al. (2022)
In vitro & In vivo	• Regulation of antioxidant/antioxidant balance and acetylcholinesterase activity. • Reduction of neurotoxic effects in zebrafish embryos.	Cansız et al. (2022)
In vivo (Mice)	• Revival of strong nitrite cleansers • Reduction of nitroxidative stress derived from PN • Blocking the development of analgesic tolerance	Doyle et al. (2009)
In vitro	• Increase in cellular survival • Increase in cellular toxicity suppression • Increase in cellular death • Increase in mitochondrial membrane potential formation • Reduction of intracellular calcium concentration and mitochondrial calcium	Amini et al. (2019)
In vitro	• Nrf 2 pathway disorder. • Mitochondrial disorders. • Potential imbalance in redox in human brain endothelial cells.	Reymond et al. (2022)

Continued on the next page …

In vitro	• Prevention of PTEN-induced putative kinase1 accumulation resulting from mitochondrial damage in neurons • Inhibition of Parkin uptake into damaged mitochondria • Suppression of mitochondrial proteins • Ubiquitination inhibition of autophagosome recognition of damaged mitochondria • Suppression of autophagy flux • Inability of damaged mitochondria to undergo degradation by lysosomes • Generation of ROS	Kong et al. (2019)
In vitro	• Impairment in the function of mitochondrial complex I	Cunha-Oliveira et al. (2013)
In vitro	• Lack of morphine effect on mitochondrial morphology	Nylander et al. (2021)
In vivo (Mice)	• Protecting brain mitochondria from oxidative stress. • Shielding against harmful effects during brain ischemia-reperfusion and neurodegenerative conditions.	Feng et al. (2008)

Nevertheless, extended exposure protects the mammalian brain from future harmful or lethal stimuli, a process commonly known as "preconditioning." Preconditioning with morphine has been shown to provide defense against brain injury in hypoxia/hypoglycemia, ischemia, and Parkinson's disease models (Harburg et al., 2007; Zhao et al., 2006). For instance, research has demonstrated that continuous exposure to a 1 µM concentration of morphine prevents neuronal apoptosis induced by staurosporine (Cui et al., 2008). In another study, researchers reduced oxidative stress in hippocampal neurons by increasing antioxidant capacity through preconditioning with morphine injections (doses of 10-30 mg/kg/day) for 5 days (Arabian et al., 2018a). Furthermore, the process of morphine conditioning with a dose of 50 µM for 24 hours leads to a reduction in mitochondrial dysfunction and prevents the generation of intracellular radicals induced by 6-hydroxydopamine at a concentration of 100 µM in laboratory conditions (Wang et al., 2018). Furthermore, the process of morphine preconditioning with a dose of 50 µM for 24 hours, reduces mitochondrial impairment and prevents the production of intracellular ROS triggered by 100 µM of 6-hydroxydopamine in laboratory conditions (Parrott, 2018).

In addition, the use of morphine (50 or 100 µM per liter) for 30 minutes has been shown to protect against neuronal toxicity induced by 6-hydroxydopamine by reversing the increase in ROS and intracellular calcium levels and reestablishing the normal mitochondrial function in cells (Elyasi et al., 2014, 2019). Nevertheless, there have been conflicting results regarding alterations in ROS levels during the preconditioning process. In a laboratory experiment, treating Purkinje cells with morphine (at a concentration of 3 µM/liter) for 30 minutes before exposing them to 20 minutes of oxygen and glucose deprivation followed by 5 hours of reperfusion, successfully prevented cell death (Lim et al., 2004). These results indicate that morphine preconditioning could potentially offer neuroprotective benefits in specific circumstances, although additional research is necessary to comprehend the underlying mechanisms comprehensively. While the specific mechanisms of this process remain uncertain, these findings suggest that activating mitochondrial ATP-sensitive potassium (mKATP) channels and promoting free radical generation are significant factors in morphine preconditioning. In tests conducted on primary cortical neurons of mice, it has been shown that being exposed to a concentration of 3 µM/liter of morphine for one hour provides protection against damage resulting from oxygen and glucose deprivation (Meng et al., 2016).

These findings indicate that non-coding RNAs play a role in regulating the process of morphine preconditioning. Therefore, morphine preconditioning protects the brain from ischemic injury by activating mTOR phosphorylation, which boosts antioxidant factors to handle oxidative stress (Kennedy & Lamming, 2016). Additionally, giving increasing doses of morphine subcutaneously (ranging from 10 to 30 mg/kg/day) for five days before cerebral ischemia has been indicated to provide protection against apoptosis induced by oxidative stress in the hippocampus (Arabian et al., 2015).

It has been shown that morphine also exerts a protective role against dopaminergic neurotoxicity caused by microglial activation in primary neuron-glia co-cultures of the mesencephalon. Morphine significantly protects against intracellular oxidative stress and neuroinflammation in neuroblastoma cell lines. It also counteracts apoptosis caused by peroxynitrite in neonatal rat astrocytes, reduces toxicity from beta-amyloid in human neuroblastoma HTB-11 cells, and lessens neurotoxicity induced by lipopolysaccharide or 1-methyl-4-phenylpyridinium in rat neuron-glia co-cultures. Additionally, morphine triggers neuroprotection against ischemia through its receptor in rats, decreasing cell death induced by ischemia in the hippocampal regions (Chen et al., 2008).

Morphine can block neurotoxicity in neuron-glia co-cultures of the mesencephalon in rats. However, this blocking mechanism does not occur through opioid receptors but instead involves decreased NMDA oxidase activity (Qian et al., 2007). Apart from its neurotoxic effects, morphine and its synthetic derivatives also demonstrate anti-cancer properties through apoptosis. Opioids impact the signaling pathways of growth factors, although other evidence indicates that cytoskeletal elements are also involved in morphine-induced cell death (Eisch and Mandyam, 2007). In an experimental rat model, a study compared the neurotoxic effects of morphine and tramadol. The results showed that morphine induces cell death in various brain regions, including the cerebellum, frontal cortex, occipital cortex, and prefrontal cortex, along with the spinal cord's CA1, CA2, and CA3 regions (Atici et al., 2004). **Table 3** illustrates morphine's protective function in the CNS.

3.0 CONCLUSIONS

Based on various studies, it is evident that morphine has both anti- and pro-effects on the nervous system. It appears that various factors, including dosage, frequency of administration, type of disease, and timing of morphine use, greatly influence the outcomes. A more precise evaluation of morphine administration can help resolve these contradictions. Given the long history

Table 3: Morphine's protective function in the CNS.

Study Design	Key Results	References
In vitro	• Prevention of neuronal apoptosis caused by cephalosporins.	Cui et al. (2008)
In vitro	• Reduction of oxidative stress in hippocampal neurons.	Arabian et al. (2018)
In vitro & In vivo	• Decrease in mitochondrial dysfunction. • Prevention of intracellular ROS production.	Wang et al. (2014)
In vitro	• Reversal of increased levels of intracellular ROS and calcium. • Restoration of mitochondrial membrane potential in cells. • Protection against neural toxicity caused by 6-hydroxydopamine.	Elyasi et al. (2014, 2019)
In vitro	• Prevention of cell death in Purkinje cells.	Lim et al. (2004)
In vitro	• Protection of primary cortical neurons in mice after oxygen and glucose deprivation injuries.	Meng et al. (2016)
In vitro	• Conditioning of morphine through phosphorylation and activation of mTOR. • Protection of the brain against ischemic damage.	Kennedy et al. (2016)
In vivo (Mice)	• Prevention of oxidative stress. • Protection against apoptosis in the hippocampus.	Arabian et al. (2015)
In vivo (Rat)	• Protective role against dopaminergic neurotoxicity. • Neuroprotection against ischemia. • Reduction of ischemia-induced cell death in the hippocampal regions.	Chen et al. (2008)
In vivo (Rat)	• Inhibition of neurotoxicity in glial-neuronal co-cultures in mesencephalic cells.	Qian et al. (2007)
In vivo (Rat)	• Induction of apoptosis in the cerebellar, frontal, occipital, prefrontal cortex, and CA1, CA2 and CA3 of spinal cord regions.	Atici et al. (2004)

of morphine use in the medical industry, morphine and its analgesic mechanisms have been investigated for many years. Nevertheless, the beneficial or harmful impacts of this traditional substance on the CNS has not been extensively investigated. As a result, there is limited evidence to support both of these functions of morphine, despite reports that emphasize its harmful effects more than its protective role.

Advanced techniques, such as genomics and proteomics, have been utilized to uncover novel roles and mechanisms of morphine. Nonetheless, the primary obstacle lies in handling and interpreting the extensive data produced by these investigations. Ultimately, the application of new technologies can significantly enhance our comprehension of morphine's function. Conversely, insights gained from molecular and cellular pathways of morphine's effects can lead to a definitive understanding of its beneficial or harmful functions in neuron cells and other systems. This knowledge will play a crucial role in reducing the negative impacts of morphine in clinical settings and in furthering the treatment and prevention of opioid addiction.

Author contributions:
S.F. contributed to the study design, while S.F. and A.M. were involved in the research implementation, result analysis, and manuscript writing. S.F., B.L.A. and A.M participated in result discussions and provided feedback on the manuscript.

Acknowledgements:
We express our deepest gratitude to Ramsar Campus of Mazandaran University of Medical Science (Ramsar, Iran).

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

References

Abdyazdani, N., Nourazarian, A., Nozad Charoudeh, H., Kazemi, M., Feizy, N., Akbarzade, M., Mehdizadeh, A., Rezaie, J., & Rahbarghazi, R. (2017). The role of morphine on rat neural stem cells viability, neuro-angiogenesis and neuro-steroidgenesis properties. *Neuroscience Letters*, *636*, 205–212. https://doi.org/10.1016/J.NEULET.2016.11.025

Aceves, M., Terminel, M. N., Okoreeh, A., Aceves, A. R., Gong, Y. M., Polanco, A., Sohrabji, F., & Hook, M. A. (2019). Morphine increases macrophages at the lesion site following spinal cord injury: Protective effects of minocycline. *Brain, Behavior, and Immunity*, *79*, 125–138. https://doi.org/10.1016/J.BBI.2019.01.023

Ali, S. F., Toshitaka, N. & Tomoji, Y. (2004). *Current status of drug dependence/abuse studies : cellular and molecular mechanisms of drugs of abuse and neurotoxicity*. New York Academy of Sciences.

Amini, K., Zhaleh, H., Tahvilian, R., & Farnia, V. (2019). Low concentration of morphine protects against cell death, oxidative stress and calcium accumulation by nicotine in PC12 cells. *Bratislavske Lekarske Listy*, *120*(4), 256–262. https://doi.org/10.4149/BLL_2019_042

Anghel, A., Jamieson, C. A. M., Ren, X., Young, J., Porche, R., Ozigbo, E., Ghods, D. E., Lee, M. L., Liu, Y., Lutfy, K., & Friedman, T. C. (2010). Gene expression profiling following short-term and long-term morphine exposure in mice uncovers genes involved in food intake. *Neuroscience*, *167*(2), 554. https://doi.org/10.1016/J.NEUROSCIENCE.2010.01.043

Arabian, M., Aboutaleb, N., Soleimani, M., Ajami, M., Habibey, R., & Pazoki-Toroudi, H. (2018). Activation of mitochondrial KATP channels mediates neuroprotection induced by chronic morphine preconditioning in hippocampal CA-1 neurons following cerebral ischemia. *Advances in Medical Sciences*, *63*(2), 213–219. https://doi.org/10.1016/J.ADVMS.2017.11.003

Arabian, M., Aboutaleb, N., Soleimani, M., Ajami, M., Habibey, R., Rezaei, Y., & Pazoki-Toroudi, H. (2018). Preconditioning with morphine protects hippocampal CA1 neurons from ischemia–reperfusion injury via activation of the mTOR pathway. *Canadian Journal of Physiology and Pharmacology*, *96*(1), 80–87. https://doi.org/10.1139/cjpp-2017-0245

Arabian, M., Aboutaleb, N., Soleimani, M., Mehrjerdi, F. Z., Ajami, M., & Pazoki-Toroudi, H. (2015). Role of morphine preconditioning and nitric oxide following brain ischemia reperfusion injury in mice. *Iranian Journal of Basic Medical Sciences*, *18*(1), 14.

Assunção-Silva, R. C., Gomes, E. D., Sousa, N., Silva, N. A., & Salgado, A. J. (2015). Hydrogels and Cell Based Therapies in Spinal Cord Injury Regeneration. *Stem Cells International*, *2015*. https://doi.org/10.1155/2015/948040

Asuni, G. P., Speidell, A., & Mocchetti, I. (2021). Neuronal apoptosis induced by morphine withdrawal is mediated by the p75 neurotrophin receptor. *Journal of Neurochemistry*, *158*(2), 169–181. https://doi.org/10.1111/JNC.15355

Atici, S., Cinel, L., Cinel, I., Doruk, N., Aktekin, M., Akca, A., Camdeviren, H., & Oral, U. (2004). Opioid neurotoxicity: comparison of morphine and tramadol in an experimental rat model. *The International Journal of Neuroscience*, *114*(8), 1001–1011. https://doi.org/10.1080/00207450490461314

Avelar, A. J., Cooper, S. Y., Wright, T. D., Wright, S. K., Richardson, M. R., & Henderson, B. J. (2022). Morphine Exposure Reduces Nicotine-Induced Upregulation of Nicotinic Receptors and Decreases Volitional Nicotine Intake in a Mouse Model. *Nicotine & Tobacco Research*, *24*(8), 1161. https://doi.org/10.1093/NTR/NTAC002

Barrow, T. M., Byun, H. M., Li, X., Smart, C., Wang, Y. X., Zhang, Y., Baccarelli, A. A., & Guo, L. (2017). The effect of morphine upon DNA methylation in ten regions of the rat brain. *Epigenetics*, *12*(12), 1038–1047. https://doi.org/10.1080/15592294.2017.1398296

Bian, Y., Wang, X., Liang, J. hui, Li, L., Wu, X., Tang, B., Leung, G. P. H., & Lee, S. M. Y. (2022). The development of behavioral sensitization induced by a single morphine exposure in adult zebrafish (Danio rerio). *Progress in Neuro-psychopharmacology & Biological Psychiatry*, *113*. https://doi.org/10.1016/J.PNPBP.2021.110456

Cansız, D., Ustundag, U. V., Unal, I., Alturfan, A. A., & Emekli-Alturfan, E. (2022). Morphine attenuates neurotoxic effects of MPTP in zebrafish embryos by regulating oxidant/antioxidant balance and acetylcholinesterase activity. *Drug and Chemical Toxicology*, *45*(6), 2439–2447. https://doi.org/10.1080/01480545.2021.1957558

Cao, Q., Benton, R. L., & Whittemore, S. R. (2002). Stem cell repair of central nervous system injury. *Journal of Neuroscience Research*, *68*(5), 501–510. https://doi.org/10.1002/JNR.10240

Chahkandi, M., Askari Phd, N., & Asadikaram, G. (2015). The Effect of Acute and Chronic Morphine on Some Blood Biochemical Parameters in an Inflammatory Condition in Gonadectomized Male Rats. *Addiction & Health*, *7*(3–4), 130.

Chambers, R. A. (2013). Adult Hippocampal Neurogenesis in the Pathogenesis of Addiction and Dual Diagnosis Disorders. *Drug and Alcohol Dependence*, *130*(0), 1. https://doi.org/10.1016/J.DRUGALCDEP.2012.12.005

Chen, K., Phan, T., Lin, A., Sardo, L., Mele, A. R., Nonnemacher, M. R., & Klase, Z. (2020). Morphine exposure exacerbates HIV-1 Tat driven changes to neuroinflammatory factors in cultured astrocytes. *PLOS ONE*, *15*(3), e0230563. https://doi.org/10.1371/JOURNAL.PONE.0230563

Chen, Q., Cui, J., Zhang, Y., & Yu, L. C. (2008). Prolonged morphine application modulates Bax and Hsp70 levels in primary rat neurons. *Neuroscience Letters*, *441*(3), 311–314. https://doi.org/10.1016/J.NEULET.2008.06.067

Chen, Y., Wang, X., Xiao, M., Kang, N., Zeng, W., & Zhang, J. (2022). Prenatal morphine exposure increases gamma oscillation and theta coherence in the rat reward system. *Neurotoxicology*, *90*, 246–255. https://doi.org/10.1016/J.NEURO.2022.04.007

Cichewicz, D. L., Haller, V. L., & Welch, S. P. (2001). Changes in Opioid and Cannabinoid Receptor Protein following Short-Term Combination Treatment with Δ9-Tetrahydrocannabinol and Morphine. *Journal of Pharmacology and Experimental Therapeutics*, *297*(1), 121–127.

Cui, J., Chen, Q., Yu, L. C., & Zhang, Y. (2008). Chronic morphine application is protective against cell death in primary human neurons. *Neuroreport*, *19*(18), 1745–1749. https://doi.org/10.1097/WNR.0B013E3283186FD7

Cunha-Oliveira, T., Silva, L., Silva, A. M., Moreno, A. J., Oliveira, C. R., & Santos, M. S. (2013). Mitochondrial complex I dysfunction induced by cocaine and cocaine plus morphine in brain and liver mitochondria. *Toxicology Letters*, *219*(3), 298–306. https://doi.org/10.1016/J.TOXLET.2013.03.025

Darvishi, F. Z., & Saadat, M. (2022). Morphine may have a role in telomere shortening. *Psychiatric Genetics*, *32*(2), 87–89. https://doi.org/10.1097/YPG.0000000000000311

Dholakiya, S. L., Aliberti, A., & Barile, F. A. (2016). Morphine sulfate concomitantly decreases neuronal differentiation and opioid receptor expression in mouse embryonic stem cells. *Toxicology Letters*, *247*, 45–55. https://doi.org/10.1016/J.TOXLET.2016.01.010

Ding, H., Kiguchi, N., Mabry, K. M., Kishioka, S., & Ko, M. C. (2023). Functional consequences of short-term exposure to opioids versus cannabinoids in nonhuman primates. *Neuropharmacology*, *223*. https://doi.org/10.1016/J.NEUROPHARM.2022.109328

Dominguez, J. E., & Habib, A. S. (2013). Prophylaxis and treatment of the side-effects of neuraxial morphine analgesia following cesarean delivery. *Current Opinion in Anaesthesiology*, *26*(3), 288–295. https://doi.org/10.1097/ACO.0B013E328360B086

Doyle, T., Bryant, L., Batinic-Haberle, I., Little, J., Cuzzocrea, S., Masini, E., Spasojevic, I., & Salvemini, D. (2009). Supraspinal inactivation of mitochondrial superoxide dismutase is a source of peroxynitrite in the development of morphine antinociceptive tolerance. *Neuroscience*, *164*(2), 702–710. https://doi.org/10.1016/J.NEUROSCIENCE.2009.07.019

Drastichova, Z., Hejnova, L., Moravcova, R., & Novotny, J. (2021). Proteomic Analysis Unveils Expressional Changes in Cytoskeleton- and Synaptic Plasticity-Associated Proteins in Rat Brain Six Months after Withdrawal from Morphine. *Life (Basel, Switzerland)*, *11*(7), 683. https://doi.org/10.3390/LIFE11070683

Eftekhar-Vaghefi, S. H., Asadi-Shekaari, M., & Esmaeili-Mahani, S. (2019). Induction of cross-tolerance between protective effect of morphine and nicotine in 6-hydroxydopamine-induce neurotoxicity in SH-SY5Y human dopaminergic neuroblastoma cells. *International Journal of Neuroscience*, *129*(2), 129–138. https://doi.org/10.1080/00207454.2018.1494169

Eisch, A. J., Barrot, M., Schad, C. A., Self, D. W., & Nestler, E. J. (2000). Opiates inhibit neurogenesis in the adult rat hippocampus. *Proceedings of the national academy of sciences of the United States of America (PNAS)*, *97*(13), 7579–7584. https://doi.org/10.1073/pnas.120552597

Eisch, A.J. & Mandyam, C.D. (2007). Adult neurogenesis: can analysis of cell cycle proteins move us "Beyond BrdU"? *Current Pharmaceutical Biotechnology*, *8*(3), 147–165. https://doi.org/10.2174/138920107780906540

Elyasi, L., Eftekhar-Vaghefi, S. H., & Esmaeili-Mahani, S. (2014). Morphine protects SH-SY5Y human neuroblastoma cells against 6-hydroxydopamine-induced cell damage: involvement of anti-oxidant, calcium blocking, and anti-apoptotic properties. *Rejuvenation Research*, *17*(3), 255–263. https://doi.org/10.1089/REJ.2013.1473

Espinosa, V. P., Liu, Y., Ferrini, M., Anghel, A., Nie, Y., Tripathi, P. V., Porche, R., Jansen, E., Stuart, R. C., Nillni, E. A., Lutfy, K., & Friedman, T. C. (2008). Differential regulation of prohormone convertase 1/3, prohormone convertase 2 and phosphorylated cyclic-AMP-response element binding protein by short-term and long-term morphine treatment: implications for understanding the "switch" to opiate addiction. *Neuroscience*, *156*(3), 788–799. https://doi.org/10.1016/J.NEUROSCIENCE.2008.07.063

Famitafreshi, H., Karimian, M., & Marefati, N. (2015). Long-term morphine addiction reduces neurogenesis and memory performance and alters emotional reactivity and anxiety levels in male rats. *Open Access Animal Physiology*, *7*, 129–136. https://doi.org/10.2147/OAAP.S87674

Fan, W., Wang, H., Zhang, Y., Loh, H. H., Law, P. Y., & Xu, C. (2018). Morphine regulates adult neurogenesis and contextual memory extinction via the PKCε/Prox1 pathway. *Neuropharmacology*, *141*, 126–138. https://doi.org/10.1016/J.NEUROPHARM.2018.08.031

Farahani, F., Pachenari, N., Mohammad Ahmadi-Soleimani, S., Azizi, H., & Semnanian, S. (2023). Acute morphine injection persistently affects the electrophysiological characteristics of rat locus coeruleus neurons. *Neuroscience Letters*, *795*. https://doi.org/10.1016/J.NEULET.2023.137048

Farrokhfar, S., Tiraihi, T., Movahedin, M., & Azizi, H. (2020). Differential gene expression by lithium chloride induction of adipose-derived stem cells into neural phenotype cells. *Iranian Journal of Basic Medical Sciences*, *23*(4), 544. https://doi.org/10.22038/IJBMS.2020.41582.9820

Feizy, N., Nourazarian, A., Rahbarghazi, R., Nozad Charoudeh, H., Abdyazdani, N., Montazersaheb, S., & Narimani, M. (2016). Morphine Inhibited the Rat Neural Stem Cell Proliferation Rate by Increasing Neuro Steroid Genesis. *Neurochemical Research*, *41*(6), 1410–1419. https://doi.org/10.1007/S11064-016-1847-7

Feng, Y., Lu, Y., Lin, X., Gao, Y., Zhao, Q., Li, W., & Wang, R. (2008). Endomorphins and morphine limit anoxia-reoxygenation-induced brain mitochondrial dysfunction in the mouse. *Life Sciences*, *82*(13–14), 752–763. https://doi.org/10.1016/J.LFS.2008.01.004

Fischer, S. J., Arguello, A. A., Charlton, J. J., Fuller, D. C., Zachariou, V., & Eisch, A. J. (2008). Morphine blood levels, dependence, and regulation of hippocampal subgranular zone proliferation rely on administration paradigm. *Neuroscience*, *151*(4), 1217–1224. https://doi.org/10.1016/J.NEUROSCIENCE.2007.11.035

Fukuda, T., Chidambaran, V., Mizuno, T., Venkatasubramanian, R., Ngamprasertwong, P., Olbrecht, V., Esslinger, H. R., Vinks, A. A., & Sadhasivam, S. (2013). OCT1 genetic variants influence the pharmacokinetics of morphine in children. *Pharmacogenomics*, *14*(10), 1141–1151. https://doi.org/10.2217/PGS.13.94

Fürst, Z., Riba, P., & Al-Khrasani, M. (2013). New approach to the neurobiological mechanisms of addiction - PubMed. *Neuropsychopharmacologia Hungarica*, *15*(4), 189–205. https://pubmed.ncbi.nlm.nih.gov/24380960/

Gabel, F., Hovhannisyan, V., Berkati, A. K., & Goumon, Y. (2022). Morphine-3-Glucuronide, Physiology and Behavior. *Frontiers in Molecular Neuroscience*, *15*. https://doi.org/10.3389/FNMOL.2022.882443

Gach, K., Wyrębska, A., Fichna, J., & Janecka, A. (2011). The role of morphine in regulation of cancer cell growth. *Naunyn-schmiedeberg's Archives of Pharmacology*, *384*(3), 221. https://doi.org/10.1007/S00210-011-0672-4

Glare, P. A., & Walsh, T. D. (1991). Clinical pharmacokinetics of morphine. *Therapeutic Drug Monitoring*, *13*(1), 1–23. https://doi.org/10.1097/00007691-199101000-00001

Guan, S., Jin, T., Han, S., Fan, W., Chu, H., & Liang, Y. (2021). Dihydroartemisinin alleviates morphine-induced neuroinflammation in BV-2 cells. *Bioengineered*, *12*(2), 9401. https://doi.org/10.1080/21655979.2021.1982311

Harburg, G. C., Hall, F. S., Harrist, A. V., Sora, I., Uhl, G. R., & Eisch, A. J. (2007). Knockout of the mu opioid receptor enhances the survival of adult-generated hippocampal granule cell neurons. *Neuroscience*, *144*(1), 77. https://doi.org/10.1016/J.NEUROSCIENCE.2006.09.018

Hauser K F, & Mangoura D. (1998). Diversity of the endogenous opioid system in development. Novel signal transduction translates multiple extracellular signals into neural cell growth and differentiation. *Perspectives on Developmental Neurobiology*, *5*(4), 437–449.

Holmes, M. M., & Galea, L. A. M. (2002). Defensive behavior and hippocampal cell proliferation: Differential modulation by naltrexone during stress. *Behavioral Neuroscience*, *116*(1), 160–168. https://doi.org/10.1037/0735-7044.116.1.160

Jaferi, A., Lane, D. A., & Pickel, V. M. (2009). Subcellular plasticity of the corticotropin-releasing factor receptor in dendrites of the mouse bed nucleus of the stria terminalis following chronic opiate exposure. *Neuroscience*, *163*(1), 143–154. https://doi.org/10.1016/J.NEUROSCIENCE.2009.06.029

Jahanian, F., Hosseininejad, S. M., Ahidashti, H. A., Bozorgi, F., Khatir, I. G., Montazar, S. H., & Azarfar, V. (2018). Efficacy and Safety of Morphine and Low Dose Ketamine for Pain Control of Patients with Long Bone Fractures: A Randomized, Double-Blind, Clinical Trial. *Bulletin of Emergency & Trauma*, *6*(1), 31. https://doi.org/10.29252/BEAT-060105

Jahanshahi, M., Shabani, R., Nikmahzar, E., & Babakordi, F. (2014). Female Rat Hippocampal Cell Density after Conditioned Place Preference. *Folia Biologica*, *60*(1), 47–51.

Jiang, C., Wang, X., Le, Q., Liu, P., Liu, C., Wang, Z., He, G., Zheng, P., Wang, F., & Ma, L. (2021). Morphine coordinates SST and PV interneurons in the prelimbic cortex to disinhibit pyramidal neurons and enhance reward. *Molecular Psychiatry*, *26*(4), 1178–1193. https://doi.org/10.1038/S41380-019-0480-7

Jimenez-Gonzalez, A., García-Concejo, A., León-Lobera, F., & Rodriguez, R. E. (2018). Morphine delays neural stem cells differentiation by facilitating Nestin overexpression. *Biochimica Et Biophysica Acta*, *1862*(3), 474–484. https://doi.org/10.1016/J.BBAGEN.2017.10.016

Jin, C., Araki, H., Nagata, M., Suemaru, K., Shibata, K., Kawasaki, H., Hamamura, T., & Gomita, Y. (2004). Withdrawal-induced c-Fos expression in the rat centromedial amygdala 24 h following a single morphine exposure. *Psychopharmacology*, *175*(4), 428–435. https://doi.org/10.1007/S00213-004-1844-4

Kahn, L., Alonso, G., Normand, E., & Manzoni, O. J. (2005). Repeated morphine treatment alters polysialylated neural cell adhesion molecule, glutamate decarboxylase-67 expression and cell proliferation in the adult rat hippocampus. *The European Journal of Neuroscience*, *21*(2), 493–500. https://doi.org/10.1111/J.1460-9568.2005.03883.X

Kashiwagi, Y., Yi, H., Liu, S., Takahashi, K., Hayashi, K., Ikegami, D., Zhu, X., Gu, J., & Hao, S. (2021). Mitochondrial biogenesis factor PGC-1α suppresses spinal morphine tolerance by reducing mitochondrial superoxide. *Experimental Neurology*, *339*. https://doi.org/10.1016/J.EXPNEUROL.2021.113622

Kennedy, B. K., & Lamming, D. W. (2016). The mechanistic Target of Rapamycin: The grand conducTOR of metabolism and aging. *Cell Metabolism*, *23*(6), 990. https://doi.org/10.1016/J.CMET.2016.05.009

Khani, F., Pourmotabbed, A., Hosseinmardi, N., Nedaei, S. E., Fathollahi, Y., & Azizi, H. (2022). Impairment of spatial memory and dorsal hippocampal synaptic plasticity in adulthood due to adolescent morphine exposure. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, *116*, 110532. https://doi.org/10.1016/J.PNPBP.2022.110532

Khazali, H., & Mahmoudi, F. (2019). Morphine and kisspeptin influences on 5-α reductase and aromatase gene expression in adult male rats. *Iranian Journal of Basic Medical sciences*, *22*(12), 1462. https://doi.org/10.22038/IJBMS.2019.14053

Kong, H., Jiang, C. Y., Hu, L., Teng, P., Zhang, Y., Pan, X. X., Sun, X. Di, & Liu, W. T. (2019). Morphine induces dysfunction of PINK1/Parkin-mediated mitophagy in spinal cord neurons implying involvement in antinociceptive tolerance. *Journal of Molecular Cell Biology*, *11*(12), 1056–1068. https://doi.org/10.1093/JMCB/MJZ002

Konno, F., & Takayanagi, I. (1982). Effect of morphine on the stimuli-induced calcium uptake into synaptosomes isolated from morphine-tolerant rats. *Japanese Journal of Pharmacology*, *32*(4), 625–632. https://doi.org/10.1254/JJP.32.625

Kupnicka, P., Kojder, K., Metryka, E., Kapczuk, P., Jeżewski, D., Gutowska, I., Goschorska, M., Chlubek, D., & Baranowska-Bosiacka, I. (2020). Morphine-element interactions - The influence of selected chemical elements on neural pathways associated with addiction. *Journal of Trace Elements in Medicine and Biology, 60*, 126495. https://doi.org/10.1016/J.JTEMB.2020.126495

Lapierre, J., Karuppan, M. K. M., Perry, M., Rodriguez, M., & El-Hage, N. (2021). Different Roles of Beclin1 in the Interaction Between Glia and Neurons after Exposure to Morphine and the HIV-Trans-Activator of Transcription (Tat) Protein. *Journal of Neuroimmune Pharmacology, 17*(3), 470–486. https://doi.org/10.1007/S11481-021-10017-4

Li, W. W., Irvine, K. A., Sahbaie, P., Guo, T. Z., Shi, X. Y., Tawfik, V. L., Kingery, W. S., & Clark, J. D. (2019). Morphine Exacerbates Postfracture Nociceptive Sensitization, Functional Impairment, and Microglial Activation in Mice. *Anesthesiology*, *130*(2), 292–308. https://doi.org/10.1097/ALN.0000000000002495

Li, Z., Liu, J., Dong, F., Chang, N., Huang, R., Xia, M., Patterson, T. A., & Hong, H. (2023). Three-Dimensional Structural Insights Have Revealed the Distinct Binding Interactions of Agonists, Partial Agonists, and Antagonists with the μ Opioid Receptor. *International Journal of Molecular Sciences*, *24*(8). https://doi.org/10.3390/IJMS24087042

Lim, Y. J., Zheng, S., & Zuo, Z. (2004). Morphine preconditions Purkinje cells against cell death under in vitro simulated ischemia-reperfusion conditions. *Anesthesiology*, *100*(3), 562–568. https://doi.org/10.1097/00000542-200403000-00015

Liu, Y., Lu, G. Y., Chen, W. Q., Li, Y. F., Wu, N., & Li, J. (2018). Agmatine inhibits chronic morphine exposure-induced impairment of hippocampal neural progenitor proliferation in adult rats. *European Journal of Pharmacology*, *818*, 50–56. https://doi.org/10.1016/J.EJPHAR.2017.10.018

Lu, G., Zhou, Q. X., Kang, S., Li, Q. L., Zhao, L. C., Chen, J. D., Sun, J. F., Cao, J., Wang, Y. J., Chen, J., Chen, X. Y., Zhong, D. F., Chi, Z. Q., Xu, L., & Liu, J. G. (2010). Chronic Morphine Treatment Impaired Hippocampal Long-Term Potentiation and Spatial Memory via Accumulation of Extracellular Adenosine Acting on Adenosine A1 Receptors. *The Journal of Neuroscience*, *30*(14), 5058. https://doi.org/10.1523/JNEUROSCI.0148-10.2010

Lyu, N., & Li, X. (2022). Effect of Exosomal Protein Expression and Electrochemical Nano Interface in Morphine Analgesia Tolerance. *Cellular and Molecular Biology*, *67*(6), 40–47. https://pubmed.ncbi.nlm.nih.gov/35818216/

Mandyam, C. D., Norris, R. D., & Eisch, A. J. (2004). Chronic morphine induces premature mitosis of proliferating cells in the adult mouse subgranular zone. *Journal of Neuroscience Research*, *76*(6), 783–794. https://doi.org/10.1002/JNR.20090

Meng, F., Li, Y., Chi, W., & Li, J. (2016). Morphine Preconditioning Downregulates MicroRNA-134 Expression Against Oxygen-Glucose Deprivation Injuries in Cultured Neurons of Mice. *Journal of Neurosurgical Anesthesiology*, *28*(3), 195–202. https://doi.org/10.1097/ANA.0000000000000204

Muchhala, K. H., Jacob, J. C., Dewey, W. L., & Akbarali, H. I. (2021). Role of β-arrestin-2 in short- and long-term opioid tolerance in the dorsal root ganglia. *European Journal of Pharmacology*, *899*, 174007. https://doi.org/10.1016/J.EJPHAR.2021.174007

Murphy, E. J. (2005). Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesthesia and Intensive Care*, *33*(3), 311–322. https://doi.org/10.1177/0310057X0503300306

Naderi, J., Samani, F., Amooheidari, A., Javanmard, S. H., Vahabzadeh, G., & Vaseghi, G. (2019). Evaluation of effects of morphine and ionizing radiation in cancer cell lines. *Journal of Cancer Research and Therapeutics*, *15*(8), S144–S152. https://doi.org/10.4103/JCRT.JCRT_48_17

Nestler, E. J. (2001). Molecular basis of long-term plasticity underlying addiction. *Nature Reviews Neuroscience 2001 2:2*, *2*(2), 119–128. https://doi.org/10.1038/35053570

Nowycky, M. C., Walters, J. R., & Roth, R. H. (1978). Dopaminergic neurons: effect of acute and chronic morphine administration on single cell activity and transmitter metabolism. *Journal of Neural Transmission*, *42*(2), 99–116. https://doi.org/10.1007/BF01675349

Nyberg, F. (2009). The Role of the Somatotrophic Axis in Neuroprotection and Neuroregeneration of the Addictive Brain. *International review of neurobiology*, *88*(C), 399–427. https://doi.org/10.1016/S0074-7742(09)88014-8

Nylander, E., Zelleroth, S., Nyberg, F., Grönbladh, A., & Hallberg, M. (2021). The effects of morphine, methadone, and fentanyl on mitochondria: A live cell imaging study. *Brain Research Bulletin*, *171*, 126–134. https://doi.org/10.1016/J.BRAINRESBULL.2021.03.009

Ofoegbu, A., & B. Ettienne, E. (2021). Pharmacogenomics and Morphine. *Journal of Clinical Pharmacology*, *61*(9), 1149–1155. https://doi.org/10.1002/JCPH.1873

Osmanlıoğlu, H. Ö., Yıldırım, M. K., Akyuva, Y., Yıldızhan, K., & Nazıroğlu, M. (2020). Morphine Induces Apoptosis, Inflammation, and Mitochondrial Oxidative Stress via Activation of TRPM2 Channel and Nitric Oxide Signaling Pathways in the Hippocampus. *Molecular Neurobiology*, *57*(8), 3376–3389. https://doi.org/10.1007/S12035-020-01975-6

Parrott, A. C. (2018). Mood Fluctuation and Psychobiological Instability: The Same Core Functions Are Disrupted by Novel Psychoactive Substances and Established Recreational Drugs. *Brain Sciences*, *8*(3). https://doi.org/10.3390/BRAINSCI8030043

Pirnik Z, Schwendt M, & Jezova D. (2001). Single dose of morphine influences plasma corticosterone and gene expression of main NMDA receptor subunit in the adrenal gland but not in the hippocampus. *Endocrine Regulations*, *35*(4), 187–193.

Qian, L., Tan, K. S., Wei, S.-J., Wu, H.-M., Xu, Z., Wilson, B., Lu, R.-B., Hong, J.-S., & Flood, P. M. (2007). Microglia-mediated neurotoxicity is inhibited by morphine through an opioid receptor-independent reduction of NADPH oxidase activity. *Journal of Immunology*, *179*(2), 1198–1209. https://doi.org/10.4049/JIMMUNOL.179.2.1198

Rahimi, S., Dadfar, B., Tavakolian, G., Asadi Rad, A., Rashid Shabkahi, A., & Siahposht-Khachaki, A. (2021). Morphine attenuates neuroinflammation and blood-brain barrier disruption following traumatic brain injury through the opioidergic system. *Brain Research Bulletin*, *176*, 103–111. https://doi.org/10.1016/J.BRAINRESBULL.2021.08.010

Reymond, S., Vujić, T., Schvartz, D., & Sanchez, J. C. (2022). Morphine-induced modulation of Nrf2-antioxidant response element signaling pathway in primary human brain microvascular endothelial cells. *Scientific Reports, 12*(1), 1–10. https://doi.org/10.1038/s41598-022-08712-0

Roch, C., & van Oorschot, B. (2020). Opioidrotation bei Tumorschmerzen. *Im Fokus Onkologie*, *23*(1), 19–21. https://doi.org/10.1007/S15015-019-0745-7

Rouhani, F., Khodarahmi, P., & Naseh, V. (2019). NGF, BDNF and Arc mRNA Expression in the Hippocampus of Rats After Administration of Morphine. *Neurochemical Research*, *44*(9), 2139–2146. https://doi.org/10.1007/S11064-019-02851-Z

Rueda-Ruzafa, L., Cruz, F., Cardona, D., Hone, A. J., Molina-Torres, G., Sánchez-Labraca, N., & Roman, P. (2020). Opioid system influences gut-brain axis: Dysbiosis and related alterations. *Pharmacological Research*, *159*, 104928. https://doi.org/10.1016/J.PHRS.2020.104928

Sakurada, T., Komatsu, T., & Sakurada, S. (2005). Mechanisms of nociception evoked by intrathecal high-dose morphine. *Neurotoxicology*, *26*(5), 801–809. https://doi.org/10.1016/J.NEURO.2004.12.011

Sargeant, T. J., Miller, J. H., & Day, D. J. (2008). Opioidergic regulation of astroglial/neuronal proliferation: where are we now? *Journal of neurochemistry*, *107*(4), 883–897. https://doi.org/10.1111/J.1471-4159.2008.05671.X

Schroeder, C. I., & Lewis, R. J. (2006). ω-Conotoxins GVIA, MVIIA and CVID: SAR and Clinical Potential. *Marine Drugs*, *4*(3), 193.

Schuster, M., Bayer, O., Heid, F., & Laufenberg-Feldmann, R. (2018). Opioid rotation in cancer pain treatment - A systematic review. *Deutsches Arzteblatt International*, *115*(9), 135–142. https://doi.org/10.3238/ARZTEBL.2018.0135

Soto-Montenegro, M. [a]L, García-Vázquez, V., Lamanna-Rama, N., López-Montoya, G., Desco, M., & Ambrosio, E. (2022). Neuroimaging reveals distinct brain glucose metabolism patterns associated with morphine consumption in Lewis and Fischer 344 rat strains. *Scientific Reports*, *12*(1). https://doi.org/10.1038/S41598-022-08698-9

Stampas, A., Pedroza, C., Bush, J. N., Ferguson, A. R., Kramer, J. L. K., & Hook, M. (2020). The first 24 h: opioid administration in people with spinal cord injury and neurologic recovery. *Spinal Cord, 58*(10), 1080–1089. https://doi.org/10.1038/s41393-020-0483-x

Teasell, R. W., Mehta, S., Aubut, J. A. L., Foulon, B., Wolfe, D. L., Hsieh, J. T. C., Townson, A. F., & Short, C. (2010). A systematic review of pharmacologic treatments of pain after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 816–831. https://doi.org/10.1016/J.APMR.2010.01.022

Terminel, M. N., Bassil, C., Rau, J., Trevino, A., Ruiz, C., Alaniz, R., & Hook, M. A. (2022). Morphine-induced changes in the function of microglia and macrophages after acute spinal cord injury. *BMC Neuroscience*, *23*(1), 1–21. https://doi.org/10.1186/S12868-022-00739-3/FIGURES/11

Thigpen, J. C., Odle, B. L., & Harirforoosh, S. (2019). Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. *European Journal of Drug Metabolism and Pharmacokinetics*, *44*(5), 591–609. https://doi.org/10.1007/S13318-019-00552-0

Ucha, M., Coria, S. M., Núñez, A. E., Santos-Toscano, R., Roura-Martínez, D., Fernández-Ruiz, J., Higuera-Matas, A., & Ambrosio, E. (2019). Morphine self-administration alters the expression of translational machinery genes in the amygdala of male Lewis rats. *Journal of Psychopharmacology*, *33*(7), 882–893. https://doi.org/10.1177/0269881119836206

Valkenburg, A. J., Van Den Bosch, G. E., De Graaf, J., Van Lingen, R. A., Weisglas-Kuperus, N., Van Rosmalen, J., Groot Jebbink, L. J. M., Tibboel, D., & Van Dijk, M. (2015). Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomized Controlled Trial. *The Journal of Pain*, *16*(9), 926–933. https://doi.org/10.1016/J.JPAIN.2015.06.007

Wang, B., Su, C. J., Liu, T. T., Zhou, Y., Feng, Y., Huang, Y., Liu, X., Wang, Z. H., Chen, L. H., Luo, W. F., & Liu, T. (2018). Neuroprotection of low-dose morphine in cellular and animal models of parkinson's disease through ameliorating endoplasmic reticulum (ER) stress and activating autophagy. *Frontiers in Molecular Neuroscience*, *11*, 306235. https://doi.org/10.3389/FNMOL.2018.00120/BIBTEX

Wang, X. M., Wang, X. J., & Han, J. S. (1989). Antagonistic effects of angiotensin II and morphine on synaptosomal calcium uptake. *Sheng Li Xue Bao*, *41*(2), 179–183.

Wang, Y. L., An, X. H., Zhang, X. Q., Liu, J. H., Wang, J. W., & Yang, Z. Y. (2020). Morphine induces the apoptosis of mouse hippocampal neurons HT-22 through upregulating miR-181-5p. *European Review for Medical and Pharmacological Sciences*, *24*(12), 7114–7121. https://doi.org/10.26355/EURREV_202006_21705

Willner, D., Cohen-Yeshurun, A., Avidan, A., Ozersky, V., Shohami, E., & Leker, R. R. (2014). Short Term Morphine Exposure In Vitro Alters Proliferation and Differentiation of Neural Progenitor Cells and Promotes Apoptosis via Mu Receptors. *PLOS ONE*, *9*(7), e103043. https://doi.org/10.1371/JOURNAL.PONE.0103043

Woller, S. A., Moreno, G. L., Hart, N., Wellman, P. J., Grau, J. W., & Hook, M. A. (2012). Analgesia or addiction? Implications for morphine use after spinal cord injury. *Journal of Neurotrauma*, *29*(8), 1650–1662. https://doi.org/10.1089/NEU.2011.2100

Yang, X., Wang, Y., Li, Q., Zhong, Y., Chen, L., Du, Y., He, J., Liao, L., Xiong, K., Yi, C. X., & Yan, J. (2018). The Main Molecular Mechanisms Underlying Methamphetamine- Induced Neurotoxicity and Implications for Pharmacological Treatment. *Frontiers in Molecular Neuroscience*, *11*, 186. https://doi.org/10.3389/FNMOL.2018.00186

Young, W. (2014). Spinal cord regeneration. *Cell Transplantation*, *23*(4–5), 573–611. https://doi.org/10.3727/096368914X678427

Zhaleh, H., Bidmeshki, P. A., & Azadbakht, M. (2020). Mesenchymal stem cell condition medium enhanced cell viability in morphine-treated cells. *Bratislavske Lekarske Listy*, *121*(4), 263–270. https://doi.org/10.4149/BLL_2020_040

Zhang, D., Zhang, H., Jin, G. Z., Zhang, K., & Zhen, X. (2008). Single dose of morphine produced a prolonged effect on dopamine neuron activities. *Molecular Pain*, *4*, 57. https://doi.org/10.1186/1744-8069-4-57

Zhang, H., Jia, M., Wang, X. W., Ye, C., Li, Y., Wang, N., Elefant, F., Ma, H., & Cui, C. (2019). Dentate gyrus μ-opioid receptor-mediated neurogenic processes are associated with alterations in morphine self-administration. *Scientific Reports*, *9*(1), 1471. https://doi.org/10.1038/S41598-018-37083-8

Zhang, X. F., Liu, Z. G., Shen, W., & Gurunathan, S. (2016). Silver Nanoparticles: Synthesis, Characterization, Properties, Applications, and Therapeutic Approaches. *International Journal of Molecular Sciences*, *17*(9), 1534. https://doi.org/10.3390/IJMS17091534

Zhang, Y., & Zhai, H. (2020). Bilobalide assuages morphine-induced addiction in hippocampal neuron cells through upregulation of microRNA-101. *Journal of Biochemical and Molecular Toxicology*, *34*(7), e22493. https://doi.org/10.1002/JBT.22493

Zhao, P., Huang, Y., & Zuo, Z. (2006). Opioid preconditioning induces opioid receptor-dependent delayed neuroprotection against ischemia in rats. *Journal of Neuropathology and Experimental Neurology*, *65*(10), 945–952. https://doi.org/10.1097/01.JNEN.0000235123.05677.4B