中国临床研究 Chin J Clin Res, April 2024, Vol.37, No.4
Cite as: Chen X, Wang Y, Wei YY. Research progress in ion channel mechanism of morphine addiction [J]. Chin J Clin Res, 2024, 37(4):497-500.
DOI: 10.13429/j.cnki.cjcr.2024.04.002

**Dr. WEI Yiyong**, an Associate Chief Physician, serves as a Master's Supervisor and Postdoctoral Collaborative Supervisor at the School of Anesthesiology, Zunyi Medical University. He is a member of the Anesthesiology Committee of the Chinese Research Hospital Association and a youth editor for the Journal of Zunyi Medical University. His research primarily focuses on myocardial protection, the mechanisms of general anesthetic drugs, and clinical anesthesia. Over the past three years, Dr. Wei has led four research projects funded by the Science and Technology Department of Guizhou Province and Science and Technology Bureau of Zunyi. He has also headed five clinical trials and co-authored two graduate textbooks. As the first author or corresponding author, Dr. Wei has published twelve papers in Science Citation Indexed journals including "*Front Pharmacol*" and "*J Neuroinflammation*", along with four papers in core Chinese journals. Additionally, he has been granted three utility patents, including one for an anesthetic administration device.

# Research progress in ion channel mechanism of morphine addiction

CHEN Xia*, WANG Yong, WEI Yiyong

**School of Anesthesiology, Zunyi Medical University, Zunyi, Guizhou 563099, China*

*Corresponding authors: WEI Yiyong, E-mail: 295502476@qq.com;*

*WANG Yong, E-mail: 13357174@qq.com*

**Abstract:** Morphine is a classic opioid analgesic drug commonly used to treat chronic pain, cancer pain, neuropathic pain, etc. However, its clinical use is severely restricted due to the risk of addiction associated with repeated use. Morphine addiction has become a major global public health issue contributing to the spread of specific diseases. However, the mechanisms of morphine addiction are still not incompletely understood. An ion channel is a protein structure on the cell membrane, similar to a gate between inside and outside the cell, selectively allowing some ions to enter or exit the cell. Many types of ion channels are involved in the addiction mechanism of morphine. Current research shows that voltage-gated, ligand-gated and mechanical-gated ion channels are all involved in the mechanism of morphine addiction. Therefore, this paper reviews the mechanism of voltage-gated, ligand-gated and mechanically gated ion channel.

**Keywords:** Morphine tolerance; Morphine addiction; Ion channel; Voltage-gated channel; Ligand-gated channel; Mechanically gated channel

**Fund program:** General Project of National Natural Science Foundation of China (81860062); Project of Science and Technology Department of Guizhou Province (ZK [2022]664); Science and Technology of Zunyi Bureau Project (HZ [2021] 46, HZ [2022] 229); Doctoral Initiation Fund Project of Zunyi Medical University [Yuan Zi (2021) No.3]

Morphine, the main alkaloid with pharmacological activity in opium poppy extract, not only exhibits potent analgesic and sedative effects, but also modulates muscle spasms and histamine release in the peripheral nervous system [1]. The adverse reactions of morphine include constipation, pruritus, respiratory depression, and asthma attacks, severely limiting its clinical application, with addiction being the most harmful consequence [2]. Research into the mechanisms of morphine addiction has been a focus, as it can contribute to mitigating morphine's side effects and developing new analgesic drugs.

Researchers have conducted a series of studies on morphine addiction from various perspectives, including molecular biology mechanisms, neurotransmitter system mechanisms, receptor mechanisms, ion channel mechanisms, etc. Among these, the ion channel mechanism is an important direction of research, serving as a crucial entry point for studying new targets and drugs. Current researches indicate that voltage-gated, ligand-gated, and mechanical-gated ion channels are all involved in the mechanism of morphine addiction. Therefore, this article provides a review of voltage-gated, ligand-gated, and mechanical-gated ion channel mechanisms for morphine addiction.

## 1. Overview of morphine addiction

Drug addiction is a chronic neurological and psychiatric disorder characterized by an excessive craving for psychoactive substances to seek pleasure or alleviate pain, leading to fundamental changes in cognition, memory, and emotion. The core clinical symptom of drug addiction is the long-term recurrent cycle of drug withdrawal and drug craving. As the drug addiction progresses, the pleasure derived from drug use diminishes, increasing the demand for psychoactive substances and exacerbating drug dependence [3].

Morphine addiction occurs when drugs such as morphine act on the body, producing rewarding effects. Its mechanism involves morphine acting on μ receptors on γ-aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA). Morphine binds to μ receptors, inhibiting GABA neurons, thereby relieving their inhibition on dopamine (DA) neurons and promoting DA release from the VTA to the nucleus accumbens (NAc), where it binds to DA receptors, ultimately producing rewarding effects [4].

## 2. Ion channel mechanisms of morphine addiction

### *2.1 Voltage gated ion channels and morphine addiction*

2.1.1 Hyperpolarization-activated,cyclic nucleotide-gated (HCN) channels and morphine addiction

HCN channels are widely distributed in the central nervous system, including important regions related to drug addiction: the NAc, prefrontal cortex (PFC), VTA, and hippocampus [5]. Belonging to the voltage-gated ion channel superfamily, they can be activated by intracellular cyclic nucleotides. Morphine can increase the production of cyclic adenosine monophosphate (cAMP) in *vitro,* which is involved in chronic morphine analgesic tolerance and regulates downstream effector HCN channels by directly binding to intracellular cyclic nucleotide binding sites located at the C-terminus. The regulatory effect of cyclic nucleotides depends on different HCN subunits, with cAMP sensitivity being higher in HCN2 and HCN4, weaker in HCN1, and absent in HCN3 channels [6]. The specific inhibitor ZD7288 blocks the spinal cord HCN channel and effectively delays morphine-induced analgesic tolerance. Enhanced reward response is associated with overexpression of HCN2 in the abdominal segmental region of morphine-sensitized rats [6]. Inhibiting HCN channels effectively reduces the development of morphine-induced chronic analgesic tolerance.

2.1.2 Small-conductance calcium-activated potassium (SK) channels and morphine addiction

SK channels are potassium channels that are $K^+$selective, voltage independent, and activated by an increase in intracellular $Ca2^+$concentration. Their $K^+$ current is an important mechanism for the formation of neuronal action potential afterhyperpolarization. The role of SK channels in action potential afterhyperpolarization determines that they are important regulatory factors for cell excitability. Therefore, they may be involved in the formation of morphine-induced pain sensitization by altering neuronal excitability [7].

The excitability of neurons in the NAc and medial prefrontal cortex (mPFC) can be influenced by the amplitude of the afterhyperpolarization, including medium afterhyperpolarization and fast afterhyperpolarization, with the former being regulated by SK channels. SK channels affect neuronal excitability by promoting afterhyperpolarization and regulating synaptic plasticity. Research on rodents indicates that the SK2 channel in the infralimbic (IL) area of the mPFC, mediated by metabotropic glutamate receptor 5 (mGlu5), regulates the disappearance of drug-seeking behavior through synaptic plasticity.

On the other hand, Rac1, a member of the Rho family of small GTPases, may modulate SK channel activity and firing patterns, affecting synaptic plasticity of neurons in the nucleus accumbens (NAc) and mPFC, and thus influencing repeated drug exposure [8]. Increased expression of the SK3 subunit in the mPFC leads to morphine withdrawal in experimental animals [7-8]. During morphine withdrawal, the activity of protein phosphatase 2 (PP2A), which enhances SK channels in the mPFC and NAc, is increased. In addition, SK channels and their upstream mechanisms also play an important role in the process of morphine withdrawal. One week after morphine withdrawal, SK channels in the mPFC are upregulated via the Rac1 signaling pathway[8].

### *2.2 Ligand gated ion channels and morphine addiction*

The synaptic plasticity of glutamatergic neurons in the NAc is a crucial factor in acute rewarding effects and addiction to opioid drugs. Enhanced NAc glutamate transmission is the basis for both physical and effective withdrawal symptoms. Acute morphine exposure increases extracellular glutamate in NAc [9]. Glutamate receptors can be classified into two categories: N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolipyric acid (AMPA). Glutamate receptors have been shown to participate in the acquisition and consolidation of addictive memory by affecting synaptic plasticity [10].

(1) AMPA receptor (AMPAR): AMPARs are members of the ligand-gated ionotropic glutamate receptor family and play a critical role in rapid excitatory synaptic transmission in the mammalian central nervous system. AMPARs are tetramers composed of GluR1-4 subunits, with most AMPARs containing GluR1 and GluR2 subunits, the GluR2 subunit being critical for Ca2+ permeability. Regulation of AMPARs is involved in synaptic plasticity associated with long-term potentiation

(LTP) and long-term depression, as well as homeostatic synaptic plasticity of excitatory synapses [11]. AMPAR lacking GluA2, homologous to GluA1, has high calcium permeability and channel conductance, and its dynamic membrane insertion is the main mechanism inducing synaptic enhancement and LTP. Exposure to opioid drugs leads to an upregulation of GluA2 function, which increases AMPAR-mediated synaptic responses, thereby promoting drug uptake. In the early stages of LTP, homologous GluA1 AMPARs are transferred to synapses, which are thought to be the cellular basis of learning and memory, as well as the mechanisms underlying many neurological disorders (including opioid addiction and chronic pain). Research has shown that CeA-GluA1 is involved in the process of morphine reward and that GluA1 adaptation plays a key role in both negative and positive associative learning [12].

(2) NMDAR receptor (NMDAR): NMDAR is a ligand-gated ion channel composed of two obligatory NR1 subunits and two regulatory NR2 (a-D) or NR3 (a-B) subunits [13]. The NR1 and NR2B subunits are involved in morphine tolerance [14]. N-methyl-D-aspartate receptor (GluN2B NMDAR) protein levels specifically increase with the expression and recovery of morphine-conditioned place preference (CPP) in the hippocampus, and selective blockade of GluN2B NMDARs can inhibit the expression of morphine CPP [15].

Studies suggest that addictive drugs stimulate presynaptic release of glutamate, leading to rapid activation of AMPARs and depolarization of postsynaptic membranes. Subsequently, NMDA receptors are activated after AMPAR-mediated depolarization. Activated NMDA receptors cause extracellular calcium influx, activating downstream protein kinases of NMDA receptors and memory-related transcription factors, regulating the expression of target genes, forming new synapses, and consolidating addictive memories [16]. Intrathecal injection of MPEP (mGluR5 antagonist) or conditional knockdown of mGluR5 can alleviate morphine-induced hyperalgesia and tolerance [17].

## *2.3 Mechanical gated ion channels and morphine addiction*

### 2.3.1 Typical transient receptor potential canonical (TRPC) 1/4/5 channels

The TRPC channels are non-selective membrane cation channels permeable to $Na^+$ and $Ca^{2+}$. Activation of these channels contributes to membrane depolarization and calcium-dependent initiation of intracellular cascades.

Research has indicated that TRPC1/4/5 channels are involved in spatial working memory and learning adaptation. Knockout of TRPC1, TRPC4, and TRPC5 proteins reduces hippocampal synaptic transmission, leading to working memory deficits. Another study has shown that TRPC4 and TRPC5 are involved in anxiety-like behavior in the amygdala and innate fear responses [18]. Chronic morphine exposure leads to upregulation of TRPC1/4/5 channels in the spinal cord. Mice lacking TRPC1/4/5 proteins show reduced analgesic tolerance and decreased pain sensitivity. TRPC1/4/5 proteins are known to form heterotetrameric channels in the mouse brain. TRPC1/4/5 channels are crucial mediators in the development of morphine-induced tolerance. The absence of TRPC1, TRPC4, and TRPC5 proteins inhibits spinal cord remodeling and chronic morphine therapy, providing a new mechanism for morphine-induced hyperalgesia and analgesic tolerance [18].

### 2.3.2 TRPC6

TRPC6 is a $Ca^{2+}$ permeable non-selective cation channel, with multiple physiological functions. TRPC6 is widely expressed in the central nervous system, including the cerebral cortex, hippocampus, and spinal cord. Chronic exposure to morphine increases the expression of TRPC6 in cerebrospinal fluid, suggesting that TRPC6 is involved in morphine dependence [19]. After morphine treatment, the activity of CaMKIIα in the spinal cord increases. Inhibiting CaMKIIα in the spinal cord can prevent or reverse morphine tolerance and dependence [19]. The activation of CaMKIIα requires elevated intracellular $Ca^{2+}$ and activated calmodulin. TRPC6 siRNA inhibits the morphine-induced increase in CaMKIIα expression, suggesting that TRPC6 may regulate morphine induction by modulating CaMKIIα expression or activity. On the other hand, CaMKIIα can phosphorylate and activate TRPC6 channels, leading to inward $Ca^{2+}$ currents. CaMKIIα-TRPC6 channels may interact in a feed-forward manner in morphine-induced tolerance and hyperalgesia [19]. Studies have found that morphine increases TRPC6 expression in the spinal cord, contributing to the development of morphine-induced tolerance and hyperalgesia [20].

### 2.3.3 Transient receptor potential vanilloid 1 (TRPV1)

TRPV1 is a non-selective cation (Ca2+) channel involved in various pathophysiological processes and can be activated by acidic pH (≤5.9), high temperature (>42℃), endocannabinoids, endogenous lipids, and capsaicin. Brain regions closely associated with drug addiction, such as the prefrontal cortex, hippocampus, VTA, and striatum, show increased TRPV1 expression [21]. The TRPV1 antagonist SB366791 inhibits the reinstatement of cocaine-seeking behavior in rats and reduces morphine-induced addictive behaviors in mice and rats, while the TRPV1 agonist capsaicin promotes morphine reward. The TRPV1 antagonist effectively prevents morphine tolerance, and the TRPV1 antagonist significantly reduces withdrawal symptoms in morphine-dependent mice [22]. Long-term exposure to morphine may promote morphine-induced tolerance and dependence by regulating downstream targets of TRPV1, such as substance P (SP) in the spinal dorsal horn and calcitonin gene-related peptide (CGRP). Acute intrathecal injection of SP or CGRP antagonists can alleviate morphine withdrawal symptoms [22]. TRPV1 receptor antagonists can effectively inhibit morphine-induced reward and dependence. In addition, rats treated with TRPV1 receptor antagonists exhibit reduced anxiety-like

behavior after morphine withdrawal [23]. TRPV1 may be a promising therapeutic target for treating morphine dependence.

## 3. Conclusion

Morphine is a classic opioid analgesic commonly used to treat chronic pain, cancer pain, neuropathic pain, etc. However, its repeated use can lead to addiction, severely restricting its use. Patients unable to tolerate pain often resort to opioid medications, but long-term use inevitably leads to dependence and tolerance, causing both physical and psychological distress, potentially leading to irreversible consequences. Research on the mechanism of morphine addiction has been a hot topic, contributing to the alleviation of morphine side effects and the development of new analgesic drugs. Currently, numerous researchers are engaged in the study of ion channel mechanisms and have made some progress, providing a starting point for the development of new analgesic drugs.

**Conflict of Interest** None

## References


[1] Wang YE, Xu KL, Lv Y, et al. Morphine: the flower of Morpheus and the fruit of perdition[J]. Univ Chem, 2022, 37(9): 191-195.**[In Chinese]**

[2] Lu ZP, Bai J. Role and mechanism of MOR in morphine addiction, immunosuppression and other diseases[J]. Chin Pharmacol Bull, 2020, 36(12): 1636-1639. **[In Chinese]**

[3] Jiang CY, Xu YL, Liu YT, et al. Correlation analysis between hair regeneration and drug addiction susceptibility in rats[J]. J Integr Technol, 2022, 11(5): 23-33. **[In Chinese]**

[4] Zhang PP, Xu WJ, Liu HF. Research Progress on mechanism of ERK signaling pathway in drug addiction[J]. Chin Pharmacol Bull, 2017, 33(1): 1-9. [In Chinese]

[5] Zhou M, Luo P, Lu Y, et al. Imbalance of HCN1 and HCN2 expression in hippocampal CA1 area impairs spatial learning and memory in rats with chronic morphine exposure[J]. Prog Neuro Psychopharmacol Biol Psychiatry, 2015, 56: 207-214.

[6] Yuan L, Luo LM, Ma XQ, et al. Chronic morphine induces cyclic adenosine monophosphate formation and hyperpolarization-activated cyclic nucleotide-gated channel expression in the spinal cord of mice[J]. Neuropharmacology, 2020, 176: 108222.

[7] Qu LA, Wang YA, Ge SN, et al. Altered activity of SK channel underpins morphine withdrawal relevant psychiatric deficiency in infralimbic to accumbens shell pathway[J]. Front Psychiatry, 2019, 10: 240.

[8] Qu LA, Wang YA, Li Y, et al. Decreased Neuronal Excitability in Medial Prefrontal Cortex during Morphine Withdrawal is associated with enhanced SK channel activity and upregulation of small GTPase Rac1[J]. Theranostics, 2020, 10(16): 7369-7383.

[9] Madayag AC, Gomez D, Anderson EM, et al. Cell-type and region-specific nucleus accumbens AMPAR plasticity associated with morphine reward, reinstatement, and spontaneous withdrawal[J]. Brain Struct Funct, 2019, 224(7): 2311-2324.

[10] Jiang WN, Jing X, Li M, et al. Corydaline and l-tetrahydropalmatine attenuate morphine-induced conditioned place preference and the changes in dopamine D2 and GluA1 AMPA receptor expression in rats[J]. Eur J Pharmacol, 2020, 884: 173397.

[11] Zhang JJ, Liu Z, Liu XD, et al. Intravenous injection of GluR2-3Y inhibits repeated morphine-primed reinstatement of drug seeking in rats[J]. Brain Sci, 2023, 13(4): 590.

[12] Cai YQ, Hou YY, Pan ZZ. GluA1 in central amygdala increases pain but inhibits opioid withdrawal-induced aversion[J]. Mol Pain, 2020, 16: 174480692091154.

[13] Liu ZG, Yu Z, Yu S, et al. A conantokin peptide con-T[M8Q]inhibits morphine dependence with high potency and low side effects[J]. Mar Drugs, 2021, 19(1): 44.

[14] Zhu QM, Wu LX, Zhang B, et al. Donepezil prevents morphine tolerance by regulating N-methyl-d-aspartate receptor, protein kinase C and CaM-dependent kinase II expression in rats[J]. Pharmacol Biochem Behav, 2021, 206: 173209.

[15] Wang XJ, Liu Y, Jia M, et al. Phosphorylated SNAP25 in the CA1 regulates morphine-associated contextual memory retrieval via increasing GluN2B-NMDAR surface localization[J]. Addict Biol, 2018, 23(5): 1067-1078.

[16] Ou JY, Zhou YT, Li C, et al. Sinomenine protects against morphine dependence through the NMDAR1/CAMKII/CREB pathway: a possible role of astrocyte-derived exosomes[J]. Molecules, 2018, 23(9): 2370.

[17] Jin DZ, Chen H, Zhou MH, et al. mGluR5 from primary sensory neurons promotes opioid-induced hyperalgesia and tolerance by interacting with and potentiating synaptic NMDA receptors[J]. J Neurosci, 2023, 43(31): 5593-5607.

[18] Chu WG, Wang FD, Sun ZC, et al. TRPC1/4/5 channels contribute to morphine-induced analgesic tolerance and hyperalgesia by enhancing spinal synaptic potentiation and structural plasticity[J]. FASEB J, 2020, 34(6): 8526-8543.

[19] Jin H, Sun YT, Guo GQ, et al. Spinal TRPC6 channels contributes to morphine-induced antinociceptive tolerance and hyperalgesia in rats[J]. Neurosci Lett, 2017, 639: 138-145.

[20] Zhu YJ, Wienecke CFR, Nachtrab G, et al. A thalamic input to the nucleus accumbens mediates opiate dependence[J]. Nature, 2016, 530(7589): 219-222.

[21] Chen SR, Chen H, Jin D,, et al. Brief opioid exposure paradoxically augments primary afferent input to spinal excitatory neurons via α2δ-1-dependent presynaptic NMDA receptors[J]. J Neurosci,2022,42(50):9315-9329.

[22] Wang XQ, Bao CY, Li ZJ, et al. Side effects of opioids are ameliorated by regulating TRPV1 receptors[J]. Int J Environ Res Public Health, 2022, 19(4): 2387.

[23] Ma SX, Kim HC, Lee SY, et al. TRPV1 modulates morphine self-administration via activation of the CaMKII-CREB pathway in the nucleus accumbens[J]. Neurochem Int, 2018, 121: 1-7.


**Submission received:** 2023-07-08 / **Revised**:2023-08-31

· 学术前沿 ·

# 吗啡成瘾的离子通道机制研究进展

陈夏[1]，　王勇[2]，　魏义勇[1,3]

1. 遵义医科大学麻醉医学院，贵州 遵义 563099；2. 贵州省六盘水市人民医院，贵州 六盘水 553000；
3. 遵义医科大学附属医院麻醉科，贵州 遵义 563000

魏义勇博士，遵义医科大学麻醉医学院硕士生导师，博士后合作导师，副主任医师。中国研究型医院学会麻醉学专业委员会委员，遵义医科大学学报青年编委。主要从事心肌保护、全身麻醉药物作用机制和临床麻醉等相关研究。近三年主持贵州省科技厅和遵义市科技局研究项目 4 项，主持临床试验 5 项，参编研究生教材 2 部。以第一作者或通信作者在“*Front Pharmacol*”、“*J Neuroinflammation*”等 SCI 收录期刊发表论文 12 篇，中文核心期刊 4 篇，获“一种麻醉科用给药装置”等实用型专利 3 项。

**摘要**：吗啡是一种经典的阿片类镇痛药物，常用于治疗慢性痛、癌痛、神经病理性疼痛等。但由于反复使用会产生成瘾，这使得其临床使用受到严重限制。吗啡成瘾已经成为导致某些疾病传播的全球性重大公共卫生问题。然而，目前吗啡成瘾的机制仍然不完全清楚。离子通道是细胞膜上的一种蛋白结构，类似于细胞内外之间的门，可选择性让一些离子进出细胞。目前的研究表明，电压门控、配体门控和机械门控等离子通道均参与了吗啡成瘾的机制。因此本文就吗啡成瘾的上述离子通道机制作一综述。

**关键词**：吗啡耐受；吗啡成瘾；离子通道；电压门控；配体门控；机械门控

**中图分类号**：R971$^{+}$.2　**文献标识码**：A　**文章编号**：1674-8182(2024)04-0497-04

# Research progress in ion channel mechanism of morphine addiction

CHEN Xia*, WANG Yong, WEI Yiyong

** School of Anesthesiology, Zunyi Medical University, Zunyi, Guizhou 563099, China*

*Corresponding authors: WEI Yiyong, E-mail: 295502476@qq.com; WANG Yong, E-mail: 13357174@qq.com*

**Abstract**: Morphine is a classic opioid analgesic drug commonly used to treat chronic pain, cancer pain, neuropathic pain, etc. But repeated use can be addictive, this makes its clinical use severely limited. Morphine addiction has become a major global public health problem leading to the spread of some diseases. However, the mechanisms of morphine addiction are still not fully understood. An ion channel is a protein structure on the cell membrane, similar to a gate between inside and outside of the cell, that selectively allows some ions to enter and exit the cell. Current research shows that voltage-gated, ligand-gated and mechanically gated ion channels are all involved in the mechanism of morphine addiction. Therefore, this paper reviews the mechanism of voltage-gated, ligand-gated and mechanically gated ion channel for morphine addiction.

**Keywords**: Morphine tolerance; Morphine addiction; Ion channel; Voltage-gated; Ligand-gated; Mechanically gated

**Fund program**: General Project of National Natural Science Foundation of China (81860062); Project of Science and Technology Department of Guizhou Province (ZK [2022]664); Science and Technology of Zunyi Bareall Project (HZ

DOI: 10.13429/j.cnki.cjcr.2024.04.002

**基金项目**：国家自然科学基金面上项目（81860062）；贵州省科技厅项目（黔科合基础-ZK［2022］一般 664）；遵义市科技局项目（HZ［2021］46，HZ［2022］229）；遵义医科大学博士启动基金项目［院字（2021）3 号］

**通信作者**：魏义勇，E-mail：295502476@qq.com；王勇，E-mail：13357174@qq.com

**出版日期**：2024-04-20

QR code for English version

[2021] 46, HZ [2022] 229); Doctoral Initiation Fund Project of Zunyi Medical University [Yuanzi (2021) No. 3]

吗啡是罂粟提取物中具有药理活性的主要生物碱,除了具有强烈的镇痛、镇静作用外,还具有调节周围神经系统肌肉痉挛和释放组胺的作用[1]。吗啡的不良反应包括便秘、皮肤瘙痒、呼吸抑制、哮喘发作等,这些副作用极大限制了其临床应用,其中危害最为严重的是吗啡导致的成瘾[2]。有关吗啡成瘾机制的研究一直是热点,研究这一科学问题,有助于为减轻吗啡的副作用及研发新型镇痛药物奠定基础。

研究者从分子生物学机制、神经递质系统机制、受体机制、离子通道机制等多个方面对吗啡成瘾展开了一系列的研究,其中离子通道机制是目前研究的重要方向,是研究新靶点和新药物的重要切入口。目前的研究表明,电压门控、配体门控和机械门控等离子通道均参与了吗啡成瘾的机制。因此本文就吗啡成瘾的上述离子通道机制作一综述。

## 1　吗啡成瘾概述

药物成瘾是一种慢性神经精神疾病,其主要症状为过度渴求摄入精神类药物,以寻求欣快或缓解痛苦,进而诱发认知、记忆和情绪的根本变化。药物成瘾的核心临床症状为药物戒断与药物渴求的长期复发性循环,随着药物成瘾病程延续,使用药物带来的快感减少,导致患者对精神药物的需求上升,进而加重了药物使用者的药物依赖[3]。

吗啡成瘾是吗啡等成瘾药物作用于机体后,产生奖赏效应,其作用机制为吗啡作用于腹侧被盖区(ventral tegmental area, VTA)中 γ-氨基丁酸(γ-aminobutyric acid, GABA)能神经元上的 μ 受体,吗啡与 μ 受体结合后抑制 GABA 能神经元,从而解除其对多巴胺(dopamine, DA)能神经元的抑制,促进 VTA 到伏隔核(nucleus accumbens, NAc)区的 DA 释放,并与 DA 受体相结合,最终引发奖赏效应[4]。

## 2　吗啡成瘾的离子通道机制

### 2.1　电压门控离子通道与吗啡成瘾

2.1.1　超极化激活环核苷酸门控非选择性阳离子(HCN)通道与吗啡成瘾　HCN 通道广泛存在于中枢神经系统,包括对药物成瘾相关的重要区域:NAc、前额叶皮质(prefrontal cortex, PFC)、VTA 和海马[5]。属于电压门控离子通道超家族,可被细胞内环核苷酸激活。吗啡可增加体外腺苷-3′,5′-环磷酸(cAMP)的生成,cAMP 参与慢性吗啡镇痛耐受,通过直接结合位于 C 末端的细胞内环核苷酸结合位点,调节下游效应器 HCN 通道。环核苷酸的调节作用取决于不同的 HCN 亚单位,其中 cAMP 敏感性在 HCN2 和 HCN4 中较高,在 HCN1 中较弱,在 HCN3 通道中缺失[6]。特异性抑制剂 ZD7288 阻断脊髓 HCN 通道,可有效延缓吗啡诱导的镇痛耐受[6]。据报道,奖赏反应的增强也与吗啡致敏大鼠腹部节段区域 HCN2 过表达有关[6]。抑制 HCN 通道可以有效地降低吗啡诱导慢性镇痛耐受的发展。

2.1.2　小电导钙激活钾(SK)通道与吗啡成瘾　SK 通道是 $K^+$选择性、电压非依赖性、通过细胞内 $Ca^{2+}$浓度升高而激活的一种钾通道,其介导的 $K^+$电流是形成神经元动作电位后超极化(afterhyperpolarization, AHP)的重要机制。SK 通道在动作电位 AHP 的作用决定了它是细胞兴奋性的重要调节因子,因此有可能通过改变神经元的兴奋性而参与吗啡痛觉敏化的形成[7]。

NAc 和内侧 PFC(medial PFC, mPFC)神经元兴奋性可能会受到 AHP 动作电位幅度的影响,包括中等 AHP (medium AHP, mAHP)和快速 AHP,前者被认为由 SK 通道调节。SK 通道通过促进 AHP 和调节突触可塑性影响神经元兴奋性。啮齿动物研究表明,mPFC 边缘区(IL)中的 SK2 通道通过代谢型谷氨酸受体 5(mGlu5)介导的突触可塑性,调节寻求药物行为的消失。另一方面,Rac1 是小 GTP 酶 Rho 家族的成员,可能调节 SK 通道活性和放电模式,影响 NAc 和 mPFC 神经元突触可塑性,进而影响反复药物暴露[8]。mPFC 中 SK3 亚单位表达增加,实验动物会发生吗啡戒断[7-8]。吗啡戒断时,mPFC 和 NAc 中,对 SK 通道发挥增强作用的蛋白磷酸酶 2A(PP2A)活性增强。此外,SK 通道及其上游机制在吗啡戒断过程中也发挥重要作用,吗啡戒断 1 周后,mPFC 中的 SK 通道被 Rac1 信号通路上调[8]。

### 2.2　配体门控离子通道与吗啡成瘾

NAc 中的谷氨酸能神经元突触可塑性是阿片类药物急性奖赏效应、阿片类药物成瘾的重要因素。NAc 谷氨酸传递增强是躯体和有效戒断症状的基础。急性吗啡暴露会增加 NAc 中的细胞外谷氨酸[9]。谷氨酸受体可分为两大类:N-甲基-D-天冬氨酸(NMDA)和 α-氨基-3-羟基-5-甲基-4-异恶唑哌酸(AMPA),多种谷氨酸受体已被证明通过影响突触形态的可塑性参与成瘾记忆的获得和巩固[10]。(1) AMPA 受体(AMPAR):AMPAR是

配体门控的离子型谷氨酸受体家族成员,在哺乳动物中枢神经系统的快速兴奋性突触传递中起着关键作用。AMPAR 是 GluR1-4 亚单位的四聚体集合,大多数 AMPAR 含有 GluR1 和 GluR2 亚单位,其中 GluR2 亚单位对 $Ca^{2+}$ 的渗透性至关重要。调节 AMPAR 参与了长时程增强(LTP)和长时程抑制的突触功能,以及兴奋性突触的稳态突触可塑性[11]。缺乏 GluA2 同源 GluA1 的 AMPAR 具有较高钙通透性和通道电导,其动态膜插入是诱导突触增强和 LTP 的主要机制。暴露于阿片类药物会通过 AMPAR 的 GluA2 上调功能,增加 AMPAR 介导的突触反应,从而促使成瘾性药物摄入。在 LTP 的早期阶段,同源 GluA1 AMPAR 转移到突触中,被认为是学习和记忆的细胞基础,也是许多神经疾病(包括阿片类药物成瘾和慢性疼痛)的机制。研究表明,CeA-GluA1 参与吗啡奖赏过程,GluA1 适应在消极和积极联想学习中都起着关键作用[12]。(2) NMDA 受体(NMDAR):NMDAR 是一种配体门控离子通道,由两个强制性 NR1 亚基和两个调节性 NR2(a-D)或 NR3(a-B)亚基组成[13]。NR1 和 NR2B 亚单位参与吗啡耐受[14]。含有 GluN2B 的 NMDAR(GluN2B-NMDAR)蛋白水平随着吗啡条件性位置偏好(CPP)在海马中的表达和恢复而特异性增加,选择性阻断 GluN2B-NMDAR 可抑制吗啡 CPP 的表达[15]。

研究表明,成瘾药物刺激突触前膜释放谷氨酸,导致 AMPARs 快速激活和突触后膜去极化。因此,在 AMPARs 介导去极化后,NMDAR 被激活。通过激活的 NMDAR 细胞外钙内流,激活 NMDAR 和记忆核转录因子的下游蛋白激酶,调节靶基因的表达并形成新的突触,导致成瘾记忆的巩固[16]。背根神经元(DRG 神经元)鞘内注射 MPEP(mGluR5 拮抗剂)或条件性敲低 mGluR5 可减轻吗啡治疗诱导的痛觉过敏和耐受[17]。

### 2.3　机械门控离子通道与吗啡成瘾

2.3.1　典型瞬时受体电位(TRPC)1/4/5 通道　TRPC 通道是非选择性的质膜阳离子通道,可渗透 $Na^{+}$ 和 $Ca^{2+}$。激活后,这些通道有助于质膜去极化和钙依赖性细胞内级联的启动。

研究发现,TRPC1/4/5 通道参与空间工作记忆和学习适应。敲除 TRPC1、TRPC4 和 TRPC5 可减少海马突触传递与工作记忆缺失。另一项研究显示,TRPC4和 TRPC5 分别参与杏仁核的焦虑样行为和天生恐惧反应[18]。慢性吗啡暴露导致脊髓中TRPC1/4/5通道上调,TRPC1/4/5 缺失小鼠表现出镇痛耐受和痛觉过敏减弱。TRPC1/4/5 通道是吗啡诱导耐受发展的关键介质。TRPC1、TRPC4 和 TRPC5 蛋白的缺失,抑制了脊髓重塑和慢性吗啡治疗,为吗啡诱导的痛觉过敏和镇痛耐受提供了新的机制[18]。

2.3.2　TRPC6　TRPC6 是一种 $Ca^{2+}$ 渗透性非选择性阳离子,具有多种生理功能的通道。TRPC6 在中枢神经系统广泛表达,包括大脑皮质、海马和脊髓中。慢性吗啡暴露增加脑脊液中 TRPC6 表达,提示 TRPC6 参与吗啡依赖[19]。吗啡治疗后脊髓中的 CaMKⅡα 活性增加。脊髓上抑制或脊髓抑制 CaMKⅡα 可以预防或逆转吗啡耐受和依赖[19]。CaMKⅡα 活化需要升高细胞内 $Ca^{2+}$ 和激活的钙调蛋白。TRPC6 siRNA 抑制吗啡诱导的 CaMKⅡα 表达增加,通过调节 CaMKⅡα 的表达或活性,提示 TRPC6 可以调节吗啡诱导。另一方面,CaMKⅡα 可以磷酸化并激活TRPC6 通道,导致 $Ca^{2+}$ 通道内流。CaMKⅡαTRPC6 通道在吗啡诱导的耐受性和痛觉过敏中可能以前馈方式相互作用[19]。研究发现,吗啡导致脊髓中 TRPC6 表达增加,参与吗啡诱导耐受性和痛觉过敏的发展[20]。

2.3.3　瞬时受体电位香草醛 1(TRPV1)　TRPV1 是一种非选择性阳离子($Ca^{2+}$)通道,可被酸性环境(pH≤ 5.9)、高温(>42 ℃)、内源性大麻素、内源性脂质和辣椒素等激活。药物成瘾密切相关的大脑区域,如额叶皮质、海马、VTA 和纹状体,TRPV1 表达增加[21]。TRPV1 拮抗剂 SB366791,抑制了大鼠可卡因寻求行为的恢复,并减少了小鼠和大鼠吗啡诱导的成瘾行为,而 TRPV1 激动剂辣椒素促进了吗啡奖赏,TRPV1 拮抗剂能有效阻止吗啡耐受,TRPV1 拮抗剂显著减少了吗啡依赖小鼠的戒断症状[22]。长期吗啡暴露可能通过调节 TRPV1 下游靶点,如脊髓背角 P 物质(SP)和降钙素基因相关肽(CGRP),促进吗啡诱导的耐受和依赖。急性鞘内注射 SP 或 CGRP 拮抗剂可减轻吗啡戒断症状[22]。TRPV1 受体拮抗剂可以有效抑制吗啡诱导的奖赏和依赖,此外,TRPV1 受体拮抗剂治疗的大鼠在戒断吗啡后表现出焦虑样行为减少[23]。TRPV1 可能是治疗吗啡依赖的一个很有前景的靶点。

## 3　结　语

吗啡是一种经典的阿片类镇痛药物,常用于治疗慢性痛、癌痛、神经病理性疼痛等。但由于反复使用会产生成瘾使得其使用受到严重限制。疼痛难以忍受的患者不得已寻求吗啡类药物,吗啡类药物的长期

使用不可避免地会出现依赖和耐受,这对于疼痛患者可导致身体和心理上的双重崩溃。有关吗啡成瘾机制的研究,一直是目前研究的热点,探讨这一问题,有助于为减轻吗啡的副作用及为研发新型镇痛药物奠定基础。当前众多研究学者从事于离子通道机制研究,并取得了一定的进展,这些离子通道是研发新型镇痛药物的切入口。

**利益冲突**　无潜在的利益冲突

## 参考文献


[1] 王玥,徐开来,吕弋,等.梦神之花,堕落之果——吗啡[J].大学化学,2022,37(9):191-195.
Wang Y, Xu KL, Lv Y, et al. Morphine: the flower of Morpheus and the fruit of perdition[J]. Univ Chem, 2022, 37(9): 191-195.

[2] 卢志鹏,白洁.μ 受体在吗啡成瘾及免疫抑制等疾病中的作用和机制[J].中国药理学通报,2020,36(12):1636-1639.
Lu ZP, Bai J. Role and mechanism of MOR in morphine addiction, immunosuppression and other diseases[J]. Chin Pharmacol Bull, 2020, 36(12): 1636-1639.

[3] 蒋辰宇,许云龙,柳昱彤,等.大鼠毛发再生与药物成瘾易感性的相关性分析[J].集成技术,2022,11(5):23-33.
Jiang CY, Xu YL, Liu YT, et al. Correlation analysis between hair regeneration and drug addiction susceptibility in rats[J]. J Integr Technol, 2022, 11(5): 23-33.

[4] 张盼盼,徐文锦,刘惠芬.中枢神经系统 ERK 信号通路在药物成瘾中的作用机制研究进展[J].中国药理学通报,2017,33(1):1-9.
Zhang PP, Xu WJ, Liu HF. Research Progress on mechanism of ERK signaling pathway in drug addiction[J]. Chin Pharmacol Bull, 2017, 33(1): 1-9.

[5] Zhou M, Luo P, Lu Y, et al. Imbalance of $HCN_1$ and $HCN_2$ expression in hippocampal CA1 area impairs spatial learning and memory in rats with chronic morphine exposure[J]. Prog Neuro Psychopharmacol Biol Psychiatry, 2015, 56: 207-214.

[6] Yuan L, Luo LM, Ma XQ, et al. Chronic morphine induces cyclic adenosine monophosphate formation and hyperpolarization-activated cyclic nucleotide-gated channel expression in the spinal cord of mice[J]. Neuropharmacology, 2020, 176: 108222.

[7] Qu LA, Wang YA, Ge SN, et al. Altered activity of SK channel underpins morphine withdrawal relevant psychiatric deficiency in infralimbic to accumbens shell pathway[J]. Front Psychiatry, 2019, 10: 240.

[8] Qu LA, Wang YA, Li Y, et al. Decreased Neuronal Excitability in Medial Prefrontal Cortex during Morphine Withdrawal is associated with enhanced SK channel activity and upregulation of small GTPase Rac1[J]. Theranostics, 2020, 10(16): 7369-7383.

[9] Madayag AC, Gomez D, Anderson EM, et al. Cell-type and region-specific nucleus accumbens AMPAR plasticity associated with morphine reward, reinstatement, and spontaneous withdrawal[J]. Brain Struct Funct, 2019, 224(7): 2311-2324.

[10] Jiang WN, Jing X, Li M, et al. Corydaline and l-tetrahydropalmatine attenuate morphine-induced conditioned place preference and the changes in dopamine $D_2$ and GluA1 AMPA receptor expression in rats[J]. Eur J Pharmacol, 2020, 884: 173397.

[11] Zhang JJ, Liu Z, Liu XD, et al. Intravenous injection of GluR2-3Y inhibits repeated morphine-primed reinstatement of drug seeking in rats[J]. Brain Sci, 2023, 13(4): 590.

[12] Cai YQ, Hou YY, Pan ZZ. GluA1 in central amygdala increases pain but inhibits opioid withdrawal-induced aversion[J]. Mol Pain, 2020, 16: 174480692091154.

[13] Liu ZG, Yu Z, Yu S, et al. A conantokin peptide con-T[M8Q] inhibits morphine dependence with high potency and low side effects[J]. Mar Drugs, 2021, 19(1): 44.

[14] Zhu QM, Wu LX, Zhang B, et al. Donepezil prevents morphine tolerance by regulating N-methyl-d-aspartate receptor, protein kinase C and CaM-dependent kinase Ⅱ expression in rats[J]. Pharmacol Biochem Behav, 2021, 206: 173209.

[15] Wang XJ, Liu Y, Jia M, et al. Phosphorylated SNAP25 in the CA1 regulates morphine-associated contextual memory retrieval via increasing GluN2B-NMDAR surface localization[J]. Addict Biol, 2018, 23(5): 1067-1078.

[16] Ou JY, Zhou YT, Li C, et al. Sinomenine protects against morphine dependence through the NMDAR1/CAMK Ⅱ/CREB pathway: a possible role of astrocyte-derived exosomes[J]. Molecules, 2018, 23(9): 2370.

[17] Jin DZ, Chen H, Zhou MH, et al. mGluR5 from primary sensory neurons promotes opioid-induced hyperalgesia and tolerance by interacting with and potentiating synaptic NMDA receptors[J]. J Neurosci, 2023, 43(31): 5593-5607.

[18] Chu WG, Wang FD, Sun ZC, et al. TRPC1/4/5 channels contribute to morphine-induced analgesic tolerance and hyperalgesia by enhancing spinal synaptic potentiation and structural plasticity[J]. FASEB J, 2020, 34(6): 8526-8543.

[19] Jin H, Sun YT, Guo GQ, et al. Spinal TRPC6 channels contributes to morphine-induced antinociceptive tolerance and hyperalgesia in rats[J]. Neurosci Lett, 2017, 639: 138-145.

[20] Zhu YJ, Wienecke CFR, Nachtrab G, et al. A thalamic input to the nucleus accumbens mediates opiate dependence[J]. Nature, 2016, 530(7589): 219-222.

[21] Chen SR, Chen H, Jin D, et al. Brief opioid exposure paradoxically augments primary afferent input to spinal excitatory neurons via α2δ-1-dependent presynaptic NMDA receptors[J]. J Neurosci, 2022, 42(50): 9315-9329.

[22] Wang XQ, Bao CY, Li ZJ, et al. Side effects of opioids are ameliorated by regulating TRPV1 receptors[J]. Int J Environ Res Public Health, 2022, 19(4): 2387.

[23] Ma SX, Kim HC, Lee SY, et al. TRPV1 modulates morphine self-administration via activation of the CaMK Ⅱ-CREB pathway in the nucleus accumbens[J]. Neurochem Int, 2018, 121: 1-7.


**收稿日期**:2023-07-08　**修回日期**:2023-08-31　**编辑**:石嘉莹