

The pathophysiological role of serotonin receptor systems in opioid analgesia and tolerance

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ABSTRACT

Continuous treatment with opioid analgesics, such as morphine, leads to the development of ant nociceptive tolerance in patients. Although a lot of information about antinociceptive, the pathophysiological mechanisms of tolerance to opioid analgesia are not yet completely understood. Proposed mechanisms for opioid analgesic tolerance comprise down-regulation of opioid receptors, reduction of sensitivity G-proteins, altered intracellular signalling pathway including nitric oxide, adenylyl cyclase, and protein kinase C. Numerous physiological and behavioural studies have shown an interaction of the serotonergic system and opioid antinociception. The serotonin (5-HT) receptor system is a necessary component of the spinal and midbrain pain modulation circuit mediating opioid analgesia. Various types of serotonin receptors demonstrate different effects on morphine analgesia. Systemic administration of opioids rise 5-HT levels in the spinal cord dorsal horn and contribute to opioid analgesia in the normal state but reduce that in neuropathic pain via spinal 5-HT₃ receptors. Spinal and supraspinal serotonergic neurons may also play a pathophysiological role in the development of morphine analgesic tolerance. Serotonin receptor subtypes show different effects on opioid tolerance. This review paper focus on the current understanding of the role of serotonin receptor systems in opioid analgesia and tolerance.

Keywords: Opioid receptors, Opioid tolerance, Serotonin receptors, Serotonin analgesia, Tolerance mechanism

INTRODUCTION

Though opioid analgesic drugs are still the principal treatment for severe chronic pain, continuous use of opioids is known to result in a decreased antinociceptive effect, also known as antinociceptive tolerance.^{1,2} Antinociceptive tolerance is described as the reduction in analgesic efficacy of a drug after a previous exposure to the same drug dose. Thus, higher doses of the drug are necessary to show the same amount of analgesic effect. High doses of opioid drugs result in important unwanted effects such as nausea, constipation, vomiting, somnolence, dizziness, and deterioration of mental vigilance.^{3,4}

The pathophysiological mechanism underlying the development of opioid analgesic tolerance maintains obscure. It has been suggested that opioid analgesic

tolerance is a result of 1) down-regulation of opioid receptors (μ , δ , and κ), 2) decreased sensitivity of heterotrimeric G-proteins, 3) changed cellular signaling pathway including nitric oxide, adenylyl cyclase or protein kinase C and 4) participation of postreceptor cellular occurrences, especially the γ -aminobutyric acid (GABA), glutamate, and monoamine neurotransmitters such as noradrenaline and serotonin (5-hydroxytryptamine, 5-HT).⁵

The rostral ventromedial medulla (RVM) forms part of a descending pathway that regulates pain transmission at the level of the spinal cord dorsal horn. In addition, RVM is a critical site for the supraspinal antinociceptive actions and analgesic tolerance to opioids. Animals with lesion of the dorsolateral funiculus (DLF) did not demonstrate enhanced neuropeptide release and antinociceptive tolerance upon sustained exposure to opioid drugs.

Injection of lidocaine into the RVM inhibited both thermal hyperalgesia and analgesic tolerance to morphine in rats.^{6,7}

Many pharmacological agents have been shown to inhibit antinociceptive tolerance. These agents include: nitric oxide (NO) synthase inhibitors, calcium channel blockers, substance P receptor (NK-1) antagonists, calcitonin gene-related peptide (CGRP) receptor antagonists, cyclooxygenase (COX) inhibitors, antagonists of the NMDA (N-methyl-D-aspartate) receptor, cholecystinin (CCK) receptor antagonists, and 5-HT receptor agonists.⁸⁻¹⁷

Serotonergic neurons are involved in the formation of spinal cord pain.¹⁸ Stimulation of serotonergic neurons decreases the pain responses through a descending inhibitory pathway in the spinal cord dorsal horn.¹⁹ The antinociceptive effect of morphine was blocked by the 5-HT receptor antagonist methysergide when injected into the periaqueductal gray (PAG) in midbrain.²⁰ Additionally, opioid induces the release of 5-HT in different serotonergic neuron areas, originated primary from the dorsal raphe nucleus (DRN).²¹ Morphine seems to act in the area of the DRN to produce raised extracellular 5-HT levels in several midbrain sites.²² It has been suggested that sustained administration of morphine leads to an increase in GABA levels and later to a reduce in serotonergic activity in the DRN neurons. Thus, it may be supposed that the dorsal and median raphe serotonergic neuron systems have significant roles in the appearance of opioid tolerance. There is argument showing a correlation between the synthesis rate of 5-HT in the midbrain and the development of tolerance,

supporting a pathophysiological role of 5-HT in opioid analgesic tolerance.^{23,24} In addition, it has been shown that 8-OH-DPAT, a specific 5-HT_{1A} receptor agonist, inhibits morphine analgesic tolerance.²⁵

This review focus on the mechanisms of mophine antinociceptive tolerance and pathophysiological role of serotonin receptor systems in opioid analgesia and tolerance.

OPIOID RECEPTOR PHYSIOLOGY

Opioid receptors have belonged to the major family of seven transmembrane G protein-coupled receptors (GPCR) with opioids as ligands.²⁶ The endogenous opioids are dynorphins, enkephalins, endorphins and nociceptin. Three large opioid receptor families, the μ -, κ , and δ - receptor subtypes, were cloned in 1990 and the nociceptin or orphanin FQ receptor (NOR), a fourth member of the opioid receptor subtype, was attached to the list in 1994 (Table 1).²⁷⁻²⁹ Opioid receptors are distributed widely in the brain, and are found in the spinal cord, heart, liver, lungs and digestive tract.³⁰

Numerous studies indicate that the pharmacological interactions between opioid receptors play a crucial role in defining their resultant physiologically behaviors.³¹ For instance, δ -agonist drugs were displayed to increase the antinociceptive potency of μ -agonists, and δ -antagonists attenuated the development of tolerance to opioid analgesia by μ -agonists.³²

Table 1: Opioid receptors subtypes, locations and functions.

Receptor	Subtypes	Location	Function
mu (μ), MOR	μ_1, μ_2, μ_3	<ul style="list-style-type: none"> - cortex - thalamus - PAG - spinal cord - peripheral sensory neurons - intestinal tract 	<ul style="list-style-type: none"> - analgesia (μ_1) - intestinal motility (μ_2) - respiratory depression (μ_2) - physical dependence (μ_1) - euphoria (μ_2) - miosis (μ_2) - vasodilation (μ_3)
delta (δ), DOR	δ_1, δ_2	<ul style="list-style-type: none"> - pontine nuclei - amygdala - olfactory bulbs - peripheral sensory neurons 	<ul style="list-style-type: none"> - analgesia - convulsant effects - antidepressant effects - physical dependence
Kappa (K), KOR	$\kappa_1, \kappa_2, \kappa_3$	<ul style="list-style-type: none"> - brain - hypothalamus - PAG - spinal cord - peripheral sensory neurons 	<ul style="list-style-type: none"> - analgesia - depression - dysphoria - miosis - neuroprotection - sedation - stress
Nociceptin Receptor, NOR	ORL ₁	<ul style="list-style-type: none"> - cortex - hippocampus - amygdala - hypothalamus - spinal cord 	<ul style="list-style-type: none"> - appetite - anxiety - depression

LY255582, an opioid antagonist, which formed effects on feeding via a heteromeric combination of μ -opioid receptor, δ -opioid receptor and κ -opioid receptor.³³ For this reason, new ligands with dual μ -/ δ -agonism or antagonism, or mixed μ -agonism/ δ -antagonism are arising as encouraging original attempts to the development of antinociceptive drugs.³²

OPIOID RECEPTOR SUBTYPES

Mu Opioid Receptor (MOR)

The MOR was the latest of the known all opioid receptors to be cloned. MOR is found high density in the cerebral cortex, amygdala, caudate putamen and PAG. MOR is located presynaptic terminals on primary afferent neurons within the dorsal horn of the spinal cord. These receptors prevent transmission of pain stimuli from A δ and C fibres.³⁴ The periaqueductal grey involves in the supraspinal control of pain signal transmission in the midbrain. The efferent PAG signals descend to the spinal cord where it acts to block pain signal in primary afferent neurons. The opioids analgesia is recommend to come about from removal of an inhibitory GABA-ergic tone in the PAG region. The fundamental inhibitory neurotransmitter GABA acts to decrease pain signal from the PAG.³⁵

Major side-effects of MOR agonists contain respiratory depression via impaired sensitivity of chemoreceptors in lungs. MOR agonists block gastrointestinal tract peristalsis and frequently cause constipation.³⁶ MORs also have effects on the immune function, thermoregulation, heart, vascular system and endocrine system. MOR knockout mice suggest significantly enhanced sensitivity to thermal pain sensations.^{34,37} None of the side-effects of opioid were shown in mice lacking the MOR. In addition, morphine did not create antinociception or respiratory depression in this mice. These findings support that both the wanted and side-effects of opioid are attributable to action at the MOR.³⁸

Delta Opioid Receptor (DOR)

The DOR was the first opioid receptor subtypes to be cloned and is found in the cerebral cortex, the nucleus accumbens and caudate putamen. DORs are located presynaptic terminal on primary afferent neurons and they prevent the release of transmitters. These receptors are involved in the analgesic actions of opioids via both spinal and supraspinal sites. DOR agonists have also been suggested to decrease intestinal tract peristaltic movements and cause unwanted effect on respiratory system.³⁹

Studies with DOR knockout mice indicated that they show hyperactive locomotor behaviour and it is presumed the receptor, under normal conditions, may depress locomotor activity. Researchers have also reported that

DOR knockout mice display depressive and anxiogenic behaviours.⁴⁰

Kappa Opioid Receptor (KOR)

The KOR was the second of the four subtypes opioid receptor to be cloned. The kappa receptor agonist is the benzomorphan ketocyclazocine, the actions of which have been shown to be distinct from those elicited by stimulation of the MOR. The activation KOR by agonists is coupled to the Gi protein in cell membrane, which substantially enhances phosphodiesterase enzyme activity in cell cytoplasm. Thus, intracellular phosphodiesterase enzyme breaks down cAMP, producing an inhibitory effect on pain signal transmission.⁴¹ The KOR effects include altering pain perception, consciousness, mood, and motor control. KOR agonists are potently analgesic agents and have been used clinically in the treatment of severe and chronic pain, consistent with MOR agonists. Spiradoline and enadoline, as a KOR agonists, have experienced clinical trials for their antinociceptive effects.^{42,43} Clinical findings suggests that spiradoline produces side-effects such as dysphoria, sedation and diuresis at doses lower than those required for antinociceptive actions. The adverse effects of KOR agonists have restricted their efficient clinical use. Nevertheless, it has been suggested that KOR agonists may have neuroprotective activity through their capacity to prevent glutamat release.

The superiority of the KOR opioid agonists over other opioid agonists is that they do not produce respiratory distress. It has been shown that KOR agonists indicate an anti-opioid activity decreasing analgesia produced by MOR opioid agonists. This anti-opioid activity is produced by a different distribution of KORs on primary neurons located within the nucleus raphe magnus (NRM). The signal from the NRM neurons creates part of the descending inhibitory control pathway acting to suppress pain transmission. The NRM consists of two type neurons (primary and secondary neurons) whose axons terminate in the dorsal horn of spinal cord. It is indicated that secondary neuron discharging induces pain transmission, while primary neurons block it.⁴⁴ Analgesia produced by exogenously applied opioids is principally through agonist actions at the MOR. It has been suggested that MORs are localized just at secondary cells of the NRM. Inhibition of the secondary neurons owing to MOR activation results in inhibition of GABA-ergic input to primary neurons and causes their disinhibition. Thus, inhibition of the primary neurons, which equates to their stimulation, is concluded analgesia produced in the spinal cord. KORs are localized solely on the primary neurons in the spinal cord and the anti-nociceptive effect of KOR agonists is caused by blocking the primary neurons.⁴⁴

Nociceptin Orphanin FQ Receptor (NOR)

The NOR opioid receptor is a member of the opioid receptors subfamily whose native ligand is a peptide known as nociceptin (N/OFQ). This nociceptin opioid receptor performs same actions to those of the usual opioids resulting in inhibition of neurotransmitter release and reduced neuronal excitability. This member of the opioid receptors is involved in the regulation of many midbrain activities, especially pain transmission, feeding, memory, learning, stress and anxiety.⁴⁵

The NOR acts as a dopamine endogenous antagonist that may act either by the blocking GABA or directly on dopamine to affect dopamine levels. NOR has been shown to have a hyperalgesic or anti-analgesic effect. NOR agonists produce pronociceptive effects when applied supraspinally. However, spinally NOR agonists cause analgesia at high doses. Anti-analgesic action of NOR agonists is the hypothesised cause for the supraspinal hyperalgesic effect, inhibiting endogenous opioid tone. Anti-opioid effect of NOR is produced by NOR localization on primary neuron cells of the NRM.⁴⁶

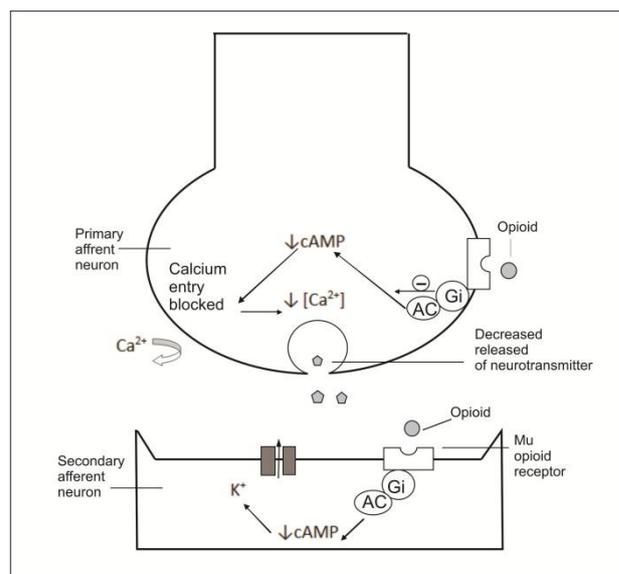
Studies suggest that the levels of nociceptin in neuron cells of NRM may act to set threshold to pain, as NOR antagonist agents have been suggested to give enhance to a permanent antinociception. NOR antagonists may have a probable future as new antinociceptive drug or may be used as an adjuvant to decrease the opioid drug dose required to analgesic actions.

OPIOID TOLERANCE MECHANISMS

Opioid tolerance is defined as a shift to the right in the dose-response curve in pharmaceutical science. In other words, an increasing dose is required long time to protect the similar level of antinociception. Sometimes, chronic diseases and cancers are the reasons for higher dose of opioid requirements.⁴⁷ Pharmacokinetic and pharmacodynamic changes cause the increase of opioid drug dose. Pharmacokinetic changes involve in alterations the rate of excretion from the body via the effects that modify metabolic activity of drugs. Metabolic enzyme induction results in a progressive decrease in serum levels of drug meanwhile the daily opioid dose remains constant. However, pharmacodynamic tolerance occurs when a decrease in effects of opioid drugs and express drug-activated alterations in the response of the neural systems.²

There are two major theories about the mechanisms of opioid tolerance. The first theory presents that opioid receptors undergo alterations that result in decreased receptor activation, with chronic exposure to opioid drugs. The supporting document indicates that the down-regulation of opioid receptor is at least partly liable for the development of tolerance to opioid analgesia. The desensitization mechanism of opioids includes the physiological alterations of the opioid receptors.⁴⁸

Heterotrimeric G protein is activated, when the opioid drug is bound to its receptor. Eventually, activation of G proteins causes attenuating excitability throughout the neuron membranes in the nociceptive pathways. This effect is formed via a reduction in cyclic adenosine monophosphate (cAMP), leading to a repression of Ca^{2+} and Na^+ channels and resulting in antinociception (Figure 1). Long time, changes in the mechanism of G protein pathway may lead to attenuated antinociception via opioid receptor desensitization.^{49,50} In experimental studies, the desensitization arises when enzymes or cellular regulatory proteins, such as adenylyl cyclase, β -arrestins, and GPCR kinases are activated by opioids in such a way that they decouple G protein from the opioid receptor in the cell membrane later reducing antinociceptive effect. Before this, opioid analgesic tolerance has been associated with opioid receptor desensitization in rats. However, actual reviews emphasize how much is left to be learned about these complex intracellular tolerance mechanisms.^{49,51} There is substantial evidence indicating that application of a mitogen-activated protein kinase (MAPK) inhibitor reduces morphine analgesic tolerance.⁵²



When the opioid is bound to the receptor, the connected G protein becomes activated. Activation of G proteins finally leads to decreasing excitability along the cell membranes of neurons in the pain pathways. This action occurs via a reduction in cyclic adenosine monophosphate (cAMP), leading to a repression of Na^+ and Ca^{2+} channels and resulting in antinociception.

Figure 1: The action mechanism of opioid receptors. Opioid receptors belong to the family of G protein-coupled receptors (GPCRs).

The second mechanism of opioid analgesic tolerance is performed through internalization of the opioid receptor from the bilayer lipid membrane of cell. The opioid receptors density situated on the nerve cell membrane is administered by endocytic mechanism. Once entered into the nerve cells the opioid receptor can no longtime

activity and is rapidly down-regulated. It is prevented the development of opioid analgesic tolerance in β -arrestin2 (a down-regulators) deficient rats and continue to have sustained opioid analgesia.⁵³ Nevertheless, numerous studies have indicated that enhanced internalization may essentially attenuated opioid tolerance by getting desensitized receptors off the membrane and leading to resensitization via recycled receptors being displaced.⁵⁴

Different opioid receptor agonist drugs have been indicated to distinct in their ability to down-regulate or desensitize opioid receptors.⁵⁵ One of these differences has been based on the intrinsic activity of the opioid agonist drugs. Every opioid has a given level of intrinsic activity for the different opioid receptors. Intrinsic activity is a notional parameter that pertains the number of receptors engaged to the size of the opioid receptor response. It is required to retain a number of receptors out of the all population to create a given effect.⁵⁶ The number of receptors that need to be occupied to generate an antinociceptive action is supposed to be reverse proportional to the intrinsic efficacy.^{57,58}

Generally, chronic treatment with morphine has been known to cause a greater rightward shift in dose response curve with lower intrinsic activity.⁵⁹ Experimental models have suggested that long-term treatment with high activity opioids, such as fentanyl, that have a important receptor stock and down-regulate a little receptors.⁵⁸ At the same time, the evidences indicate high activity opioids virtually activate more G protein coupled receptor kinases than low activity opioids.⁶⁰ On the other hand, animal studies suggest that melanocortin 4 receptor antagonists attenuate tolerance to morphine analgesia in rats. Melatonin is a hormone secreted by the pineal gland and inhibits morphine-induced hyperalgesia via the PKC pathway in rats.²⁷ The endocrine hormone melatonin reverses morphine tolerance by inhibiting microglia activation and HSP27 expression.⁶¹ The orexin 1 receptor

is intensely localized the hypothalamus and regulates appetite. Blockade of orexin type 1 receptors prevents the development of morphine analgesic tolerance in the brainstem.⁶²

SEROTONIN RECEPTORS

The serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter and biochemically derived from the amino acid tryptophan and one of the most ancient signaling molecules. 5-HT is localized in various cell types, such as enterochromaffin cells and blood platelets and the central nervous system cells.⁶³ 5-HT is an important regulator of a wide variety of behaviors such as feelings of well-being and happiness.⁶⁴

The 5-HT receptors are located on the cell membrane of nerve cells and a family of G protein-coupled receptors (GPCRs). With the exception of the 5-HT₃, these receptors are a ligand-gated ion channels and found in the peripheral and central neurons.^{65,66} The 5-HT receptors are divided into seven different classes (5-HT₁ to 5-HT₇) according to their structural and transmission characteristics (Table 2). These receptors intercede both inhibitory and excitatory neurotransmission in neuronal circuits. The membrane 5-HT receptors are activated by the 5-HT molecule, which modulates the release of many neurotransmitters and hormones, including epinephrine, GABA, dopamine, acetylcholine, cortisol, prolactin, substance P, oxytocin and vasopressin.⁶⁷ Furthermore, the 5-HT receptors regulate different neurological and physiological processes such as appetite, aggression, mood, anxiety, cognition, learning, memory, nausea, thermoregulation and sleep. At the same time, these receptors are the target of a diversity of biochemical drugs, including several antipsychotics, antidepressants, antiemetics, gastroprokinetic, hallucinogens and antimigraine agents.⁶⁴

Table 2: Serotonin receptors subtypes.

Receptor Subtypes	Signaling Mechanism	Distribution	Effects
5-HT _{1A}	Gi, ↓ cAMP	Raphe nuclei, hippocampus	Regulates sleep, feeding and anxiety
5-HT _{1B}	Gi, ↓ cAMP	Substantia nigra, globus pallidus, basal ganglia	Neuronal inhibition, behavioral changes
5-HT _{1D}	Gi, ↓ cAMP	Brain	Vasoconstriction
5-HT _{1E}	Gi, ↓ cAMP	Cortex, hippocampus	Memory
5-HT _{1F}	Gi, ↓ cAMP	Globus pallidus, putamen	Anxiety, vasoconstriction
5-HT _{2A}	Gq, ↑ IP ₃	Platelets, cerebral cortex	Cellular excitaton, muscle contraction
5-HT _{2B}	Gq, ↑ IP ₃	Stomach	Appetite
5-HT _{2C}	Gq, ↑ IP ₃	Hippocampus, substantia nigra	Anxiety
5-HT ₃	Na ⁺ -K ⁺ ion channel	Area postrema, enteric nerves	Vomiting
5-HT ₄	Gs, ↑ cAMP	Cortex, smooth muscle	Gut motility
5-HT _{5A,B}	Gi, ↓ cAMP	Brain	Locomotion, sleep
5-HT ₆	Gs, ↑ cAMP	Brain	Cognition, learning
5-HT ₇	Gs, ↑ cAMP	Brain	Mood, memory, sleep

The 5-HT₁ family includes five receptor subtypes that are largely coupled to Gi proteins and inhibit adenylate cyclase enzyme. 5-HT₁ receptor subtypes are highly localized in the hippocampus, basal ganglia and raphe nuclei. The Gq protein receptor 5-HT₂ activate phospholipase C and is localized in the cortex, hippocampus, basal ganglia and medulla spinalis.⁶⁸ 5-HT₄, 5-HT₆, and 5-HT₇ receptors bind to Gs proteins and are positively associated with adenylate cyclase enzyme. The 5-HT₄ receptor subtypes are fundamentally expressed in the hippocampus and basal ganglia, 5-HT₆ receptors in the hippocampus, amygdala, striatum and cortex, and 5-HT₇ receptors in the amygdala, hippocampus and hypothalamus. Besides, subtypes of the 5-HT₅ receptor are localized in the hypothalamus, hippocampus, cerebellum and cortex.

Finally, the 5-HT₃ receptor belongs to the ligand-gated ion channels and consequently differs structurally from all other 5-HT receptors, and stimulation of this receptor leads to the opening of a cation channel such as sodium, potassium and calcium.⁶⁹ 5-HT₃ receptors are highly localized in both peripherally and centrally neurons, in the substantia gelatinosa of the spinal cord, in the brainstem and cortex, and limbic areas, such as the entorhinal cortex, hippocampus and amygdala.^{68,70}

Serotonin and pain

Serotonergic neurons are highly expressed in the raphe nuclei of the brainstem and project to the spinal cord and forebrain. The raphe nuclei of the brainstem are divided in two groups structurally and functionally. The rostral group of raphe includes median raphe nucleus (MRN) and dorsal raphe nucleus (DRN). In addition, the caudal group comprises the raphe pallidus and the nucleus raphe magnus (NRM).⁷¹ The afferent fibers to the raphe nuclei originate from the hypothalamus, limbic system, and prefrontal cortex.⁷² The NRM neuron fibers project mainly to the spinal cord dorsal horn.⁷¹

It has been well established that 5-HT producing neurons contribute to descending pain control pathways.^{73,74} Experimental studies suggest that this pain control pathways derived from the raphe nuclei have a significant role in serotonergic pain regulation.⁷⁵ Neurons in the rostralventromedial medulla (RVM), give arise to significant facilitatory and inhibitory serotonergic projections. These serotonergic neurons continue in the dorsolateral funiculus and terminate usually in the dorsal horn neurons in laminae I, II, IV and V in spinal cord.⁷⁶ Injections of 5-HT-receptor agonists into the spinal cord have shown inhibitory and facilitatory activity on the pain behavior in animals. Systemic administration of 5-HT mostly decreases nociceptive transmission and pain behavior in experimental animals.⁷⁷ Excitatory effects have also been reported, mediated via 5-HT₇ receptors, and possibly caused by increases in cyclic AMP levels.⁷⁸ Neuronal 5-HT receptors are highly localized on primary afferent neuron terminals, excitatory and inhibitory

interneurons in the spinal cord. 5-HT_{1A} and 5-HT_{1B} receptors are present at high densities in dorsal horn neurons, for example on wide dynamic range (WDR) neurons. Activated 5-HT_{1A} receptors cause opening of K⁺ and a closing of Ca²⁺ channels through coupling negatively to adenylate cyclase. Their activation should thus directly hyperpolarize substantia gelatinosa neurons and produce an inhibitory effect on the pain transmission.⁷⁹ 5-HT₂ receptors are positively coupled to phospholipase C, and thus exert excitatory influences on neuronal activity. The antinociceptive effects of 5-HT_{2A} subtype would have to be caused by the activation of inhibitory interneurons.⁸⁰ The ionotropic 5-HT₃ receptor increases neuronal excitability, and has been found to mediate descending facilitation through serotonergic pathways. In accordance, ondansetron (5-HT₃ antagonist) decreases pain transmission onto nociceptive stimuli after nerve cell damage in rats.⁸¹ In the animal model, it has been suggested that 5-HT_{1B}, 5-HT_{2C}, 5-HT₃ and 5-HT₄ receptors are involved in serotonin mediated analgesia.⁸²

The central nociceptive control system is arranged by in the periaqueductal grey (PAG) neurons. The PAG is a crucial section and includes several pain control activity.⁷⁴ Various pain stimuli activates the serotonergic neurons in the RVM and enhances 5-HT release in the spinal cord. Additionally, the serotonergic neurons in the medial and dorsal raphe nuclei have also been shown to be substantial in pain control mechanism.⁷⁶ The evidences suggest that the ascending serotonergic neurons might also support to pain regulation by different mechanism.⁸³ In addition, some evidence indicates that cortical 5-HT receptors are involved in descending pain regulation.⁸⁴

Several studies indicate that spinal 5-HT receptors have antinociceptive effect, pronociceptive effect or no effect.^{77,85,86} Exactly, this demonstrates that distinct areas and distinct proportions of 5-HT receptors could explain in different ways for the regulation of nociception. Intrathecally administered WAY 100635 (5-HT_{1A} receptor antagonist) with sub-effective doses of 5-HT increases the analgesia in the paw pressure test in rats. Conversely, WAY 100635 deactivates the analgesic effect in the formalin test, an animal pain model.⁸⁷ In addition, the evidences suggest that intrathecal administration of 8-OH-DPAT (5-HT_{1A} receptor agonist) creates antinociception in the formalin test and pronociception in the paw pressure pain test.⁸⁸ On the other hand, dysfunction in the central serotonin systems increases pain sensations.⁸⁹ The antipsychotic and serotonin 5-HT_{1A} receptor agonist aripiprazole induces antinociceptive effects.⁹⁰ Recently, it has been reported that tegaserod, a 5-HT₄ receptor agonist, modulate visceral pain transmission. Tegaserod activates supraspinal 5-HT₄ receptors which initiates the release of opioids at supraspinal site. Subsequently, opioids activate descending noradrenergic pathways to the spinal cord, and produce analgesia.⁹¹ Intraperitoneal administration duloxetine (a 5-HT reuptake inhibitors) inhibits post-operative pain by increasing spinal 5-HT levels and

activating spinal 5-HT_{2A} receptor.⁹² Nefopam is a non-opioid analgesic drug, used to control postoperative pain. Intrathecal nefopam is effective in the attenuation of neuropathic pain and nefopam increases the level of 5-HT. In addition, the 5-HT₇ receptors involve in the antinociceptive action of nefopam in the spinal cord.⁹³ Furthermore, an animal pain model suggests that spinal neuron 5-HT_{5A} receptors are involved in 5-HT-induced analgesia in rats.⁹⁴

Serotonin receptors and opioid antinociceptive tolerance

Numerous electrophysiological and behavioral studies have shown an interaction of the serotonergic system and morphine analgesia. Serotonergic pathways are thought to be functionally distinct from but to interact with the opioid-mediated pain modulatory circuit.⁹⁵ 5-HT in the NRM may be necessary for the action of morphine.⁹⁶ Morphine has direct actions at the 5-HT₃ receptor, suppressing 5-HT-induced currents in neurons in a competitive way.⁹⁷ Administered systemic morphine produces analgesia mediated by 5-HT₇ receptors in the spinal cord in mice.⁹⁸ It has been also reported that between the serotonergic and GABAergic systems involve the interactions in opioid analgesia.⁹⁹ Acute administration of morphine increases the release of 5-HT principally from projection areas of the DRN and MRN.¹⁰⁰ However, chronic administration of morphine reduces the release of 5-HT from the serotonergic nerve terminals.¹⁰¹

Various experimental studies have suggested that descending inhibition of pain transmission by the morphine depends on central serotonergic neurons.^{102,103} The midbrain serotonergic system is a necessary constituent of the central nociceptive regulatory circuitry mediating opioid analgesic effect. *Lmx1b^{f/f/p}* mice which lack supraspinal serotonergic neurons have no antinociceptive effect after administration of a kappa opioid receptor agonist at supraspinal and spinal locations.¹⁰⁴ Interestingly, tramadol, a drug successfully used in pain management, acts through a combination of μ -opioid receptor and 5-HT_{1A} receptors.¹⁰⁵ Opioids produce their antinociceptive effect partly via activation on central serotonergic neurons.¹⁰⁶ Systemic administration of morphine causes the release of 5-HT in different brainstem locations and the spinal cord dorsal horn.^{21,107} Though the mechanism of morphine stimulated the 5-HT release remains obscure, it has been shown the involvement of excitatory neurotransmitter and GABA.^{100,106} Furthermore, 5-HT_{1A} and 5-HT_{1B} receptors are involved in regulation spinal pain transmission, and morphine analgesia could be inhibited by administration of either mianserin (a 5-HT_{1C} antagonist) or spiperone (a 5-HT_{1A} antagonist).^{108,109} These findings indicate a complex interaction between opioid action and 5-HT receptor subtypes in the spinal cord.

Different types of serotonin receptors show different effects on morphine analgesia. Administration of morphine stimulates the release 5-HT in the spinal cord neurons and the increase in 5-HT supports morphine analgesia normally but reduces that via spinal 5-HT₃ receptor subtypes in neuropathic pain model.¹¹⁰ The 5-HT₇, a subtype of serotonin receptor, play a significant role in mediating opioid and non-opioid type stress analgesia.¹¹¹ Surprisingly, repeated administration of fluoxetine reduces morphine antinociception in hypertensive and normal rats.¹¹² It has been reported that blockade of 5-HT₇ receptors inhibit the opioid analgesia.¹¹³ In addition, evidences indicate that the activation 5-HT₇ receptors decrease morphine withdrawal.¹¹⁴ Further, coadministration of maprotiline (5-HT re-uptake inhibitor) increases the morphine analgesia by 4-fold in rats.¹¹⁵

Spinal and supraspinal serotonergic neurons may also play a pathophysiological role in the development of tolerance to morphine. For example, coadministration of fluoxetine, amitriptyline and zimelidine (selective 5-HT uptake inhibitors) with morphine prevents the morphine analgesic tolerance.^{17,116} Conversely, administered with either 1-tryptophan, the 5-HT precursor, accelerates the development of morphine tolerance.¹¹⁷ These conflicting findings could probably be caused by a distinct 5-HT density in different synapses. These conflicting findings could also be owing to the distinct projections of 5-HT neurons arising from either the MRN or the raphe nucleus. Administration of 5-HT_{1A} receptor agonist 8-OH-DPAT to dorsal raphe nucleus attenuated morphine analgesic tolerance, however administration of the similar doses of 8-OH-DPAT to the median raphe nucleus did not change morphine analgesic tolerance.²³ The activation of 5-HT_{1A} receptors causes a varied level of neuroprotection in distinct experimental models of nerve cell damage. Therefore, injection of 8-OH-DPAT inhibits morphine-induced apoptosis dorsal raphe nucleus and attenuates morphine tolerance in rats.²⁵ Recent experimental studies suggest that the 5-HT₃ receptor participates in opioid antinociceptive tolerance. Unlike other receptors, 5-HT₃ receptor subtype is a ligand-gated ion channel including five monomers which form a structure centrally permeable to positive ions. The 5-HT₃ antagonist ondansetron administered with morphine prevents morphine tolerance in mice.¹¹⁸ In mice with skin cancer, 5-HT_{1A} receptor partial agonist buspiron reduces tolerance to analgesic effect of morphine.¹¹⁹ After activation of the 5-HT_{2A} receptor, administration of 5-HT with morphine results in receptor internalization, down-regulation and desensitization of the opioid receptor.¹²⁰

CONCLUSION

The mechanisms of opioid analgesic tolerance are not yet exactly understood, although the existence of a great number of information on the subject. Opioid tolerance is a complicated phenomenon mediated by different cellular and behavioral alterations. Several factors can cause the

development of tolerance to morphine. These factors include down-regulation of opioid receptors, desensitization of G-proteins, altered intracellular signaling and postreceptor neural events. Serotonin receptor system plays a pathophysiological role in the development tolerance to opioid analgesia. Until now, several studies indicate that 5-HT receptor subtypes produce diverse effects on opioid tolerance.

On the other hand, analgesic tolerance is a restricting factor along opioid therapy in clinical application. Patients should be given security that morphine analgesic tolerance is not a serious problem and that morphine will maintain to relieve their chronic pain for several years. Therefore, the capability to control the tolerance process is a necessary step in designing suitable pharmacologic method for the treatment of persistent chronic pain. Serotonin receptor agonist or antagonist drugs can be minimized by the development of opioid tolerance.

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