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Morphine Tolerance Effects on Neurotransmitters and Related Receptors: Definition, Overview and Update

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Authors' contributions

This work was carried out in collaboration between both authors. Author SM designed the study, wrote the manuscript, and wrote the first draft of the manuscript. Author SMK managed the literature searches and edition. Both authors read and approved the final manuscript.

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ABSTRACT

Morphine is the essential opioid drug that use in the clinic to attenuate chronic and severe pain. However long-term administration of morphine leads to the development of anti-nociceptive morphine tolerance. Mechanisms that involved in morphine tolerance are complicated and affect a different part of CNS and change neural circuits. One of the most critical candidates for the development of morphine tolerance are neurotransmitters Which makes the communication between neurons and establish neural circuits. The most prominent neurotransmitters that involved in the development of morphine tolerance are NMDA one of the most popular excitatory neurotransmitter, GABA most important inhibitory neurotransmitter in CNS, and monoaminergic neurotransmitters: dopamine, noradrenaline, adrenaline and serotonin have a lot of crucial roles in CNS. Also, Changes that occur in the level of opioid receptors, neurotransmitters and its receptors make alternation cross-talk between neurons. Understanding these changes help us to have an overall concept about the development of morphine tolerance.

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1. INTRODUCTION

Opioids are used to treat acute and chronic pain that induced by injury or inflammation. Most opioid used in the clinic to attenuate pain is Morphine. In chronic pain, it can mitigate and facilitate life for patients that involve with this type of pain. Morphine is a useful and powerful drug for pain relief, but long-term use of Morphine has a lot of adverse effects for example nausea, sedation, vomiting, constipation, physical dependence, tolerance, and respiratory depression [1]. Most crucial adverse effect of Morphine consumption in the long term are tolerance and dependence. Tolerance and dependence limit the use of morphine in chronic pain, which reduces their analgesic efficacy and is related to neuroadaptive changes and persistent neural adaptation [2]. Mechanisms of opioid tolerance are complex and involve many factors at the levels of cells, receptors, neural networks and non-neural cells especially microglia [3,4]. Even though many studies on the mechanisms of development of morphine tolerance as well as its devices are not precise. The purpose of this paper is to review the neurotransmitter mechanisms involved in the development of opioid tolerance to achieve a comprehensive result in the attenuation of tolerance to morphine in the long-term prescription.

2. PHARMACOLOGY AND MECHANISMS OF MORPHINE

Morphine was isolated in 1804 by the Wilhelm Adam Serturner, and named “morphium” [5]. Morphine is metabolized by demethylation, glucuronidation. Glucuronidation is the main method of metabolism, producing morphine-6 glucuronide (M6G) and morphine-3 glucuronide (M3G) in a ratio of 6:1, and about 5% of the drug is demethylated and produced normorphine. Glucuronidation occurs almost immediately after morphine enters the serum in both hepatic and extrahepatic sites, that a limited amount of intrahepatic recycling occurs [6]. M6G is the most potent morphine metabolite and has analgesic effect with interaction with opioid receptors. M3G metabolite has complex pharmacologic activities, it has a partial antagonism in morphine analgesia. The increase of M6G is associated with an increased of morphine side effects (respiratory depression, nausea, vomiting) [7,8]. M3G in high concentrations is believed to potentially lead to hyperalgesia. Role of M3G and other metabolites is still controversial but might include the development of morphine-resistant pain, allodynia, and tolerance [7]. M6G binds to μ-receptors and is half as potent an analgesic as morphine in humans [8]. Morphine also may be metabolized into small amounts of normorphine, codeine, and hydromorphone. Morphine is a phenanthrene opioid receptor agonist. Its main effect is binding to μ-opioid receptors in the central nervous system [9]. Analgesia is mediated by activation of G protein-coupled μ-opioid receptors [10] which are expressed throughout the central nervous system. Within the dorsal spinal cord, μ opioid receptors are found on pre and postsynaptic nociceptive neurons, astrocytes and microglia [11]. Morphine can cross the blood-brain barrier (BBB), but because of poor lipid solubility, protein binding, rapid conjugation with glucuronic acid, it does not cross easily to BBB. Diacetylmorphine, which is derived from morphine, crosses the blood-brain barrier more easily than morphine [5,10]. There are three major classes of opioid receptors that mediate distinct effects: mu (μ), delta (δ) and kappa (κ) [12]. All these receptors mediate spinal analgesia. Particularly, μ opioid receptor subtype 1 mediates also supraspinal analgesia[12]. The opioid receptors are coupled to inhibitory G proteins. The receptor activation has many consequences, including inhibition of adenylate cyclase with reduction of cAMP and other second messengers. Opioids increase the conduction of potassium and hyperpolarize cells and inhibiting calcium influx. This process reduces the excitability of cells and decreasing the release of neurotransmitters [11,12]. Activation of the μ-opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression [11,13]. At spinal level, analgesic effect is produced by inhibiting the release of mediators of pain pathway such as substance P, glutamate and nitric oxide from nociceptive afferent neurons [14,15]. At supraspinal level, opioid analgesics bind to μ receptor located on GABAergic neurons. Usually, these neurons project to the descending inhibitory neurons of the brainstem and inhibit them. Inhibition of GABAergic neuron induced by binding of opioid analgesics to opioid receptor allows the activation of descending pathway inhibitory serotoninergic neurons and finally produces analgesia [16]. Morphine may

also interact with descending adrenergic system and induce analgesia [17].

3. TOLERANCE, DEPENDENCE AND WITHDRAWAL

Morphine is an active drug to reduce pain, especially in chronic pain but for long-term use, it has many side effects. Common side effects include sedation, dizziness, nausea, vomiting, constipation, tolerance, dependence, and respiratory depression. Also if we stop or decrease morphine dosage in chronic administration of morphine causes withdrawal syndrome in patients. Withdrawal symptoms occur only in patients who have developed tolerance. Physical dependence is the development of an altered physiological state that is revealed by an opioid withdrawal syndrome involving autonomic and somatic hyperactivity [1]. Tolerance, dependence and withdrawal behaviours are a most significant side effect of chronic administration of morphine. Tolerance may be defined as a reduction in sensitivity to an agent following repeated exposure, while dependence is generally thought of as the absolute requirement for the agent to maintain normal physiological function. Dependence presents in different forms that are defined by the presence of a withdrawal reaction (physical relationship) and the presence of a "drug-craving" component (psychic dependence) [18]. Opioid tolerance is characterised by a progressive lack of response to opioids that can be overcome by escalating doses to achieve similar pain relief [19]. Understanding is the most critical factor in the creation of dependence and withdrawal and happens before this phenomena. Patience is a neurological adaptation in which the sensitivity of opioid receptors decreases. Physiologically, it means that Opioid tolerance occurs because the brain cells that have opioid receptors on them gradually become less responsive to the opioid stimulation [20]. It says that it's necessary to increase the dose of opioid to achieve the desired analgesic effect of the drug. Opioids at high doses cause several severe side effects and are fatal at extreme doses. Opioid tolerance, combined with the side effects at high opioid doses, significantly limits the clinical use of opioid analgesics to efficiently and sufficiently control pain, resulting in a possible forced termination of opioid treatment and replacement by other less effective alternatives, leaving millions of chronic pain patients under-treated [21].

4. MECHANISMS OF TOLERANCE AND DEPENDENCE

4.1 Opioid receptor Desensitisation and Internalisation

Desensitization is defined as a progressive reduction of signal transduction that occurs more or less rapidly after opioid receptor (OR) activation depending on the agonist and the signalling pathway. The rapid desensitisation is mainly observed on the regulation of ion channel conductance from sec to several minutes while a sustained desensitisation is slightly observed on the management of enzymes after minutes to several tens of minutes [22]. Some Studies report the OR desensitisation in cellular tolerance. When rats are chronically exposed to morphine study shows a reduction of morphine receptor activity on the outward potassium current compared to innocent animals that are not reversible even after six h in free- morphine medium; this is cellular tolerance [23]. In contrast, desensitisation may be defined as a reduction of signal transduction from OR after acute activation by agonists that recovers when cells or tissues are placed in agonist- free medium [24,25]. The number of OR is regulated by two processes: endocytosis and export of synthesised receptors. When agonists stimulate OR internalisation, one could expect a reduction in signal transduction. Studies show that a lot of mechanisms involved in desensitisation and internalisation. The essential tools are OR phosphorylation by PKC, and other protein kinases like Calcium-Calmodulin Kinase, Phospholipase D and p38 Mitogen-Activated Protein Kinase and arrestins proteins that involved OR regulation. This mechanisms finally cause cellular adaptation to morphine or other opioid drugs.

4.2 Role of NMDA in Morphine Tolerance

NMDA is a crucial excitatory neurotransmitter in CNS and has a lot of role in brain and spinal cord. NMDA receptor triggers by excitatory glutamate neurotransmitter. The activation of NMDA receptors has been associated with hyperalgesia [26]. The studies showed that long-term administration of morphine induces hyperalgesia [26,27]. The most studies Emphasize that NMDA has a critical role in development of tolerance to antinociceptive effect of morphine and NMDA hyperactivity caused hyperalgesia in morphine tolerance

[28,29] NMDA inhibitors like Ketamine, Memantine ,Mk-801 attenuate hyperalgesia and development of morphine tolerance and also activation of other ionotropic receptors of NMDA (AMPA and Kainate) in spinal cord could induce hyperalgesia like neuropathic [27-30]. Activation of NMDA receptor increase intracellular Ca that facilitation of calcium-regulated intracellular protein kinase C, and crosstalk of neural mechanisms of pain and tolerance[26]. Prolonged morphine administration caused NMDA hyperactivity that induces apoptotic cell death in the dorsal horn of spinal cord and finally neurotoxicity and hyperalgesia [31,32]. The NMDA receptor is the most critical reason in the development of neuronal plasticity because the administration of NMDA receptor antagonists inhibits side effects such as morphine analgesic tolerance and hyperalgesia [33]. Inoue et al. [34] in mutant mice that delete specific gene GluR_1 that code NMDA receptors showed that decrease of NMDA receptors in PAG and VTA attenuate morphine tolerance and dependence. Also, This study showed that NMDA receptors in PAG and VTA play a critical role in the development of analgesic tolerance, and the receptor in Nucleus accumbans plays a specific role in the development of physical dependence to chronic morphine.

4.3 Role of GABA in Morphine Tolerance

GABA is a most important inhibitory neurotransmitter in CNS that could be affected by morphine analgesia and long-term administration of morphine also could make changes in GABA systems [35]. Most studies on GABA suggest its important role in the process of morphine tolerance [36-39]. In supraspinal studies acute morphine administration induce significant increased GABA but in chronic administration, there were significant decreases in both GABA level [40]. Siroosi et al. showed that GABA transporter-1(GAT-1), which removes GABA from the synaptic cleft, overexpress in morphine tolerance in the spinal cord. The GAT-1 inhibitor ethyl-nipecotate improved the antinociceptive effect of morphine in long-term administration [41]. Repeated administration of morphine induces adaptations that alter both presynaptic GABA and postsynaptic $GABA_A$ receptor function [42]. In another study showed that $GABA_B$ receptors also play an important role in morphine tolerance [43-45]. Another study showed that microinjection of Baclofen in Lucus cereleus (LC) as $GABA_B$ agonist could attenuate naloxone withdrawal syndrome in morphine tolerate rats[46] because in withdrawal syndrome LC neurons show augmented activity and $GABA_B$ agonist could suppress this hyperactivity of neurons in LC with an increase of k conductance [47,48]. Also, it seems that benzodiazepines play an important role in morphine tolerance and boost the anti-nociceptive effect of in continuous treatment by morphine [49-51]. So many studies show that during the development of morphine tolerance GABA and it's receptors function and even enzymes that metabolise it change in the different level of CNS and These changes can be one the reason of morphine tolerance.

4.4 Role of Dopamine in Morphine Tolerance

Dopamine is the neurotransmitter that involved with the reinforcing and reward of drugs of abuse like opioids and has an important role in changes of neuron pathways in addiction. Dopamine has also been implicated in the development of tolerance and dependence to opioids Morphine as an opioid drug has a relationship in its function with the dopaminergic system [52]. Some effect of morphine hyperlocomotion and reward related to the dopaminergic system [53,54]. The studies showed that activation of opioid receptors on dopaminergic neurons in the striatum and nucleus accumbens [55] striatum [56] mesolimbic [52] and mesocortex [57] play an important role in morphine tolerance and dependence [58,59]. The dopaminergic mesolimbic system has a prominent role in the development of rewarding actions of opiates and neuro-adaptive changes in opioid tolerance [60]. Long administration of morphine affects dopaminergic neurons, those related to nucleus accumbans [61,62]. Chronic treatment with morphine to mice unable to synthesize dopamine failed to induce analgesia in tail flick test, in contrast, dopamine-deficient mice display a robust conditioned place preference for morphine which it means dopamine is a crucial role in morphine analgesia, but that dopamine is not required for morphine-induced reward in place preference and other pathways also involved in reward behaviors [63]. It has been considered that the mesolimbic dopaminergic system is profoundly affected by its functions during chronic opiate administration. The mesolimbic dopaminergic system is modified in its activity after withdrawal from a chronic morphine administration [64]. The studies suggested that dopamine in mesolimbic [65] and nucleus accumbans [66] after morphine injection

dramatically increase but after morphine withdrawal dopamine immediately reduced and this reduction may induce negative affective state (dysphoria) after morphine withdrawal [65]. In another study observed Both the activation and blockade of D2 dopamine receptors led to a decreased of tolerance to morphine-induced antinociception [67]. This study suggested that D2-Receptor may influence both inhibitory and facilitatory on nociceptive and anti-nociceptive mechanisms. Studies also indicate that bromocriptine [68] and RU 24926 [69] as a D2-receptor agonist could attenuate morphine tolerance. In one study Blockade of D2 receptors produces withdrawal behaviours in opioid-dependent animals. Furthermore, D1 receptor antagonist couldn't produce withdrawal sign in opioid-dependent animals these data suggest an important role of D2 as compared to D1 receptors in the expression of morphine withdrawal signs [70]. All of these studies suggested that dopamine level and its function change with morphine treatment and these changes related to morphine administration or morphine withdrawal. Any way Dopamine and opioid drugs like morphine have interaction together and opioid drugs could change dopamine, and it functions in different parts of CNS.

4.5 Role of Serotonin in Morphine Tolerance

The serotonergic system as one of the neurotransmitters of a monoaminergic system that involved in descending inhibitory pathway which modulate pain in spinal level. It is well established that part of the analgesic effects of morphine caused by the serotonergic system. Co-administration of fenfluramine, a selective 5-HT uptake inhibitor, inhibits the development of morphine tolerance [71]. Studies reported that acute morphine injection enhances serotonin turnover by an increase in its synthesis, release, and metabolism in whole brain areas [72,73] especially in the dorsal raphe nucleus and median raphe nucleus [74] but in chronic morphine administration, a release of 5-HT from the nerve terminals is decreased. Co-administration of morphine with serotonin/norepinephrine reuptake inhibitors (amitriptyline and venlafaxine) improve the morphine anti-nociceptive effect and attenuate the development of morphine tolerance.It has been suggested that Chronic morphine administration causes an increase in GABA release and subsequently decrease in serotonin release in the dorsal raphe nucleus [75]. Central serotonergic system is a key role in supraspinal pain modulatory that mediate by opioids [76]. It 's well established that central 5-HT neurons are required for analgesia effect of opioids [71]. For MOR(μ receptor) and DOR (δ receptor) induced spinal analgesia 5-HT neurons to play an important role, but KOR-induced spinal analgesia is independent of 5-HT neural function. KOR (κ receptor) analgesia completely depends on supraspinal 5-HT neurons [76]. Morphine induces the release of 5-HT in several parts of CNS that are the source region of 5-HT mainly from the median or dorsal raphe [77,78]. Pretreatment with a 5-HT receptor antagonist attenuates the anti-nociceptive effect of intrathecal morphine [79]. 5-HT1A and 5-HT1B receptor subtypes are involved in modulating spinal nociception [80]. Morphine-induced analgesia could be blocked by intrathecal injection spiperone, a 5-HT1A antagonist, or mianserin, a 5-HT1C/2 antagonist spinal cord [81]. In Another study indicates that development of morphine tolerance results in up-regulation of 5-HT2 receptors while in morphine-withdrawal rats up-regulation of 5-HT1 receptors on the membranes in the cerebral cortex was observed [82]. Also, other study suggested that direct stimulation of 5-HT1A receptors in the dorsal raphe nucleus of the rat prolongs the development of tolerance to the analgesic effect of morphine [83]. These studies indicate complicated interplay of different subtypes of 5-HT receptors in the development of morphine tolerance. 5-HT neurons could induce the release of other neurotransmitters and neuropeptides that could interact with the opioid system and modulate analgesia effect of opioids [21,84]. Synergistic interactions between spinal and supraspinal actions of serotonin were observed that suggested it's important in morphine spinal analgesia-induced [85].

4.6 Role of Norepinephrine and Epinephrine in Morphine Tolerance

Studies reported that activation of hypothalamic–pituitary–adrenal (HPA) axis modulates the analgesic effect of morphine and has an essential role in the development of morphine tolerance [86,87]. ACTH directly acts on the adrenal medulla and increases the activity of dopamine beta-hydroxylase and tyrosine hydroxylase. Epinephrine and norepinephrine result in the release of ACTH, from the anterior lobe of pituitary gland [87]. It has been reported in stressful situations such as chronic pain like

pain that induced by subcutaneous injection of formalin could attenuate morphine tolerance [88,89]. Some studies suggested that release ACTH and following it increase of epinephrine have an inhibitory effect on the development of morphine tolerance and also the reversal of developed tolerance [90,91]. Also decreased expression of α2A and α2C adrenoceptors following chronic administration of morphine were observed [92]. Unlike morphine tolerance in withdrawal, a situation reported norepinephrine turnover, increases during naloxone-precipitated withdrawal [93]. Also, production of the norepinephrine metabolite 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) in brain regions that innervated by the locus coeruleus was increased during naloxone-induced withdrawal in chronic administration of morphine and administration of clonidine as α2 agonist reversed the increase of MHPG [94]. It has been reported co-administration of morphine with serotonin/norepinephrine reuptake inhibitors (amitriptyline and venlafaxine)increased the analgesic effects of morphine and attenuated the morphine tolerance [75]. It's reported that β2 adrenergic antagonism could improve morphine sensitivity in long-term morphine administration. In this study observed that morphine over-express of substance P and CGRP and co-administration of butoxamine as β2 agonist and morphine during the chronic treatment phase could decrease both the mRNA precursor and peptide levels [95].

5. CONCLUSION

In summary, recent studies based on our understanding showed that in morphine tolerance neurotransmitters have an essential role in the development of this state (Fig. 1). Long-term administration of morphine cause interference with neurotransmitters and their receptors function and not only does not reduce pain but also induces hyperalgesia in some studies. In fact in morphine tolerance cross-talk between neurons be impaired because neurotransmitters change and it's possible that happen neuro-plasticity, and neuroadaptive change as in some studies has been seen. It can also be said that homeostasis in some part of CNS does not work well for example clearance of neurotransmitters or their synthesis could be changed. In spite of extensive studies, morphine tolerance needs more research to clear it's mechanisms in CNS to improve these imbalances in morphine tolerance and overcome this condition.

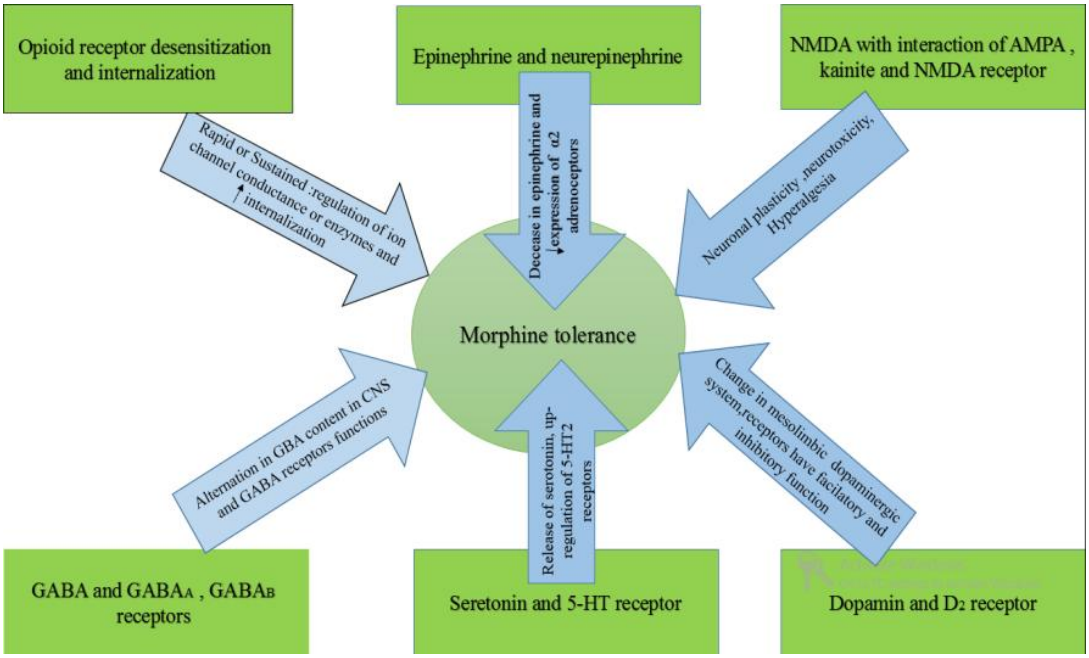

Fig. 1. Summary of different neurotransmitters interaction and their changes in morphine tolerance

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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