



# Neural mechanisms underlying morphine withdrawal in addicted patients: a review

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### ARTICLE INFO

#### Article type

Review article

#### Article history

Received: 3 May 2014

Revised: 5 Aug 2014

Accepted: 12 Aug 2014

#### Keywords

Morphine dependence

Morphine withdrawal

Morphine withdrawal syndrome

Neural mechanisms

### ABSTRACT

Morphine is one of the most potent alkaloid in opium, which has substantial medical uses and needs and it is the first active principle purified from herbal source. Morphine has commonly been used for relief of moderate to severe pain as it acts directly on the central nervous system; nonetheless, its chronic abuse increases tolerance and physical dependence, which is commonly known as opiate addiction. Morphine withdrawal syndrome is physiological and behavioral symptoms that stem from prolonged exposure to morphine. A majority of brain regions are hypofunctional over prolonged abstinence and acute morphine withdrawal. Furthermore, several neural mechanisms are likely to contribute to morphine withdrawal. The present review summarizes the literature pertaining to neural mechanisms underlying morphine withdrawal. Despite the fact that morphine withdrawal is a complex process, it is suggested that neural mechanisms play key roles in morphine withdrawal.

Please cite this paper as:

Babbadiashar N, Vaseghi G, Rafieian-Kopaei M, Andalib S, Eshraghi A, Masoudian N. Neural mechanisms underlying morphine withdrawal in addicted patients: a review. *Rev Clin Med.* 2015;2(3):151-157.

## Introduction

Morphine is the first active principle purified from herbal source (1,2). Investigation on its structure-activity relationship has discovered 200 morphine derivatives (e.g., codeine and related drugs) and synthesis of morphine-derived antagonist drugs (e.g., naloxone, naltrexone and nalorphine) (3). Morphine is a natural product but has high potential for addiction, tolerance, and psychological dependence. It is postulated that physiological dependence develops in several months (4). Morphine receptors are opioid receptors and categorized according to their selectivity in binding and pharmacological assays (5)

such as mu-receptors (6) and delta-receptors (7). In addition, of all the classes of opioid receptors, the kappa types are the most complex (8).

Morphine has been traditionally utilized to treat severe and chronic pain (9), for instance myocardial-infraction (MI) pain (10). It suppresses the respiratory activity, and irregular breathing; even so, the main cause of death in morphine poisoning is respiratory depression (3). As a consequence of peripheral vasodilatation, peripheral resistance may decrease. Additionally, morphine declines intestinal secretion and increases intestinal fluid absorption,

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which inbrings about the constipation (3). High doses of morphine impair finger tapping and the ability of maintaining a low constant level of isometric force (impaired motor control) (11,12). It was also demonstrated that morphine plays a crucial role in learning and memory (13). Passive avoidance learning, which is normally assessed by shuttle box (14), is affected by Morphine (15). Morphine withdrawal syndrome results from adaptations' response on multiple levels with different mechanism. Although little is known, several neural mechanisms have thus far been shown to be involved in morphine withdrawal. This paper reviews the findings regarding the withdrawal phenomenon and its contributory mechanisms.

## Literature review

### 1. Morphine dependence and tolerance

Dependence refers to a set of changes in the homeostasis of an organism if the drug is stopped. Several hypotheses have explained the contributory mechanisms of development of morphine tolerance (16) for example, blockade of glutamate action, phosphorylation and the receptor conformation changes (17), decoupling of receptors from G-proteins and the receptor desensitization (18,19),  $\mu$ -opioid receptor internalization and/or receptor down-regulation and up-regulation of the cAMP pathway (20). Moreover, cholecystokinin (CCK) mediates some counter-regulatory pathways in opioid tolerance. CCK-antagonist medicines, such as proglumide, have been found to develop the tolerance of morphine (21).

### 2. Morphine Withdrawal

Opiates are amongst the most useful medications, despite their usage as recreational drugs (22). Chronic misuse of such drugs leads to tolerance and physical dependence called as opiate addiction. Withdrawal syndrome is also found as physiological and behavioral symptoms subsequent to prolonged exposure to morphine (23). Prolonged exposure to opiates was demonstrated to disrupt neural function (24). Cognitive deficit is also present even following subsiding somatic withdrawal signs resulting from impairment of brain function by chronic misuse (25). Abrupt cessation of morphine usage results in the prototypical withdrawal syndrome, which is not fatal by itself, although suicide, heart attacks, strokes, seizures proceeding to status epilepticus and influences of extreme dehydration may produce fatal outcomes.

The withdrawal symptoms owing to morphine addiction are typically seen shortly prior to the time of the next scheduled dose, sometimes within a few hours (normally between 6–12 hours) following the last administration. In this regard, severe depression

and vomiting are very common. Systolic and diastolic blood pressure and heart rate increase over the acute withdrawal period. As well as to muscle spasms, severe pain in the bones and muscles of the back and extremities will be appeared. A suitable narcotic may be administered to reverse the withdrawal symptoms at any points over this process. Major withdrawal symptoms peak 48 to 96 hours subsequent to the last dose and subside after 8 to 12 hours (26).

### 2.1. Morphine withdrawal and brain function

Most of brain regions show decreased function in prolonged abstinence and acute morphine withdrawal. Memory deficit following morphine withdrawal results in drug relapse (21,27). Cortical and limbic activities are suppressed in the withdrawal that may pertain to the memory impairment (25). It was shown that hippocampus plays an important role in memory processing and a high density of glucocorticoid receptors exists in this region of the brain (28). Recent investigations have highlighted the contribution of corticosterone and its receptor antagonist to prevention of morphine withdrawal memory deficit. High concentration of corticosterone in the withdrawal impairs object recognition task that is reversed by methyrapone and mifepristone (29,30). Interestingly, a functional interaction between opioids receptors and adenoreceptors is present in modulating central processes (31), which may contribute to the modulation of memory (32). Morphine withdrawal impairs fear extinction, which may be due to chronic histamine deficiency and the brain histamine level contributes to cognitive deficit subsequent to morphine withdrawal (33). High concentration of brain cortisol was shown to cause neuronal damage and memory loss (34). Cortisol brings about indirect memory impairment through stimulative amino acids rather than the direct impact (35). Therefore, corticosterone concentration growth in the brain may explain recognition impairment subsequent to morphine withdrawal (36). Furthermore, the intensity of morphine withdrawal symptoms is associated with the extent of development of physical dependence. The level of increase of naloxone-induced serum corticosterone concentration is thus associated with the level of development of physical dependence (36). Morphine abstinence can activate A2 cells, that is, adrenergic nerve axis in nuclei of solitary tract, which thereafter stimulates adrenergic receptors in paraventricular nucleus in order to liberate corticotropin-releasing hormone (CRH). CRH also acts at the pituitary gland in the way of humeral transmission for liberation of adrenocorticotrophic hormone (ACTH) that, in turn, liberates corticosteroid from the adrenal cortex (37). This corroborates the findings that indicate adrenergic blocking agents inhibit ACTH secretion arising from morphine withdrawal (37).

## 2.2. The effect of calcium on morphine withdrawal

Calcium channel blockers of the dihydropyridine group such as verapamil (38), nifedipine, nitrendipine, and nimodipine (39) can inhibit naloxone-precipitated withdrawal symptoms. Effects of the nimodipine, L-type calcium channel antagonist has been studied on memory loss caused by spontaneous morphine withdrawal in mice (40). However, it was shown that nifedipine inhibited the signs of naloxone-precipitated withdrawal, which was not statistically significant, and the difference might be owing to different methodology applied. Another study in rats in which naloxone was not used for withdrawal, showed various withdrawal symptoms, involving writhing, squealing, diarrhea, teeth chattering, eyelid ptosis, and wet -type shaking 18 hours following the end of morphine administration (41). Both central and peripheral mechanisms were demonstrated to serve important roles in the inhibition of morphine abstinence syndrome using calcium channel blockers; such impacts result from an action independent of opioid receptors (41). In addition, blockade of L-type voltage-dependent calcium channels by means of calcium channel blockers attenuates morphine withdrawal syndrome. T-type voltage dependent calcium channels play a crucial role in the development of morphine dependence and withdrawal (42).

## 2.3. Glucocorticoids and morphine withdrawal

Morphine withdrawal can activate hypothalamic pituitary-adrenal (HPA) system (42). It was reported that corticosterone is augmented in the brain and blood 4 hours following the last dose of morphine in morphine-dependent mice (19). Thereby, an increase in concentration of corticosterone in the brain may be a plausible explanation for recognition impairment caused by morphine withdrawal (29). Glucocorticoids exert genomic and non-genomic influences upon neuronal function (43). Role of glucocorticoid inhibitors has been established in neurons (19). Chronic use of morphine increases the density of dihydropyridine sensitive calcium channels and their antagonists can thus alleviate symptoms of morphine withdrawal.

## 2.4. Cannabinoid and morphine withdrawal

Morphine withdrawal activates of endocannabinoid system and results in cognitive deficits (44,45). Chronic usage of cannabinoid agonists has been demonstrated to impair memory (46). The evidence from multiple investigations suggests that activation of the cannabinoid system in the brain is involved in the impairment of spatial and working memories (47,48). Prolonged morphine abuse increases the density of cannabinoid CB<sub>1</sub> receptor mRNA in brain regions activated during morphine withdrawal (49). Chronic exposure to the cannabinoid agonist may

also disrupt memory (50).

CB<sub>1</sub> receptors contribute to physical dependence and may be activated over drug withdrawal (51). SR<sub>141716</sub>, a cannabinoid receptor antagonist, and URB<sub>599</sub>, a cannabinoid blocking reuptake, inhibit extinction of conditioned aversion produced by naloxone-precipitated morphine withdrawal (52).

## 2.5. Adenosine kinase inhibitors and morphine withdrawal

Adenosine receptor activation through adenosine kinase inhibitor treatment attenuates opiate withdrawal and can be helpful while treating drug withdrawal syndromes (53).

## 2.6. Co-administration of nalbuphine, (kappa-agonist) and morphine

Morphine has widely been used for treatment of various types of chronic pain. Nevertheless, development of tolerance and dependence on morphine by repeated application is a major concern in pain therapy. It was shown that combined treatment of nalbuphine with morphine affects the development of tolerance and dependence on morphine. The use of nalbuphine, kappa-agonist may be a useful adjunct therapy for prevention of morphine-induced undesirable impacts during management of some types of chronic pain. It was demonstrated that a combined treatment of morphine and nalbuphine (10:1) resulted in a decreased morphine dependence (54). The elevation of [3H]MK-801 binding in frontal cortex, dentate gyrus, and cerebellum following chronic morphine infusion was suppressed by the co-administration of nalbuphine. The elevation of NR1 expression by morphine reduced by the co-administration of nalbuphine in rat cortex (54). These results indicate that the co-administration of nalbuphine with morphine during chronic pain management may be one of the treatments for decreasing development of tolerance to and dependence on morphine (54).

## 2.7. Morphine tolerance, withdrawal-induced hyperalgesia, and associated spinal inflammatory immune responses by propentofylline

The activation of glial cells and increased expression of proinflammatory cytokine at the spinal cord participate in development of morphine tolerance, and morphine withdrawal-induced hyperalgesia. The role of propentofylline, a glial modulator, in the expression of analgesic tolerance and withdrawal-induced hyperalgesia was assessed in chronic morphine-treated rats (55). Consequently, repeated subcutaneous injections of morphine may induce glial activation and increased levels of proinflammatory cytokine at the lumbar spinal cord. Furthermore, there was a temporal correlation between glial activation and increased cytokine levels and expression

of tolerance of morphine and hyperalgesia. It was also shown that propentofylline declined the hyperalgesia development and expression of spinal analgesic tolerance to morphine. There was a declined glial activation and proinflammatory cytokines at the L5 lumbar spinal cord with the administration of propentofylline during induction of morphine tolerance. These findings may confirm that spinal glia and proinflammatory cytokines are involved in the mechanisms of morphine tolerance and corresponding abnormal pain sensitivity (55).

### **2.8. Morphine withdrawal signs and a GABA B receptor agonist in the locus coeruleus of rats**

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the CNS (56). Activation of gamma-aminobutyric acid B (GABA B) receptor mechanisms in the Locus Coeruleus (LC) may decline precipitated withdrawal symptoms of chronic morphine usage (57). The impacts of intra-LC injection of GABA B receptor-interacting agents have been assessed on naloxone-induced withdrawal signs of morphine-dependent rats (57). The GABA (B) receptor agonist and antagonists were administered 5 min before naloxone injection. Baclofen, a GABA B receptor agonist, reduced the triphasic waves (TWs) in a dose-dependent manner, although CGP<sub>35348</sub> which is a GABA (B) receptor antagonist, failed to exert any influences. Baclofen influences were, however, reversed by CGP<sub>35348</sub> (57).

### **2.9. Morphine withdrawal signs and muscimol in the locus coeruleus of rats**

It was demonstrated the influences of muscimol were antagonized by GABA B but not by GABA A receptor antagonists (58). The impacts of intra-LC injection of a GABA A receptor agonist were evaluated upon naloxone-induced withdrawal signs of morphine-dependent rats and 20 different withdrawal signs were tested. The total withdrawal score was then calculated and used as an index of withdrawal intensity. The GABA A agonist and antagonists were injected 15 and 30 min prior to naloxone injection, respectively. Muscimol, a GABA A agonist (25, 50, and 100 ng/site), reduced the total withdrawal score in a dose-independent manner; however, bicuculline (0.367, 3.67, and 36.7 ng/site), a GABA A antagonist, and CGP<sub>35348</sub> (48.6 ng/site), a GABA B antagonist, failed to exert any influences. Muscimol impacts were also reversed by CGP<sub>35348</sub> (48.6 ng/site) but not by bicuculline (36.7 ng/site) (58).

### **2.10. Morphine withdrawal signs and the GABA B receptor agonist baclofen**

Baclofen demonstrates some potential in the opioid withdrawal treatment and GABA B receptors are likely to be implicated in such a withdrawal

(59). The influence of the GABA B receptor agonist, baclofen on naloxone-induced withdrawal signs was assessed in morphine-dependent rats as well as modification by the antagonist, 3-aminopropyl-cyclohexylmethylphosphinic acid (CGP46381) (59). The morphine was administered by means of mini-osmotic pumps for 7 days for induction of physical dependence. In morphine-dependent rats, baclofen (20 mg kg<sup>-1</sup>) declined stereotyped head movements, chewing, chatter, ptosis, and body weight loss, induced by naloxone (10 mg kg<sup>-1</sup>). CGP<sub>46381</sub> (20 mg kg<sup>-1</sup>) reversed the impacts exerted by baclofen on stereotyped head movements, ptosis, and weight loss and reversed the influence of baclofen on chewing to some degree (59).

### **2.11. Ibogaine attenuation of morphine withdrawal in mice: role of glutamate N-methyl-D-aspartate receptors.**

Ibogaine (IBO) is an alkaloid that exerts an inhibitory influence upon opiate withdrawal symptoms and the complex process resulting in morphine withdrawal includes an IBO-sensitive functional and transitory change of glutamate N-methyl-D-aspartate (NMDA) receptor (60). The NMDA receptors was shown in the physiology of drug addiction; and IBO hence acts as a noncompetitive NMDA antagonist (60). Recently, the impacts of IBO on naloxone-induced withdrawal syndrome in morphine-dependent mice, focusing on the role of NMDA receptors have been assessed (60). The authors reported that jumping, which is a major behavioral expression of the withdrawal, was inhibited by IBO significantly ( $P < 0.01$ ) (40 and 80 mg/kg, 64.2% and 96.9% inhibition, respectively) and MK<sub>801</sub> (0.15 and 0.30 mg/kg, 67.3% and 97.7%, respectively) which was administered before naloxone. Concurrent administration of the lower doses of IBO (40 mg/kg) and MK<sub>801</sub> (0.15 mg/kg) brought about 94.7% inhibition of jumping, which was comparable to the influences of higher doses of either IBO or MK<sub>801</sub>. Moreover, IBO and MK<sub>801</sub> inhibited NMDA-induced (99.0% and 71.0%, respectively) jumping significantly when administered 30 min (but not 24 hr) prior to NMDA in non-addictive mice. The results showed no significant differences in [<sup>3</sup>H]MK<sub>801</sub> binding to cortical membranes from naive animals, morphine-dependent animals, or morphine-dependent animals treated with IBO or MK<sub>801</sub> (60).

### **2.12. Ketorolac prevents recurrent withdrawal induced hyperalgesia but does not inhibit tolerance to spinal morphine**

Recurrent withdrawal was shown to be associated with hyperalgesia, although this exerts no influence upon the tolerance development;



ketorolac protects against recurrent withdrawal induced hyperalgesia without significantly changing spinal morphine tolerance (61).

In rats, the effect of subcutaneous or intrathecal treatment of ketorolac upon recurrent withdrawal created hyperalgesia and tolerance to spinal morphine was tested. Animals were infused with morphine intrathecally, and subcutaneous naloxone was daily administered for recurrent withdrawal purpose. Escape latencies on hot box were found to be reduced in rats subjected to withdrawal. However, this reduction was reversed by subcutaneous ketorolac pretreatment. Recurrent withdrawal also failed to influence the magnitude of spinal morphine tolerance. All morphine infused rats experienced similar changes in their dose responses to spinal morphine, effective dose-50 values, and tolerance ratios in comparison with control group. These changes were not influenced by the ketorolac administered subcutaneously. The impact of ketorolac upon tolerance was also assessed by means of directly delivering ketorolac to the spinal cord, and the authors reported similar alterations in the daily latency, percentage of area under the curve, and percentage of maximal possible influences amongst groups infused with morphine, regardless of intrathecal ketorolac treatment. Table 1 illustrates neural mechanisms in morphine withdrawal.

## Conclusion

Positive and negative reinforcement as key components are present in many types of drug addiction. Continued usage of drug stems from positive reinforcement of drug taking and negative reinforcement results from withdrawal along with quitting drug. The mesocorticolimbic dopamine mechanism, which originates in the ventral tegmental region and projects to terminal regions such as prefrontal cortex, amygdala, and accumbens, is an important neural network wherein drug-induced neuroadaptations occur, resulting in both types of reinforcement. The reinforcing influences of substance abuse contribute to increased dopaminergic neurotransmission (62) in the Acb (63). Animals lever-press in order to keep increased DA rates over cocaine self-administration (64). However, declined accumbal DA rates are associated with morphine withdrawal (65).

Drug abstinence gives rise to physical withdrawal in addition to psychological withdrawal. Interestingly, these components of withdrawal are mediated through distinct neural systems. It has been shown that opiate antagonists in the LC (66) and the periaqueductal gray (67) precipitate robust somatic withdrawal syndromes in morphine-dependent animals; be that as it may, infusions into the Acb generates a few somatic symptoms exclusively (67). In morphine dependent animals, direct administration of opiate antagonists into the Acb and amygdala brings about psychological withdrawal as indicated by the decline

**Table 1.** Outline of underlying neural mechanisms in morphine withdrawal

1	Calcium channel blockers of the dihydropyridine group (e.g. nifedipine, nitrendipine, and nimodipine) can inhibit naloxone-precipitated withdrawal symptoms
2	An increase in concentration of corticosterone in the brain may be a plausible explanation for recognition impairment caused by morphine withdrawal.
3	Morphine withdrawal leads to the activation of endocannabinoid system and cognitive deficits.
4	Adenosine receptor activation through adenosine kinase inhibitor treatment attenuates opiate withdrawal.
5	Nalbuphine with morphine affects the development of tolerance and dependence on morphine.
6	The activation of glial cells and increased expression of proinflammatory cytokine at the spinal cord are present in the development of morphine tolerance, and morphine withdrawal-induced hyperalgesia.
7	Activation of GABA (B) receptor mechanisms in the locus coeruleus (LC) may decline precipitated withdrawal symptoms of chronic morphine usage.
8	Influences of muscimol are antagonized by gamma-amino-butyric acid type B but not by GABAA receptor antagonists.
9	Baclofen demonstrates some potential in the opioid withdrawal treatment and GABAB receptors are likely to be implicated in such a withdrawal.
10	IBO exerts an inhibitory influence upon opiate withdrawal symptoms and the complex process resulting in morphine withdrawal includes an IBO-sensitive functional and transitory change of glutamate NMDA receptors.
11	Ketorolac prevents recurrent withdrawal induced hyperalgesia but does not inhibit tolerance to spinal morphine.

of lever pressing for food (68) and conditioned place aversion (69). Nevertheless, some overlap lies in these neural systems. By way of illustration, direct administration of opioid antagonists in the amygdala of morphine-dependent animals was shown to contribute to moderate physical withdrawal (67). Additionally, systemic DA agonist administration lowers both conditioned place aversions and physical withdrawal symptoms in morphine-dependent animals that were treated with naloxone; however, increasing phosphorylation of GluR1 in the Acb (70), which indirectly implicates the Acb in both withdrawal components.

Morphine chronic misuse leads to opiate addiction. A wide range of symptoms can occur after stopping or dramatically reducing morphine subsequent to the heavy and prolonged use. As has been argued above, it is tempting to suggest that neural mechanisms serve key roles in morphine withdrawal.

### Acknowledgement

We would like to thank Clinical Research Development Center of Ghaem Hospital for their assistant in this manuscript.

### Conflict of Interest

The authors declare no conflict of interest.

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