

## Morphine-Induced Place Preference: Interactions with Neurotransmitter Systems

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### Abstract

This review gives an overview of our recent findings and developments in research on brain mechanisms of morphine reward from studies using the place preference conditioning paradigm. Intracranial place conditioning methodology has become a valuable and firmly established and very widely used tool in behavioural pharmacology and drug reward mechanisms. Several studies have established that morphine induces a conditioned preference for the place in which it has been administered in rats. Transmitter systems that have been investigated with respect to their involvement in morphine reward mechanisms include dopamine, GABA, acetylcholine, adrenalin and nitric oxide, the motivational significance of which has been examined either directly, by using respective agonist or antagonist drugs. Although, considerable evidence suggested that the mesocorticolimbic DA system, which originates in the VTA and projects to the Nac, various limbic and cortical areas is a major neural substrate of the rewarding effects produced by morphine, but the role of other brain sites such as hippocampus and amygdala also exist. Overall, our intracranial place conditioning studies showed that there are a number of receptors, neuronal pathways and discrete central nervous system sites involved in the morphine reward mechanisms.

**Keywords:** Morphine; Conditioned place preference; Neurotransmitters; Reward mechanisms.

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### Introduction

The behavioral evidence shows that opiate addiction is a complex phenomenon involving many biological and social factors (1), and was also suggested that learning and memory play an important role in the development of opiate tolerance and dependence (2, 3). Conditioned place preference (CPP), a behavioral task

often used to measure reinforcing properties of drugs, has been used to measure memory or learning of simple stimulus–reward associations (4). Several studies suggested that morphine induces a conditioned preference for the place in which it has been administered in rats (for a review see [5]). In accord with previous studies (6, 7), our data indicated that morphine induced a significant CPP, dose dependently.

It seems that the mesolimbic dopaminergic pathway projecting from the ventral tegmental area to the nucleus accumbens is a critical site

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for the initiation of psychological dependence on opioids (8). Intracranial place conditioning studies have been used to show that there are a number of receptors, neuronal pathways and discrete central nervous system (CNS) sites involved in the brain reward mechanisms (for a review see [9]). Thus, it was postulated that opiates have more than one site of rewarding action, which may include the VTA (10-12), the Nac (13), the hippocampus (3, 14), the amygdala (3, 15), the medial prefrontal cortex, the lateral hypothalamus (9) and the periaqueductal gray (16).

Among the CNS regions examined, there was evidence suggesting that the mesocorticolimbic DA system, which originates in the VTA and projects to the Nac, various limbic and cortical areas is a major neural substrate of the rewarding effects produced by morphine (11, 12). It has been demonstrated that injection of morphine into the VTA produces conditioned place preference, suggesting that activating opioid receptors throughout the VTA is rewarding (9, 11, 17, 18). On the other hand, there are some reports showing that unilateral infusion of the mu-opioid agonist DAMGO into the VTA produced CPP, whereas infusion of the Kappa-opioid agonist U50, 488H produced conditioned place aversion (19). Activating mu-opioid receptors within the VTA is reinforcing but that activating kappa-opioid receptors could affect different neuronal ensembles to produce place aversion (9).

Nucleus accumbens (NAc) also is a neuroanatomical substrate mediating the rewarding effects of morphine. Van Der Kooy et al. (20) reported that unilateral injections of morphine into the NAc produced CPP in rats. Contrary to these results, Olmstead and Franklin (11) reported that unilateral injection of 1.5 nmol morphine into either the shell or core of the NAc did not produce conditioned place preference. It seems that the lack of effect found by Olmstead and Franklin may be a result of using a low dose of morphine. The investigations of Bals-Kubik et al. (19) also showed that the intra-NAc administration of a kappa-opioid agonist produced conditioned place aversion (CPA). Thus, it has been suggested that activating of opioid receptors within the NAc may be positively reinforcing.

Decker and McGaugh (21) reported that morphine inhibits cholinergic activity in the hippocampus. Synaptic acetylcholine (ACh) release in the VTA has an excitatory function on DA neuronal activity (22). Although other evidences suggested that the mesolimbic dopaminergic system is necessary for the acquisition of morphine-induced CPP (23), the role of other neurotransmitter systems such as GABA (24), nitric oxide (25, 26) and glutamate (27) also exist.

Some conditioned place preference (CPP) studies suggested that the amygdala may play an important role in the reward produced by drugs of abuse (3, 28). The amygdaloid complex is composed of several different nuclei and cortical areas that are linked to each other and also to other brain regions via organized pathways (29). Among the diverse nuclei of the amygdala, it appears that the central and basolateral amygdala (CeA and BLA) are involved in arousal, expression of emotions and forming associations between environmental stimuli, the formation and expression of stimulus-reward associations and affective states, typically involving autonomic responses (30-32). The CeA is a part of the extended amygdala that connects anatomically with the nucleus accumbens (NAc) and receives dense dopaminergic afferents from the ventral tegmental area (VTA). It also has more DA terminals relative to other amygdaloid nuclei (33). Furthermore, BLA connects anatomically with Nac (34) and shares reciprocal connections with VTA (35). The basolateral amygdala (BLA), being the main part of the amygdaloid body, is a key subregion of the amygdala involved in several neurotransmitter systems such as dopamine (36), glutamate (37) and ACh (38) have been implicated in amygdala dependent mediation of stimulus-reward associations. Amygdala is important for learning tasks such as CPP that use appetitive motivation and the reinforcement is of high affective value (4). Findings in our previous experiments indicated that the amygdala has an important role in mediation of morphine-induced place preference (24, 39-41).

It was already reported that unilateral injections of the mu-opioid agonist DAMGO or morphine into the medial prefrontal cortex (MPF) did not have any effect on CPP, whereas

injections of a kappa-opioid agonist produced CPA (11, 19). Thus, it has been suggested that the MPF is involved in brain mechanisms mediating drug reward. Moreover, considerable evidence also suggested that the lateral hypothalamus may be another site supporting the reinforcing actions of morphine and mu-opioid agonists (for a review see [9]).

#### **Involvement of dopaminergic system**

Some researchers claimed that the activation of different subtypes of DA receptors could be essential for the opiate reward (for a review see [5]). Furthermore, a pivotal role for dopaminergic mechanisms in opioid-induced CPP was proposed (42). Dopamine (DA) exerts its action by binding to specific membrane receptors (43). The DA receptor subtypes are divided into two major subclasses: D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) (for a review see [44]). It has been suggested that the involvement of DA in opioid-induced place preference is mediated through DA receptors (40, 41). For example, the CPP produced by morphine is abolished by pretreatment with a dopamine D<sub>1</sub> receptor antagonist (45). Morphine-induced place preference is also attenuated by 6-hydroxydopamine lesion of the Nac (46). Opioids have the ability to increase DA release in the Nac (42). Moreover, injection of opioids into the VTA elicits a CPP (19) and increase DA release in the Nac (47).

Our previous experiments showed that the injection of the DA receptor agonists (D<sub>1</sub> receptor agonist: SKF38393 or D<sub>2</sub> receptor agonist: quinpirole) or antagonists (D<sub>1</sub> receptor antagonist: SCH 23390 or D<sub>2</sub> receptor antagonist: sulpiride) into the central amygdala (40, 41) or dorsal hippocampus (48) could potentiate either or inhibit morphine-induced place preference, respectively. Since pretreatment with SCH 23390 or sulpiride reversed the SKF 38393 or quinpirole response, respectively, thus, we suggest that the effect of SKF 38393 or quinpirole may be mediated through the dopamine receptors of the central amygdala or dorsal hippocampus. The distribution of D<sub>1</sub> and D<sub>2</sub> DA receptors in the nuclei of the rat amygdaloid complex estimated by quantitative light microscopy has the highest density of

[<sup>125</sup>I]iodosulpiride (DA D<sub>2</sub> receptor antagonist) binding sites in the CeA (49). Considering the anatomy and functions of the CeA, it is likely that it influences the mesocorticolimbic dopaminergic system (originating with cell bodies in the VTA that project to the Nac) that mediates opiate reward (40, 41, 50). As the CeA also projects back to the VTA and the Nac, it is likely to have an important role in the control of motivation and the effects of drug conditioned cues (33, 51). It should be noted that in our experiments (41, 48), intracranial injections of quinpirole had biphasic effects on the acquisition of CPP induced by morphine. We showed that quinpirole potentiated the acquisition of CPP induced by the lower doses of morphine (0.5 and 2.5 mg/kg), while it decreased the response induced by the higher dose (7.5 mg/kg) of morphine. Since the administration of the DA D<sub>2</sub> receptor antagonist, attenuated the potentiation or inhibition induced by quinpirole, the effect of quinpirole may be produced through a DA D<sub>2</sub> receptor mechanism. Hodge et al. (52) showed similar biphasic effects by elicited quinpirole. They reported that the microinjection of quinpirole into the Nac produced a biphasic effect on alcohol self-administration. Since the DA D<sub>2</sub>/D<sub>3</sub> receptor agonist, quinpirole, exhibits an affinity for DA D<sub>3</sub> receptors at higher doses, it appears likely that the dose-related differential action is due to the various D<sub>2</sub>-like receptor subtypes. It has further been demonstrated that the activation of DA D<sub>2</sub> and D<sub>3</sub> receptor subtypes have opposing functional consequences on behaviors (53). The activation of pre-synaptic (terminal) DA D<sub>2</sub> receptors inhibits both the DA synthesis and release. Some studies also suggest that DA D<sub>3</sub> receptors might function as both release- and synthesis-inhibiting autoreceptors in some systems (54). Therefore, we suggested that the biphasic effect of quinpirole on the acquisition of morphine-induced CPP may be either due to pre- or post-synaptic stimulation of DA D<sub>2</sub>-like receptors or may be mediated through activation of different DA receptors.

De Fonseca and colleagues (6) showed that DA has an effective role in the expression of morphine-induced place preference. The expression of morphine-induced CPP may be related to decrease in DA release in the test

session. This decrease stimulates the drug-seeking behavior evoked by environmental cues associated with morphine administration. The opposite effects of the lower and higher doses of quinpirole on the expression of the morphine-induced CPP may be related to the affinity of the drug to the DA D<sub>2</sub>/D<sub>3</sub> receptors that may change the DA levels. Intra-CeA administration of sulpiride by itself also decreased the expression of morphine-induced CPP. Sulpiride may block presynaptic DA D<sub>2</sub> receptors, and so releases DA, which, in turn, activates postsynaptic DA receptors and thus reduces the expression of morphine-induced CPP. In general, our studies demonstrated for the first time that DA D<sub>2</sub> receptors in the CeA have an important role in the acquisition and expression of morphine-induced CPP. Recent studies also support this hypothesis that the DA D<sub>2</sub> receptor could be as important as the DA D<sub>1</sub> receptors in morphine reward (8).

#### **Involvement of GABAergic system**

Some studies strongly suggested that opiates actions on a GABAergic in both the VTA and the Nac play critical roles (55). Opiates inhibit VTA GABAergic interneurons to decrease GABA release, which subsequently disinhibits VTA DA neurons, leading to an increase in Nac DA release (56). The inhibitory functions of GABA in the brain are mediated by two distinct classes of receptors, namely the GABA<sub>A/C</sub> and GABA<sub>B</sub> receptors. The GABA<sub>A/C</sub> receptors are ligand-gated Cl<sup>-</sup> channel that mediate the fast synaptic inhibition. The GABA<sub>B</sub> receptors are linked to K<sup>+</sup> channel via G protein and mediate slow onset and prolonged effects of GABA in the CNS (57, 58).

In a number of mammalian species, including rats, mice and monkeys have been shown that GABA<sub>B</sub> receptors modulate memory processes in learning paradigms (59). It has been also suggested that the involvement of GABA in opioid reward is mediated especially through GABA<sub>A</sub> receptors (60). Our previous study showed that the injection of the GABA<sub>A</sub> receptor agonist, muscimol into the BLA (24) significantly decreased the acquisition of morphine-induced place preference. Considering that the projection from the BLA to the Nac may act to modulate DA levels in the Nac (61), there may

be a possibility that muscimol could attenuate the morphine response through dopaminergic mechanism. Xi and Stein (56) suggested the hypothesis that GABA<sub>A</sub> receptors are located on both dopaminergic projection neurons and GABAergic interneurons in the VTA such that activating them individually will produce opposite effects on mesolimbic DA release: either direct inhibition or indirect disinhibition, respectively. It has also been suggested that the BLA may exert an inhibitory effect on the Nac, during conditions of Nac activation. Therefore, it seems that the bilateral injection of muscimol into the BLA in the presence of morphine may have an inhibitory effect on the Nac and decrease morphine reward.

In the other study, we injected the GABA<sub>B</sub> receptor agonist, baclofen into the dorsal hippocampus (62) and obtained the results as the same as muscimol response. These results are in consistence with previous observations showing that the rewarding effect of morphine, as assessed by morphine-induced place preference suppressed by microinjection of baclofen into the VTA (10). In addition, some studies reported that GABA<sub>B</sub> receptor agonists decrease cocaine reward (63, 64). It has been also shown that lesions of the dorsal hippocampus, but not the ventral hippocampus, attenuate cocaine-CCP (65). Furthermore, it has been suggested that GABA<sub>B</sub> receptor agonists attenuate the reinforcing effects of cocaine, nicotine, heroin and ethanol through a modulation of dopamine transmission (66). Baclofen has been shown to decrease the activity of dopamine neurons and decrease extracellular dopamine levels in the VTA and nucleus accumbens (67). The activation of the mesolimbic dopamine (DA) system by morphine is essential for morphine reward, and also intra-CA1 injection of baclofen induced inhibition of morphine CPP, thus it seems that the inhibitory effect of baclofen to be also produced via an interaction with dopamine system.

On the other hand, our investigations indicated that microinjection of the GABA<sub>A</sub> receptors antagonist, bicuculline into the BLA, during acquisition of place preference, increased the morphine CPP. It has been suggested that blockade of postsynaptic GABA<sub>A</sub> receptors by bicuculline, which increases brain GABA

levels, may accelerate the development of morphine dependence (68). Furthermore, GABA antagonists can activate VTA DA neurons and increase DA release in the Nac (69). Yan (70) also reported that local application of bicuculline increases dopamine release in the Nac via a receptor mediated process. Considering the previous results and that the BLA projects to the Nac, there may be a possibility that in our data (24), bicuculline in the BLA potentiates the dopamine properties of morphine in the Nac through such a pathway. Our results also showed that pretreatment with bicuculline during conditioning, attenuated the decrease of morphine reward by muscimol. Therefore, the muscimol response may be mediated through GABA<sub>A</sub> receptors. These results are consistent with previous observations that showed microinjection of muscimol into VTA produced a dose-dependent increase in motor activity. This effect was antagonized by intrategmental injection of bicuculline or peripheral administration of haloperidol (71), suggesting that the effects of bicuculline on accumbal dopamine levels were mediated through GABA<sub>A</sub> receptors (72). It is also interesting to note that the bilateral microinjection of GABA<sub>B</sub> receptors antagonist, phaclofen into the dorsal hippocampus can significantly increase morphine-induced place preference (62). It has also reported that pretreatment with phaclofen during conditioning, attenuated the decrease of morphine reward by baclofen. Therefore, GABA<sub>B</sub> receptor mechanism is involved in the inhibition of morphine-induced CPP.

Furthermore, in a set of experiments, we also tested the effects of the intra-BLA administration of muscimol or bicuculline on the expression of morphine-induced place preference (24). The results showed that administration of bicuculline, but not muscimol, before testing prevented the expression of morphine-induced place preference. Since bicuculline potentiated acquisition of morphine-induced CPP and attenuated the expression of the opioid effect, therefore, GABA<sub>A</sub> receptors in the BLA may be differentially involved in the acquisition and expression of morphine CPP. We also examined the effects of intra-dorsal hippocampus administration of the GABA<sub>B</sub> receptor agonist

or antagonist on the expression of morphine CPP. The results showed that administration of baclofen, but not phaclofen, before testing prevented the expression of morphine-induced place preference. Since baclofen attenuated acquisition and expression of morphine-induced CPP, therefore, GABA<sub>B</sub> receptors in the CA1 regions of dorsal hippocampus may interact with dopaminergic system and thus can reduce the expression of morphine reward. Thus, our findings support the role of GABA<sub>A</sub> and GABA<sub>B</sub> receptors in the actions of morphine and further suggest that dorsal hippocampus and amygdala GABAergic system may be relevant to the rewarding effects of drugs of abuse and are involved in mediating morphine CPP.

#### **Involvement of cholinergic system**

It is well known that there exists an interaction between opioid and the cholinergic systems (73-75). Moreover, it is also reported that  $\mu$  and  $\delta$  receptors located on cholinergic terminals, are normally under tonic inhibition by the opiate system (76). Decker and McGaugh (21) reported that morphine inhibits cholinergic activity in the hippocampus. Synaptic acetylcholine (ACh) release in the VTA has an excitatory function on DA neuronal activity (22, 77).

Our previous studies showed that bilateral injections of the cholinesterase inhibitor, physostigmine or the nicotinic acetylcholine receptor agonist, nicotine into the dorsal hippocampus (78) or amygdala (40) during acquisition of place preference, potentiated the morphine-induced place preference. It has been reported that combined administration of morphine and physostigmine results in a strong, highly significant antinociceptive effect (79). Basile and coworkers (80) demonstrated that the rewarding effects of morphine, as measured in the CPP paradigm, are reduced in M<sub>5</sub> muscarinic receptor-deficient mice. It may be possible that physostigmine in combination with morphine induces its rewarding effect through muscarinic receptor mechanisms. On the other hand, it has been suggested that central nicotinic receptor stimulation, especially those located in the VTA, increases dopamine release in the nucleus accumbens (81-84). Both nicotine and morphine may produce a reinforcing effect due

to facilitating dopaminergic transmission (85). Considering the fact that there is an interaction between nicotinic receptors and opioid systems in controlling the release of dopamine and the induction of reward, it seems likely that intra-dorsal hippocampus, -amygdala or -VTA administration of nicotine potentiates dopamine properties of morphine.

In several investigations, we reported that the blockade of muscarinic or nicotinic receptors of dorsal hippocampus (78) or amugdala (40) by atropine or mecamlamine inhibited the morphine-induced place preference. Furthermore, our data in previous studies revealed that administration of atropine or mecamlamine reversed the physostigmine or nicotine response respectively; and therefore the effect of physostigmine may be mediated through muscarinic receptors. In agreement with our data, other investigators have shown that injections of atropine into the VTA inhibited brain stimulation reward (86). It has also indicated that administration of mecamlamine disrupts cocaine-induced place preference (87) as well as decreasing alcohol's effects on the mesolimbic dopamine system (88, 89). It has been suggested that the central nicotinic receptors appear to facilitate the rewarding and reinforcing effects and mecamlamine blocks the nicotine-induced behavioral responses (90-95). Nicotine-induced accumbal dopamine release was inhibited by mecamlamine (84). Our data may be similar to results obtained by Garcia-Rebollo and coworkers (96) who showed that the administration of nicotine in the CA1 region of dorsal hippocampus has a detrimental dose-dependent effect on acquisition of the lever-press response in alcohol drinkers and antagonized by mecamlamine co-administration.

#### **Involvement of nitric oxide**

Nitric oxide (NO) is formed enzymatically from L-arginine, a nitric oxide (NO) precursor by NO synthase (NOS) following the activation of NMDA receptor (97). NO has been documented to participate in numerous physiological and pathophysiological processes (98). The synaptic transmission in the central and peripheral nervous system seems to be modulated by NO (99). NO is a neurotransmitter in the central

nervous system, and an important messenger molecule in a number of organ systems (100). NO has some known implications in opiates dependence, as NOS inhibitors attenuate signs of opiates withdrawal (100) and prevent morphine tolerance (101). NO is involved in the rewarding properties of opiates (102). Both activation and inhibition of nitric oxide synthesis may alter morphine induced place preference (103, 104). Thus, NO is assumed to play a role in the place preference induced by morphine. There is an interaction between the NO system and the dopaminergic neuronal system (105). In addition, previous studies suggested that endogenous nitric oxide (NO) could play a role in the modulation of dopaminergic effects elicited by morphine (104, 106).

Nucleus accumbens is one of the regions in which the diffusible gas NO has been implicated in the control of dopamine release (107). It is determined that dopamine D<sub>3</sub> receptor density is modified following NO generation and the density of high affinity dopamine D<sub>2</sub> receptors decreases in the nucleus accumbens and NO is very much involved in the expression of the associative increase in extracellular dopamine in the nucleus accumbens (108). In the shell of the nucleus accumbens, NOS is localized to the cytoplasm of spiny somata and dendrites some of which contain *N*-Methyl-D-aspartate (NMDA) receptors (107). Furthermore, pharmacological studies also suggested that glutamate releases NO through activation of NMDA receptor thus implying that NMDA receptors are present on cells producing NO (109). It is also revealed that glutamate receptor antagonists can block the acquisition and/or expression of morphine reward and antagonism of NMDA receptor functions within the nucleus accumbens is shown to reduce the expression of the psychostimulant and reinforcing properties of cocaine (110).

Our previous studies also showed that the injection of L-arginine into the ventral tegmental area (111), nucleus accumbens (26), dorsal hippocampus (103) or central amygdale (25) significantly potentiated morphine-induced place preference. It has been reported that L-arginine induced dopamine release from the striatum in vivo that can be markedly reduced by NOS inhibitors (112). Also endogenously produced

NO is involved in stimulating dopamine release following activation of NMDA receptors located on dopaminergic nerve terminals in the nucleus accumbens. Since NO is a membrane-permanent gas, which can diffuse out to act on neighboring neurons, it is likely that NO synthesized in neurons postsynaptic to mesolimbic dopamine fibers may influence presynaptic processes to stimulate dopamine release in the nucleus accumbens (113). Furthermore, it has recently been reported that the associative type of sensitization to d-amphetamine is expressed as an NO-dependent dramatic increases in extracellular dopamine in the nucleus accumbens (114). Therefore, our data may be in agreement with a previous report that NO stimulated dopamine release in the nucleus accumbens (115).

On the other hand our investigations indicated that intra-VTA, -NAc or -CeA administration of *N*<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) decreased the conditioned place preference induced by morphine and also the response of different doses of L-arginine was decreased by L-NAME. The results are in agreement with previous data that showed the blockade of NO synthesis with L-NAME reduced the reinforcing properties of cocaine (110). Intraperitoneal administration of NOS inhibitor, L-NOARG (L-N-nitroarginine), before and during the chronic administration of morphine has been also shown to block the acquisition of morphine place preference (104), while administration of a NOS inhibitor never showed any significant effect of place preference (104). Another neuronal NOS inhibitor, 7-nitronidazole has also been shown to block conditioned place preference induced by cocaine (102), nicotine (116) and alcohol (117). The possibility may exist that L-NAME decreases the dopamine release in the nucleus accumbens by morphine, thus attenuation of morphine-induced place preference can be observed. This can be also supported by our data which shows pretreatment with L-NAME reversed the increase in morphine place preference by administration of L-arginine in the conditioning sessions (26). Therefore, it can be concluded that acquisition of morphine place preference might be mediated via activation of the NO system in the nucleus accumbens in the present experiments. our results also showed that NO may be involved

in the acquisition and expression of morphine-induced place preference.

### **Involvement of adrenergic**

Several studies have shown that the alpha-adrenergic and opioid systems can interact in a complex manner. Morphine tends to inhibit noradrenaline release from human neuroblastoma cells (118). There are also reports showing that opioids increase the turnover of norepinephrine (119).

The noradrenergic and opioid systems have been shown to be involved in the development and expression of opioid dependence (for a review, see [120]). The rats tolerant to the antinociceptive effects of morphine showed cross-tolerance to the effect of norepinephrine (121) and  $\alpha_2$ -adrenoceptor agonist, clonidine (122). Furthermore, rats tolerant to the antinociceptive effect of clonidine showed cross-tolerance to the effects of morphine (123). Clonidine also attenuated some of the signs of morphine withdrawal in rats (124) as well as the signs of morphine withdrawal in humans (125). Acute administration of the adrenoceptor antagonist, yohimbine, increased the physical effects of morphine withdrawal in rats (126), suggesting that  $\alpha_2$ -adrenoceptors are involved in the development of physical dependence upon opioids (127). It has also been shown that signs of discriminative-stimulus (128) and development of conditioned opiate withdrawal effects of morphine (129) may be enhanced by clonidine.

Although there is a report that indicates no important role for noradrenergic pathways in CPP (130), evidence from many different studies revealed that adrenergic drugs are involved in CPP over a range of doses. For example, it has indicated that  $\alpha_2$  adrenergic agonists and antagonists can induce CPP or CPA (see review [5]). Morphine-induced CPP may be related to dopaminergic mechanism(s) (41) and several studies in mice and rats revealed the existence of interactions between adrenergic and dopaminergic systems (131). Several other studies (131- 133) showed that phenylephrine or clonidine inhibits and also prazosin or yohimbine increases the expression of morphine-induced CPP. These results indicated that both agonists

of  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors have similar effects and thus, there is the possibility that activation of these receptors inhibit the expression of morphine CPP. In contrast, the data showed that the adrenoceptor antagonists enhanced the morphine response. The conditioned opiate withdrawal represents the negative reinforcement properties of opiates (129), while the CPP paradigm is developed to investigate the positive reinforcement properties of natural rewards and abused drugs (5, 130, 134). Because the adrenoceptor agonists and antagonists alter the morphine effect in our previous study (133), one may conclude that brain adrenergic systems have an important role in the expression of conditioned reward induced by morphine. Several studies showed that clonidine decreased, while yohimbine increased the acquisition of morphine conditioning (5, 132, 135). Overall, in agreement with others (131, 132), the obtained results indicated involvement of alpha adrenoceptors in the expression and acquisition of morphine CPP.  $\alpha_2$ -adrenoceptor agonist, clonidine, acts primarily at presynaptic noradrenergic autoreceptors to decrease noradrenaline activity. It alleviated the behavioral symptoms of opiate withdrawal in rats and humans. Clonidine also blocked the rewarding effect of morphine in opiate-withdrawn rats as well as the aversive properties of the withdrawal itself (136). It has been shown that the drug could produce CPP (5) or CPA (135). Yohimbine, the  $\alpha_2$ -adrenoceptor antagonist, which is clinically available and used to treat erectile impotence (137), was found to produce CPA. Moreover, the  $\alpha_1$ -adrenoceptor antagonist prazosin, which has been shown to have a preference for  $\alpha_2$ -adrenoceptor subtypes (138), did not produce any effect in this respect (5).

### Conclusion

Conditioned place preference (CPP), a task often used to measure reinforcing properties of drugs, such as morphine. There are a number of receptors, neuronal pathways and discrete central nervous system sites involved in the morphine reward mechanisms. However, it seems that the mesolimbic dopaminergic pathway projecting from the ventral tegmental area to the nucleus

accumbens is a critical site for the initiation of psychological dependence on opioids, but our studies demonstrated that other neurotransmitter systems may be involved in the morphine reward.

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