RESEARCH PAPER

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Effects of morphine on conditioned place preference and pain are independent of uptake-2

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Morphine changes neurotransmitter release, including norepinephrine, dopamine, and serotonin. Decynium-22 (D22) inhibits an alternative neurotransmitter removal pathway, namely uptake-2. Uptake-2 includes plasma membrane monoamine transporter (PMAT) and organic cation transporters that have a low affinity, but high capacity for uptake of various monoamines such as norepinephrine, dopamine, and serotonin. This study was done to assess the effect of uptake-2 inhibition on morphine-induced conditioned place preference (CPP) and analgesia. In this study, the effects of morphine and/or D22 on CPP were evaluated following intraperitoneal injection in mice. Afterward, changes in motor activity were evaluated by the open field test. Using the tail-flick model, the effects of D22 and/or morphine were evaluated on the pain threshold. The results showed that 20 mg/kg of morphine induced a place preference response. D22, at the dose of 0.03 mg/kg, caused place avoidance, while at the dose of 0.3 mg/kg, it produced a notable place preference response. Co-administration of D22 and morphine showed that morphine reversed the CPP aversion induced by D22 at the lowest dose. Motor activity did not alter. In the tail-flick test, morphine, at the dose of 3 mg/kg but not 1 mg/kg, increased the pain threshold. D22 induced significant analgesic responses. Co-administration of D22 and morphine caused considerable analgesic effects. The findings revealed that D22 induced both conditioned aversion and preference depending on the dose while morphine induced CPP. Both drugs produced analgesia.

Key words: decynium-22, morphine, conditioned place preference, tail-flick, pain

INTRODUCTION

Opioid addiction is an important global public health issue classified as a chronic and relapsing brain disease (Alavi et al., 2016). Morphine is one of the most efficient analgesics with a high abuse incidence (Lupina et al., 2020). Many studies have been devoted to finding efficient interventions to reduce physical and psychological dependence following opioid administration while maintaining their analgesic effects (Bu et al., 2015; Kourosh-Arami et al., 2020).

It was reported that various neurotransmitters such as dopamine, serotonin, and norepinephrine play essential roles in the rewarding response of psychoactive compounds (Takamatsu et al., 2011) and opioids (Pourtaqi et al., 2017). Norepinephrine transporter (NET), serotonin transporter (SERT), and dopamine transporter (DAT) are considered as uptake-1 that show high selectivity but low capacity for neurotransmitters clearance. Administration of morphine is reported with functional interactions between dopaminergic, adrenergic, and serotonergic systems (Sierra et al., 2020). Monoamine transporters are markedly involved in the pharmacological effects of morphine. In accordance, fluoxetine, a SERT blocker, increased morphine-induced analgesia and suppressed its anti-nociceptive tolerance and physical dependence (Alboghobeish et al., 2019). Similarly, venlafaxine, a SERT/NET inhibitor, prevented mor-

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phine-induced conditioned place preference (CPP) (Lu et al., 2001).

Uptake-2 is described as a low affinity but high capacity non-selective transport system of monoamine clearance (Koepsell, 2020). This process consists of different organic cation transporters such as plasma membrane monoamine transporter (PMAT) and organic cation transporters (OCT1, OCT2, and OCT3) (Fraser-Spears et al., 2019). These transporters are densely expressed in the brain, especially in the striatum and nucleus accumbens, which are associated with the rewarding effects of morphine (Sweet, 2021). PMAT and organic cation transporters (OCTs) are also expressed outside the brain and transport endogenous monoamines, including dopamine, serotonin, and norepinephrine (Koepsell, 2013). Furthermore, many psychoactive substances including morphine act as substrates for OCTs and PMAT (Tzvetkov et al., 2013; Bönisch, 2021; Maier et al., 2021).

Decynium-22, (D22, 1-ethyl-2-[(1-ethyl-2(1H)-quinolinylidene) methyl] quinolinium iodide), is a cation derivative of quinoline that inhibits OCTs and PMAT transporters. Recently, it was shown that D22 inhibits the development of CPP by amphetamine, as a well-known drug with significant abuse liability (Clauss et al., 2021).

Since the relationship between OCTs and PMAT transporters and the rewarding effects of morphine has not been investigated yet, we tested the effect of uptake-2 inhibition by D22 on pain and reward and assessed its possible interaction with the rewarding and analgesic effects of morphine.

METHODS

Animals

Since the goal of the present study was to assess the potential interaction between decynium-22 (D22, Sigma-Aldrich, Germany) and morphine (Daroupakhsh, Iran), but not the effect of sex on the putative interaction of these drugs, only male mice were used to avoid complexities involved with estrous in females. D22 is a potent inhibitor of PMAT and OCT 1, 2, and 3. D22 powder was dissolved in 1 ml Tween-80, 1 ml dimethyl sulfoxide (DMSO), and 8 ml sterile saline 0.9%. Morphine was dissolved in sterile saline 0.9%. Male albino mice (25–33 g) were housed under temperature-controlled (23±2°C) conditions with 12 h day/night cycle. Seven mice were involved in each experiment group. Mice were allowed unlimited access to food and water except during the tests. The experimental procedure was performed according to the Ethics and Animal Care Committee of Mashhad University of Medical Sciences protocol (No. 951589).

Experimental procedure

CPP procedure

Based on our previous studies, the CPP paradigm was performed over seven consecutive days consisted of pre-conditioning (two days), conditioning (four days), and post-conditioning (one day) phases (Alavi et al., 2016; Etemad et al., 2020). For all of the experiments, the animals were tested at the same time each day. The CPP apparatus included 2 equal-sized chambers (15 cm × 15 cm × 15 cm) being connected by a movable guillotine door (7 cm × 15 cm × 15 cm). The light intensity in the center of each chamber was 30 lux. Place conditioning was performed by an unbiased protocol. The walls and floors of the chambers differed in color and netted shape (black and white lines with fine floor *vs.* white wall and coarse floor). When the guillotine door was opened, mice were allowed to explore freely and when closed, it restricted the movement in one compartment. The activity of the mice in each compartment was recorded by a camera installed above the chambers.

Phase 1: pre-conditioning

In this two-day phase (D1-D2), each animal was placed separately in the central part to move between the chambers freely. Then, the time spent by the mice in each chamber on the second day was measured for 15 min. According to the CPP setup, the mice did not have any preference for either of the chambers.

Phase 2: conditioning

The second phase contained a four-day schedule (D3-D6). These 45-min sessions were conducted twice each day with 6-h interval saline pairing (black with white lines) chamber and drug pairing (white) chamber. The control group of animals received vehicle instead of the drug in all sessions.

Phase 3: post-conditioning

On the test day (D7), the movable door was removed and the animals explored both chambers for 15 min. On this day, mice did not receive any treatment. Similar to the pre-conditioning phase, the total time spent in the chambers was recorded. The change of preference, as the difference between the explora-

tion time in the post-conditioning phase and pre-conditioning phase in the drug-paired chamber, was calculated (Fig. 1).

Induction of CPP by morphine and D22

Firstly, we measured the effects of 10 and 20 mg/kg of morphine sulfate (intraperitoneal; i.p.) on place preference. The mice were treated with morphine and saline on alternate sessions. During the mornings of D3 and D5 and afternoons of D4 and D6, morphine was administered and the animals were placed for 45 min in the white chamber. In the afternoons of D3 and D5 and mornings of D4 and D6, saline 0.9% (10 ml/kg, i.p.) was injected, and mice were placed in the chamber with black and white lines for 45 min. The control group received only saline injections in morning and afternoon intervals. We used this method according to the previous studies (Rivera et al., 2019; Brice-Tutt et al., 2020, Nwaneshiudu et al., 2020).

We also measured the effects of D22 (0.03, 0.1, and 0.3 mg/kg, i.p.) and D22 vehicle on place preference with a similar to the above-explained protocol for the morphine-induced CPP. The doses for D22 were chosen according to the previous studies (Horton et al., 2013; Marcinkiewcz et al., 2015).

The mice of three groups received D22 (0.03, 0.1, and 0.3 mg/kg, i.p.) 30 min before morphine injection (10 mg/kg, i.p.) in the conditioning phase. The control group received D22 vehicle (instead of D22) 30 min before morphine administration.

Motor activity procedure

The motor activity of each mouse was recorded immediately after the CPP test by the open field experiment. The field size was (45 cm × 45 cm × 45 cm) made of black Plexiglas. Motor activity was measured using a camera and related software (MazeRouter, Iran). Measurement of motor activity helps to justify non-specific mechanisms interacting with the CPP test (Alavi et al., 2016).

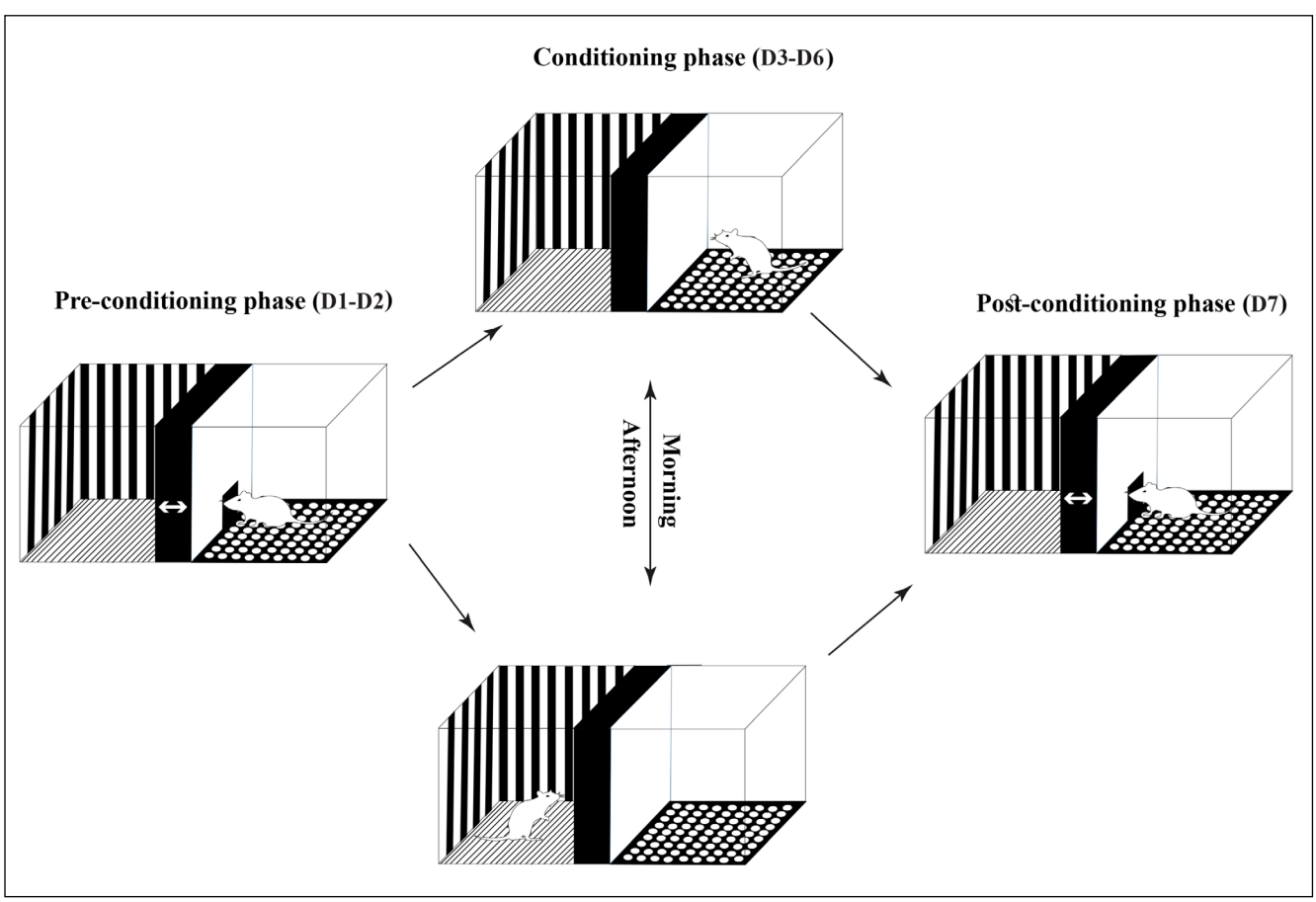

Fig. 1. The schematic of CPP procedure. CPP consisted of three phases: pre-conditioning (days 1-2), conditioning (days 3-6), and post-conditioning (day 7).

Tail-flick test

The tail-flick model is a test of acute pain in which intense heat is exposed to the tail of a mouse or rat (Hasanein et al., 2009; Katyal et al., 2012). In this test, radiant heat is directed to the dorsal surface of the tail with a cut-off time of 10 seconds. By using a tail-flick apparatus, the latency time of the tail-flick responses before (0) and at 15, 30, 45, and 60 min after drug administrations were recorded.

Statistical analysis

All data were expressed as mean ± SEM. One-way ANOVA was applied for the comparison of the means of morphine groups on CPP. The results of D22/D22 morphine-induced CPP and tail-flick latencies were analyzed using two-way ANOVA. Following a significant *F*-value, *post hoc* analysis (Tukey) was executed. P<0.05 was considered statistically significant.

RESULTS

Effects of morphine on CPP

A one-way ANOVA revealed a significant difference between groups on morphine induced preference ($F_{2,21}$=8.923, *P*=0.0016). Fig. 2A presents CPP following morphine treatment. Injection of 20 mg/kg morphine in the conditioning phase caused a significant preference (*P*<0.01) compared to the animals that received saline, although 10 mg/kg morphine-treated mice did not show considerable preference compared with the control group (Fig. 2A). Fig. 2B shows that, in comparison with the control group, morphine treatments did not alter locomotor activity in the conditioning phase, significantly.

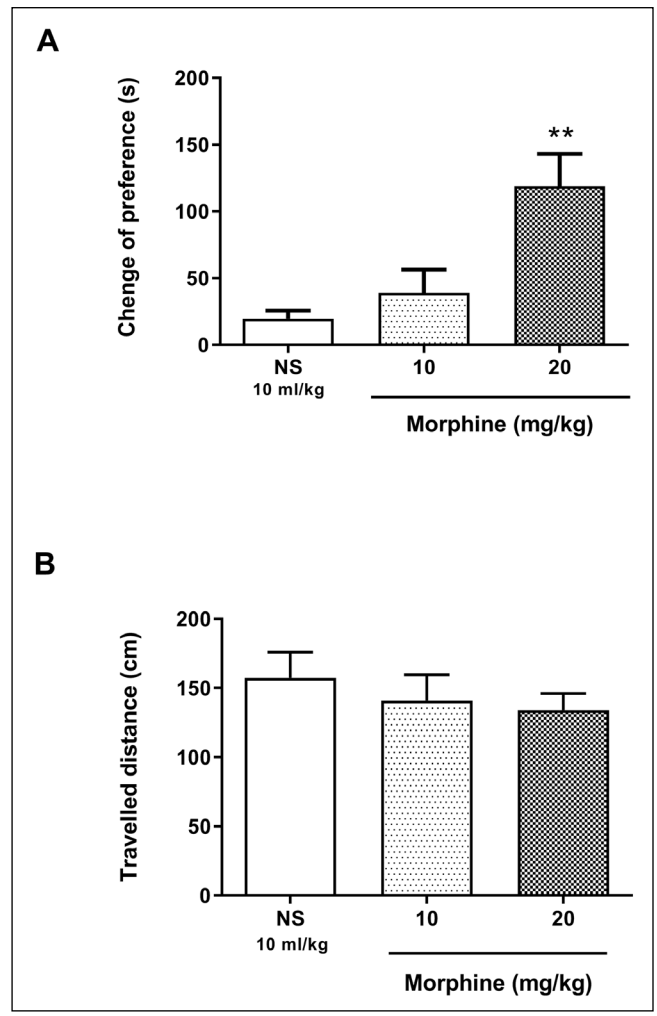

Fig. 2. (A) The effect of intraperitoneal injection of morphine (10 and 20 mg/kg) on place preference. Change of preference: the difference between the times that animals spent on pre-and post-conditioning sessions in the drug-paired chamber. (B) The effect of morphine on motor activity immediately after the post-conditioning session. Data are means ± SEM of seven mice per group. **P<0.01 compared with the saline-treated group. NS: normal saline.

Effects of D22 and D22/morphine on CPP

We analyzed the effect of D22 (0.03, 0.1, and 0.3 mg/kg), *per se,* or in combination with morphine on preference by two-way ANOVA test (dose effect: $F_{3,48}$=70.35, *P*<0.0001; treatment effect: $F_{1,48}$=17.31, *P*<0.0001; interaction effect: $F_{3,48}$=32.86, *P*<0.0001; Fig. 3A). Subsequent analysis indicated that administration of 0.03 mg/kg of D22 decreased preference (caused aversion) in the conditioning phase (*P*<0.001, Fig. 3A1) compared to vehicle group. Administration of D22 at the dose of 0.1 mg/kg did not change CPP, while D22 at the dose of 0.3 mg/kg, in contrast to the lowest dose, increased CPP (*P*<0.001, Fig. 3A1) in comparison to vehicle-treated animals.

As shown in Fig. 3A2, administration of morphine (10 mg/kg) did not induce significant CPP in combination with the aforementioned doses of D22 compared to animals who received only morphine (vehicle group).

Further analysis with Tukey's *post hoc* test showed that administration of 0.03 mg/kg of D22 and the ineffective dose of morphine on CPP (10 mg/kg) enhanced preference (*P*<0.001, Fig. 3A) in comparison with 0.03 mg/kg of D22, *per se*. However, administration of morphine (10 mg/kg) with D22, at the doses of 0.1 and 0.3 mg/kg, did not change the effect of D22 on CPP (Fig. 3A).

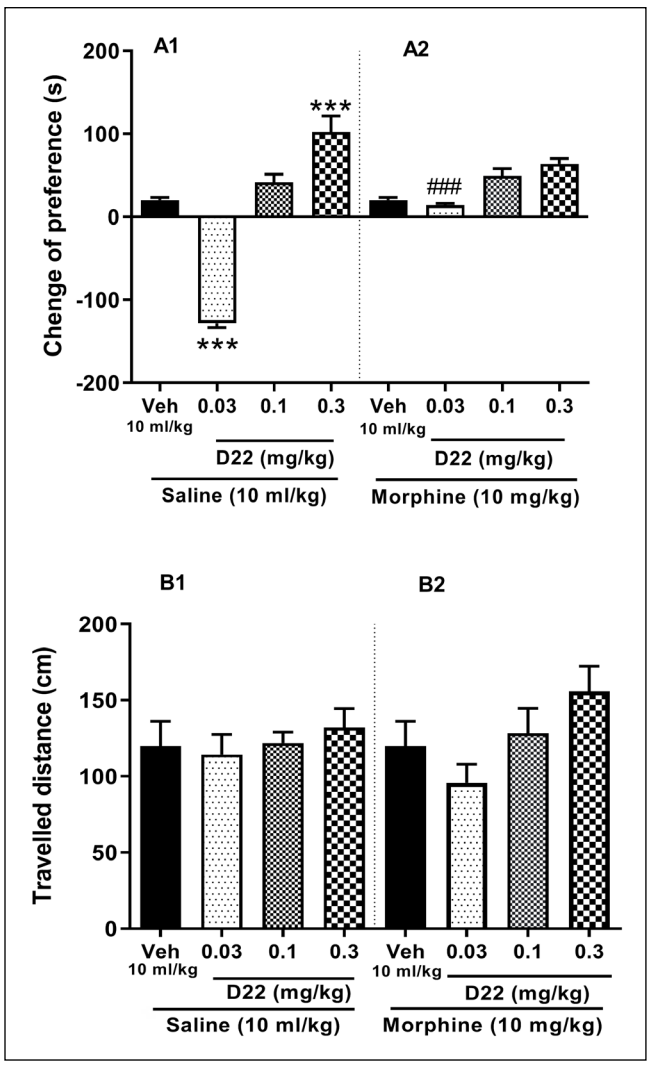

Fig. 3. (A1) The effects of D22 (0.03, 0.1, and 0.3 mg/kg, i.p.) with saline (10 ml/kg, i.p.) or (A2) morphine (10 mg/kg, i.p.) on CPP. Change of preference: the difference between the times that animals spent on pre- and post-conditioning sessions in the drug-paired chamber. (B1) The effect of D22 with saline (10 ml/kg, i.p.) or (B2) morphine (10 mg/kg, i.p.) on the motor activity immediately after the post-conditioning session. Data are means ± SEM of seven mice per group. ***P<0.001 compared with the vehicle-treated group and ###P<0.001 compared with the respective group in the D22/saline-treated group.

The open field results showed that D22 did not alter the locomotor activity of the animals implying that the effects of D22 on CPP were independent of possible locomotor activity alteration (Fig. 3B).

Effects of morphine, D22, and D22 plus morphine on pain threshold

The effect of morphine (1 and 3 mg/kg) on the pain threshold in the tail-flick test is presented in Fig. 4A. Analysis of data with two-way ANOVA showed that there is a significant difference between morphine groups on pain threshold (treatment effect: $F_{2,90}$=323.5, P<0.0001; time effect: $F_{4,90}$=74.61, P<0.0001; interaction effect: $F_{8,90}$=66.98, P<0.0001; Fig. 4A). Morphine, at the dose of 3 mg/kg, caused a significant (P<0.001) analgesic effect after 30, 45, and 60 min in comparison with the saline group. The lower dose of morphine (1 mg/kg) did not induce analgesia (Fig. 4A).

Analysis of data with two-way ANOVA revealed that there is a significant difference between D22 groups on pain threshold (treatment effect: $F_{3,120}$=92.06, P<0.0001; time effect: $F_{4,120}$=59.18, P<0.0001; interaction effect: $F_{12,120}$=16.81, P<0.0001; Fig. 4B). As shown in Fig. 4B, D22 at the dose of 0.1 mg/kg at 15, 30, 45, and 60 min after injection showed a notable analgesic effect (P<0.001) in comparison to vehicle. Similarly, D22 at the dose of 0.3 mg/kg at all times, except 45 min, significantly enhanced the pain threshold (P<0.001). This implies that D22 induced a significant anti-nociceptive effect.

Two-way ANOVA indicated that there is significant difference between D22/morphine groups on pain threshold (treatment effect: $F_{3,120}$=92.69, P<0.0001; time effect: $F_{4,120}$=17.42, P<0.0001; interaction effect: $F_{12,120}$=13.38, P<0.0001; Fig. 4C). Animals that received 0.03 of D22 plus morphine (1 mg/kg) had significant decrease in pain thresholds at 45 and 60 min after injection than their respective D22-treated control animals (P<0.05 and P<0.001). Mice who treated with 0.1 mg/kg of D22 plus morphine (1 mg/kg) showed significant increase in nociceptive threshold at 15 and 30 min after administration (P<0.001 and P<0.05 respectively). The higher dose of D22 (0.3 mg/kg) plus morphine (1 mg/kg) caused an analgesic effect after 15, 30, 45 and 60 min of injection compared with the control group (15 and 60 min: P<0.05, 30 and 45 min: P<0.001, Fig. 4C).

DISCUSSION

The present study demonstrated that D22, as a potent uptake-2 inhibitor, induced both aversion and place preference at low and high doses, respectively. D22 also induced significant analgesia in the tail-flick test. There was not an important interaction between D22 and morphine in the modulation of pain and CPP.

CPP is a well-known animal model for the evaluation of reward-related behaviors (Gibula-Bruzda et al., 2015; Qian et al., 2020). Many drugs with addictive properties, including amphetamines, cocaine, heroin, and morphine induce significant CPP (Park et al., 2014; Mori et al., 2016). In agreement with the literature

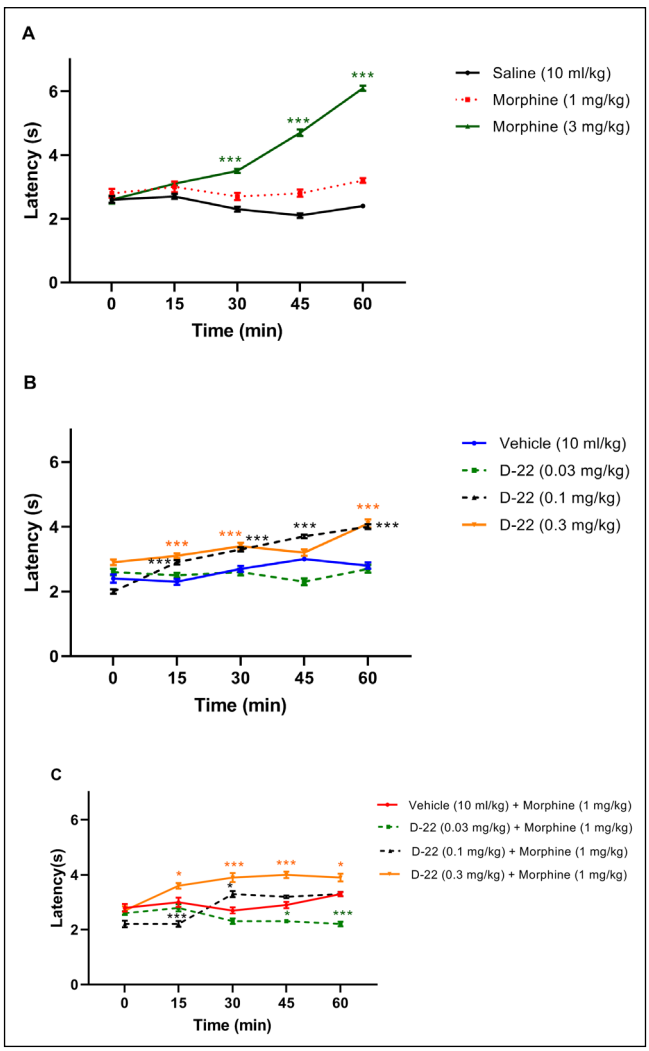

Fig. 4. (A) The effect of injection of morphine (1 and 3 mg/kg) on time-course of thermal-induced pain in the tail-flick test. *P<0.05 and ***P<0.001 compared with the saline-treated group. (B) The effect of different doses of D22 (0.03, 0.1, and 0.3 mg/kg, i.p.) on time-course of thermal-induced pain in the tail-flick test. ***P<0.001 compared with the vehicle-treated group. (C) Co-administration of different doses of D22 (0.03, 0.1, and 0.3 mg/kg, i.p.) with ineffective dose of morphine on pain (1 mg/kg) on time-course of thermal-induced nociception in tail-flick test at 0, 15, 30, 45, and 60 min after morphine administration. Data are means ± SEM of seven mice per group. *P<0.05 and ***P<0.001 compared with the baseline time.

(Ribeiro Do Couto et al., 2003) and our previous study (Etemad et al., 2020), morphine promoted condititiong in the CPP task at the dose of 20, but not 10 mg/kg, in mice. This effect of morphine was without significant alteration in motor activity. This finding implies that morphine elicited reward-related behaviors with no significant change in locomotion as a confounding parameter.

D22 has been reported to inhibit uptake-2, which is involved in the termination of dopamine, serotonin, and norepinephrine biological activities. In the present study, the dual and paradoxical effects of D22 on CPP may be attributed to its effects on dopamine. Many studies are showing that dopamine activity, depending on various factors, may promote preference or aversion. As an example, dopamine activity was reported to be involved in aversive learning (Sellings et al., 2008; Weitemier et al., 2009). On the other hand, nicotine (Risinger et al., 1995), amphetamine (Fudala et al., 1990; Wang et al., 2010), caffeine (Brockwell et al., 1991), and cocaine (Mayer et al., 1993) have been reported with both aversive and rewarding effects. Interestingly, aversive and rewarding doses of nicotine were reported to produce completely different cellular firing patterns in the nucleus accumbens (Sun et al., 2014). As another hypothesis, the balance between dopamine and serotonin has been reported as a key factor in the expression of learned behavior, including preference or aversion (Weitemier and Murphy, 2009). As mentioned, D22 also enhances serotonin activity *via* blockade of uptake-2 and provokes significant antidepressant-like effects. So, its potential use as antidepressant medication, similar to selective serotonin reuptake inhibitors (SSRIs), has been evaluated and documented (Horton et al., 2013; Jin et al., 2019). Previous studies imply that SSRIs can induce CPP (Subhan et al., 2000). So, we suggest that D22-induced aversion, at the lowest dose, and induction of CPP, at the highest dose, were mediated by the complex interaction of D22 with dopamine and serotonin. In addition, D22, induced analgesia dose-dependently. Similarly, the analgesic effect of tricyclic antidepressants has been reported (Spiegel et al., 1983; Rojas-Corrales et al., 2003). These drugs block neuronal norepinephrine and serotonin reuptake and finally enhance their concentrations in the synapses. Interestingly, the pharmacological depletion of monoamines in the nervous system abolished the analgesic effect of tricyclic antidepressants. So, it may be suggested that D22, *via* inhibition of uptake-2, induced similar monoamine-dependent analgesia.

In addition to uptake-1, uptake-2 has been recognized as an important system for the termination of neurotransmitter functions in the nervous system (Koepsell, 2013). Accordingly, this system has been proposed as an important target for the treatment of various neurological disorders. Uptake-2 includes a group of broadly-specific organic cation transporters, such as the organic cation transporter (OCT) family and plasma membrane monoamine transporter (PMAT) (Fraser-Spears et al., 2019). This system includes uptake of serotonin, dopamine, and norepinephrine as the main brain monoamines (Koepsell, 2013). OCTs and PMAT are located on the neurons of the hippocampus, occipital cortex, nucleus accumbens, and caudate nucleus

that are considered as key brain regions in the modulation of reward-related behaviors (Koepsell, 2020).

D22 is an inhibitor of OCT3, OCT2, OCT1, and PMAT (Koepsell et al., 2007; Koepsell, 2021). Recently, Clauss and co-workers (2021) reported that D22 at the dose of 0.1 mg/kg blocked amphetamine-induced CPP in wild-type mice. CPP for amphetamine did not develop in male OCT3 knockout mice, and D22 was without effect. While PMAT knockout mice developed CPP for amphetamine, it was not suppressed by D22 in female PMAT knockout animals. Thus, OCT3 and PMAT may play an important, sex-dependent role in the ability of D22 to inhibit amphetamine CPP in intact animals.

Dopaminergic pathways have been suggested as key mechanisms in the induction of opioid reward-related behaviors (Kalivas et al., 1991). However, the key role of dopamine in reward has been questioned (Hnasko et al., 2005). Serotonin, norepinephrine, gamma-aminobutyric acid, adenosine, and cholecystokinin are involved in morphine-induced tolerance and dependence, as well (Bhargava et al., 1994). In accordance, morphine has been reported to increase serotonin release from the raphe nucleus (Tao et al., 1995). Considering the interaction of the opioid system with various neurotransmitters, including monoamines, we hypothesized that D22, as a potent uptake-2 inhibitor, may interfere with the main pharmacological effects of morphine: analgesia and reward. As mentioned, morphine induced analgesia and CPP, at the doses of 3 and 20 mg/kg, respectively. We evaluated the effect of D22, at different doses, on ineffective doses of morphine on tail-flick (1 mg/kg) and CPP (10 mg/kg); no significant interaction was found between D22 and morphine in either experiment. However, D22, at the dose of 0.03 mg/kg, as the lowest dose, did not exhibit aversion when combined with the ineffective dose of morphine. We did not see such interaction at the higher doses or in the tail-flick test and cannot provide supporting evidence for such finding, but it means that a potential interaction between these drugs may exist.

The interaction of D22, at the lowest dose, with morphine, may be explained by previous studies showing that failure of OCT1 increases the pharmacological effects of morphine as it has been reported as a substrate for OCT1 (Tzvetkov et al., 2013; Zhu et al., 2018). In accordance, it was reported that humans carrying loss-of-function OCT1 polymorphisms had higher plasma levels of morphine as much as 56% after codeine administration in comparison with non-carrier controls (Tzvetkov et al., 2013). Similarly, lower morphine clearance, higher incidence of respiratory depression, and postoperative nausea and vomiting during and after surgeries have been attributed to OCT1 polymorphisms in Caucasian children (Balyan et al., 2017). In contrast, a recent study showed that OCT1 polymorphisms did not change morphine and its major metabolites levels in adult surgical patients (Kuhlmann et al., 2022). These findings suggest that a potential interaction between morphine and uptake-2 exists that needs further investigations to uncover its significance in clinical practice.

CONCLUSION

The present study demonstrated that D22 induced variable results in the CPP test, but morphine induced significant CPP. Moreover, morphine turned the aversive effect of D22 into a rewarding effect in the CPP task. Both drugs induced significant analgesic effects. Co-administration of highest dose of D22 and morphine showed significant interaction in pain modulation.

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