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Experimental Research Article

Kisspeptin-13 attenuates the rewarding but not the reinstatement effects of methamphetamine in the conditioned place preference test in rats

Somayeh Nazari[1], Mobina Gheibi[2], Hamed Ghazvini[3], Raheleh Rafaiee[3], Seyedeh Masoumeh Seyedhosseini Tamijani[3*]

1. Student Research Committee, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran
2. Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran
3. Department of Neuroscience, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran

ABSTRACT

Introduction: Methamphetamine (MA) addiction is a major global public health concern, yet there is currently no approved medication that effectively treats this addiction. Kisspeptin is a neuropeptide that has a role in the reproductive system, metabolism and energy balance, and metastasis suppression in different types of cancers. The kisspeptin receptors, GPR54 are widely distributed in the brain's memory-related structures. Previous studies have revealed that the opioid system contributes to the addictive effects of MA. Additionally, preclinical studies have shown that a derivative of kisspeptin possesses anti-opioid properties. This study aimed to clarify the role of kisspeptin-13 (KP-13) on reward and reinstatement-related memory associated with MA in the conditioned place preference test.

Methods: We evaluated pre-treatment with intracerebroventricular KP-13 for 3 consecutive days (2.5 µl/nostril, once a day) in a conditioned place preference test induced by MA. MA was administered intraperitoneally at a dose ranging from 1 to 7 mg/kg, once daily, beginning at 1 mg/kg on day one and increasing by 1 mg/kg per day up to the day 7.

Results: We found that KP-13 suppresses the reward behavior in MA-treated rats, while it has no significant effect on reinstatement behavior after one week of MA cessation, which could be attributed to the ineffective dose of KP-13.

Conclusion: The findings indicate that KP-13 alters the rewarding and motivating effects of MA. Further research involving both multiple and single administrations of KP-13 before the reinstatement test is necessary to throw light on its impact on withdrawal-related reinstatement.

Keywords:
Kisspeptin-13
Methamphetamine
Reward
Reinstatement
Condition place preference

Introduction

Methamphetamine (MA) is known as the most addictive drug with a high potential for abuse. The abuse of this illicit psychostimulant has significantly increasedin the years (Moenk and Matuszewich 2012). Currently, there are no FDA-approved medications for metham-

* Corresponding author: Seyedeh Masoumeh Seyedhosseini Tamijani, m.seyedhoseini@mazums.ac.ir
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phetamine addiction (Stauffer et al., 2020). Both pharmacological and behavioral/psychosocial approaches are not completely effective. Chronic use in MA abusers is associated with behavioral disorders such as learning and memory deficits, anxiety, drug craving, reinstatement, and psychosis (Ekhtiari et al., 2016). The psychostimulant addiction is caused by the destruction of neuronal circuits that modulate desire and motivation. The mesolimbic pathway as a reward circuit plays an essential role in MA-induced rewarding effects by increasing dopamine in the limbic system such as the nucleus accumbens (Thorn et al., 2012). The MA increases dopamine in synaptic cleft by suppressing of dopamine transporters, enhancing the release of dopamine from synaptic vesicles and decreasing dopamine metabolism by inhibition of monoamine oxidases (Kotlinska et al., 2008; Thorn et al., 2012). Preclinical studies have shown that increasing the release of dopamine by MA can increase the activity of opioid receptors in the reward circuit. In accord with preclinical studies, molecular studies have also demonstrated the change in mRNA level of endogenous opioid receptors in the reward circuit after repeated administration of psychostimulants (Chiu et al., 2006; Magendzo and Bustos 2003).

The RF-amide peptides are a family of neuropeptides (Gibula-Tarlowska et al., 2019a; Kotlinska et al., 2008). Neuropeptide FF (NPFF) was the first identified RF-amide peptide in the central nervous system of mammals, known as an anti-opioid modulator influencing the expression of morphine and cocaine-induced reward (Kotlinska et al., 2007; Kotlinska et al., 2008). Kisspeptin is another member of the RF-amide peptide family and its receptor is G protein-coupled receptor 54 (GPR54 or KISS1R). Kisspeptin precursor, encoded by *KISS1*/*Kiss1* gene, is a propeptide that has 145 amino acids. The proteolytic action of this product generates kisspeptin 54 (KP-54), which is subsequently cleaved into several active isoforms, including kisspeptin 10 (KP-10), kisspeptin 13 (KP-13), kisspeptin 14 (KP-14). Reproductive studies in humans and animals have demonstrated that KP-13 plays an essential role in regulating gonadotropin-releasing hormone (GnRH) during puberty, the onset of reproductive maturity, and fertility (Delmas et al., 2018; Ibos et al., 2021).

Kissorphin (KSO), as a new derivate of KP-10, has been shown to act like NPFF. It does not affect GnRH secretion through GPR54 (Takino et al., 2003), but possesses anti-opioid activity. Milton et al. reported that the biological activity of the KSO peptide is antagonized by RF9 (NPFF receptor antagonist) in human neuronal SH-SY5Y cells (Milton et al., 2012). Kisspeptin derivatives are primarily located in the hippocampal dentate gyrus within the central nervous system. This region is responsible for learning, spatial orientation and memory consolidation, making it particularly relevant to the addiction process. Memory processes are known to play a significant role in the development and maintenance of addiction to psychoactive substances such as ethanol, cocaine, morphine, and other similar substances (Oishi et al., 2011). In addition, several studies have reported that NPFF and Kisspeptins (KPs) exert anti-addictive effects in conditioned place preference (Gibula-Tarlowska et al., 2019b; Kotlinska et al., 2007; Kotlinska et al., 2008). Therefore, based on these data, we hypothesized that KP-13 may possess anti-addictive properties. Earlier, the role of KP-13 in cognitive function such as learning and memory had been identified but its role in MA addiction has not been investigated so far.

In this study, we examined whether KP-13, as a member of RF-amide peptide family attenuates the rewarding and reinstatement effects of methamphetamine in the conditioned place preference (CPP) test.

Materials and Methods

Animals

Adult male Wistar rats weighing (200-270 g) were obtained from the Institute for Laboratory Animal Research of Mazandaran University of Medical Sciences. Subjects were housed under standard conditions (12h light/12h dark with a constant room temperature of 21±2◦C and 50 ± 10% humidity) with free access to standard nutriments and tap water. The rats were acclimatized for 7 days before the beginning of the experiments. All procedures were conducted in accordance with the ethical guidelines set by the Research Ethic Committee of Mazandaran University of Medical Sciences, Sari, Iran (IR.MAZUMS.REC.1398.6037).

Drugs

MA hydrochloride was synthesized in the laboratory of Medicinal Chemistry, Tehran University of Medical Sciences, Iran, with 99.2% purity. The KP-13 was obtained from Bachem (Basel, Switzerland). MA was freshly dissolved in 0.9% saline solution before each

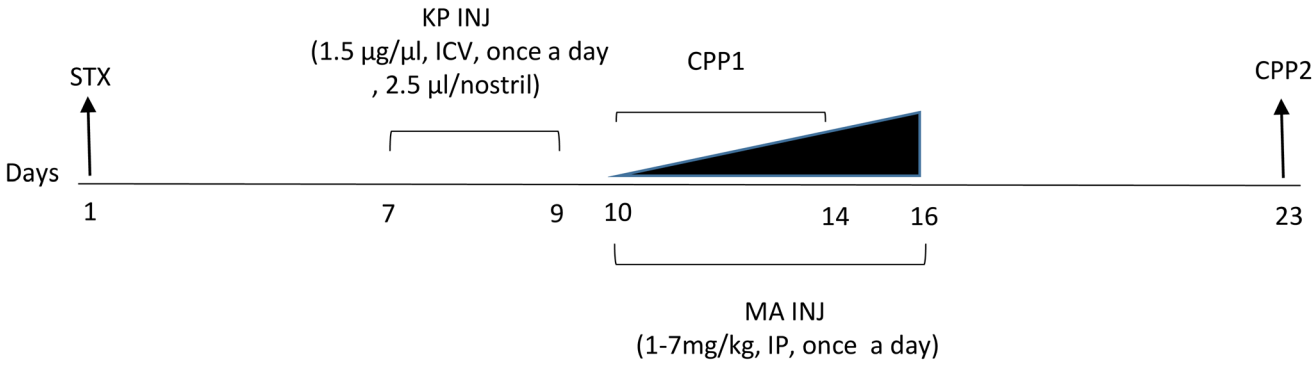

FIGURE 1. Experimental design.

intraperitoneal injection. The KP-13 was dissolved in sterile pyrogen-free 0.9% saline and injected intracerebroventricular (ICV).

Stereotaxic Surgery

The animal was anesthetized by intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10mg/kg). For intracerebroventricular (ICV) administration of either KP-13 or saline into the right lateral ventricle of the brain, subjects underwent stereotaxic surgery. The cannula was positioned according to the Paxinos and Watson, Atlas (AP: −0. 5, L: 1.6, DV: −4.2) and fixed in the skull with dental cement. All central microinjections were performed over 5 min using a 30-gauge stainless steel injector, which was connected to a Hamilton syringe by polyethylene tubing (PE-20).

Drug administration, and experimental design

After 7 days of recovery from surgery, rats were divided randomly into 4 groups (n = 7-9/group): 1) The saline group received ICV saline for 3 days and followed by intraperitoneal saline for 7 days, 2) MA group received ICV saline for 3 days and followed by intraperitoneal repeated doses of MA (1-7 mg/kg, once a day at 5h intervals, beginning at 1 mg/kg on day 1 and escalated 1mg/kg per day, for the next 6 consecutive days), 3) KP-13+MA group treated with ICV KP-13 (1.5 µg/µl, once a day) for 3 days followed by MA injection same as MA group. 4) The KP-13 group was treated with ICV KP-13 (1.5 µg/µl) for 3 days, followed by saline injection for 7 days. Based on the timeline depicted in Figure 1, each group participated in the conditioned place preference (CPP) assessment on two separate occasions, labeled as CPP1 and CPP2. CPP1 was conducted between the 10th to 15th days of the experiment, while CPP2 was carried out on the 23rd day. One hour before the start of the behavioral tests, animals were brought to the test room.

Conditioned place preference (CPP) test

CPP1 was performed to elucidate the rewarding effects of MA in animals. We used a three chamber wooden CPP device. The device comprised two equally sized chambers (30×30×40 cm) connected by another chamber (30×15×40 cm) called the null chamber. The two chambers had distinct features. The left one had vertical white and black stripes while the right one had horizontal white and black stripes. Additionally, they had different floors.

CPP1 procedures had three different phases: pre-conditioning phase, conditioning phase, and post-conditioning phase. Seven days after MA/saline cessation, CPP2 was repeated same as post-conditioning phase to assess the reinstatement behavior (Anooshe et al., 2021; Rafaiee et al., 2023), (Ebrahimi et al., 2021) (Fig. 1).

Preconditioning phase: Before MA injection on day 10 of the experiments, a preconditioning phase was conducted. The rats were placed in the null chamber and allowed to move freely in all chambers for 10 minutes. A camera located 2 meters above the device recorded the time spent by each rat in each chamber. Recorded videos were analyzed offline by experimenter. The rats that exhibited compartment preference were eliminated from the study because they should not spend more than 80% of the total test time in one chamber (Anooshe et al., 2021; Ebrahimi et al., 2021).

Conditioning phase (Acquisition): This phase was initiated 24 hours after the preconditioning phase and consisted of a three-day schedule of conditioning sessions.

For conditioning, an increasing dosage regimen of MA was used. During this phase, rats were given daily doses of either MA (1 to 3 mg/kg) or saline in the morning and evening, with the timing alternating daily. After each injection, the rats were immediately placed in either the drug-paired chamber or the saline-paired chamber. Accordingly, on the first day of the conditioning phase, rats were injected with 1mg/kg of MA in the morning and confined to the MA-paired chamber for 45 min. After 5h intervals, rats received saline and were confined to a saline-paired chamber for 45 min. On the second day of the conditioning phase, the administration time of MA and saline was changed and rats were treated with 2mg/kg of MA. On the third day of the conditioning phase, the administration time of MA and saline was the same as the first day of the conditioning phase, and the drug dose was increased to 3 mg/kg (Anooshe et al., 2021; Rafaiee et al., 2023; Rezaeian et al., 2020). After the conditioning phase, the injection regimen continued with a dose of 4 mg/kg the next day, increasing by 1 mg/kg per day until it was terminated at a dose of 7 mg/kg.

Post-conditioning phase (Expression): The day after conditioning phase, post-conditioning phase was carried out. Each rat was allowed to freely explore all of the chambers for 10 min before any injection and then the injections were done as previously described. One week later, after MA cessation, CPP2 was performed to evaluate reinstatement behavior. The CPP2 procedure was done the same as post-conditioning phase. To determine the change in preference, the amount of time spent in the MA-paired chamber during the post-conditioning phase (CPP1) was subtracted from the time spent in that same chamber during the pre-conditioning phase. Similarly, for CPP2, the change in preference was calculated by subtracting the time spent in the MA-paired chamber from the time spent in that same chamber during pre-conditioning phase (Rafaiee et al., 2023; Rezaeian et al., 2020).

Statistical analysis

The analysis of data performed by analysis of variance (ANOVA) and comparison between groups were followed by post hoc Tukey's test. Data were expressed as mean ± SEM and P-values less than 0.05 ($P < 0.05$) were set to be statistically significant. The analyses were conducted in IBM SPSS Statistics 26 software.

Results

The effect of KP-13 on the MA-induced reward

Rats in MA-treated groups received MA as an escalating paradigm consisting of once a day intraperitoneal injection of 1-7mg/kg after pre-treatment with KP-13. During pre-conditioning phase, the time spent in chambers did not differ between all experimental groups [$F_{(3, 32)} = 1.082$, $P > 0.05$], Fig. 2. This data suggested that there was no preference for any chamber between the

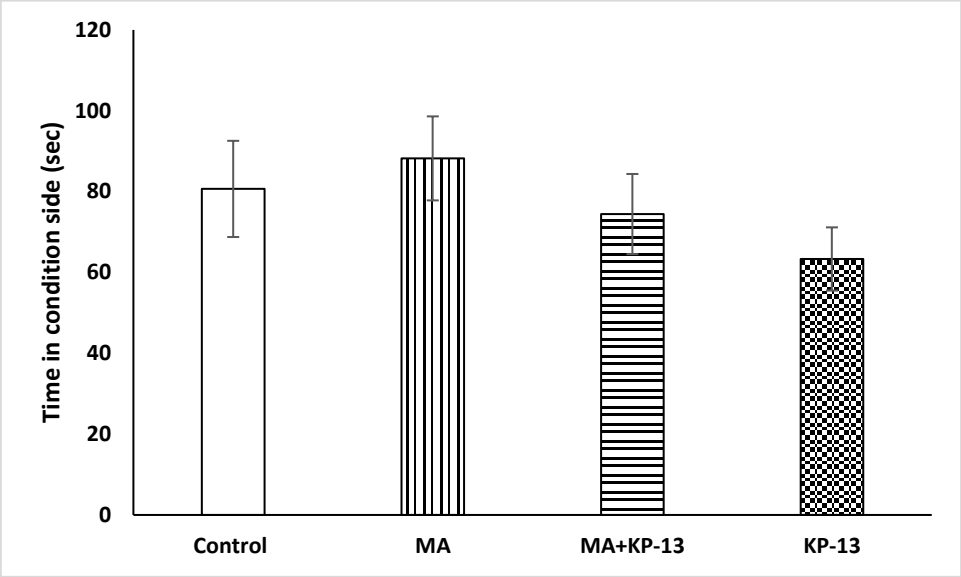

FIGURE 2. The time spent in the conditioned side prior to MA exposure during the pre-conditioning phase of the CPP test. The differences between all experimental groups were analyzed by ANOVA, followed by post hoc Tukey's test. Data are expressed as mean±SEM (n=7-9).

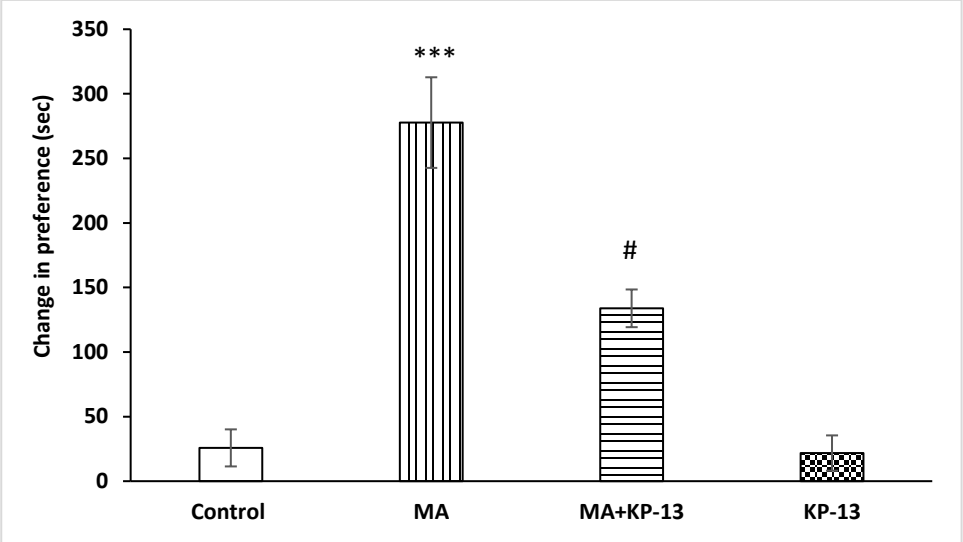

FIGURE 4. The effect of KP-13 on the change in preference following MA exposure in the CPP1 during the post-conditioning phase. The differences between all experimental groups were analyzed by ANOVA, followed by post hoc Tukey's test. Data are expressed as mean±SEM (n=7-9). ***P < 0.001 vs control group; # P < 0.05 vs MA group.

groups.

A one-way ANOVA, followed by the post hoc Tukey test revealed a significant difference between groups in the change of preference [$F_{(3, 30)} = 20.22$, $P < 0.001$], (Fig. 3). The post-hoc analysis showed preference for conditioned side of MA group was increased considerably compared to those of the control group ($p < 0.001$) that indicating the rewarding effect of MA. Pre-treatment with KP-13 prevented MA-induced reward in the kp-13+MA group ($p < 0.05$). The animals spent less time in the conditioned compartment compared to the MA group. There was no significant difference in the change of preference between the KP-13 group and the control group ($p > 0.05$).

The effect of KP-13 on MA-induced reinstatement

The one-way ANOVA showed a significant difference between groups in their change of preference after discontinuing MA for one week in CPP2 [$F_{(3, 31)} = 10.21$, $P < 0.001$], (Fig. 4). The post-hoc analysis revealed that rats in MA-treated group spent more time in condition side compared with control group ($p < 0.001$), suggestive of high resistance to extinction and reinstatement effect of drug. KP-13 administration could not decrease preference time in the MA-paired chamber in comparison with MA group. Also, the control and KP-13 groups were not significantly different in the change in preference.

Discussion

In the present study, we investigated the effects of KP-13 when centrally administered on the rewarding and reinstatement behavior caused by an escalating dose of MA (1-7mg/kg, IP, once daily) in the CPP test. Our findings revealed that while KP-13 decreased the rewarding response to MA, it did not affect the reinstatement of the drug. The applied doses of KP-13 and MA did not influence locomotor activity (data not shown) (Khonacha et al., 2019; Seyedhosseini Tamijani et al., 2018; Valian et al., 2018). It seems that the current results are consistent with previous research, which have demonstrated the anti-addictive properties of KP derivatives. Gibula-Tarlowska et al. reported that Kissorphin, a new derivative of KP-10, suppressed the acquisition, expression, and reinstatement caused by morphine in CPP test (Gibula-Tarlowska et al., 2019b). Additionally, the research team discovered that Kissorphin was able to inhibit the rewarding response of ethanol in CPP tests (Gibula-Tarlowska et al., 2019a). The results of the study showed that the observed effect was dependent on the binding of Kissorphin to the NPFF receptor. As previously mentioned, neuropeptide NPFF has anti-opioid properties, indicating that KP-13 potentially has the same physiological effect as neuropeptide NPFF through the NPFFR pathways (Gibula-Bruzda et al., 2017). It has been reported that central administration of NPFF in morphine-dependent rats precipitates the

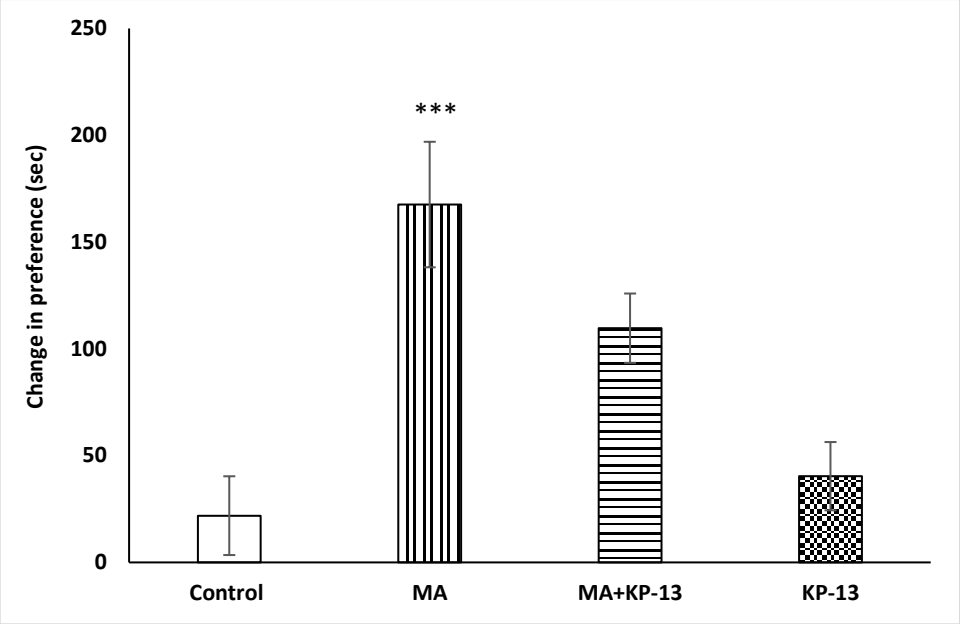

FIGURE 4. The effect of KP-13 on the change in preference following MA exposure during CPP2. The differences between all experimental groups were analyzed by ANOVA, followed by post hoc Tukey's test. Data are expressed as mean±SEM (n=7-9). ***P < 0.001 vs control group.

withdrawal symptoms (Malin et al., 1990). In confirmation of these observations, the research carried out by Katalia and his colleagues showed that ICV injection of NPFF decreased the expression of morphine-induced CPP (Kotlinska et al., 2007). Studies have shown that the length of the kisspeptin derivative plays a role in how well it binds to the NPFF receptors. For example, KP-54, which is longer, has low affinity, whereas shorter analogs like KP-13 and KP-8 have moderate and high affinities, respectively. The activation of NPFF receptors by kisspeptin is related to the similarity in structure of kisspeptins to neuropeptide NPFF (Ibos et al., 2021; Lyubimov et al., 2010).

Numerous studies suggest that the use of psychostimulants can affect and interact with the opioid system in various ways. In one instance, when repeatedly given MA, behavioral sensitization was reduced in mice lacking a μ-opioid receptor (Shen et al., 2010). This effect is associated with the decrease of tyrosine hydroxylase expression in the nigrostriatal pathway (Park et al., 2012), suggesting the interaction of the opioid system with the dopaminergic system that is dramatically affected by MA. Based on previous observations and the findings of this study, it can be inferred that KP-13, through its anti-opioid activity, can suppress the rewarding effects of MA in the CPP test.

Another possible explanation for the anti-rewarding effect of KP-13 is its involvement in learning and memory processes. The CPP test is an associative memory model that is used to study drug- seeking and maladaptive reward-based learning. It examines the link between environment and the rewarding effects of drugs. This association is critical because certain stimuli, like those associated with drug use, can easily trigger cravings, drug-seeking behavior, and reinstatement even after a prolonged period of abstinence (Everitt 2014). The kisspeptin and its receptor, known as the G-protein coupled receptor (GPR)-54 receptor, are present in high levels in various areas of the brain, including the medial amygdala, medial frontal gyrus, cingulate, hippocampus, accumbens, parahippocampal gyrus, striatum, and thalamus. These structures are related to cognitive functions such as learning, memory, and behavior (Melka et al., 2021; Mills et al., 2018; Mills et al., 2019; Patel and Smith, 2020). The widespread distribution of the KP receptors in these brain regions suggests that the neuropeptide may play a role in these functions. It has been demonstrated that central administration of KP-13 attenuated memory deficits in animal models of Alzheimer's disease (Jiang et al., 2015; Khonacha et al., 2019). On the other hand, many clinical and preclinical studies have highlighted the negative impact of MA on cogni-

tive function (Khodamoradi et al., 2022; Peters et al., 2023; Rezayof et al., 2023; Seyedhosseini Tamijani et al., 2018; Tamijani et al., 2023). Our findings indicate that the use of KP-13 led to a decrease in MA-induced CPP. Please be conscious that the anti-rewarding effects of KP-13 may be because of disturbing memory rather improving the distinction between the conditioned side and the other one.

It has been observed that kp-13 alleviated the conditioned place preference (CPP) induced by MA, causing the subjects to be unable to distinguish between the two compartments. Therefore, it is suggested that the effects of kp-13 in the CPP paradigm are linked to an anti-reward mechanism rather than a memory-enhancing one.

Conclusion

It was found that administering KP-13 prior to MA treatment possessed an anti-rewarding effect, though not able to prevent reinstatement behavior. These findings provide a better understanding of the pharmacological role of KP-13 and introduce innovative pharmacological strategies to address methamphetamine dependence.

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Author Contributions

"Conceptualization, SMST.; methodology, SN., MG., HG., and SMST.; formal analysis, RR., and HG.; writing—original draft preparation, SMST., and RR. All authors have read and agreed to the published version of the manuscript".

Conflict of interest

The authors declare no conflict of interest.

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