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Research article

Intra-accumbal administration of AMN082, a metabotropic glutamate receptor type 7 allosteric agonist, inhibits the acquisition but not the expression of morphine-induced conditioned place preference in rats

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ABSTRACT

The nucleus accumbens (NAc) plays a primary role in opioid reward. The actions of glutamate are mediated by the activation of ionotropic and metabotropic glutamate receptors (mGluRs). Previous documents have shown the extensive distributions of the different types of mGluRs, including mGluR7, in regions that are involved in opioid reward, such as the NAc. In this study, seventy male Wistar rats were used to investigate the role of mGluR7 receptors in the NAc on the acquisition and expression of morphine-induced conditioned place preference (CPP). In Experiment 1, to determine the effect of AMN082, a selective mGluR7 allosteric agonist, on the acquisition of morphine-induced conditioned place preference (CPP), the rats bilaterally received AMN082 (1, 3 and 5 μg/0.5 μL DMSO) during three-day conditioning by morphine (5 mg/kg). In Experiment 2, the rats bilaterally received AMN082 (5 μg/0.5 μL DMSO) 5 min prior to the post-conditioning test to investigate the effect of AMN082 on the expression of morphine-induced CPP. The results showed that the intra-accumbal injection of AMN082 prevents the acquisition of morphine-induced CPP in a dose-dependent manner. However, intra-accumbal injection of AMN082 had no effect on the expression of morphine-induced CPP. The findings propose that the mGluR7 in the NAc inhibits the acquisition of morphine-induced CPP that could be mediated by inhibition of NMDA receptors in the NAc.

1. Introduction

The rewarding effects of drugs play a critical role in the acquisition and expression of drug abuse [9]. Glutamatergic neurotransmission in the mesocorticolimbic pathway has been hypothesized to be involved in the various effects of morphine dependency [1,18]. The actions of glutamate (Glu), the most important excitatory neurotransmitter in the mammalian central nervous system, are mediated by the activation of ionotropic and metabotropic glutamate receptors (mGluRs) [7]. The mGluR group III includes mGluR4, mGluR7, and mGluR8, which are coupled with the Gi/o proteins [14]. The mGluR7 has high density in brain regions involved in reward like the nucleus accumbens (NAc) [10], ventral pallidum (VP) [12], and ventral tegmental area (VTA) [2].This anatomical distribution of mGluR7 suggests that this receptor plays a critical role in drug dependence. The mGluR7 is primarily localized presynaptically and is involved in the regulation of Glu and GABA [10]. Moreover, postsynaptic mGluR7 may be involved in the regulation of NMDA receptor trafficking and function [4].

Previous documents have shown that Glu in the NAc plays a critical role in the opioid reward, including its expression [1], extinction [1,3], and reinstatement [3,22] of morphine-induced CPP. It is thought that NAc facilitates reward-seeking by integrating dopaminergic reinforcement signals with glutamate-encoded environmental stimuli. Stuber et al. presented the electrophysiological evidence for glutamate release by mature dopamine neurons projecting to the NAc shell. These data documented the inimitable ability of NAc-projecting dopamine neurons to synchronously activate both dopamine and glutamate receptors may have crucial implications for the ability to respond to motivational stimuli [21]. Also, it has been shown that dopaminergic neurons nin the VTA that project into the NAc co-release Glu so synchronously activate both dopamine and Glu receptors in the NAc. Based on these, Glu in the NAc may play a crucial role in the ability to respond to motivational stimuli.

The mGluR7 is involved in opioid-related behaviors in the reward system [5,23]; however, the role of intra-accumbal mGluR7 in the acquisition and expression of morphine has not been established. Therefore, the present document considered the effects of mGluR7 agonist within the NAc on the acquisition and expression of morphine-induced

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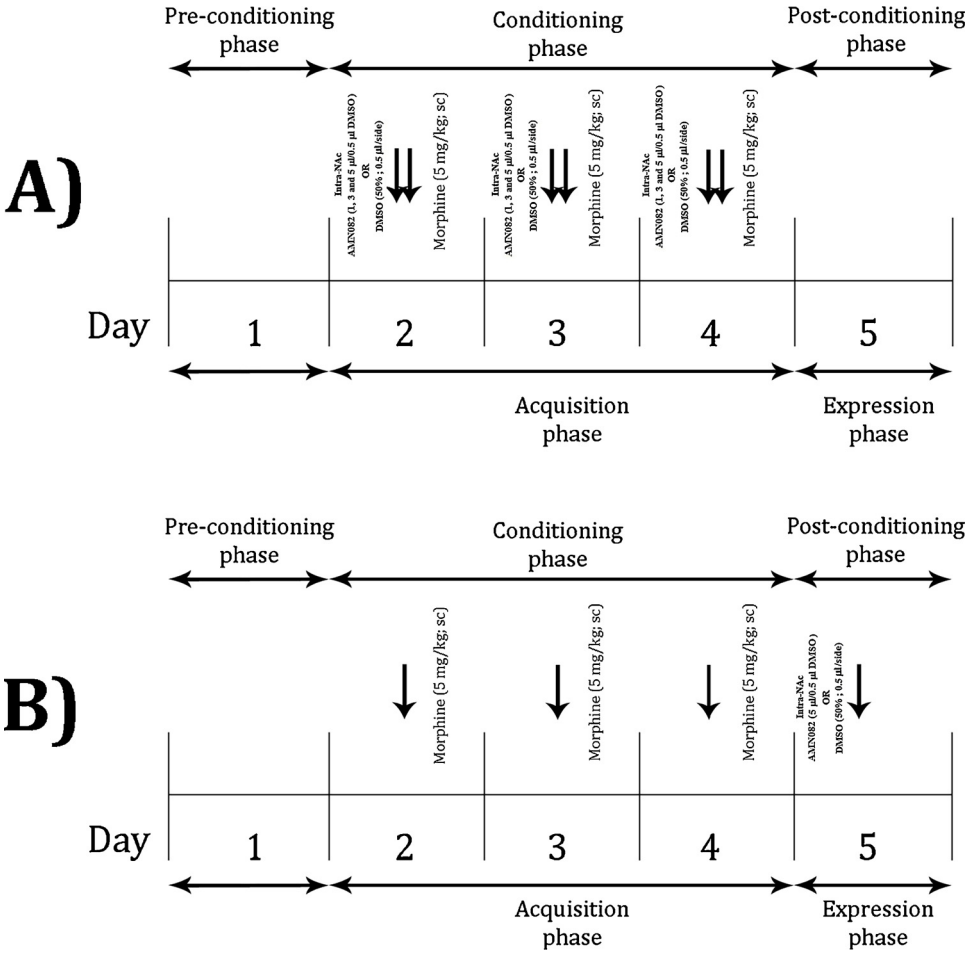

Fig. 1. Graphical scheme to show behavioral protocol ***(A)*** to investigate the role of AMN082 in the acquisition of morphine-induced CPP, the animals received AMN082 (1, 3 and 5 µg/0.5 µL) of these 5 min before the rats received an effective dose of morphine (5 mg/kg), and ***(B)*** to investigate the role of AMN082 in the expression of morphine-induced CPP, the animals received the highest dose AMN082 (5 µg/0.5 µL) 5 min before CPP test.

CPP in rats.

2. Materials and methods

2.1. Animal

Seventy male albino Wistar rats (200–250 g) were obtained from the Pasteur Institute (Tehran, Iran) and used in these experiments. They were maintained on a reverse 12/12 h light/dark cycle and had access to freely available food and water in their home cages (temperature 22 °C ± 2 °C). All experiments were performed in accordance with the guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996) and were approved by the Research and Ethics Committee of Hamadan University of Medical Sciences.

2.2. Drugs

Morphine sulfate (Temad, Iran) was dissolved in normal saline (0.9% NaCl), and AMN082, a selective mGluR7 allosteric agonist, (Abcam, USA) was dissolved in DMSO (50%) [8].

2.3. Surgical preparation and drug administration

The rats were anesthetized with intraperitoneal injection of a mixture containing Ketamine 10% (100 mg/kg) and Xylazine 2% (10 mg/kg). The stereotaxic coordinates for the NAc were as follows: AP = 1.5 mm posterior to bregma, ML = 1.4 mm lateral to midline, and DV = 7.5 mm below the skull surface [15]. The guide cannula was maintained in the place (1 mm above the NAc) by using stainless steel screw tightened to the skull and dental acrylic cement. The rats were maintained and allowed to recover from surgery for 5–7 days. The injection unit was organized from a polyethylene tube (PE-10) connected to a 5-µl Hamilton syringe and a 30-gauge needle with 13 mm length in the tip. The tube was filled with the appropriate drug concentration, and the needle was put in the cannula, and then, 0.5 µL drug solution was injected bilaterally in 60s. The injector cannula was left in place for another the 60 s in order to avoid drug backflow.

2.4. Behavioral test: conditioned place preference apparatus and paradigm

The conditioning apparatus comprised of three compartments; two compartments were similar in size (30 cm* 40 cm* 30 cm) but different in cue and texture, in which each compartment wall was striped horizontally or vertically with different floors texture. The third compartment (null compartment) was just a protruded tunnel which connects the two main compartments. In this apparatus, rats showed no consistent preference for none of the large compartments, which supports our unbiased conditioned place preference (CPP) paradigm [1,18]. The mean time spent in these two large compartments/chambers, and differences scores in different treatment groups at the baseline presented in a table to make sure that there were no differences between animals at the pre-conditioning phase (Electronic supplementary Table 1) According to our previous documents, the condition place preference