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Research report

Influence of cholinesterase inhibitors, donepezil and rivastigmine on the acquisition, expression, and reinstatement of morphine-induced conditioned place preference in rats

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HIGHLIGHTS

- Morphine-induced rewarding effects in conditioned place preference paradigm.
- Morphine effects were more effectively attenuated by rivastigmine than by donepezil.
- Mecamylamine reversed donepezil and rivastigmine effects on morphine reinstatement.
- Nicotinic acetylcholine receptors are involved in morphine seeking after abstinence.
- Donepezil and rivastigmine may be useful in therapy of morphine dependence.

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ABSTRACT

The influence of systemic administration of cholinesterase inhibitors, donepezil and rivastigmine on the acquisition, expression, and reinstatement of morphine-induced conditioned place preference (CPP) was examined in rats. Additionally, this study aimed to compare the effects of donepezil, which selectively inhibits acetylcholinesterase, and rivastigmine, which inhibits both acetylcholinesterase and butyrylcholinesterase on morphine reward. Morphine-induced CPP (unbiased method) was induced by four injections of morphine (5 mg/kg, i.p.). Donepezil (0.5, 1, and 3 mg/kg, i.p.) or rivastigmine (0.03, 0.5, and 1 mg/kg, i.p.) were given 20 min before morphine during conditioning phase and 20 min before the expression or reinstatement of morphine-induced CPP. Our results indicated that both inhibitors of cholinesterase attenuated the acquisition and expression of morphine CPP. The results were more significant after rivastigmine due to a broader inhibitory spectrum of this drug. Moreover, donepezil (1 mg/kg) and rivastigmine (0.5 mg/kg) attenuated the morphine CPP reinstated by priming injection of 5 mg/kg morphine. These properties of both cholinesterase inhibitors were reversed by mecamylamine (3 mg/kg, i.p.), a nicotinic acetylcholine receptor antagonist but not scopolamine (0.5 mg/kg, i.p.), a muscarinic acetylcholine receptor antagonist. All effects of cholinesterase inhibitors were observed at the doses that had no effects on locomotor activity of animals. Our results suggest beneficial role of cholinesterase inhibitors in reduction of morphine reward and morphine-induced seeking behavior. Finally, we found that the efficacy of cholinesterase inhibitors in attenuating reinstatement of morphine CPP provoked by priming injection may be due to stimulation of nicotinic acetylcholine receptors.

1. Introduction

Opioids are not only taken and/or abused to experience alterations in mood or sensory perception but also for medical reasons, such as, e.g. pain relief, diarrhea or cough. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), opioids are still the prominent drugs of abuse, which makes them

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an important area of searching for new treatment strategies [17]. Conventional strategies for treating opioid abuse include cognitive/behavioral therapy, maintenance therapy, and medically managed withdrawal. These strategies deal with the addictive state, but recently many efforts have focused toward development of preventive therapy against addiction. One possible approach is to reduce the rewarding properties of abused drugs, which in case of prescription pharmaceuticals, such as opioid analgesics, is clearly a worthwhile endeavor [8].

Opioid substances are well known for their rewarding properties. Rats will readily self-administer morphine or other opioid drugs [7,15,20,41]. The mesolimbic dopamine system projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and is a key neuronal substrate regulating drug reinforcement [55]. However, the VTA receives cholinergic input from the laterodorsal and pedunculopontine tegmental nuclei that directly and indirectly influence the activity of dopamine neurons [30,36,37,54]. It has been indicated that these cholinergic inputs regulate the rewarding effects of opioids because lesions of cholinergic neurons in the pedunculopontine tegmental nucleus have been shown to disrupt morphine-induced conditioned place preference (CPP), and to reduce heroin self-administration in drug-naive rats [6,42,43]. Furthermore, dopamine neurons and axons' terminals express muscarinic and nicotinic cholinergic receptors, and stimulation of these receptors elicits dopaminergic cells firing, mesolimbic dopamine release, what can promote reinforcement [24,30,39]. It has been found that the activity of dopaminergic neurons in the NAc is also modulated by cholinergic interneurons [9,14]. Drugs, such as morphine [45,46], remifentanil [11] or cocaine [28,50] alter cholinergic transmission in the NAc but these studies differ in the direction of changes or in interpretation of the alterations. In addition, it has been observed that acetylcholine and dopamine act jointly but oppositely on the NAc circuit. Thus, not only immunotoxin-mediated ablation of the NAc cholinergic neurons enhanced the sensitivity to morphine in the CPP, but also potentiated negative reinforcement of morphine withdrawal in the conditioned place aversion [25]. In contrast, pretreatment with the acetylcholinesterase inhibitor donepezil can prevent cocaine- or morphine-induced CPP in mice [25]. Taken together, these findings suggest that cholinergic transmission in the VTA and NAc modulates the mesolimbic dopamine projection and may regulate rewarding effects elicited by addictive drugs [35,57].

Synaptic levels of acetylcholine are regulated by cholinesterases that inactivate acetylcholine. The mammalian brain contains two forms of cholinesterases, acetylcholinesterase and butyrylcholinesterase [4,19]. Although the physiologic importance of butyrylcholinesterase is unclear, it contributes to degradation of acetylcholine [10]. Treatment with acetylcholinesterase inhibitors increases acetylcholine levels. Donepezil is a centrally acting, reversible cholinesterase inhibitor that is approved by the U.S. Food and Drug Administration (FDA) for treatment of Alzheimer's disease, and is relatively selective for inhibition of acetylcholinesterase but no other cholinesterases [16,32]. Rivastigmine is a highly potent agent that blocks both acetylcholinesterase and butyrylcholinesterase [40].

Here, we investigated an influence of cholinesterase inhibitors, donepezil and rivastigmine on the acquisition, expression, and reinstatement of morphine-induced CPP in rats. In addition, we compared the effects of donepezil, which selectively inhibits acetylcholinesterase, and rivastigmine, which inhibits both acetylcholinesterase and butyrylcholinesterase, on this effect of morphine. Involvement of nicotinic acetylcholine receptors or muscarinic acetylcholine receptors in the effects of cholinesterase inhibitors on the reinstatement of morphine-induced CPP was also investigated.

2. Materials and methods

2.1. Animals

Male Wistar rats (HZL, Warsaw, Poland; weighing 200–250 g) were housed for at least 1 week before the experiment. The animals were maintained under the standard laboratory conditions (22 °C, 12-h light:12-h dark cycle) and grouped ten per cage. Food (Agropol, Motycz, Poland) and water were available *ad libitum* in home cages. The experiments were performed between 9:00 am and 5:00 pm. All experimental procedures and housing conditions were approved by the Local Ethics Committee and carried out according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, the European Community Council Directive for Care and Use of Laboratory Animals.

2.2. Drugs

In this study, the drugs used were as follows: morphine hydrochloride (Polfa, Kutno, Poland), donepezil hydrochloride (Sigma–Aldrich, St. Louis, MO), rivastigmine (Sigma–Aldrich, St. Louis, MO), scopolamine hydrochloride (Sigma–Aldrich, St. Louis, MO,) and mecamylamine hydrochloride (Abcam Biochemicals, Bristol, UK). All drugs were dissolved in sterile saline and injected intraperitoneally (i.p.) in a volume of 2 ml/kg. Control groups received saline injections in the same volume and by the same route.

2.3. Apparatus

The CPP experiments were performed in eight identical rectangular wooden boxes. The boxes were divided into two large compartments (size 65 cm × 35 cm × 30 cm) and were distinguished by color (white vs. black) and floor texture (smooth vs. striped) connected by a central gray square compartment (dimensions 10 cm × 10 cm × 30 cm). During habituation, post-conditioning test, extinction, and reinstatement the rats were free to move between the two compartments through a square hole. During conditioning, this opening was closed by insertion of a wooden diaphragm. Time spent on each side was measured with the video-tracking program (Karnet, Lublin, Poland).

2.4. CPP procedures

The CPP procedure consisted of five different phases: habituation (2 days), conditioning (8 days), expression (post-conditioning test, 1 day), extinction (5 days) and reinstatement test (1 day). The effects of donepezil and rivastigmine were studied on conditioning, expression, and reinstatement of morphine-induced CPP.

2.5. Habituation

Habituation (days 1–2): each day the rats were placed in the central gray square compartment of the CPP apparatus and allowed to freely explore the compartments for 15 min in order to become habituated. On the second day (i.e. the pre-conditioning test), the time spent in each compartment was recorded with a computer. No injections were given during these sessions. Rats that spent 150 s more in one large compartment than in the other, were considered to have compartment bias and were excluded from subsequent testing. Approximately 10% of the rats were excluded based on these criteria.