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Opposite effects of MK-801 on the expression of food and morphine-induced conditioned place preference in rats

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Abstract

Behavioural studies have provided strong evidence for common substrates in the rewards of natural and addictive substances, but it is still unclear whether there is a common glutamatergic NMDA receptor mechanism involved in the processing of reward for both. The present study was designed to investigate the effects of MK-801 (0.1 mg/kg) on the expression of place preference conditioned with food and morphine (5.0 mg/kg) in rats. The data indicates that MK-801 potentiates the expression of food-induced conditioned place preference (CPP) but retards that of morphine CPP. It also demonstrates that the opposite effects of MK-801 on food and morphine CPP expression were caused neither by hyperactivity nor by the impairment of memory retrieval. These results suggest that MK-801 enhances food craving and inhibits morphine craving in rats, and that the roles of glutamatergic NMDA receptor mechanisms in the reward processing of natural reinforcers and addictive drugs may be dissociable.

Keywords

MK-801, morphine, food, expression of CPP, craving

Introduction

Most addictive drugs, regardless of their different chemical structures, share common behavioural features, e.g., Conditioned Place Preference (CPP) (Tzschentke, 1998; Bardo and Bevins, 2000), psychomotor activity (Wise and Bozarth, 1987), and self-administration (Gardner, 2000). It is suggested that some addictive substances might exert their action via common neural substrates, or even share, in part, common neural substrates with natural reward, since the brain evolved to respond, not to addictive drugs, but to natural rewards (Wise, 1997; Bardo, 1998; Di Chiara *et al.*, 1998; Schroeder *et al.*, 2001; Zheng *et al.*, 2004). Although the roles of dopamine and opioid in the behavioural consequences of natural rewards and addictive substances have been well established (Kelley *et al.*, 2002; Cannon and Bseikri, 2004), researches on other important neurochemical systems associated with reward, e.g., the glutamatergic NMDA receptor system, are still relatively sparse. In particular, whether common glutamatergic NMDA receptor mechanisms are involved in the reward process of natural reinforcers and addictive substances needs to be clarified.

Glutamatergic receptors, especially NMDA receptors, contribute to mediating the behavioural and neurochemical effects of addictive drugs (Bisaga and Popik, 2000; Spanagel, 2003). For example, the noncompetitive NMDA receptor antagonist MK-801 prevents the development of behavioural sensitization (Jeziorski *et al.*, 1994), inhibits the induction and expression of conditioned place preference (Tzschentke and Schmidt, 1997; Scheggi *et al.*, 2002), and impairs the acquisition of intravenous self-administration (Schenk *et al.*, 1993; Shoaib *et al.*, 1995). Paradoxically, an increase in the reward value of addictive drugs by MK-801 was also reported (Ranaldi *et al.*, 1996; Tzschentke and Schmidt, 1997). In contrast to the wealth of evidence concerning the role of MK-801 with addictive substances, fewer reports target the

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involvement of MK-801 in natural rewards. Several studies showed that MK-801 increased food intake in rats (Burns and Ritter, 1997; Treece *et al.*, 1998; Covasa *et al.*, 2000, 2003), but reduced the breaking points in responding for food in the PR procedure (Buffalo *et al.*, 1994). MK-801 prevented the development of CPP induced by novelty reward in rats (Bevins and Bardo, 1999). Thus, the cross talk of MK-801 (and NMDA glutamatergic synapses) in the reward proccesing of natural and addictive substances needs to be further addressed.

The CPP paradigm has been used extensively to investigate the anatomical and neurochemical substrates of natural reward and drug addiction (Tzschentke, 1998; Bardo and Bevins, 2000), and the time spent in the drug-associated compartment during the expression phase are thought to be an indirect measure of drug craving (Markou *et al.*, 1993; Bardo and Bevins, 2000), which can trigger relapse in abstinent individuals, and is closely related to drug-seeking behaviours. In the present study, we examined the effects of MK-801 on the expression of food and morphine-induced conditioned place preferences. The specific objectives of the present experiment were: (1) to determine whether a common glutamatergic mechanism is involved in the processing of natural rewards and addictive drugs; (2) to find out whether the increases in food intake induced by MK-801 is caused by enhancement of food craving; (3) to provide more evidence about the role of the glutamatergic system in natural rewards.

Materials and methods

Animals and housing

Forty-eight male Sprague–Dawley rats (Charles River laboratories of Beijing, China), weighing 240–280 g at the beginning of the experiment, were housed individually in stainless metal mesh cages (25 cm × 22.5 cm × 30 cm) in a controlled temperature (20–24 °C) colony room with a 12:12 h light–dark (light on at 08:00) cycle. Food and water were available in the home cage ad libitum during adaptation periods. Rats were then food restricted to reduce their body weight to 80–85% of their beginning weight. All experiments were conducted in the light phase (08:00–18:00). Rats were gently handled three times before the formal experiment began. The experimental protocol and procedures were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Apparatus

The conditioned place preference test was conducted in four identical three-compartment rectangular plastic chambers, measuring 80 cm × 40 cm × 50 cm (l × w × h), with two equal size end compartments (33 cm × 40 cm × 50 cm) separated by a black central area (14 cm × 40 cm × 50 cm), a 10 cm × 10 cm opening was centred at a lower part of the board between the central area and end compartment. The two end compartments had distinct visual and tactile cues, one with red stripe walls and a smooth floor, and the other with black walls and a grid floor. A video camera was suspended on the ceiling to track the rats in four chambers, and the location of each rat recorded by the camera was input into the computer system to analyse the time spent in each chamber.

Drugs

Morphine hydrochloride (Qinghai pharmaceutical, China), MK-801 (Sigma, St Louis, USA), and physiological saline (NaCl 0.9%) were used in the experiments. Drugs were diluted in physiological saline, and morphine was in the dose of 5.0 mg/kg (s.c.), MK-801 was in the dose of 0.1 mg/kg (i.p.), which is optimal to increase food intake (Burns and Ritter, 1998). The injection volume for each drug was 1.0 ml/kg.

Procedures

The CPP procedures were based on a previous study with minor modifications (Popik and Danysz, 1997). The procedures consisted of four phases: adaptation, pretest, conditioning and posttest. On day 1 (adaptation), the rats were given access to the apparatus for 30 min to reduce the novelty and stress; during the pretest sessions (Day 2 and Day 3) the rats were placed individually into the central compartment and allowed to explore the apparatus freely, the time spent and distance travelled by the animal in each compartment was recorded for 15 min (900 s). The average time of these 2 days was used as the initial preference score; the pretest data indicated that the rats showed no preference for any compartment. The subsequent conditioning sessions lasted for 6 successive days, on days 4, 6 and 8, during food training, half of the rats were confined to the smooth floor compartment and the others were placed into the grid floor compartment for 60 min with the opening closed and with 14 g of food pellets scattered on both sides. During morphine training, half of the rats received a morphine (5.0 mg/kg, s.c.) injection prior to placement in the smooth side and the others had morphine paired on the grid side; for the control group, all the rats received saline injections on both sides. On day 5, 7 and 9, all the rats in the food group received no food supply in the reverse compartment, and the rats in the morphine and control group were injected with saline in the reverse compartment. Posttest began on day 10, 15 min before being placed into the central compartment, half the rats in each group received an MK-801 (0.1 mg/kg) injection and the other ones received saline, the time spent and distance travelled by the rats were recorded during the session, which lasted 15 min (900 s).

Data analysis

The time spent in the associated compartments of the apparatus before, and after, conditioning was analysed by a 2 × 3 × 2 three-way, one repeated measures ANOVA analysis (data were expressed as mean ± SEM), with 'test' (preconditioning, test) as a within-subject factor, 'reinforcement' (saline, food, morphine) and 'treatment' (saline, MK-801) as between-subject factors. A 2 × 3 two-way ANOVA was used to examine the changes in distance travelled after different treatments (data were expressed as mean ± SEM), with 'reinforcement' (saline, food, morphine) and

'treatment' (saline, MK-801) as between-subject factors. Post-hoc tests (LSD) were applied to test between-group differences whenever indicated by ANOVA results. One data point was missing in the food group because of track system error.

Results

Effects of MK-801 on the expression of food CPP

Effects of MK-801 on the expression of food CPP are summarized in Fig. 1. Three-way repeated measures ANOVA revealed a significant 'test' × 'reinforcement' × 'treatment' interaction [$F(2,42) = 5.12$, $p < 0.01$]. During the drug-free (saline) posttest (left panel of Fig. 1), there was a significant 'test' × 'reinforcement' interaction [$F(2,21) = 14.02$, $p < 0.01$], and appreciable differences among groups after conditioning [$F(2,21) = 16.94$, $p < 0.01$]. The rats significantly preferred the food-associated compartment [$t(21) = 2.049$, $p < 0.05$]. These results indicated an obvious food CPP. To assess the effect of MK-801 on the expression of the food CPP, the rats were injected with MK-801 (0.1 mg/kg) 15 min before the posttest. During the MK-801 posttest (right panel of Fig. 1), a notable interaction between 'reinforcement' × 'test' [$F(2,20) = 3.58$, $p < 0.05$] and a significant difference among the groups [$F(2,20) = 3.92$, $p < 0.05$] were observed after MK-801 injection, the rats also spent more time in the food-associated side [$t(21) = 2.333$, $p < 0.05$]. These data suggested a significant food CPP was still preserved after MK-801 injection, and moreover, MK-801 potentiated the expression of the food-induced CPP [$F(1,43) = 3.39$, $p = 0.07$], which was further confirmed by a significant 'treatment' × 'test' interaction after conditioning [$F(2,41) = 7.74$, $p < 0.01$] (left panel of Fig. 3).

Effects of MK-801 on the expression of morphine CPP

Effects of MK-801 on the expression of morphine-induced CPP are summarized in Fig. 2. During the drug-free (saline) posttest (left panel of Fig. 2), a significant 'test' × 'reinforcement' interaction [$F(2,21) = 14.02$, $p < 0.01$] and a strong difference among groups after conditioning [$F(2,21) = 16.94$, $p < 0.01$] were observed, and the post hoc analyses demonstrated that the rats significantly preferred the morphine-associated compartment [$t(21) = 5.742$, $p < 0.01$]. These data indicated an obvious morphine CPP. However, during the MK-801 posttest (right panel of Fig. 2), the rats showed no preference for the morphine-paired compartment [$t(21) = 0.753$, $p > 0.05$], which was confirmed by a significant 'treatment' and 'test' interaction after conditioning in the morphine group [$F(2,41) = 7.74$, $p < 0.01$] (left panel of Fig. 3). These results suggested that MK-801 blocked completely the expression of the morphine CPP.

Effects of MK-801 on locomotor activity of the rats in food and morphine groups

Fig. 4 depicts the effects of MK-801 on locomotor activity of the rats in both groups. During the preconditioning test there was no difference in the distance travelled by the rats in the apparatus [$F(5,42) = 0.103$, $p > 0.05$], however during the posttest (Fig. 4), a significant main effect of 'treatment' [$F(1,42) = 30.68$, $p < 0.01$]

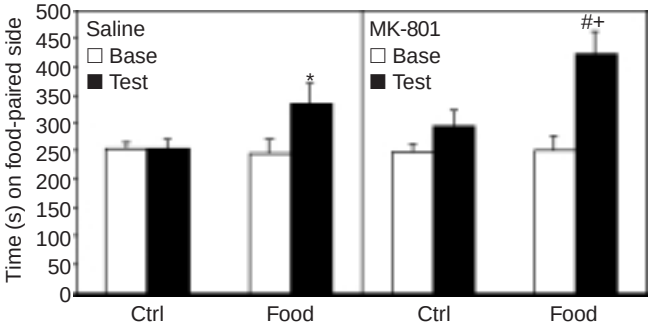

Figure 1 Effect of MK-801 on the expression of food CPP in rats. Data presented are time (mean ± SEM, seconds) spent in the food-associated compartment before (open bars) and after (filled bars) six conditioning sessions. Left panel depicts the data of rats receiving saline during the posttest after conditioning, right panel shows the data of animals administrated MK-801 (0.1 mg/kg) 15 min prior to placement in the CPP expression test. In each panel, the first pair of bars shows the data of animals injected with saline in both sides, and the second pair of bars shows the data of rats receiving vehicle in one side and food in the other side. Each bar represents 8 rats per group. Symbols: * $p < 0.05$, # $p < 0.01$ compared with the control group, respectively, + $p = 0.07$, compared with food group in saline test. See text for details.

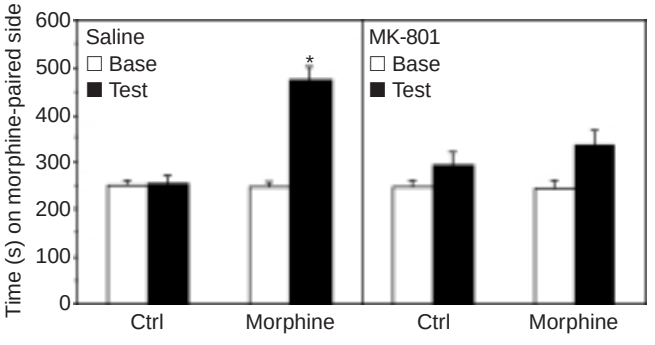

Figure 2 Effect of MK-801 on the expression of CPP induced by morphine in rats. Data presented are time (mean ± SEM, seconds) spent in the morphine-associated compartment before (open bars) and after (filled bars) six conditioning sessions. Left panel depicts the data of rats receiving saline during the posttest after conditioning; right panel shows the data of animals injected with MK-801 (0.1 mg/kg) 15 min prior to placement in the apparatus in the CPP expression test. In each panel, the first pair of bars shows the data of animals injected with saline in both compartments, and the second pair of bars shows the data of rats receiving vehicle in one side and morphine in the other side. Each bar represents 8 rats per group. Symbols: * $p < 0.01$, compared with the control group. See text for details.

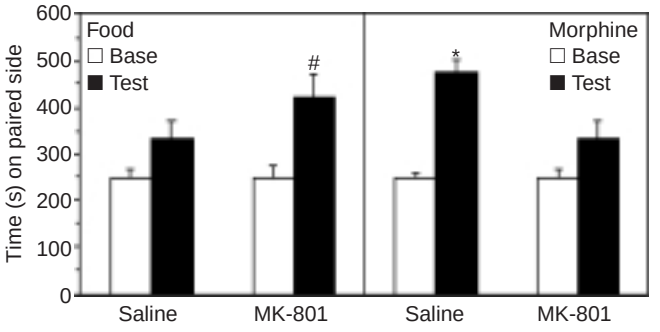

Figure 3 Opposite effects of MK-801 on the expression of food and morphine CPP in rats. Data presented are time (mean ± SEM, seconds) spent in the food and morphine-associated compartments before (open bars) and after (filled bars) six conditioning sessions. Left panel depicts the data of the rats in morphine group during the saline and MK-801 posttest after conditioning, right panel shows the data of animals in the food group during the saline and MK-801 CPP expression test. In each panel, the first pair of bars shows the data of animals injected with saline in the posttest, and the second pair of bars shows the data of rats receiving MK-801 during the posttest. Each bar represents 8 rats per group. Symbols: * $p < 0.01$, # $p = 0.07$ compared with the saline-treated rats, respectively. See text for details.

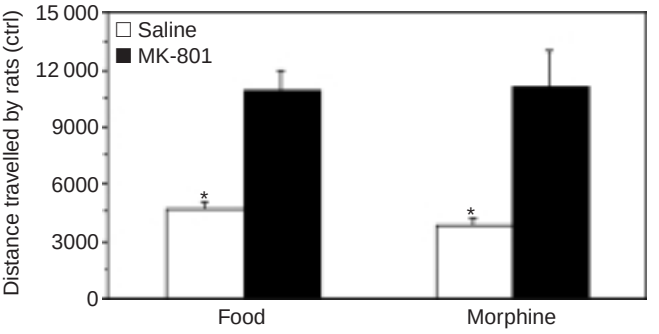

Figure 4 Effects of MK-801 on the locomotor activity of the rats. Data presented are distance (mean ± SEM, cm) travelled by rats in the apparatus during the posttest injected with saline (open bars) and MK-801 (filled bars) 15 min prior to placement into the apparatus. The first pairs of bars depict the data of the rats receiving vehicle in one side and food in the other side, the second pairs of bars summarize the data of rats given morphine in one compartment and saline in the other. Each bar represents 8 rats per group. Symbols: * $p < 0.05$, compared with the control group. See text for details.

was observed, the results indicate that the rats treated with MK-801 increased their locomotor activity significantly. But no significant 'reinforcement' × 'treatment' interaction [$F(2,41) = 2.62$, $p > 0.05$] was observed, demonstrating that there was no difference in distance travelled by the rats between the food and morphine groups after MK-801 injection [$t(21) = 0.103$, $p > 0.05$] (Fig. 4).

Discussions

The main findings of the present study were as follows: first, systemic injection with MK-801 potentiated the expression of food-induced CPP (Fig. 1); and second, MK-801 blocked the expression of morphine CPP (Fig. 2). This latter outcome is consistent with previous findings (Popik and Danysz, 1997; Tzschentke and Schmidt, 1997; Popik *et al.*, 2003). Therefore, the present results suggest that the role of glutamatergic NMDA receptor mechanisms in the processing of reward properties of natural rewards and addictive drugs may be dissociable. This conclusion is further supported by other studies showing that memantine and ACPC (NMDA antagonists) inhibit the expression of morphine-induced CPPs but have no effect on the expression of food-induced CPPs (Popik and Danysz, 1997; Papp *et al.*, 2002; Popik *et al.*, 2003). In particular, the results in the current experiments extend previous findings by demonstrating that the NMDA receptor antagonist MK-801 enhances the expression of food-induced CPP.

The CPP paradigm has been used extensively to investigate the anatomical and neurochemical substrates of natural reward and drug addiction (Tzschentke, 1998; Bardo and Bevins, 2000). Usually, the expression of CPP has been suggested as one of the animal models for drug craving (Markou *et al.*, 1993; Cervo and Samanin, 1995; Bardo and Bevins, 2000; Shi *et al.*, 2003), the magnitude of expression of CPP depending on both reward or craving and memory retrieval processes (White and Carr, 1985). Therefore, before drawing the obvious inference that MK-801 enhanced the craving for food and inhibited the morphine craving, we should consider some alternative explanations.

First, MK-801 is known to impair spatial and nonspatial learning in rats (Ahlander *et al.*, 1999; Riedel *et al.*, 2003; Roberts and Shapiro, 2002). Therefore, the blockade of expression of the morphine CPP could arise if MK-801 impaired the retrieval of memory. But, in most of these studies, the disruptive effects of MK-801 on learning could not be disassociated from sensorimotor disturbances (Ahlander *et al.*, 1999). In fact, after considering the sensorimotor disturbances caused by MK-801, the impairment of learning almost vanished (Cain *et al.*, 1996; Saucier *et al.*, 1996; Keith and Galizio, 1997). Moreover, other lines of studies support the idea that MK-801 does not impair the retrieval process (Heale and Harley, 1990; Venable and Kelly, 1990; Uekita and Okaichi, 2005). Most importantly, if there was any effect of MK-801 on memory retrieval, it seems impossible that MK-801 would just impair the retrieval of morphine-related memory, but spare the retrieval of food-related memory. Therefore, impairment of memory retrieval can be excluded as an explanation of the above dissociated role of the drug MK-801.

Second, the present results could not be attributed to motor disturbance elicited by MK-801, although behavioural hyperactivity and sensorimotor disturbances have been observed after treatment with it at the dose range of 0.05 to 0.1 mg/kg or more (Lehmann

and Geyer, 1991; Ögren and Goldstein, 1994; Irifune *et al.*, 1995). Sensorimotor disturbance would cause rats to be unable to discriminate the different context cues in the apparatus, and therefore, they would spend their time equally among the compartments, which would lead to the abolishment of CPP. As expected, the rats, both in the food and morphine groups in the present experiment, showed hyperactivity after injection with MK-801 (Fig. 3); but there was no difference of locomotor activity between them. Hence, if behavioural hyperactivity interrupted the expression of CPP, it would not differentially interfere with the expression of place preference conditioned with food and morphine. Thus, the hypothesis that hyperactivity after treatment with MK-801 caused the dissociation of expression of place preference conditioned with food and morphine appears untenable.

From above analysis of alternative explanations, we infer that the most tenable account of the results in the current experiment is that MK-801 increased the craving for food, but inhibited morphine craving, which is in accordance with previous studies that acamprosate (an NMDA antagonist) can prevent craving for morphine (Spanagel *et al.*, 1998; Kratzer *et al.*, 2003). These results suggest that NMDA antagonists may be promising anti-craving drugs in the treatment of opiate addiction. In the case of MK-801, the enhancement of food craving is a new finding. Although the increase of food intake by MK-801 is well established (Burns and Ritter, 1997; Treece *et al.*, 1998; Covasa *et al.*, 2000, 2003), the potential mechanism is not clear. Most studies demonstrate that MK-801 increases food intake by delaying the satiation signals transmission from the periphery to the central nervous system (Burns and Ritter, 1998; Covasa *et al.*, 2000, 2003). We present here new evidence that MK-801 could increase food intake by enhancing food craving.

The finding, MK-801 increases food craving, appears to contradict with the previous result that MK-801 reduced motivation in the PR procedure (Buffalo *et al.*, 1994). However, what is measured in the CPP and PR paradigms is different. In PR procedure, motivation (indexed by breaking point) consisted of the craving prior to the food delivery and the reinforcing consequences of food after delivery; if MK-801 disrupts the reinforcement of food it will reduce the food motivation. Furthermore, MK-801-induced hyperactivity may compete with pressing the lever and eating (Wellman *et al.*, 2005), which also can decrease the breaking point. The differential effect on food motivation and craving is not special to MK-801, naloxone has a similar effect. Naloxone decreases the breaking point in PR procedure (Glass *et al.*, 1999), but has no effect on speed of run in runway paradigm or number of presses on the lever to get the first pellet (Kirkham *et al.*, 1986; Rudski *et al.*, 1994). Therefore, it seems reasonable that MK-801 potentiates food craving but reduces the breaking points in PR procedure.

Neural substrates involved in the natural rewards and addictive substances have been the targets of a growing body of pre-clinical researches. Collectively, some evidence supports that drug of abuse and natural reinforcers mostly recruit the common biological substrates, the possibilities of obtaining such dissociation remains an open issue. However, as found in the present experiment, a dissociation between natural and addictive reinforcement has been demonstrated in the electrophysiological studies. Selective neuronal subpopulations in the nucleus accumbens were found to be differentially activitated by natural rewards (water and food) and cocaine reinforcement (Carelli *et al.*, 2000, 2002). And recently, Baunez *et al*. (2005) established that the rats enhanced food motivation but decreased cocaine motivation after the lesions of subthalamic nucleus. These results suggest that different parallel microcircuits mediate response for natural and addictive reward. Furthermore, there are glutamatergic connections between subthalamic nucleus (STN) and prefrontal cortex (Afasharpour, 1985), NMDA receptors are found in the STN (Ball *et al.*, 1994). And the behavioural effects induced by NMDA receptor blockade in the subthalamic nucleus were similar to those observed after a neurotoxic lesion of the STN (Baunez and Robbins, 1997, 1999). Therefore, NMDA receptors in subthalamic nucleus may exert an opposite effect on natural and addictive reward. And it needs to be tested further.

In summary, the results in the present study indicate that MK-801 increased food craving, but inhibited the morphine craving in the CPP paradigm. It is suggested that the role of glutamatergic NMDA receptor mechanisms in the reward processing of natural rewards and addictive drugs can be dissociated, and that NMDA receptor antagonists might be potential anti-craving drugs in the treatment of opiate addiction.

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