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Research Report

Acute systemic blockade of D2 receptors does not accelerate the extinction of cocaine-associated place preference

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ABSTRACT

Facilitation of extinction can be used as a therapeutic tool in treatment of both post-traumatic stress disorder and drug addiction. The present study examined whether the blockade of D2 receptors before each extinction trial would accelerate the extinction of cocaine-induced place preference. Male Wistar rats were initially conditioned and tested for a cocaine-associated place-preference (20 mg/kg). On the following day after the initial test, the animals were submitted to extinction training. This training consisted of daily sessions in which the subjects were alternatively confined during 30 min in the saline and cocaine-associated environment. However, 30 min before each extinction trial the animals received a systemic injection of D2 antagonist sulpiride. While one group was treated with a dose of 50 mg/kg (ip), the other group was treated with a dose of 100 mg/kg. An additional control group received injections of saline during extinction trials. Twenty-four hours after the last extinction trial, the animals were tested again for their preferences to cocaine and saline associated environments. Since one round of extinction trial was not sufficient to produce extinction of cocaine associated place preference, the animals were submitted to a second cycle of extinction trials and test. The systemic administration of the two doses of sulpiride (50 and 100 mg/kg) 30 min before each conditioning did not enhance the extinction of cocaine-associated place preference. This finding suggests that the D2 receptors are not involved in a acute protocol of extinction of cocaine-induced place preference.

1. Introduction

The conditioned place preference is an animal model, dependent upon learning and memory, used to evaluate the reinforcing properties of drugs of abuse. This model is a kind of Pavlovian conditioning in which the animals learn to associate environmental cues (conditioned stimulus) with the rewarding properties of the drug (unconditioned stimulus). After several alternating pairings between a compartment and drug treatment, the animals prefer, in the test day and in a free drug-state, to spend more time in drug-paired environment. The drug–environment association is subject to attenuation after repeated presentations of the conditioned stimulus (environment) in the absence of the unconditioned stimulus (injection of a drug of abuse). This reduction of conditioned response is due to the consolidation and expression of an association between the environment and the affective state produced by an extinction

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trials treatment (for review, see Bardo and Bevins, 2000; Tzschentke, 2007).

Extinction is considered a new learning in which conditioned response to a conditioned stimulus gradually decreases when the unconditioned stimulus is omitted. However, the original trace of memory is still present, since extinguished responses to a conditioned stimulus can spontaneously recover with the passage of time (Quirk and Mueller, 2008). Although extinction did not erase definitely the original trace of memory, it can be used as a therapeutic tool for treatment of both post-traumatic stress disorder (Milad et al., 2006) and in relapse of addictive behavior (Havermans and Jansen, 2003). Importantly, previous studies (Botreau et al., 2006; Schroeder and Packard, 2004; Parker et al., 2004) have shown that it is possible accelerate the extinction of both cocaine- and amphetamine-associated place preference using, respectively, a partial NMDA glutamatergic agonist (d-cycloserine), a cholinergic agonist (oxotremorine) and two cannabinoids agonists (Δ^9-tetrahydrocannabinol and cannabidiol).

Dopaminergic neurotransmission has an important role in the acquisition and consolidation of both aversive and appetitive learning (Pezze and Feldon, 2004; Mirenowicz and Schultz; 1994; Wise, 2004; Cheng and Feenstra, 2006). Moreover, dopaminergic neurotransmission is also involved in the extinction of aversive tasks, since Fernandez Espejo (2003) showed that lesion of dopaminergic terminals of pre-frontal cortex impaired long-term extinction of contextual fear conditioning. Other studies have found that it is possible to facilitate the extinction of both aversive and appetitive tasks using D2 antagonists. For instance, in the auditory fear conditioning, the systemic blockade of D2-receptors accelerated the extinction in a subsequent test (Ponnusamy et al., 2005). In the same study, quinpirole, a D2-agonist, partially blocked the extinction of this memory. In relation to appetitive tasks, the D2 antagonism (pimozide), in a way similar to extinction, devalued stimuli associated with sucrose taking under a heterogeneous chain schedule, reducing seeking responses to reinforcer (Johnston et al., 2001).

Since dopamine is involved in both acquisition and consolidation of drug-related memories and is required for habit learning (Everitt and Robbins, 2006; Yin and Knowlton, 2006; Volkow et al., 2006) related to compulsive use of drugs of abuse, one could hypothesize that this neurotransmitter is also involved in the extinction of association between environmental cues and reinforcing properties of cocaine. Therefore, if dopamine has a role in the extinction of drug–environment association, one possible strategy that could be utilized in the treatment of cocaine addiction would be the use of dopaminergic antagonists in order to facilitate extinction. Since previous study (Kosten et al., 1996) has found that a short-term treatment of haloperidol (antagonist D2), during conditioning, attenuated the expression of cocaine-associated place preference, the aim of this study was to investigate the possible effects of the systemic administration of sulpiride, a D2 antagonist and an atypical anti-psychotic drug, on extinction of a cocaine-induced place preference. Our working hypothesis is that the blockade of D2 receptors could accelerate the extinction of cocaine-associated place preference.

2. Results

The control group of animals treated with saline in both compartments during conditioning was not included in this work, since early experiments from our laboratory have shown that these animals treated with saline during conditioning still preferred the initial compartment chosen in habituation in the testing phase.

Fig. 1 shows the mean time ± S.E.M. spent in the cocaine-paired compartment during the habituation (before conditioning) and test phase, following conditioning. This figure showed that the 25 animals conditioned with cocaine learned to associate the environment with the reinforcing properties of cocaine. A *t*-paired test showed that animals spent significantly more time in cocaine-paired compartment during testing phase when compared to habituation phase ($p<0.001$).

Fig. 2 shows the increase in time spent in cocaine-paired compartment on testing session when compared to habituation session. A two-way ANOVA, with treatment (saline, sulpiride 50 and sulpiride 100) and increase in time spent in cocaine-paired compartment as factors, revealed a significant effect of the difference in the time spent in cocaine-paired compartment ($F_{(2,\ 44)}=4.01$; $p=0.02$). The Newman–Keuls *post-hoc* test showed that the increase in time spent in the cocaine-paired compartment in test 3 was significantly lesser when compared to test 1 ($p=0.01$). This result showed that animals really extinguished the association between the environmental cues and the reinforcing properties of cocaine. However, no statistical difference was found among groups ($F_{(2,22)}=0.\ 178$; $p=0.83$) and no interaction was found between groups and phases ($F_{(4,44)}=0{,}20$; $p=0{,}93$).

Regarding locomotor activity, the mean and ± S.E.M. of number of times that animals crossed one compartment to other for saline group were 12.88 ± 0.76; 14.88 ± 2.01, 10.13 ± 1.36 and 8.87 ± 2.23 during, respectively, habituation, test 1, test 2 and test 3. For the group injected with sulpiride 50 mg/kg, the mean time ± S.E.M. of number of times that animals crossed one compartment to other were 13.63 ± 1.91, 16.38 ± 1.77, 13.25 ± 0.94 and 10.13 ± 1.65 during, respectively, habituation, test 1, test 2 and test 3. Finally, for the group sulpiride 100 mg/kg, the number of times that animals crossed one

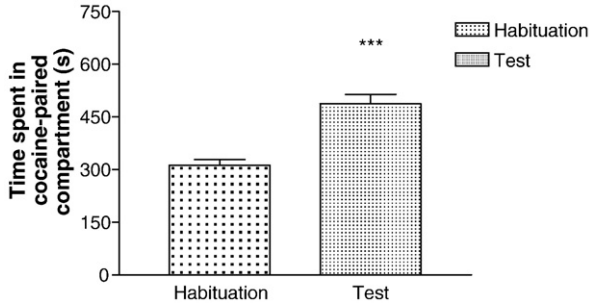

Fig. 1 – The mean time ± S.E.M. spent in cocaine-paired compartment during the habituation and test 1 of animals that received an intraperitoneal injection of cocaine (20.0 mg/kg). *($p<0.001$, $n=25$).**