Pharmacological Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Enduring effects of tacrine on cocaine-reinforced behavior: Analysis by conditioned-place preference, temporal separation from drug reward, and reinstatement

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ARTICLE INFO

Article history:
Received 22 December 2014
Received in revised form 7 April 2015
Accepted 7 April 2015
Available online xxx

Keywords:
Acetylcholine
Acetylcholinesterase inhibitors
Cocaine
Liver toxicity
Self-administration
Reinforcement (psychology)
Reward
Tacrine

ABSTRACT

Previous work by our laboratory has shown that tacrine can produce long-lasting reductions in cocaine-reinforced behavior, when administered to rats as daily intravenous infusions over four days. Tacrine causes dose-related liver toxicity in different species, and its manufacture for human use was recently discontinued. This study was conducted to further characterize its actions on cocaine reward. Cocaine-experienced animals that had no contact with drug over one week resumed self-administration at levels similar to their initial baseline. When tacrine was administered over four days which were preceded and followed by washout periods to allow elimination of cocaine and tacrine respectively, subsequent cocaine self-administration was attenuated by more than one-half. Tacrine administered at 10 mg/kg-day as a chronic infusion by osmotic pump did not modify cocaine-induced increases in locomotor activity or conditioned-place preference. In rats that exhibited persistent attenuation of cocaine-self-administration after receiving tacrine, cocaine-induced reinstatement was also attenuated. No changes in plasma measures of renal or hepatic function were observed in rats receiving tacrine. In conclusion, pretreatment with tacrine can decrease cocaine-motivated behavior measured by self-administration or reinstatement, but not conditioned-place preference. Reductions in cocaine self-administration following pretreatment with tacrine do not require direct interaction with cocaine and are not secondary to either liver or kidney toxicity.

1. Introduction

Behaviors motivated by psychostimulant reinforcement are known for their persistence over time [1,2]. Within the first three months of initiating treatment for cocaine dependence, most patients will relapse to drug abuse [3]. This persistence is paralleled by observations from animal models. Rats typically either continue a stable pattern of drug intake, or increase drug taking during chronic self-administration of either cocaine [4] or amphetamine [5]. In the absence of drug treatments that interfere with stimulant reinforcement, animals in our laboratory typically maintain a consistent pattern of daily cocaine self-administration. Given the robust persistence psychostimulant-motivated behavior over time, alternative treatment approaches are needed.

Poor outcomes in substance abuse and other mental health disorders often stem from lack of compliance with medications prescribed as treatment. Such individuals often lack insight for the negative consequences of addictive behaviors [6], and do not see the need to take prescribed medications. Recent clinical trials indicate that approximately one-third of medication doses being used to treatment psychostimulant abuse are not taken [7]. This rate is almost certainly much higher in real-world patients who are not enrolled in a clinical trial, and are not receiving frequent coaching and monitoring. Despite many drug trials, no medications are either currently approved by the Food and Drug Administration or generally accepted as a means of preventing relapse in patients who abuse cocaine or other psychostimulants.

Although cholinesterase inhibitors have not been successful in modifying cocaine abuse in humans, only limited dose levels have been administered in laboratory [8] or outpatient based studies [9]. Administration of cholinesterase inhibitors in rats can produce two

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http://dx.doi.org/10.1016/j.phrs.2015.04.003
1043-6618/

different effects on cocaine-reinforced behavior. Acute bolus dosing causes reductions in self-administration that resolve by the following day [10]. In contrast, after delivery as a series of 21-h infusions, cocaine self-administration is decreased in some animals over a period of weeks following tacrine treatment [11]. Doses of tacrine that produced reductions in drug self-administration at 1–3 days later, were more than three-fold more potent in modifying cocaine relative to food reinforcement. The long-lasting nature of tacrine-induced decreases in drug reinforcement, described as persistent attenuation, could offer a useful approach to the treatment of substance abuse disorders. If persistent attenuation could be produced in humans, continuous treatment with anti-addictive medications may not be needed, decreasing the importance of self-motivated compliant behavior.

Stimulants such as cocaine are known to produce both reinforcing and aversive effects. In addition to drug-induced euphoria, humans receiving intravenous cocaine in a laboratory setting also report 'bad' drug effects, dysphoria, and other negative somatic symptoms [12]. Taste aversions in response to flavors paired with addictive or aversive compounds are among the most enduring forms of learned behaviors [13]. If tacrine and other cholinesterase inhibitors were to enhance cocaine's aversive properties, this could explain its long-lasting negative actions on drug reward.

Although actual liver injury is rare, clinically significant increases in plasma liver enzymes occurred in approximately one-fourth of Alzheimer's-disease patients treated with tacrine [14]. Based on this, monitoring of liver function has been recommended beginning at four weeks following initiation of tacrine treatment in humans. Because of the potential for liver toxicity, use of tacrine steadily declined and its manufacture was recently discontinued. It is possible that hepatic inflammation could have aversive properties which may contribute to behavioral actions of tacrine.

The present studies were conducted to better characterize tacrine's persistent effects on cocaine reward. If its long-term actions were caused by a direct interaction with cocaine, these should be prevented by administering cocaine and tacrine at different times. A related hypothesis is that intravenous cocaine becomes aversive in some animals receiving tacrine treatment. If so, combined administration of both drugs should exhibit aversive effects that can be detected using conditioned-place preference. After extinction, cocaine and other drugs of abuse can cause pronounced increases in non-reinforced responding, which serves as an animal model of human drug craving. Tacrine treatment may be effective by modifying these delayed actions of cocaine. Given its history of hepatic toxicity, it is possible that a subset of rats that exhibit tacrine-induced persistent attenuation have associated changes in liver function that underlie this effect. To differentiate these mechanisms, we determined effects of tacrine on cocaine-induced conditioned-place preference, reinstatement, and measured hepatic and renal function in rats that received tacrine and exhibited persistent attenuation.

2. Materials and methods

2.1. Animals

For all studies, male Wistar rats (Charles River Laboratories, Raleigh, NC) were transferred to our Facility at 9 weeks of age. Animals were evaluated according to standards outlined in the NIH Guide for Care and Use of Laboratory Animals (NIH publication no. 86-23, 1996), with procedures approved by the local Animal Care and Use Committee. To facilitate operant responding, rats were maintained under a reversed light–dark cycle (14 h of darkness beginning at 9:00 AM, and 10 lighted hours). Starting at 10 weeks of age, animals were single-housed with drinking water available ad libitum and restriction of food as outlined below.

2.2. Experiment 1, temporal separation of tacrine treatment from drug reward

This experiment was designed to examine effects of tacrine that was separated by significant delays from prior and subsequent cocaine self-administration. As soon as rats exhibited a stable pattern of self-administration under fixed-ratio-5 (FR-5) with a 20-s time out (see below), sessions were discontinued over 24 h and rats were left undisturbed in home cages, attached to a fluid swivel and steel-coil tether. This initial washout interval was assessed as more than adequate to allow clearance of plasma cocaine, which has a half-life of less than 20 min in rats [15]. Beginning on the following day, 10 mg/kg-day of tacrine or vehicle (saline) was administered as a chronic infusion over 4 days, delivered intravenously at 4.0 ml per day. After completion of these infusions, rats were then left undisturbed in home cages for an additional two days. This second washout period permitted complete clearance of tacrine, which has a half-life of less than 2 h in rat brain [16]. Cocaine self-administration was then re-initiated under FR-5 with a 20-s time-out period. To determine persistent effects of tacrine, the pattern of self-administration was monitored over six additional sessions. Afterwards, catheters were tested for patency in rats meeting criterion for persistent attenuation. This was accomplished by observing for rapid ataxia or loss of consciousness following intravenous injection of one or two 5.0 mg doses of pentobarbital.

2.2.1. Self-administration apparatus

The test boxes and computer interface utilized have previously been described in detail [11]. Food reinforcement (45 mg pellets) was provided by a pellet dispenser, with intravenous drug injections supplied by a pneumatic syringe that delivered a volume of 30 μL within 1 s. Pneumatic syringes were connected to animals by a liquid swivel and metal-spring tether.

Presentation of food or drug reinforcers was accompanied by a 2-s tone and continuous illumination of a cue light. After delivery of either reinforcer, responding had no consequence during a time-out period in which the cue light was continuously illuminated. A 5-s time-out period was used initially, with this interval gradually extended to 20 s as animals completed training, prior to tacrine treatment. After completion of the time-out period, the cue light was flashed for 0.75 s every 3 s, indicating contingent reinforcement was again available. Test boxes were equipped with two identical levers, with only responding on the left-hand (active) lever counted toward delivery of reinforcers. Responses on a right-hand (inactive) lever had no effect on reinforcement.

2.2.2. Initial food reinforcement

To facilitate acquisition of cocaine self-administration, rats were initially trained to respond for food reinforcement, with food intake limited during these studies. Rats were deprived of food over 48 h prior to their initial food self-administration session. Afterwards, daily allowances of standard rat chow were set at 14.8 gm, which was continued until the completion of experiments. Initially, 45 mg food pellets were available under a fixed-ratio-1 (FR-1) schedule for 20 min, in which each lever press led to delivery of one pellet. Daily sessions were continued until 50 pellets were obtained under FR-1 during one session. Two additional 20-min sessions were conducted in which food pellets were made available under a progressive-ratio schedule, to expose animals to an increased response requirement. A PR 9-4 progressive ratio schedule was utilized in these sessions with a time-out of 5 s [17], which incremented response requirement in the following pattern: 1, 1, 1, 2, 2, 2, 3, 3, 4, 4, 5, 5, 6, 6, 7, 7, 8, 9, 9, 10, 11, 11, 12, 13, etc.

Please cite this article in press as: K. Grasing, et al., Enduring effects of tacrine on cocaine-reinforced behavior: Analysis by conditioned-place preference, temporal separation from drug reward, and reinstatement, Pharmacol Res (2015), http://dx.doi.org/10.1016/j.phrs.2015.04.003