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Research article

Replacement treatment during extinction training with the atypical dopamine uptake inhibitor, JHW-007, reduces relapse to methamphetamine seeking

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ABSTRACT

There are currently no approved medications to effectively counteract the effects of methamphetamine (METH), reduce its abuse and prolong abstinence from it. Data accumulated in recent years have shown that a range of *N*-substituted benztropine (BZT) analogues possesses psychopharmacological features consistent with those of a potential replacement or "substitute" treatment for stimulant addiction. On the other hand, the evidence that antidepressant therapy may effectively prevent relapse to stimulant seeking is controversial. Here, we compared in rats the ability of the BZT analogue and high affinity dopamine (DA) reuptake inhibitor, JHW-007, and the antidepressant, trazodone, administered during extinction sessions after chronic METH self-administration, to alter METH-primed reinstatement of drug seeking. The data showed that trazodone produced paradoxical effects on lever pressing during extinction of METH self-administration, decreasing active, but increasing inactive, lever pressing. JHW-007 did not have any observable effects on extinction training. Importantly, JHW-007 significantly attenuated METH-primed reinstatement, whereas trazodone enhanced it. These findings lend support to the candidacy of selective DA uptake blockers, such as JHW-007, as potential treatments for METH addiction, but not to the use of antidepressant medication as a single therapeutic approach for relapse prevention.

1. Introduction

Methamphetamine (METH) is an amphetamine derivative with widespread global use as a recreational psychostimulant drug. METH produces feelings of increased confidence, disinhibition, euphoria, heightened alertness and energy and can, after chronic exposure, lead to addiction [1]. Compared to amphetamine, METH passes more readily through the blood-brain barrier and has a much longer half-life, producing psychostimulant effects for up to 12 h [2]. METH binds to the transporter proteins for dopamine (DA), serotonin (5-HT) and norepinephrine (NE) [3] and is also internalised by presynaptic terminals [4]. METH produces large elevations in extracellular DA concentrations both through vesicular release and by causing reverse transport of DA through the DA transporter (DAT) [4,5]. Although the reuptake of NE and 5-HT are affected by METH, the psychostimulant and euphoric effects induced by METH, as well as the long-term neuroadaptations produced by its repeated use, are primarily mediated by the DA system [6–8]. Currently, there are no approved and effective medications to aid in the detoxification and treatment of METH addiction.

The replacement approach in addiction therapy refers to the substitution of an abused drug for a less potent, less addictive medication with properties similar to those of the drug. Ultimately, the goal of this approach is to reduce the dose of the substituted drug over time until the individual is no longer dependent and abstinence can be maintained without severe withdrawal symptoms or craving. This approach has shown considerable efficacy in reducing craving and facilitate abstinence from nicotine (e.g. nicotine patches) [9] and heroin (e.g. oral methadone) [10]. In the case of stimulant addiction, such approach fuelled the development of long-acting DA uptake inhibitors that could act as a substitute by re-stabilising DA transmission [11,12]. The discovery of *N*-substituted benztropine (BZT) analogues, a class of highly selective DA uptake inhibitors, marked a significant development in this area. These compounds readily cross the blood-brain barrier and produce increases in extracellular DA for much longer periods of time than cocaine [13] due to a different mode of interaction with the DAT [14]. The atypical binding profile of BZT analogues to the DAT appears to be responsible for their reduced ability to produce subjective effects similar to cocaine [15]. One of such BZT derivatives, JHW-007, a high affinity DAT inhibitor largely devoid of psychostimulant effects [16,17], prevented the sensitization and synaptic changes induced by

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amphetamine in the nucleus accumbens [18], and reduced METH self-administration [19,20] in rats. In an interesting experiment with a related BZT analogue, AHN-1055, we previously showed that replacement treatment attenuated cocaine-primed reinstatement of drug seeking behaviour when such treatment was given as a self-administered substitute during extinction [21]. However, whether such substitution approach may be effective at reducing relapse to METH seeking is not known.

The present experiments were designed to assess in rats the ability of the BZT analogue, JHW-007, administered prior to extinction sessions, to reduce METH-primed reinstatement of drug seeking. Previous studies have shown that antidepressant treatment can also modulate METH seeking after extinction training [22,23]. Thus, for comparison, we also administered the antidepressant, trazodone, a phenylpiperazine compound of the serotonin antagonist and reuptake inhibitor (SARI) class, and similarly evaluated its ability to alter METH-primed reinstatement of drug seeking.

2. Materials and methods

2.1. Subjects

Subjects were 30, 8–10 weeks old male Long Evans rats bred at the Animal facility of the Department of Psychology, University of Canterbury. Rats were housed in groups of four in polycarbonate cages (45 × 24 × 20 cm) on a reverse 12 h light/dark cycle (lights on at 8 PM) under standard conditions of temperature (22 ± 2 °C) and humidity (45–55%). Rats received approximately 20 g of standard rat chow per day and kept at 100% of free feeding weight throughout the experiments. All procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory animals, and were approved by the Animal Ethics Committee of the University of Canterbury (protocols 37R and 38R).

2.2. Pharmacological treatments

METH hydrochloride (BDG Synthesis, Wellington) was dissolved in 0.9% saline. JHW-007 (synthesized by Dr Juan Murga, University Jaime I, Spain) and trazodone (Sigma, NZ), were dissolved through sonication in 0.9% saline and 20% dimethylsulfoxide (DMSO) and injected at doses of 5 mg/kg i.p. and 10 mg/kg i.p., respectively, during the substitution phase. Doses were selected according to previous research findings (see Discussion section). Control rats received vehicle injections i.p. with the same solvents. All compounds were prepared fresh daily and administered i.p. at a volume of 1 ml/kg during both the extinction and reinstatement phases. For the self-administration experiments rats received 0.05 mg/kg/infusion of METH in 100 µl boluses. For the reinstatement experiments, the dose of METH was 0.75 mg/kg i.p.

2.3. Operant self-administration chambers

Drug self-administration procedures were conducted in operant self-administration chambers (Panlab S.L., Barcelona, Spain) fitted with two metal response levers protruding approximately 1 cm from the chamber wall and serving as active and inactive levers. Active lever presses resulted in intravenous infusions of saline or METH, from an infusion pump placed outside of the chamber, while inactive lever presses had no programmed consequences. Chambers were also equipped with a general house light and 4 cm diameter stimulus light located above the active lever which illuminated for all active reinforcements.

2.4. Surgery

In preparation for surgery, rats were pre-treated with the antibiotic, cephalexin (50 mg/kg s.c), and habituated to the operant chambers for 15 min each day with both active and inactive levers removed so as not to interfere with the training process. Immediately prior to surgery, rats were anesthetized with Avertin (2,2,2-tribromoethanol, 12.5 mg/ml, in 2.5% tertiary amyl alcohol, 2 ml/100 g weight). The right jugular vein was isolated and sterile catheters (O/D 0.63 mm, I/D 0.30 mm, Camcaths, Cambridge, UK) inserted 3.2 cm into the vein. The catheter tubing was secured to the tissue by sutures and the opposite end was pushed through to exit the skin between the scapulae. This end was secured in place with sutures and a mesh collar attached to a threaded tip which was sealed with a protective cap of plastic tubing. Post-operatively, animals were treated with the analgesic, carprofen (5 mg/kg s.c), to minimise discomfort and with sodium lactate (5 ml s.c) to ensure adequate hydration. Cephalexin was also administered post-operatively and sodium lactate was given during recovery as required. Rats were housed individually following surgery and allowed to recover for seven days before commencing self-administration pre-training.

2.5. Behavioural training

The self-administration procedure consisted of four phases: pre-training, training, extinction/treatment and reinstatement. Methods were as described previously [24,21]. Rats (n = 7 per group) were initially pre-trained to lever press for METH on extended sessions lasting approximately 12 h on a fixed-ratio 1 (FR1) schedule of reinforcement. A time-out period of one sec was used throughout so as to prevent multiple infusions. Priming injections were not given during training. For control purposes, an additional group of rats (n = 9) was trained to receive saline infusions. Once rats reached the criterion of 30 reinforcements in a FR1 session, they progressed to a fixed-ratio (FR2) schedule, and finally to a fixed-ratio 3 (FR3) when the same criterion of 30 reinforcements was achieved. The computer program (Packwin, Panlab, S.L., Barcelona, Spain) recorded information on the total number of active and inactive lever presses and active reinforcements per session. Before and after each self-administration session, rats had their catheters flushed with heparinised saline (0.1 ml, 70 U.I./ml) to help maintain catheter patency. Food and water was available in the chambers during extended sessions.

Once rats met the criterion of 30 active reinforcements during an extended FR3 session, they began self-administration training during 90 min FR3 sessions for 10 consecutive days to stabilise responding. A minimum of 15 active reinforcements was needed with less than 20% variance during the last three days of training in order to begin extinction. Following stable responding at FR3, rats were withdrawn from METH for 10 consecutive days during the extinction phase. Concurrently, rats received one of three treatments in a randomised between-groups design: vehicle, JHW-007 and trazodone were administered 60 min prior to the start of the extinction sessions and were then placed in the chambers receiving infusions of saline after presses on the active lever whilst no consequences followed presses on the inactive lever. The vehicle, JHW-007 and trazodone groups were matched in terms of performance during the training phase. By the last extinction session, a criterion of 10 or less active lever presses was required prior to introducing the tests of reinstatement.

METH-induced reinstatement was assessed across two consecutive days. During these sessions, the stimulus light and the infusion pump were disconnected in order to avoid the potential influence of conditioned cues and presses on the active or inactive lever had no programmed consequences. On day 1, rats received saline (i.p.) and were immediately introduced in the operant chambers. This session acted as a control comparison for the METH reinstatement tests, which was conducted the following day. These saline sessions were performed before METH sessions for all animals so as to minimise potential carry-over effects of METH. Like saline, METH treatment was administered i.p. prior to placing the rats in the self-administration chambers. Both reinstatement sessions lasted 3 h with the infusion pump disconnected, therefore both levers produced no consequences when pressed,