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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,

however, active and inactive lever presses were still recorded.

2.6. Statistical analysis

Data were analysed by analysis of variance (ANOVA) with repeated measures when a within-subjects design was in use, followed by post hoc comparisons with the method of Fisher (Protected Least Significance Test) using the sampling error from the overall ANOVA as denominator. Statistical significance was set at $\alpha = 0.05$ for all experiments. All statistical analyses were performed using StatView 5.0 (SAS Institute, NC, USA).

3. Results

3.1. Self-administration training and extinction

METH sustained robust self-administration behaviour, whereas saline infusions did not. All animals self-administering METH showed significantly higher rates of responding on the active lever compared to controls (n = 9) ($F_{[3,27]} = 20.126$, $p < 0.001$), while there were no significant differences between all groups for inactive lever presses ($F_{[3,27]} = 0.485$, $p = 0.884$). Before assignment to the vehicle, JHW-007 or trazodone treatments, groups were matched for responses rates during the METH self-administration acquisition phase (Fig. 1A).

Before each extinction session animals were injected with vehicle, JHW-007 or trazodone. We observed a significant effect of extinction day ($F_{[3,27]} = 14.236$, $p < 0.001$) and a significant interaction effect between active lever presses and treatment group ($F_{[3,27]} = 1.567$, $p = 0.042$). On the first day of extinction the vehicle and JHW-007 groups exhibited a ca. 2-fold decrease in response rates on the active lever relative to the rates observed during METH training. Interestingly, rats treated with trazodone responded significantly less than these two groups ($p < 0.05$). Both the vehicle and JHW-007 groups showed a gradual decline in active lever presses throughout extinction, with the control group maintaining a very low and steady baseline. Animals receiving trazodone treatment exhibited a much sharper decrease in responding on the active lever than the vehicle and JHW-007 groups and by day 3 of extinction their responses matched those of the control group (Fig. 1B).

Analysis of response rates on the inactive lever during extinction training revealed a significant effect of the treatments ($F_{[3,27]} = 5.971$, $p = 0.003$). Surprisingly, rats treated with trazodone, which had shown reduced responding on the active lever during extinction, significantly increased responding on the inactive lever during the same phase, compared to rats receiving control treatment ($p < 0.05$ across several sessions).

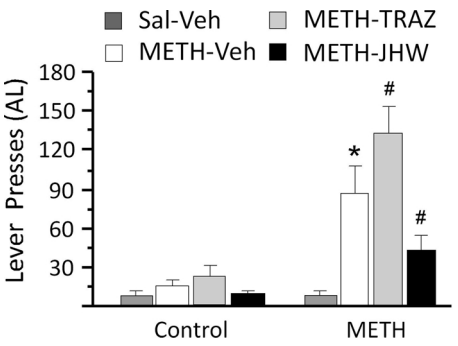

Fig. 2. *METH-primed reinstatement of drug seeking after JHW-007, trazodone or vehicle substitution during extinction training.* In the reinstatement tests, rats received saline or METH prime treatment and drug seeking behaviour was measured. METH treatment produced robust reinstatement of responding in the METH-paired lever in rats previously exposed to saline during extinction training (METH-Veh). JHW-007 treatment during extinction sessions significantly reduced METH-primed reinstatement (METH-JHW), whereas trazodone increased it (METH-TRAZ). Data points represent means ± SEM. *, $p < 0.05$ versus Sal-Veh; #, $p < 0.05$ versus METH-Veh.

3.2. Reinstatement tests

Following extinction training, priming injections of METH produced reinstatement of drug seeking behaviour. Tests of saline- and MA-induced reinstatement produced a significant interaction effect in the main ANOVA ($F_{[3,26]} = 6.838$, $p = 0.002$). As hypothesised, the JHW-007 group showed a significant attenuation of METH-seeking compared to the saline group ($p < 0.05$). Conversely, rats treated with trazodone during the extinction phase showed increased METH seeking relative to those treated with saline (Fig. 2).

4. Discussion

The present experiments were conducted to assess the effects of the atypical DA reuptake blocker, JHW-007, and the antidepressant, trazodone, administered before extinction training, on METH-primed reinstatement of METH seeking. The results showed that trazodone seemed to accelerate the extinction of METH self-administration but potentiated METH-primed reinstatement of drug seeking behaviour. On the contrary, JHW-007 did not affect response rates during extinction compared to treatment with vehicle, yet it significantly reduced relapse to METH seeking. These findings support the candidacy of DA uptake inhibitors of the BZT class as potential pharmacological interventions in METH addiction.

Although multiple transmitter systems and receptor adaptations are likely to be implicated in METH reinforcement and the processes linked

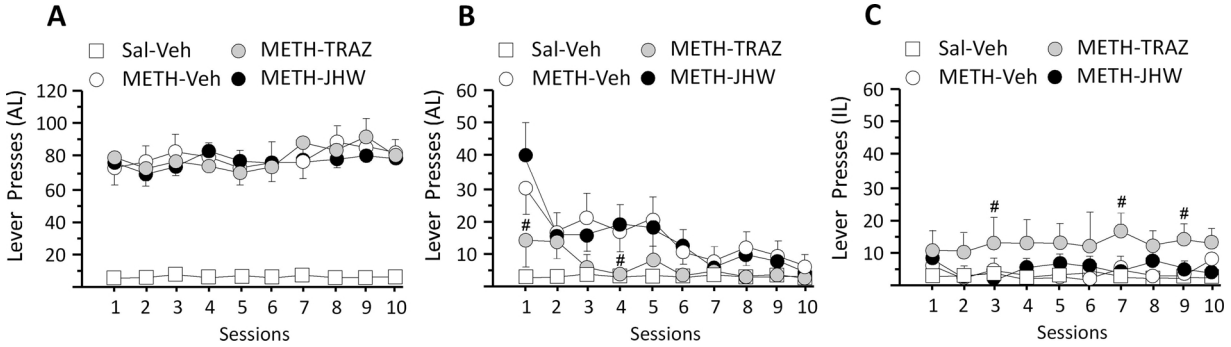

Fig. 1. *Training and extinction of METH self-administration in rats receiving JHW-007, trazodone or vehicle substitution during extinction.* Rats were trained on METH self-administration under fixed-ratio schedules until they reached stable performance on a FR3 schedule for 10 consecutive days (A), before being assigned to one of four extinction treatment groups. Acquisition curves are depicted for all four METH groups to show that response rates were matched prior to extinction training. During extinction, the decline in responding on the active lever following METH self-administration did not differ between the vehicle (METH-Veh) and the JHW-007 (METH-JHW) groups. By contrast, rats treated with trazodone (METH-TRAZ) showed reduced levels of responding compared to the METH-Veh group (B). Response rates on the inactive lever were significantly increased in the group that trained on METH self-administration and later received trazodone during extinction training (C). Data points represent means ± SEM. #, $p < 0.05$ compared to METH-sal.

to withdrawal and relapse, alterations in DA transmission are thought to play a key role. Preclinical research has shown that chronic METH exposure leads to a variety of lasting changes in the DA system, including decreases in DA levels, tyrosine hydroxylase activity, DAT expression and DA uptake [25,1]. Notably, decreased DA transmission has been associated with propensity to relapse in METH abusers [7]. Consequently, considerable efforts have been made for more than two decades to identify compounds with an ability to interact with the DAT without producing strong psychostimulant effects, as a means to reduce the effects of cocaine or METH and suppress craving and relapse following detoxification [11,12]. A variety of compounds with such desirable features were developed, including *N*-substituted BZT analogues, tropanes and substituted piperazines. The combination of a tropane ring, which is present in the cocaine molecule, with a diphenyl ether molecule, found in the GBR compounds such as GBR 12909, provided a template for the design of a new generation of dopamine uptake inhibitors. In particular, chloro or fluoro para or meta-substitution on the phenyl rings of the parent BZT molecule produced a series of compounds with high affinity for the DAT [26–28]. Such compounds exhibited a slow onset of action and prolonged effects on DA transmission, which was largely due to a different mode of action at the DAT, binding to different domains within it and producing different conformational changes in its structure [29–31]. Among other promising compounds, one of such *N*-substituted BZT analogues, JHW-007, showed nearly 10-fold higher affinity for the DAT (K_i = 25 nM) than cocaine and negligible activity at the NET (K_i = 1330 nM) and SERT (K_i = 1730 nM) [32], together with a slower rate of DAT occupancy and receptor offset [16,12]. Moreover, JHW-007 was able to block cocaine stimulant effects [16,33], cocaine place preference [33], amphetamine sensitization [18] and METH self-administration [19,20], while not sustaining responding in a self-administration task [17]. These findings strongly suggest that JHW-007 could be an effective substitute treatment for METH. The results of the current experiments demonstrated that JHW-007 treatment did not alter extinction rates after chronic METH self-administration but significantly attenuated METH-primed reinstatement of drug seeking. Given that elimination half-life for JHW-007 (10 mg/kg i.v.) is 5.35 h [13], it is most unlikely that residual effects of JHW-007 account for this observation. We have shown previously that JHW-007 prevented METH-induced increment in dendritic arborisation, lengthening of dendritic processes and increase in spine density, as well as augmentation of asymmetric synapses, in the nucleus accumbens [18]. Therefore, JHW-007 treatment may attenuate some of the neuroadaptations associated with drug withdrawal that contribute to drug seeking and relapse following drug discontinuation. Although we acknowledge that only one dose of JHW-007 was used as treatment, the dose we selected was lower (i.e., reduced by half) than that which effectively blocks METH-induced locomotor activity and METH self-administration [19], suggesting that higher doses of JHW-007 could have indeed produced a more complete blockade of METH-primed reinstatement in the current experiments. Previous evidence has shown that treatment with another BZT derivative, AHN-1055, either self-administered or received passively in the self-administration context (i.e., yoked procedure) dose-dependently attenuated cocaine-primed reinstatement of cocaine seeking [21]. Therefore, the present findings are consistent with the notion that re-stabilising DA transmission after chronic drug exposure may afford protection against relapse. A distinct possibility is that such replacement treatment prevents some of the long-term adaptations in DAT expression that occur after METH self-administration and withdrawal and are associated with reinstatement [34], though this hypothesis remains to be tested experimentally.

Trazodone, a triazolopyridine derivative, is an effective antidepressant which possesses some anxiolytic and hypnotic properties and displays a complex pharmacological profile due to its multifunctional and combined agonist/antagonist actions on the 5-HT system. Although the mechanisms contributing to its therapeutic efficacy as an antidepressant are not fully understood, trazodone produces actions on 5-HT transmission consistent with current selective serotonin reuptake inhibitors (SSRI) medications, including blockade of the SERT, moderate agonistic affinity for 5-HT1A receptors and antagonist action at 5-HT2/1C receptors [35]; [36]. In addition, trazodone metabolism leads to the formation of m-chlorophenylpiperazine (mCPP), an active metabolite with psychopharmacological properties [37]. The evidence in favour of antidepressant treatment as a means to prevent relapse to drug seeking has been rather mixed. The atypical antidepressant, mirtazapine, which enhances histaminergic transmission and augments 5-HT release through complex actions at activated norepinephrine α_2 receptors, reduced cue-induced reinstatement of METH seeking in rats [22]. Conversely, also in rats, curcumin, a major active principle of *Curcuma longa*, which possesses antidepressant properties and elevates 5-HT transmission [38], increased METH sensitization and enhanced cue-induced reinstatement of METH seeking when administered chronically during the extinction phase [23]. Adding to this complexity, the data in regards to the effects of antidepressant treatment on cocaine relapse have also been inconsistent. In monkeys, cocaine-primed reinstatement and cocaine-elicited dopamine overflow were attenuated following chronic treatment with the SSRI, fluoxetine [39]. However, in rats, while both fluoxetine and *d*-fenfluramine attenuated cue-reinstated cocaine-seeking behaviour, neither drug reliably altered cocaine-seeking reinstated by cocaine priming [40]. These conflicting results are likely to reflect differences in antidepressant pharmacology, treatment regimens, species and reinstatement procedures. In the present experiments, trazodone, compared to vehicle treatment, accelerated the decrease in operant responding during extinction of METH self-administration, but increased METH-primed reinstatement of METH seeking. The attenuation of METH seeking during extinction is consistent with the inhibitory effects of fluoxetine on cocaine seeking during this phase [40]. Although we only used one dose of trazodone as treatment, which is a limitation we acknowledge, the dose selected has been previously shown to enhance 5-HT transmission after chronic administration in rats [41] and is below the doses that produce strong sedation or catalepsy [42], although increases in non-REM sleep have been reported after chronic treatment [43]. Moreover, this dose of trazodone ameliorates stress-induced deficits in rotarod performance [44]. The present finding that trazodone paradoxically increased responding on the inactive lever during extinction training suggests that sedation and/or motor inhibition did not account for the reduction in response rates on the active lever observed both during extinction and reinstatement phases. The reducing effects of trazodone treatment on METH seeking during extinction training can only be attributed to other psychoactive effects of trazodone, facilitation of response generalisation being one potential explanation. Adding further complexity, we observed that prior trazodone exposure potentiated METH-primed drug seeking in the reinstatement tests, suggesting that antidepressant medication is not effective at preventing drug-primed relapse. This is consistent with data indicating that METH abusers display sustained craving and even enhanced propensity to relapse following antidepressant therapy [45].

In summary, the present data indicate that the atypical DA uptake blocker, JHW-007, exhibited desirable properties in a METH model of relapse, significantly attenuating METH-primed reinstatement of drug seeking behaviour, whereas the antidepressant, trazodone, produced the opposite effect. Despite the fact that trazodone was able to reduce METH seeking during extinction training, the current results suggest that targeting the DA system, either directly or indirectly, and not the serotonin system, may be a more effective approach to drug relapse prevention.

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References

[1] W.J. Panenka, R.M. Procyshyn, T. Lecomte, G.W. MacEwan, S.W. Flynn, W.G. Honer, A.M. Barr, Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings, Drug Alcohol Depend. 129 (2013) 167–179.

[2] C.C. Cruickshank, K.R. Dyer, A review of the clinical pharmacology of methamphetamine, Addiction 104 (2009) 1085–1099.

[3] D.D. Han, H.H. Gu, Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs, BMC Pharmacol. 6 (2006) 6.

[4] A.E. Fleckenstein, T.J. Volz, E.L. Riddle, J.W. Gibb, G.R. Hanson, New insights into the mechanism of action of amphetamines, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 681–698.

[5] J.S. Goodwin, G.A. Larson, J. Swant, N. Sen, J.A. Javitch, N.R. Zahniser, L.J. De Felice, H. Khoshbouei, Amphetamine and methamphetamine differentially affect dopamine transporters in vitro and in vivo, J. Biol. Chem. 284 (2009) 2978–2989.

[6] W.C. Drevets, C. Gautier, J.C. Price, D.J. Kupfer, P.E. Kinahan, A.A. Grace, J.L. Price, C.A. Mathis, Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria, Biol. Psychiatry 49 (2001) 81–96.

[7] G.J. Wang, L. Smith, N.D. Volkow, F. Telang, J. Logan, D. Tomasi, C.T. Wong, W. Hoffman, M. Jayne, N. Alia-Klein, P. Thanos, J.S. Fowler, Decreased dopamine activity predicts relapse in methamphetamine abusers, Mol. Psychiatry 17 (2012) 918–925.

[8] A.H. Ashok, Y. Mizuno, N.D. Volkow, O.D. Howes, Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis, JAMA Psychiatry 74 (5) (2017) 511–519.

[9] L.F. Stead, R. Perera, C. Bullen, D. Mant, J. Hartmann-Boyce, K. Cahill, T. Lancaster, Nicotine replacement therapy for smoking cessation, Cochrane Database Syst. Rev. 11 (2012) CD000146.

[10] R.P. Mattick, C. Breen, J. Kimber, M. Davoli, Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence, Cochrane Database Syst. Rev. (2009) CD002209.

[11] R.B. Rothman, M.H. Baumann, T.E. Prisinzano, A.H. Newman, Dopamine transport inhibitors based on GBR12909 and benztropine as potential medications to treat cocaine addiction, Biochem. Pharmacol. 75 (2008) 2–16.

[12] G. Tanda, A.H. Newman, J.L. Katz, Discovery of drugs to treat cocaine dependence: behavioral and neurochemical effects of atypical dopamine transport inhibitors, Adv. Pharmacol. 57 (2009) 253–289.

[13] S. Raje, J. Cao, A.H. Newman, H. Gao, N.D. Eddington, Evaluation of the blood-brain barrier transport, population pharmacokinetics, and brain distribution of benztropine analogs and cocaine using in vitro and in vivo techniques, J. Pharmacol. Exp. Ther. 307 (2003) 801–808.

[14] C.J. Loland, R.I. Desai, M.F. Zou, J. Cao, P. Grundt, K. Gerstbrein, H.H. Sitte, A.H. Newman, J.L. Katz, U. Gether, Relationship between conformational changes in the dopamine transporter and cocaine-like subjective effects of uptake inhibitors, Mol. Pharmacol. 73 (2008) 813–823.

[15] S.J. Kohut, T. Hiranita, S.K. Hong, A.L. Ebbs, V. Tronci, J. Green, L. Garces-Ramirez, L.E. Chun, M. Mereu, A.H. Newman, J.L. Katz, G. Tanda, Preference for distinct functional conformations of the dopamine transporter alters the relationship between subjective effects of cocaine and stimulation of mesolimbic dopamine, Biol. Psychiatry 76 (2014) 802–809.

[16] R.I. Desai, T.A. Kopajtic, M. Koffarnus, A.H. Newman, J.L. Katz, Identification of a dopamine transporter ligand that blocks the stimulant effects of cocaine, J. Neurosci. 25 (2005) 1889–1893.

[17] T. Hiranita, P.L. Soto, A.H. Newman, J.L. Katz, Assessment of reinforcing effects of benztropine analogs and their effects on cocaine self-administration in rats: comparisons with monoamine uptake inhibitors, J. Pharmacol. Exp. Ther. 329 (2009) 677–686.

[18] C. Velazquez-Sanchez, J.M. Garcia-Verdugo, J. Murga, J.J. Canales, The atypical dopamine transport inhibitor, JHW 007, prevents amphetamine-induced sensitization and synaptic reorganization within the nucleus accumbens, Prog. Neuropsychopharmacol. Biol. Psychiatry 44 (2013) 73–80.

[19] A. Ferragud, C. Velazquez-Sanchez, J.J. Canales, Modulation of methamphetamine's locomotor stimulation and self-administration by JHW 007, an atypical dopamine reuptake blocker, Eur. J. Pharmacol. 731 (2014) 73–79.

[20] T. Hiranita, S.J. Kohut, P.L. Soto, G. Tanda, T.A. Kopajtic, J.L. Katz, Preclinical efficacy of N-substituted benztropine analogs as antagonists of methamphetamine self-administration in rats, J. Pharmacol. Exp. Ther. 348 (2014) 174–191.

[21] C. Velazquez-Sanchez, A. Ferragud, A. Ramos-Miguel, J.A. Garcia-Sevilla, J.J. Canales, Substituting a long-acting dopamine uptake inhibitor for cocaine prevents relapse to cocaine seeking, Addict. Biol. 18 (2013) 633–643.

[22] S.M. Graves, T.C. Napier, Mirtazapine alters cue-associated methamphetamine seeking in rats, Biol. Psychiatry 69 (2011) 275–281.

[23] C. Zhao, Z. Lou, B. Zimmer, Z. Yu, P. Li, B. Ma, Y. Sun, K. Huang, W. Zhou, Y. Liu, Chronic treatment with curcumin enhances methamphetamine locomotor sensitization and cue-induced reinstatement of methamphetamine self-administration, Pharmacol. Biochem. Behav. 102 (2012) 555–561.

[24] A. Ferragud, C. Velazquez-Sanchez, V. Hernandez-Rabaza, A. Nacher, V. Merino, M. Carda, J. Murga, J.J. Canales, A dopamine transport inhibitor with markedly low abuse liability suppresses cocaine self-administration in the rat, Psychopharmacology (Berl.) 207 (2009) 281–289.

[25] A.M. Barr, W.J. Panenka, G.W. MacEwan, A.E. Thornton, D.J. Lang, W.G. Honer, T. Lecomte, The need for speed: an update on methamphetamine addiction, J. Psychiatry Neurosci. 31 (2006) 301–313.

[26] A.H. Newman, A.C. Allen, S. Izenwasser, J.L. Katz, Novel 3 alpha-(diphenylmethoxy)tropane analogs: potent dopamine uptake inhibitors without cocaine-like behavioral profiles, J. Med. Chem. 37 (1994) 2258–2261.

[27] G.E. Agoston, J.H. Wu, S. Izenwasser, C. George, J. Katz, R.H. Kline, A.H. Newman, Novel N-substituted 3 alpha-[bis(4'-fluorophenyl)methoxy]tropane analogues: selective ligands for the dopamine transporter, J. Med. Chem. 40 (1997) 4329–4339.

[28] S.M. Li, T.A. Kopajtic, M.J. O'Callaghan, G.E. Agoston, J. Cao, A.H. Newman, J.L. Katz, N-substituted benztropine analogs: selective dopamine transporter ligands with a fast onset of action and minimal cocaine-like behavioral effects, J. Pharmacol. Exp. Ther. 336 (2011) 575–585.

[29] T. Beuming, J. Kniazeff, M.L. Bergmann, L. Shi, L. Gracia, K. Raniszewska, A.H. Newman, J.A. Javitch, H. Weinstein, U. Gether, C.J. Loland, The binding sites for cocaine and dopamine in the dopamine transporter overlap, Nat. Neurosci. 11 (2008) 780–789.

[30] M. Indarte, J.D. Madura, C.K. Surratt, Dopamine transporter comparative molecular modeling and binding site prediction using the LeuT(Aa) leucine transporter as a template, Proteins 70 (2008) 1033–1046.

[31] H. Bisgaard, M.A. Larsen, S. Mazier, T. Beuming, A.H. Newman, H. Weinstein, L. Shi, C.J. Loland, U. Gether, The binding sites for benztropines and dopamine in the dopamine transporter overlap, Neuropharmacology 60 (2011) 182–190.

[32] T.A. Kopajtic, Y. Liu, C.K. Surratt, D.M. Donovan, A.H. Newman, J.L. Katz, Dopamine transporter-dependent and −independent striatal binding of the benztropine analog JHW 007, a cocaine antagonist with low abuse liability, J. Pharmacol. Exp. Ther. 335 (2010) 703–714.

[33] C. Velazquez-Sanchez, A. Ferragud, J. Murga, M. Carda, J.J. Canales, The high affinity dopamine uptake inhibitor, JHW 007, blocks cocaine-induced reward, locomotor stimulation and sensitization, Eur. Neuropsychopharmacol. 20 (2010) 501–508.

[34] M. Schwendt, A. Rocha, R.E. See, A.M. Pacchioni, J.F. McGinty, P.W. Kalivas, Extended methamphetamine self-administration in rats results in a selective reduction of dopamine transporter levels in the prefrontal cortex and dorsal striatum not accompanied by marked monoaminergic depletion, J. Pharmacol. Exp. Ther. 331 (2009) 555–562.

[35] G.J. Marek, C.J. McDougle, L.H. Price, L.S. Seiden, A comparison of trazodone and fluoxetine: implications for a serotonergic mechanism of antidepressant action, Psychopharmacology (Berl.) 109 (1992) 2–11.

[36] M. Haria, A. Fitton, D. McTavish, Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders, Drugs Aging 4 (1994) 331–355.

[37] R.B. Rothman, M.H. Baumann, Serotonin releasing agents neurochemical, therapeutic and adverse effects, Pharmacol. Biochem. Behav. 71 (2002) 825–836.

[38] S.K. Kulkarni, M.K. Bhutani, M. Bishnoi, Antidepressant activity of curcumin: involvement of serotonin and dopamine system, Psychopharmacology (Berl.) 201 (2008) 435–442.

[39] E.K. Sawyer, J. Mun, J.A. Nye, H.L. Kimmel, R.J. Voll, J.S. Stehouwer, K.C. Rice, M.M. Goodman, L.L. Howell, Neurobiological changes mediating the effects of chronic fluoxetine on cocaine use, Neuropsychopharmacology 37 (2012) 1816–1824.

[40] J.J. Burmeister, E.M. Lungren, J.L. Neisewander, Effects of fluoxetine and d-fenfluramine on cocaine-seeking behavior in rats, Psychopharmacology (Berl.) 168 (2003) 146–154.

[41] R. Ghanbari, M. El Mansari, P. Blier, Sustained administration of trazodone enhances serotonergic neurotransmission: in vivo electrophysiological study in the rat brain, J. Pharmacol. Exp. Ther. 335 (2010) 197–206.

[42] J.J. Balsara, S.A. Jadhav, R.K. Gaonkar, R.V. Gaikwad, J.H. Jadhav, Effects of the antidepressant trazodone, a 5-HT 2A/2C receptor antagonist, on dopamine-dependent behaviors in rats, Psychopharmacology (Berl.) 179 (2005) 597–605.

[43] Z. Lelkes, F. Obal Jr., P. Alfoldi, A. Erdos, G. Rubicsek, G. Benedek, Effects of acute and chronic treatment with trazodone, an antidepressant, on the sleep-wake activity in rats, Pharmacol. Res. 30 (1994) 105–115.

[44] K. Mizoguchi, M. Yuzurihara, A. Ishige, H. Sasaki, T. Tabira, Chronic stress impairs rotarod performance in rats: implications for depressive state, Pharmacol. Biochem. Behav. 71 (2002) 79–84.

[45] T. Zorick, C.A. Sugar, G. Hellemann, S. Shoptaw, E.D. London, Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine, Drug Alcohol Depend. 118 (2011) 500–503.