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Tetrabenazine inhibition of monoamine uptake and methamphetamine behavioral effects: Locomotor activity, drug discrimination and self-administration

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ABSTRACT

Tetrabenazine (TBZ), a benzoquinolizine derivative, binds with high affinity to the vesicular monoamine transporter-2 (VMAT2), inhibiting uptake of cytosolic monoamines. The current study aimed to provide preclinical evidence supporting the potential use of TBZ as a treatment for methamphetamine abuse. Effects of TBZ on function of the dopamine transporter (DAT) and serotonin transporter (SERT) in striatal and hippocampal synaptosomes, respectively, and on VMAT2 function in isolated striatal synaptic vesicles were determined. Effect of TBZ (acute, 0.1–3.0 mg/kg, s.c.; repeated, 1.0 mg/kg for 7 days) on locomotor activity in methamphetamine-sensitized rats was assessed. Ability of TBZ (0.1–3.0 mg/kg; s.c.) or vehicle to decrease the discriminative effect of methamphetamine also was determined. Ability of TBZ (acute, 0.1–1.0 mg/kg, s.c.; repeated, 0.1 or 1.0 mg/kg for 7 days) to specifically decrease methamphetamine self-administration was determined; for comparison, a separate group of rats was assessed for effects of TBZ on food-maintained responding. Results show that TBZ was 11-fold more potent inhibiting DAT than SERT, and 2.5-fold more potent inhibiting VMAT2 than DAT. Results from behavioral studies showed that the lowest dose of TBZ transiently increased methamphetamine self-administration, whereas higher TBZ doses decreased methamphetamine self-administration. Also, TBZ at high doses decreased methamphetamine locomotor sensitization and discriminative stimulus effects, as well as food-maintained responding. Thus, despite acting as a potent VMAT2 inhibitor, these preclinical results indicate that TBZ lacks behavioral specificity as an inhibitor of methamphetamine-induced reinforcement, diminishing its viability as a suitable treatment for methamphetamine abuse.

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1. Introduction

Methamphetamine continues to be a prominent drug of abuse. According to the 2008 National Survey on Drug Use and Health, 850,000 Americans age 12 and older used methamphetamine at least once in the year prior to being surveyed, with past month users reaching 314,000 (Substance Abuse and Mental Health Services Administration, 2009). Between 1 and 2% of high school youth reported using methamphetamine at least once in the year prior to being surveyed (Johnston et al., 2009). As such, the discovery and development of pharmacotherapies for methamphetamine abuse remains critical, with current treatment strategies to promote abstinence relying mainly on behavioral interventions such as contingency management (Prendergast et al., 2006; Roll et al., 2006; Shoptaw et al., 2006). However, a pharmacological treatment for methamphetamine abuse would be highly beneficial to augment current treatment strategies, and thus, medication development remains an active research area.

Pharmacological actions of methamphetamine include: (1) augmentation of vesicular dopamine (DA) release from the vesicles and inhibition of the vesicular monoamine transporter-2 (VMAT2), resulting in decreased accumulation of DA into synaptic vesicles and increased cytosolic DA; (2) inhibition of monoamine oxidase (MAO), preventing the metabolism of cytosolic DA; and (3) reversal of the dopamine transporter (DAT), contributing to increased extracellular DA concentrations (Mantle et al., 1976; Sulzer et al., 1995; Brown et al., 2000, 2001; Fleckenstein et al., 2007). In concert, these actions of methamphetamine produce an increase in extracellular DA, which has been shown to be critical for its rewarding effects (Vollm et al., 2004).

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Based on the mechanism of action of methamphetamine, VMAT2 has been identified as a potential pharmacological target for the treatment of methamphetamine abuse (Dwoskin and Crooks, 2002; Zheng et al., 2006). Inhibition of VMAT2 would be expected to redistribute DA from the vesicular to cytosolic pool, where it is metabolized by intracellular MAO, which may reduce the concentration of cytosolic DA available for methamphetamine-induced reverse transport of DAT, and thereby, attenuate the increase in extracellular DA mediating reward. Consistent with this possibility, heterozygous VMAT2 knockout mice display decreased amphetamine-evoked striatal DA release (Wang et al., 1997) and diminished amphetamine conditioned place preference (Takahashi et al., 1997). The VMAT2 inhibitor, lobeline, decreases both methamphetamine-evoked DA release and methamphetamine self-administration in outbred rats (Harrod et al., 2001, 2003; Miller et al., 2001). However, lobeline also acts as a potent antagonist at nicotinic receptors, and less potently inhibits DAT function (Miller et al., 2000; Zheng et al., 2005; Wilhelm et al., 2008). Lobelane, a des-oxy lobeline analog, inhibits VMAT2 more potently and selectively than its parent compound (Miller et al., 2004; Zheng et al., 2005), and similarly decreases methamphetamine-evoked DA release and methamphetamine self-administration (Neugebauer et al., 2007; Nickell et al., 2010). The latter findings provide preclinical support for VMAT2 as a pharmacotherapeutic target for the treatment of methamphetamine abuse. Unfortunately, tolerance develops rapidly to the lobelane-induced decrease in methamphetamine self-administration (Neugebauer et al., 2007), revealing a pharmacological profile not suitable for clinical use.

Since the benzoquinolizine derivative, tetrabenazine (TBZ; Xenazine®) potently and reversibly binds to VMAT2 (Scherman et al., 1983; Erickson et al., 1996) and has been approved recently by the FDA for the treatment of chorea and other symptoms associated with Huntington's disease (Yero and Rey, 2008), the current study assessed the preclinical effects of tetrabenazine on DAT, serotonin transporter (SERT) and VMAT2 function and on methamphetamine-induced behavioral effects, including hyperactivity, discriminative stimulus effects and self-administration. The aim was to evaluate its preclinical profile as a potential treatment for methamphetamine abuse.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (250–275 g) were obtained from Harlan Industries (Indianapolis, IN, USA) and housed individually with *ad libitum* access to food (2018 Teklad Global 18% Protein Rodent Diet, Harlan; Madison, WI) and water in their home cage, except where noted, and were maintained in a temperature-controlled colony room on a 12:12-h light/dark cycle (lights on at 0700 h). Rats were handled and acclimated to the colony room for at least 1 week prior to the start of the behavioral experiments. Behavioral testing was conducted during the light cycle. Experimental protocols were in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

2.2. Materials

D-Methamphetamine HCl was purchased from Sigma (St. Louis, MO) and was prepared in 0.9% NaCl (saline). Tetrabenazine and (2*R*,3*S*,11b*S*)-2-ethyl-3-isobutyl-9,10-dimethoxy-2,2,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-a]isoquinolin-2-ol (Ro4-1284) were generous gifts from Hoffman-LaRoche Inc. (Nutley, NJ). TBZ was prepared in vehicle (20 mM HCl, adjusted to pH 4 with phosphoric acid). Ketamine and diazepam were purchased from N.L.S. Animal Health (Pittsburgh, PA). [^{3}H]DA (specific activity, 28.0 Ci/mmol), and [^{3}H]5-hydroxytryptamine (5-HT; specific activity, 30.0 Ci/mmol) were purchased from PerkinElmer Life and Analytical Sciences (Boston, MA). [^{3}H]Dihydrotetrabenazine (DTBZ; specific activity, 20.0 Ci/mmol) was obtained from American Radiolabeled Chemicals, Inc. (St. Louis, MO). Bovine serum albumin (BSA), L-ascorbic acid, disodiumethylenediamine tetraacetate (EDTA), ethylene glycol tetraacetate (EGTA), L-(+) tartaric acid, N-[2-hydroxyethyl] piperazine-N′-[2-ethanesulfonic acid] (HEPES), 3-hydroxytyramine (DA), sucrose, magnesium sulfate ($MgSO_4$), D-glucose, sodium bicarbonate ($NaHCO_3$), pargyline, polyethyleneimine (PEI), fluoxetine HCl, 1-(2-(bis-(4-fluorophenyl)methoxy)ethyl)-4-(3-phenylpropyl)piperazine (GBR 12909), catechol and adenosine 5′-triphosphate magnesium salt (ATP-Mg^{2+}) were purchased from Sigma-Aldrich (St. Louis, MO). All other commercial chemicals were purchased from Fisher Scientific Co. (Pittsburgh, PA).

2.3. Synaptosomal [^{3}H]DA and [^{3}H]5-HT uptake

TBZ-induced inhibition of [^{3}H]DA and [^{3}H]5-HT uptake into rat striatal and hippocampal synaptosomes, respectively, was determined using modifications of a previously described method (Teng et al., 1997). Brain regions were homogenized in 20 ml of ice-cold 0.32 M sucrose solution containing 5 mM $NaHCO_3$ (pH 7.4) with 16 up-and-down strokes of a Teflon pestle homogenizer ("clearance, 0.005"). Homogenates were centrifuged (2000*g* for 10 min at 4 °C), and resulting supernatants centrifuged (20,000*g* for 17 min at 4 °C). Pellets were resuspended in 1.5 ml of Krebs' buffer (125 mM NaCl, 5 mM KCl, 1.5 mM $MgSO_4$, 1.25 mM $CaCl_2$, 1.5 mM KH_2PO_4, 10 mM α-D-glucose, 25 mM HEPES, 0.1 mM EDTA, with 0.1 mM pargyline and 0.1 mM ascorbic acid, saturated with 95% O_2/5% CO_2, pH 7.4). Synaptosomal suspensions (20 μg protein/50 μl) were added to duplicate tubes containing 50 μl TBZ (9 concentrations, 1 nM–0.1 mM, final concentration) and 350 μl of buffer and incubated at 34 °C for 5 min in a total volume of 450 μl. Samples were placed on ice and 50 μl of [^{3}H]DA or [^{3}H]5-HT (10 nM; final concentration), was added to each tube for a final total volume of 500 μl. Reactions proceeded for 10 min at 34 °C and were terminated by the addition of 3 ml of ice-cold Krebs' buffer. Nonspecific [^{3}H]DA and [^{3}H]5-HT uptake were determined in the presence of 10 μM GBR 12909 and 10 μM fluoxetine, respectively. Samples were rapidly filtered through Whatman GF/B filters using a cell harvester (MP-43RS; Brandel Inc.). Filters were washed 3 times with 4 ml of ice-cold Krebs' buffer containing catechol (1 μM). Complete counting cocktail was added to the filters and radioactivity determined by liquid scintillation spectrometry (B1600 TR scintillation counter; PerkinElmer, Inc.).

2.4. [^{3}H]DA uptake into synaptic vesicles

TBZ-induced inhibition of [^{3}H]DA uptake into isolated rat striatal vesicle preparations was determined using modifications of a previously described method (Teng et al., 1997). Briefly, rat striata were homogenized with 10 up-and-down strokes of a Teflon pestle homogenizer (clearance, 0.008″) in 14 ml of 0.32 M sucrose solution. Homogenates were centrifuged (2000*g* for 10 min at 4 °C), and the resulting supernatants were centrifuged again (10,000*g* for 30 min at 4 °C). Pellets were resuspended in 2 ml of 0.32 M sucrose solution and subjected to osmotic shock by adding 7 ml of ice-cold water, followed by immediate restoration of osmolarity by adding 900 μl of 0.25 M HEPES buffer and 900 μl of 1.0 M potassium tartrate solution. Samples were centrifuged (20,000*g* for 20 min at 4 °C), and the resulting supernatants centrifuged again (55,000*g* for 1 h at 4 °C), followed by addition of 100 μl of 10 mM MgSO4, 100 μl of 0.25 M HEPES and 100 μl of 1.0 M potassium tartrate solution prior to the final centrifugation (100,000*g* for 45 min at 4 °C). Final pellets were resuspended in 2.4 ml of assay buffer (25 mM HEPES, 100 mM potassium tartrate, 50 μM EGTA, 100 μM EDTA, 1.7 mM ascorbic acid, 2 mM ATP-Mg^{2+}, pH 7.4). Aliquots of the vesicular suspension (100 μl) were added to tubes containing assay buffer, various concentrations of TBZ (1 nM–100 μM) and 0.1 μM [^{3}H]DA for a final volume of 500 μl. Nonspecific uptake was determined in the presence of Ro4-1284 (10 μM). Reactions were processed as previously described.

To determine the mechanism of inhibition of [^{3}H]DA uptake for TBZ, kinetic analyses were performed. The concentration (35 nM) of TBZ utilized for the kinetic analysis approximated the K_i concentration previously determined in the inhibition assays. Nonspecific uptake was determined in the presence of Ro4-1284 (10 μM). Incubations were initiated by the addition of 50 μl of the vesicular suspension to 150 μl assay buffer, 25 μl of TBZ or Ro4-1284 and 25 μl of a range of concentrations of [^{3}H]DA (0.001–5.0 μM). Following an 8-min incubation period uptake was terminated by filtration, and radioactivity retained by the filters was determined as described previously.

2.5. Behavioral apparatus

Locomotor activity was recorded automatically using an animal activity monitoring system with Versamax System software (AccuScan Instruments Inc., Columbus, OH). Rats were placed in monitoring chambers (42 × 42 × 30 cm) made of clear acrylic walls and floor. Each chamber incorporated a horizontal 16 × 16 grid of photo beam sensors, with each beam 2.5 cm apart and 7 cm above the chamber floor. Horizontal activity was expressed as total distance traveled (cm).

Drug discrimination and self-administration were conducted in operant conditioning chambers (ENV-001; Med Associates, St Albans, VT), housed in sound-attenuated outer chambers, and using a Med Associates Interface model SG-503 with MED-IV software. The end walls of each operant conditioning chamber were aluminum, the front and back walls were made of clear Plexiglas and the floor consisted of 18 stainless steel rods (4.8 mm in diameter and placed 1.6 cm apart). Located in the bottom center of one of the end walls was an opening (5 × 4.2 cm) to a recessed food tray. Located on either side of the food tray was a response lever. A 28-V white cue light was located 6 cm above each response lever. A 28-V white house light was centered 20 cm above the floor on the wall opposite the response levers. An infusion pump (Med Associates) delivered drug via a silastic tube attached to a swivel mounted on the outside of the back wall.

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