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Effects of *N*-phenylpropyl-*N*′-substituted piperazine sigma receptor ligands on cocaine-induced hyperactivity in mice

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ABSTRACT

The present study examined *N*-phenylpropyl-*N*′-substituted piperazine sigma receptor ligands on cocaine-induced changes in locomotor activity in mice. Previous reports indicate that *N*-phenylpropyl-*N*′-(4-methoxybenzyl)piperazine (Nahas-3h), *N*-phenylpropyl-*N*′-(4-methoxyphenethyl)piperazine (YZ-067), and *N*-phenylpropyl-*N*′-(3-methoxyphenethyl)piperazine (YZ-185) bind with high affinity (Ki values ≈ 1 nM) to σ_1 sigma receptors. YZ-067 and YZ-185 are known to attenuate cocaine-induced convulsions, while Nahas-3h has not been tested in behavioral studies. Nahas-3h significantly attenuated cocaine-induced hyperactivity. YZ-067 decreased the effect of cocaine in a dose-dependent manner. Interestingly, YZ-185 inhibited cocaine's effect at higher doses, but enhanced cocaine's effect at a low dose. The YZ-185 inhibition of cocaine-induced hyperactivity was not surmounted by increasing the cocaine dose. Overall, this study is consistent with previous work showing the ability of certain sigma receptor ligands to affect cocaine-induced hyperactivity. Further, subtle alterations of ligand structure and the specific dosage levels employed influence the behavioral effects observed, with a 3-methoxy substituent apparently conferring the ability of a ligand to enhance cocaine's locomotor stimulatory effects.

1. Introduction

Acute cocaine administration to rodents produces a transient and dose-dependent increase in locomotor activity (Uhl et al., 2002). Observation of locomotor activity changes is one way that the behavioral properties of cocaine can be examined in a rodent model and the role of varied molecular targets on cocaine's effects can be determined. The behavioral effects of cocaine have historically been attributed to its ability to bind to and block the dopamine transporter (Kuhar et al., 1991; Sotnikova et al., 2006). However, studies using pharmacological transporter blockade or genetic manipulation of the transporter have shown that the dopamine transporter is not the sole target responsible for cocaine's locomotor-activating effects (Hall et al., 2009; Morice et al., 2010; Trinh et al., 2003). Additional neural targets likely contribute to cocaine's efficacy to increase locomotor activity.

Several lines of research suggest that sigma receptors are a target for cocaine's behavioral effects (Katz et al., 2011; Matsumoto et al., 2003). Sigma receptors are found in the central nervous system and regulate neurotransmitter signaling in pathways related to cocaine's locomotor-activating properties (Hayashi et al., 2010; Walker et al., 1990). Two types of sigma receptors, σ_1 and σ_2, have been classified based on ligand binding and structural biology studies. Cocaine binds to sigma receptors (Sharkey et al., 1988), although its affinity in vitro (Table 1) is several orders of magnitude less than the affinity of the ligands typically used to probe sigma receptors (Matsumoto et al., 2004; Nahas et al., 2008). Multiple structural classes of sigma receptor ligands block the locomotor-activating effects of cocaine in rodents at ligand doses that do not have a significant intrinsic effect on basal locomotor behavior (McCracken et al., 1999; Menkel et al., 1991; Rodvelt et al., 2011a).

The *N*-phenylpropyl-*N*′-substituted piperazines are sigma receptor ligands that have anti-cocaine activity. Matsumoto et al. (2004) reported that *N*-phenylpropyl-*N*′-(4-methoxyphenethyl)piperazine (YZ-067, Fig. 1) and *N*-phenylpropyl-*N*′-(3-methoxyphenethyl)piperazine (YZ-185, Fig. 1) bound to sigma receptors (Table 1) with modest selectivity for the σ_1 sigma receptor type over the σ_2 type. Both YZ-067 and YZ-185 attenuated (~25–95%) cocaine (60 mg/kg)-induced seizures in

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Table 1
Binding affinities and selectivities of *N*-phenylpropyl-*N*′-substituted piperazines for σ_1 and σ_2 sigma receptors.

	N′-piperazine substitution	σ_1 (nM)	σ_2 (nM)	Selectivity (σ_2/σ_1)	Citation
Nahas-3h	4-methoxybenzyl	0.76 (±0.07)	32.8 (±2.93)	43.7	Nahas et al. (2008)
YZ-067	4-methoxyphenethyl	1.3 (±0.3)	28.6 (±1.9)	22	Matsumoto et al. (2004)
YZ-185	3-methoxyphenethyl	1.4 (±0.2)	10.2 (±0.5)	7.3	Matsumoto et al. (2004)
SA4503	3,4-methoxyphenethyl	4.63 (±0.21)	63.09 (±4.33)	13.6	Lever et al. (2006)
Cocaine		2000 (±200)	31,000 (±400)	15	Matsumoto et al. (2002)

Values represent mean (±S.E.M.) Ki values as reported by the citations in the table. Selectivity is the ligand's Ki value for the σ_2 sigma receptor divided by the Ki value for the σ_1 sigma receptor.

mice (Matsumoto et al., 2004) and the goal of the present study was to determine if these ligands could alter cocaine-induced hyperactivity in mice. The present study also investigated *N*-phenylpropyl-*N*′-(4-methoxybenzyl)piperazine (Nahas-3h, Fig. 1), a ligand that exhibits higher selectivity for σ_1 over σ_2 sites than reported for YZ-067 and YZ-185 (Table 1). Nahas-3h has not been examined in a behavioral study. Nahas-3h, YZ-067 and YZ-185 are close structural congeners of 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazine (SA4503, Fig. 1), a σ_1 sigma receptor ligand that attenuates cocaine-induced hyperactivity in mice (Rodvelt et al., 2011a).

2. Material and methods

2.1. Drugs and chemicals

Nahas-3h dihydrochloride salt (Nahas-3h · 2HCl, molecular weight = 397.38 g/mol); YZ-067 dihydrochloride salt, quarter hydrate (YZ-067 · 2HCl · 1/4H_2O, molecular weight = 415.91 g/mol); and YZ-185 dihydrochloride salt, quarter hydrate (YZ-185 · HCl · 1/4H_2O, molecular weight = 415.91 g/mol) were synthesized as described previously (Matsumoto et al., 2004; Nahas et al., 2008) and exhibited appropriate spectral data and combustion analyses. Cocaine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). All drugs were prepared in saline (0.9% w/v) vehicle. Drug doses in the manuscript are expressed as free base weight.

2.2. Apparatus

Locomotor activity was measured by open-field activity monitors (Model# ENV-515, Med Associates Inc.; Georgia, VT) interfaced to a computer running Med Associates Activity Monitor (ver. 4.31) software. Each monitor consisted of a transparent box surrounded by banks of infrared sensors that were connected to the computer.

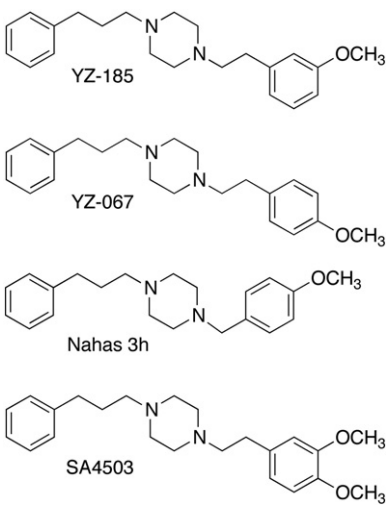

Fig. 1. *N*-phenylpropyl-*N*′-substituted piperazine structures.

2.3. Animals

Male CD-1 mice (Charles River, 20–22 g at arrival) were housed 4 or 5 mice per cage with standard rodent chow and water available ad libitum. The colony was maintained under a 12-h/12-h light/dark cycle and all experiments were conducted during the light phase of the cycle. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Missouri.

2.4. Locomotor activity procedures

The effect of Nahas-3h, YZ-067, and YZ-185 on cocaine-induced hyperactivity was evaluated by procedures similar to those previously described (Rodvelt et al., 2011a). Mice (n = 7–11 mice/group) were acclimated to the monitors for 30–60 min on two consecutive days. On the third consecutive day, mice were placed into monitors for 45 min, injected (i.p.) with Nahas-3h (0.316, 3.16, or 31.6 μmol/kg), YZ-067 (0.1, 0.316, 3.16, 10.0, or 31.6 μmol/kg) or YZ-185 (0.1, 0.316, 3.16, or 31.6 μmol/kg) or saline vehicle. Mice were returned to the monitor for 15 min, injected (i.p.) with 20 mg/kg cocaine (66 μmol/kg) or saline vehicle, and then returned to the monitor for 60 min. The 15 min period between sigma ligand and cocaine injection was selected to allow comparison of the present results to previous findings: YZ-067 and YZ-185 attenuated seizures when injected 15 min prior to cocaine (Matsumoto et al., 2004) and SA4503 attenuated cocaine-induced hyperactivity when administered 15 min before the stimulant (Rodvelt et al., 2011a). The 20 mg/kg cocaine dose was selected based on the results of previous experiments (Rodvelt et al., 2011a) in which mice were administered 10, 20 or 30 mg/kg cocaine or saline and locomotor activity was measured: A dose-dependent increase in activity was observed, with a ~3-fold increase in activity in mice administered 20 mg/kg cocaine compared to those administered saline.

Based on the results of the experiment with YZ-185 and 20 mg/kg cocaine (see Section 3.3), a follow-up experiment was conducted where mice were injected (i.p.) with 31.6 μmol/kg YZ-185, followed by a larger (30 mg/kg) cocaine dose.

Distance traveled (in cm) during the 60-min period after cocaine or saline injection was analyzed. Separate statistical analyses were performed for Nahas-3h, YZ-067 and YZ-185. In these analyses, a 3-way repeated measures analysis of variance (RM-ANOVA) was performed with Sigma Ligand Dose and Cocaine Dose as between-group factors and Time (twelve 5-min intervals) as a within-subjects factor. Where appropriate ($p < 0.05$), simple main effect and Tukey post-hoc analyses were performed. To evaluate the dose–response relationship, the total distance traveled during the 60-min period after cocaine injection was summed for each mouse, and these data were analyzed by linear regression.

3. Results

3.1. Effect of Nahas-3h on cocaine-induced hyperactivity

Distance traveled for mice administered Nahas-3h is presented in Fig. 2. Analyses revealed a significant 3-way interaction of Nahas-3h Dose, Cocaine Dose, and Time ($F(33,649) = 1.73$, $p < 0.05$). Post hoc