Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 86 (2007) 86–91
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Effects of UMB24 and (±)-SM 21, putative σ_2-preferring antagonists, on behavioral toxic and stimulant effects of cocaine in mice

Rae R. Matsumoto [a,b,*], Buddy Pouw [a], Aisha L. Mack [a], Antawan Daniels [a], Andrew Coop [c]

[a] Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, USA
[b] Department of Pharmacology, School of Pharmacy, University of Mississippi, 303 Faser Hall, University, MS 38677, USA
[c] Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD 21201, USA

Received 18 August 2006; received in revised form 28 November 2006; accepted 9 December 2006
Available online 22 December 2006

Abstract

Earlier studies have demonstrated that antagonism of σ_1 receptors attenuates the convulsive, lethal, locomotor stimulatory and rewarding actions of cocaine in mice. In contrast, the contribution of σ_2 receptors is unclear because experimental tools to selectively target this subtype are unavailable. To begin addressing this need, we characterized UMB24 (1-(2-phenethyl)-4-(2-pyridyl)-piperazine) and (±)-SM 21 (3α-tropanyl-2-(4-chorophenoxy)butyrate) in receptor binding and behavioral studies. Receptor binding studies confirmed that UMB24 and (±)-SM 21 display preferential affinity for σ_2 over σ_1 receptors. In behavioral studies, pretreatment of Swiss Webster mice with UMB24 or (±)-SM 21 significantly attenuated cocaine-induced convulsions and locomotor activity, but not lethality. When administered alone, (±)-SM 21 produced no significant effects compared to control injections of saline, but UMB24 had locomotor depressant actions. Together, the data suggest that σ_2 receptor antagonists have the potential to attenuate some of the behavioral effects of cocaine, and further development of more selective, high affinity ligands are warranted.

Keywords: Cocaine; σ receptors; UMB24; (±)-SM 21; Convulsions; Locomotor activity

1. Introduction

σ receptors are unique proteins with an amino acid sequence, drug selectivity pattern, and anatomical distribution that is distinctly different from other mammalian proteins (Guitart et al., 2004; Matsumoto et al., 2003). There are two established subtypes, σ_1 and σ_2, which are localized in many motor, limbic, and endocrine regions of the brain (Bouchard and Quirion, 1997).

Cocaine interacts with σ receptors at concentrations that can be achieved in vivo (Sharkey et al., 1988). Pharmacological antagonists and antisense oligonucleotides with a high degree of selectivity for σ receptors attenuate a number of cocaine-induced behaviors, suggesting that these receptors are promising targets for the development of pharmacotherapies to treat cocaine abuse (Matsumoto et al., 2002, 2003; Maurice et al., 2002). Of the two established σ receptor subtypes, the existing data support a role for σ_1 receptors in mediating anticocaine effects, but the contributions of σ_2 receptors are less clear.

One of the difficulties in evaluating the role of σ_2 receptors is the dearth of selective pharmacological antagonists for this subtype and the lack of an amino acid sequence from which antisense oligonucleotides that target these receptors can be developed. Although reports of σ_2 ligands abound in the literature (Bertha et al., 1995; Bowen et al., 1995a,b; Kassiou et al., 2005; Mach et al., 1995; Maeda et al., 2002; Maier and Wunsch, 2002; Perregaard et al., 1995; Vangveravong et al., 2006), the primary criterion for these claims appears to be reasonable affinity for this receptor subtype relative to σ_1, with little consideration for selectivity as compared to non-σ binding sites. In addition, the few σ_2 compounds that have been tested in functional studies appear to act as agonists (Bowen et al., 1995a,b; Crawford et al., 2002; Vilner and Bowen, 2000). One exception is (±)-SM 21 (3α-tropanyl-2-(4-chorophenoxy)butyrate), a σ_2 preferring compound, which produces antagonist

* Corresponding author. Department of Pharmacology, School of Pharmacy, University of Mississippi, 303 Faser Hall, University, MS 38677, USA. Tel.: +1 662 915 1466; fax: +1 662 915 5148.
E-mail address: rmatsumo@olemiss.edu (R.R. Matsumoto).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.12.011

actions against dystonic head movements and cocaine-induced behaviors in rodents (Ghelardini et al., 2000; Matsumoto and Mack, 2001). Both of these endpoints have been shown in earlier studies to possess a strong σ receptor-mediated component (Matsumoto et al., 1995, 2003).

Recently, AC927 (phenethylpiperidine), a mixed $\sigma_{1/2}$ compound, was shown to produce antagonist actions through σ_2 receptors under in vitro conditions (Crawford et al., 2002). Among piperazine analogs of AC927 which were subsequently developed, UMB24 (1-(2-phenethyl)-4-(2-pyridyl)-piperazine) has been reported as a potential lead for the development of selective σ_2 receptor agents (Maeda et al., 2002). Due to its structural relationship to AC927, it was conceivable that UMB24 also possessed antagonist actions at σ_2 receptors. Therefore, in the present study, UMB24 was further characterized to evaluate its relative selectivity for σ_2 receptors and its ability to attenuate cocaine-induced behaviors in mice. The putative σ_2-preferring antagonist (±)-SM 21 was used as a reference compound for these studies (Ghelardini et al., 2000; Matsumoto and Mack, 2001).

2. Methods

2.1. Drugs and chemicals

UMB24 (1-(2-phenethyl)-4-(2-pyridyl)-piperazine) was synthesized as described previously (Maeda et al., 2002). (±)-SM 21 maleate was purchased from Tocris (Ballwin, MO). The structures of these compounds are shown in Fig. 1. Cocaine hydrochloride was obtained from Sigma (St. Louis, MO). The radioligands were procured from Dupont/New England Nuclear/Perkin Elmer (Boston, MA). All other chemicals and reagents were obtained from standard commercial suppliers (Aldrich, Milwaukee, WI; Sigma, St. Louis, MO).

2.2. Animals

Male, Sprague Dawley rats (150–200 g, Harlan, Indianapolis, IN) were used for the receptor binding studies. Male, Swiss Webster mice (23–33 g, Harlan, Indianapolis, IN; Charles River, Portage, MI) were used for the behavioral experiments. The animals were housed in groups with a 12:12 h light/dark cycle and ad libitum food and water. The mice were randomly assigned to experimental groups, with at least two different shipments being tested on separate days to form the final data set for each dose/drug group. All procedures were performed as approved by the Institutional Animal Care and Use Committees at the University of Oklahoma Health Sciences Center and the University of Mississippi.

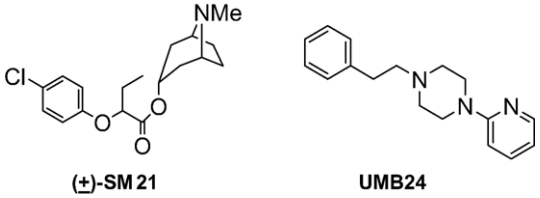

Fig. 1. Chemical structures of UMB24 and (±)-SM 21.

2.3. Radioligand binding studies

UMB24 and (±)-SM 21 were evaluated in competition binding assays using rat brain homogenates (400–500 μg protein, unless specified otherwise) and methods previously described (Matsumoto et al., 2002). Briefly, σ_1 receptors were labeled using 5 nM [^{3}H](+)-pentazocine. σ_2 receptors were labeled with 3 nM [^{3}H]di-o-tolylguanidine, in the presence of 300 nM (+)-pentazocine to mask σ_1 receptors. Nonspecific binding was determined in the presence of 10 μM haloperidol. Twelve concentrations of test ligand (0.05–10,000 nM) were incubated for 120 min at 25 °C to evaluate their ability to displace the binding of the radioligand.

The affinities of the compounds for dopamine, serotonin, and norepinephrine transporters were also determined because cocaine interacts with these monoamine transporters. The membrane preparation and assay conditions were modified slightly from those previously described (Boja et al., 1994). Briefly, dopamine transporters were assayed in 2 mg wet weight rat striatal tissue using 0.5 nM [^{3}H]WIN35,428; nonspecific binding was determined with 50 μM cocaine. Serotonin transporters were assayed in 1.5 mg wet weight rat brainstem tissue using 0.2 nM [^{3}H]paroxetine; nonspecific binding was determined with 1.5 μM imipramine. Norepinephrine transporters were assayed in 8 mg wet weight rat cerebral cortical tissue using [^{3}H]nisoxetine; nonspecific binding was determined with 4 μM desipramine.

In addition, the relative selectivities of UMB24 and (±)-SM 21 were determined for dopamine receptors, opioid receptors, and phencyclidine sites on NMDA receptors because many historic σ receptor ligands interact with them (Guitart et al., 2004). The affinities of these compounds for 5-HT$_2$ receptors were also examined because antagonists at these sites are capable of attenuating the toxicity of cocaine (Ritz and George, 1997). The affinities of the ligands were measured in homogenates from rat brain minus cerebellum using previously published methods (Matsumoto et al., 1995). Briefly, dopamine (D_2) receptors were labeled with 5 nM [^{3}H](−)-sulpiride; nonspecific binding was determined with 1 μM haloperidol. Opioid (κ) receptors were labeled with 2 nM [^{3}H]bremazocine; nonspecific binding was determined with 10 μM levallorphan. NMDA receptors were labeled with 5 nM [^{3}H]TCP (1-[1-(2-thienyl)cyclohexyl]piperidine); nonspecific binding was determined with 10 μM cyclazocine. 5-HT$_2$ receptors were labeled with 2 nM [^{3}H]ketanserin; nonspecific binding was determined with 1 μM mianserin. The incubations were performed for 60 min at 25 °C for the dopamine and opioid receptor assays, 30 min at 37 °C for the 5-HT$_2$ receptor assays, and for 60 min at 4 °C for the NMDA receptor assays.

All assays were terminated with the addition of ice-cold buffer and vacuum filtration through glass fiber filters. Counts were extracted from the filters using Ecoscint cocktail (National Diagnostics, Manville, NJ) for at least 8 h prior to counting.

2.4. Cocaine-induced behavioral toxicity

Cocaine-induced convulsions and lethality were evaluated in separate studies. For the convulsion studies, each mouse ($n=85$) was pretreated with UMB24 (0–10 mg/kg, i.p.) or (±)-SM 21 (0–10 mg/kg, i.p.), followed 15 min later with a convulsive dose of cocaine (70 mg/kg, i.p.). For the lethality studies, each mouse ($n=83$) was pretreated with UMB24 (0–50 mg/kg, i.p.) or (±)-SM 21 (0–20 mg/kg, i.p.), followed 15 min later with a lethal dose of cocaine (125 mg/kg, i.p.). The cocaine doses represent the lowest ones that reliably produced convulsions or death in 100% of the animals. Mice were monitored over a 30 min period for the occurrence of convulsions (operationally defined as a loss of righting reflexes for at least 5 s together with the presence of clonic limb movements) or death. Fisher's exact tests were used to analyze the data.

2.5. Cocaine-induced locomotor activity

The locomotor studies were conducted as described previously (Matsumoto et al., 2002). Following a habituation period in the testing chamber of an automated activity monitor (San Diego Instruments, San Diego, CA, USA), each mouse ($n=102$) was injected with UMB24 (0–1 mg/kg, i.p.) or (±)-SM 21 (0–1 mg/kg, i.p.) alone or followed 15 min later with a locomotor stimulatory dose of cocaine (10 mg/kg, i.p.). Horizontal locomotor activity was then quantified for 30 min as the number of disruptions made by each mouse in the 4×4 photobeam array surrounding each testing chamber. The dose of cocaine used is the lowest one that produced maximal effects in earlier dose response characterizations (McCracken et al., 1999).

3. Results

3.1. Radioligand binding assays

The affinities of UMB24 and (±)-SM 21 for σ_2 receptors, compared to other binding sites of interest, are summarized in Table 1. The competition binding studies confirmed that UMB24 and (±)-SM 21 have preferential affinity for σ_2 receptors, as compared to σ_1 receptors (Mach et al., 1999; Maeda et al., 2002). (±)-SM 21 exhibited nearly 10-fold preferential affinity for σ_2 receptors, as compared to σ_1 receptors, while UMB24 exhibited only about a 2-fold preference.

Table 1
Binding affinities of σ_2 receptor preferring compounds (K_i in nM)

Sigma receptor subtypes:				
	σ_1 receptor	σ_2 receptor		
UMB24	322±32	170±5		
(±)-SM 21	1050±63	145±7		
Monoamine transporters:				
	Dopamine	5-HT	Norepinephrine	
UMB24	3476±298	2933±52	3560±628	
(±)-SM 21	176±30	>10 000	2005±325	
Other receptors:				
	Opioid (κ)	NMDA	Dopamine (D_2)	5-HT$_2$
UMB24	>10 000	>10 000	305±26	595±55
(±)-SM 21	>10 000	>10 000	885±34	476±7

Competition binding assays were performed in rat brain homogenates using standard methods. Values represent mean ± SEM from at least three assays, each performed in duplicate. Values of >10 000 indicate that there was less than 30% displacement of the radioligand at that concentration.

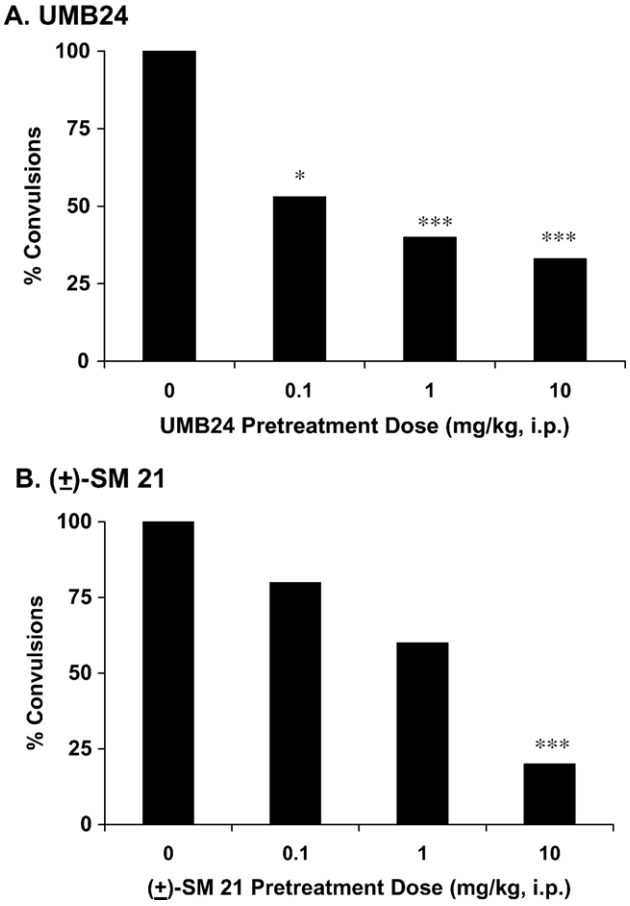

Fig. 2. Effects of UMB24 and (±)-SM 21 on cocaine-induced convulsions. Male, Swiss Webster mice were pretreated with UMB24 or (±)-SM 21 (0–10 mg/kg, i.p.) followed 15 min later with a convulsive dose of cocaine (70 mg/kg, i.p.). UMB24 and (±)-SM 21 significantly attenuated cocaine-induced convulsions (*$p<0.05$, **$p<0.01$, ***$p<0.005$).

In contrast to their nanomolar affinities for σ_2 receptors, the compounds for the most part had micromolar affinities for monoamine transporters. The exception was (±)-SM 21, which exhibited similar affinity for dopamine transporters as σ_2 receptors (Table 1). UMB24 and (±)-SM 21 did not display measurable binding to opioid or NMDA receptors, although they had moderate affinities for dopamine D_2 and 5-HT$_2$ receptors.

3.2. Cocaine-induced behavioral toxicity

The ability of UMB24 and (±)-SM 21 to attenuate cocaine-induced convulsions is summarized in Fig. 2. Fisher's exact tests revealed that pretreatment of mice with UMB24 or (±)-SM 21 attenuated cocaine-induced convulsions in a dose-dependent

manner ($p<0.005$). However, none of the tested doses of UMB24 or (±)-SM 21 attenuated cocaine-induced lethality, even at doses higher than those used to reduce cocaine-induced convulsions.

3.3. Cocaine-induced locomotor activity

The effects of UMB24 and (±)-SM 21 on basal and cocaine-induced locomotor activity are summarized in Fig. 3. Pretreatment of mice with UMB24 significantly attenuated the hyperactivity elicited by cocaine (F (2, 31)=3.49, $p<0.05$). Post-hoc Dunnett's tests revealed that the reduction in cocaine-induced behavior was significant at the 1 mg/kg dose of UMB24 ($q=2.62$, $p<0.05$). The putative σ_2 receptor antagonist (±)-SM 21 also significantly attenuated cocaine-induced locomotor activity (F (2, 23)=5.01, $p<0.05$). Post-hoc Dunnett's test confirmed that the antagonism of cocaine-induced behavior was significant for both doses of (±)-SM 21: 0.1 mg/kg ($q=2.81$, $p<0.05$) and 1 mg/kg ($q=2.53$, $p<0.05$).

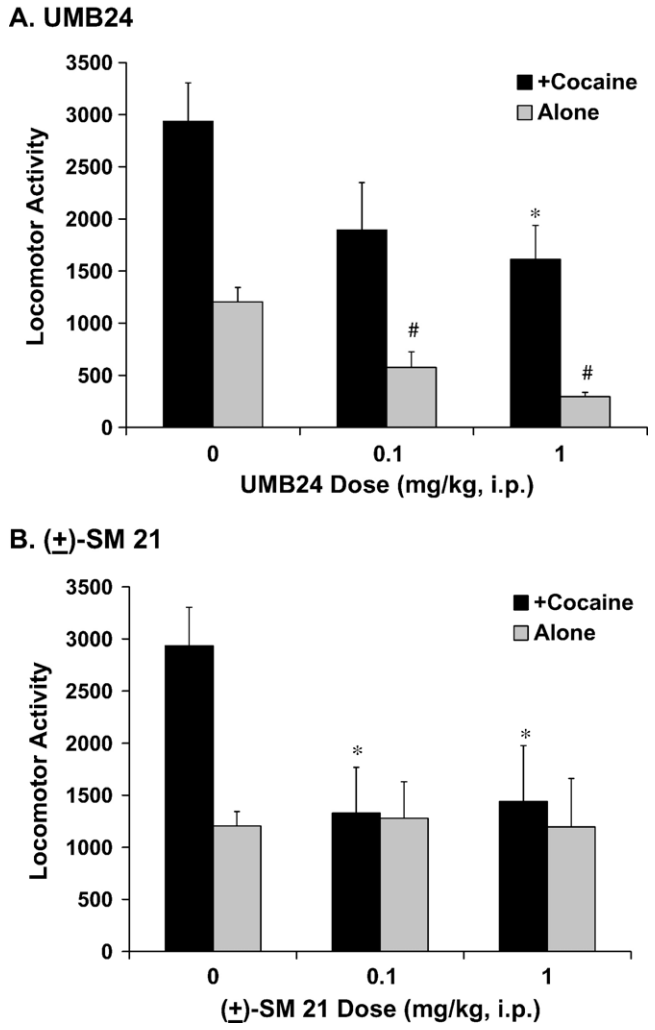

Fig. 3. Effects of UMB24 and (±)-SM 21 on basal and cocaine-induced locomotor activity. Male, Swiss Webster mice were injected (i.p.) with UMB24 or (±)-SM 21 (0, 0.1 or 1 mg/kg, i.p.) alone or as a 15 min pretreatment to a locomotor stimulatory dose of cocaine (10 mg/kg, i.p.). Horizontal locomotor activity was quantified for 30 min using an automated activity monitoring system. UMB24 produced a significant locomotor depressant effect on its own ($^{\#}p<0.01$), and also attenuated cocaine-induced locomotor activity ($^{*}p<0.05$). (±)-SM 21 had no significant effect of its own on locomotor activity, although it significantly attenuated cocaine-induced locomotor activity ($^{*}p<0.05$).

In addition to reducing the locomotor activity elicited by cocaine, UMB24 alone significantly decreased basal activity (F (2, 36)=24.16, $p<0.0005$). Post-hoc Dunnett's tests revealed that basal locomotor activity differed significantly from the saline control for both doses of UMB24: 0.1 mg/kg ($q=3.46$, $p<0.01$) and 1 mg/kg ($q=6.91$, $p<0.01$). In contrast, significant alterations in basal locomotor activity were not observed with (±)-SM 21 (F (2, 26)=0.025, n.s.).

4. Discussion

The σ_2 preferring compounds, UMB24 and (±)-SM 21, produced similar effects against cocaine-induced behaviors. UMB24 and (±)-SM 21 both significantly attenuated cocaine-induced convulsions and locomotor activity. However, the compounds did not prevent the lethal effects of cocaine. One reason that the σ_2 preferring ligands may not have prevented cocaine-induced lethality is that important target organs such as the heart are enriched in σ_1 receptors. Over 90% of the σ receptors in the heart are of the σ_1 subtype (Matsumoto et al., 2001; Novakova et al., 1995), which may contribute to the ability of σ_1, but perhaps not σ_2, antagonists to attenuate cocaine-induced lethality. In contrast, the ability of UMB24 and (±)-SM 21 to attenuate cocaine-induced convulsions and locomotor activity suggests that σ_2 receptors can be targeted to mitigate many cocaine-induced behaviors.

Earlier studies showed that pretreatment of mice with (±)-SM 21 prevented cocaine-induced convulsions, but that the efficacy of the intervention plateaued around 50% protection (Matsumoto and Mack, 2001). However, in the present study, both UMB24 and (±)-SM 21 dose dependently attenuated cocaine-induced convulsions, suggesting that antagonism of σ_2 receptors contributes to the anticonvulsive actions of σ receptor ligands. When compared to one another, UMB24 produced better protective actions than (±)-SM 21 against cocaine-induced convulsions. The protective actions of UMB24 occurred across as wider range of doses and the protected animals had a greater tendency to look normal. In contrast, (±)-SM 21-treated mice that did not meet the criterion for cocaine-induced convulsions tended to exhibit noticeable seizure-related behaviors such as pronounced locomotor excitation with ataxia. A possible reason that (±)-SM 21 may not provide as good of a protective effect against cocaine-induced convulsions, as compared to UMB24, involves its weaker affinity for σ_1 receptors. Earlier studies have shown that σ_1 receptor antagonists provide significant protection against cocaine-induced convulsions (Matsumoto et al., 2003). Therefore, compounds that elicit antagonist actions through both σ_1 and σ_2 receptors may convey better protective effects against cocaine-induced convulsions than targeting either subtype alone.

The ability of UMB24 and (±)-SM 21 to prevent cocaine-induced locomotor activity occurred at low doses, and this is consistent with reports that the σ_2 subtype has an important role in motor function (Walker et al., 1993). However, the two compounds differed in their effects on basal locomotor activity.

In contrast to (±)-SM 21, which attenuated cocaine-induced locomotor activity at doses that alone had no effects on basal locomotor activity, UMB24 alone produced locomotor depressant actions. Potential explanations for the different effects on basal activity levels most likely relate to the non-σ mediated actions of the compounds. First, UMB24 has higher affinity for dopamine D_2 receptors, compared to (±)-SM 21. If UMB24 is an antagonist at D_2 receptors, it would explain the locomotor depressant actions under basal conditions (Zhang and Creese, 1993). Second, (±)-SM 21 has higher affinity for dopamine transporters, as compared to UMB24. It is therefore possible that competing interactions between dopamine transporters and σ_2 receptors underlie the pattern of results. Compounds that bind to dopamine transporters tend to inhibit dopamine uptake and produce cocaine-like actions (Uhl et al., 2002), making it likely that (±)-SM 21 possesses some locomotor stimulant actions through dopamine transporters. Since σ_2 receptor agonists can stimulate locomotor activity (Walker et al., 1993), it is possible that under certain conditions, locomotor depressant actions could result through σ_2 receptor-mediated antagonism of tonic locomotor tone. If σ_2 antagonists depress basal locomotor activity under the conditions of our study, competing stimulant effects through dopamine transporters may mask potential locomotor depressant actions of (±)-SM 21 under basal conditions. Although additional studies are needed to further define the contribution of each of these mechanisms to basal locomotor function, the data with regard to cocaine are clear. Low doses of both UMB24 and (±)-SM 21 attenuate cocaine-induced locomotor activity, suggesting the importance of the σ_2 subtype in mediating the locomotor stimulant actions of cocaine.

The results observed herein suggest that future studies to resolve racemic SM 21 for further characterization of each isomer are warranted. These characterizations should provide valuable insight into configurations that convey favorable affinity and selectivity for σ_2 receptors, as compared to σ_1 receptors and non-σ binding sites. Additional modifications to improve the affinity and selectivity of UMB24 for σ_2 receptors also represent a potential avenue for further investigations.

When taken together, the data suggest that UMB24 and (±)-SM 21 can attenuate cocaine-induced behaviors through functional antagonism of σ_2 receptors. However, conclusive statements regarding the role of σ_2 receptors in the actions of cocaine must await additional studies using truly selective and high affinity σ_2 receptor compounds. Future efforts to improve the selectivity and affinity of UMB24 and (±)-SM 21 could lead to the development of true σ_2 receptor antagonists, which would allow a conclusive determination of the role of this subtype in the actions of cocaine.

Acknowledgements

We appreciate the technical assistance of Veena Shetty and Erika Ayala. This project was supported by grants from the National Institute on Drug Abuse (DA11979, DA13978) and an Independent Scientist Award for AC (DA19634). AD received support from NIDA as a post-baccalaureate fellow; ALM and EA were participants in the NIDA Summer Fellows Program.

References

Bertha CM, Vilner BJ, Mattson MV, Bowen WD, Becketts K, Xu H, et al. (E)-8-Benzylidene derivatives of 2-methyl-5-(3-hydroxyphenyl)morphans: highly selective ligands for the sigma 2 receptor subtype. J Med Chem 1995;38:4776–85.

Boja JW, Kuhar MJ, Kopajtic T, Yang E, Abraham P, Lewin AH, et al. Secondary amine analogues of 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters and N-norcocaine exhibit enhanced affinity for serotonin and norepinephrine transporters. J Med Chem 1994;37:1220–3.

Bouchard P, Quirion R. [^{3}H]1,3-Di(2-tolyl)guanidine and [^{3}H](+)-pentazocine binding sites in the rat brain: autoradiographic visualization of the putative sigma$_1$ and sigma$_2$ receptor subtypes. Neuroscience 1997;6:467–77.

Bowen WD, Bertha CM, Vilner BJ, Rice KC. CB-64D and CB-184: ligands with high σ_2 receptor affinity and subtype selectivity. Eur J Pharmacol 1995a;278:257–60.

Bowen WD, Vilner BJ, Williams W, Bertha CM, Kuehne ME, Jacobson AE. Ibogaine and its congeners are sigma 2 receptor-selective ligands with moderate affinity. Eur J Pharmacol 1995b;279:R1–3.

Crawford KW, Coop A, Bowen WD. σ_2 receptors regulate changes in sphingolipid levels in breast tumor cells. Eur J Pharmacol 2002;443:207–9.

Ghelardini C, Galeotti N, Bartolini A. Pharmacological identification of SM-21, the novel σ_2 antagonist. Pharmacol Biochem Behav 2000;67:659–62.

Guitart X, Codony X, Monroy X. Sigma receptors: biology and therapeutic potential. Psychopharmacology 2004;174:301–19.

Kassiou M, Dannals RF, Liu X, Wong DF, Ravert HT, Scheffel UA. Synthesis and in vivo evaluation of a new PET radioligand for studying sigma-2 receptors. Bioorg Med Chem 2005;13:3623–6.

Mach RH, Smith CR, Childers SR. Ibogaine possesses a selective affinity for sigma 2 receptors. Life Sci 1995;57:PL57–62.

Mach RH, Wu L, West T, Whirrett BR, Childers SR. The analgesic tropane anaogue (±)-SM 21 has a high affinity for σ_2 receptors. Life Sci 1999;64:PL131–7.

Maeda DY, Williams W, Kim WE, Thatcher LN, Bowen WD, Coop A. N-Arylalkylpiperidines as high-affinity sigma-1 and sigma-2 receptor ligands: phenylpropylamines as potential leads for selective sigma-2 agents. Bioorg Med Chem Lett 2002;2:497–500.

Maier CA, Wunsch B. Novel spriopiperidines as high potent and subtype selective sigma-receptor ligands. Part 1. J Med Chem 2002;45:438–48.

Matsumoto RR, Mack AL. (±)-SM 21 attenuates the convulsive and locomotor stimulatory effects of cocaine in mice. Eur J Pharmacol 2001;417:R1–2.

Matsumoto RR, Bowen WD, Tom MA, Vo VN, Truong DD, de Costa BR. Characterization of two novel σ receptor lignads: antidystonic effects in rats suggest s receptor antagonism. Eur J Pharmacol 1995;280:301–10.

Matsumoto RR, Hewett KL, Pouw B, Bowen WD, Husbands SM, Cao JJ, et al. Rimcazole analogs attenuate the convulsive effects of cocaine: correlation with binding to sigma receptors rather than dopamine transporters. Neuropharmacology 2001;41:878–86.

Matsumoto RR, McCracken KA, Pouw B, Zhang Y, Bowen WD. Involvement of sigma receptors in the behavioral effects of cocaine: evidence from novel ligands and antisense oligodeoxynucleotides. Neuroharmacology 2002;42:1043–55.

Matsumoto RR, Liu Y, Lerner M, Howard EW, Brackett DJ. σ Receptors: potential medications development target for anti-cocaine agents. Eur J Pharmacol 2003;469:1–12.

Maurice T, Martin-Fardon R, Romieu P, Matsumoto RR. Sigma$_1$ (σ_1) receptor antagonists represent a new strategy against cocaine addiction and toxicity. Neurosci Biobehav Rev 2002;26:499–527.

McCracken KA, Bowen WD, de Costa BR, Matsumoto RR. Two novel σ receptor ligands, BD1047 and LR172, attenuate cocaine-induced toxicity and locomotor activity. Eur J Pharmacol 1999;370:225–32.

Novakova M, Ela C, Barg J, Vogel E, Hasin Y, Eilam Y. Ionotropic action of sigma receptor ligands in isolated cardiac myocytes from adult rats. Eur J Pharmacol 1995;286:19–30.

Perregaard J, Moltzen EK, Meier E, Sanchez C. Sigma ligands with subnanomolar affinity and preference for the σ_2 binding site. 1. 3-(omega-aminoalkyl)-1H-indoles. J Med Chem 1995;38:1998–2008.

Ritz MC, George FR. Cocaine-induced convulsions: pharmacological antagonism at serotonergic, muscarinic and sigma receptors. Psychopharmacology 1997;129:299–310.

Sharkey J, Glen KA, Wolfe S, Kuhar MJ. Cocaine binding at σ receptors. Eur J Pharmacol 1988;149:171–4.

Uhl GR, Hall FS, Sora I. Cocaine reward, movement and monoamine transporters. Mol Psychiatry 2002;7:21–6.

Vangveravong S, Xu J, Zeng C, Mach RH. Synthesis of N-substituted 9-azabicyclo[3.3.1]nonan-3α-yl-carbamate analogs as σ_2 receptor ligands. Bioorg Med Chem 2006;14:6988–97.

Vilner BJ, Bowen WD. Modulation of cellular calcium by sigma-2 receptors: release from intracellular stores in human SK-N-SH neuroblastoma cells. J Pharmacol Exp Ther 2000;292:900–11.

Walker JM, Bowen WD, Patrick SL, Williams WE, Mascarella SW, Bai X, et al. A comparison of (−)-deoxybenzomorphans devoid of opiate activity with their dextrorotatory phenolic counterparts suggests role of σ_2 receptors in motor function. Eur J Pharmacol 1993;231:61–8.

Zhang M, Creese I. Antisense oligodeoxynucleotide reduces brain dopamine D_2 receptors: behavioral correlates. Neurosci Lett 1993;161:223–6.