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Trishomocubanes: Novel σ ligands modulate cocaine-induced behavioural effects

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Abstract

Trishomocubane analogues TC1 (*N*-(3′-fluorophenyl)ethyl-4-azahexacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol) and TC4 (*N*-(3′-fluorophenyl)methyl-4-azahexacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ol) were evaluated for their modulatory effects on locomotor activity as well as interactions with cocaine-induced responses. TC1 and TC4 have high affinity and moderate to high selectivity for σ_1 (Ki=10 nM, σ_1/σ_2=0.03) and σ_2 (Ki=20 nM, σ_1/σ_2=7.6) receptor subtypes respectively. Both compounds have negligible affinity for the dopamine (DAT), serotonin (SERT), and norepinephrine (NET) transporters. In behavioural studies, TC1 produced a dose-related inhibition in spontaneous locomotor activity measured in a Digiscan apparatus. TC1 attenuated the stimulatory locomotor effect of 20 mg/kg cocaine with a half-maximal depressant activity (ID_{50}) of 38.6 mg/kg. TC1 (dose range of 25 to 100 mg/kg) also partially substituted for the effect of cocaine (10 mg/kg) in a discriminative stimulus task, involving the trained discrimination between cocaine and saline using a two-lever choice method. Following a dose of 50 mg/kg TC1, a maximum of 31% substitution was reached. The response rate was reduced to 56% of vehicle control following a TC1 dose of 100 mg/kg. These behavioural effects suggest that TC1 can act as an antagonist via the σ_1 receptor. In contrast to TC1, TC4 produced a stimulant effect in locomotor activity with the ED_{50} estimated at 0.94 mg/kg. In addition, TC4 failed to inhibit cocaine-induced stimulation; neither did it substitute for the discriminative stimulus effects of cocaine. TC4 thus appears to interact predominantly with the σ_2 receptor subtype (σ_1/σ_2=7.6) which may result in dopamine stimulation independent of the effects of cocaine. The differential effect of TC1 and TC4 warrants further study of the mechanism of these actions. Present data also suggests a potential role for trishomocubane analogues in developing medication or research tools for cocaine addiction.

Keywords: σ receptors; Cocaine; Polycyclic; Trishomocubanes

1. Introduction

Sigma (σ) receptors, first discovered in 1976 (Martin et al., 1976) comprise two subtypes, namely σ_1 and σ_2 (Hellewell and Bowen, 1990), which are found in the central nervous system (CNS) and in peripheral organs. σ receptors have been implicated in the modulation of central neurotransmitter systems, including noradrenergic, glutamatergic and dopaminergic (Gonzalez-Alvear and Werling, 1994; Weatherspoon and Werling, 1999) and have been reported to block stimulant effects of cocaine (Izenwasser et al., 1993; Menkel et al., 1991; Witkin et al., 1993). Several σ receptor ligands have been shown to attenuate cocaine-induced toxicity and locomotor activity (McCracken et al., 1999), including σ_1 ligands, such as rimcazole (Cao et al., 2003), (+)SKF 10047 (Ritz and George, 1997), BD1063, BD1008, BD1060, BD1067 (Matsumoto et al., 2004, 2001), NE100 and BD1047 (Romieu et al., 2000),

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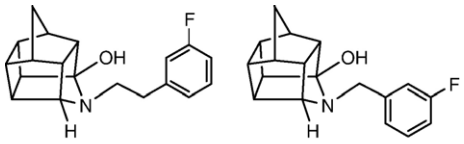

Fig. 1. Trishomocubanes chemical structures; TC1 and TC4.

BMY14802 (Ujike et al., 1996), (+)-3-PPP (Ujike et al., 1992), as well as the σ_2 ligands ibogaine (Itzhak and Ali, 1998), and SM21 (Matsumoto and Mack, 2001). There is also evidence that the σ_1 related neuroactive steroids, DHEA and pregnenolone, modulate cocaine-induced reward (Romieu et al., 2003). The purported mechanisms of action are interaction of σ ligands with dopamine transporter (DAT), sensitization of σ receptors by cocaine administration, direct antagonism of σ receptors or a combination. These findings suggest that σ receptors may be potential targets for development of anti-cocaine agents.

We have previously developed a series of novel σ receptor ligands based on a trishomocubane motif (Liu et al., 2001a) (Fig. 1). Selected compounds from this series were examined in competitive binding studies in which all molecules blocked the specific binding of a radiolabelled σ ligand (4-[^{123}I]IBP) *in vivo* in the brain as well as in peripheral organs (Liu et al., 2005a). In functional studies, four of the analogues, including TC1 and TC4, attenuated amphetamine-stimulated dopamine release *in vitro*, thereby identifying them as σ_2 receptor agonists in that assay (Liu et al., 2001a,b).

In the present study, the 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol trishomocubanes TC1, a high affinity σ_1 receptor ligand (Ki=10 nM, σ_1/σ_2=0.03), and TC4, a high affinity σ_2 ligand (Ki=20 nM, σ_1/σ_2=7.6) (Fig. 1), were evaluated for their behavioural effects on locomotor activity as well as interactions with cocaine-induced actions.

2. Material and methods

2.1. Drugs

Trishomocubane analogues were synthesized in The Adrien Albert Medicinal Chemistry Laboratory, the Department of Pharmacology at the University of Sydney (Liu et al., 2001a).

2.2. Animals

For studies of spontaneous locomotor activity male Swiss-Webster mice (Hsd:ND4, aged 2-3 month) were used. For studies of the discriminative-stimulus effects of cocaine, six male Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg) from saline using a two-lever choice methodology. All procedures were carried out in accordance to institutional approvals for animal experimentation within the Department of Pharmacology and Neuroscience, University of North Texas Health Science Center at Fort Worth (contract No. N01DA-7-8076 and N01DA-2-8822).

2.3. Methods

Locomotor activity was measured using 40 Digiscan locomotor activity testing chambers (40.5×40.5×30.5 cm) housed in sets of two, within sound-attenuating chambers. A panel of infrared beams (16 beams) and corresponding photodetectors were located in the horizontal direction along the sides of each activity chamber. A 7.5-W incandescent light above each chamber provided dim illumination. Fans provided an 80-dB ambient noise level within the chamber. Separate groups of 8 non-habituated male Swiss-Webster mice (Hsd: ND4, aged 2–3 mo.) were injected via the intraperitoneal (i.p.) route with either vehicle (2% methylcellulose) or test compound (TC1 or TC4) at selected doses, immediately (for TC4 study) or 20 min prior (for TC1 study) to locomotor activity testing. In all studies horizontal activity (interruption of photocell beams) was measured for 1-h within 10-min periods.

Compound and cocaine interaction studies were performed using the same apparatus. Twenty minutes following i.p. injection of vehicle or test compound (TC1 or TC4) at selected doses, groups of 8 non-habituated male Swiss-Webster mice (Hsd:ND4, aged 2–3 mo.) were injected i.p. with either 0.9% saline or 20 mg/kg cocaine and placed in the Digiscan apparatus for a 1-h session.

Discriminative stimulus effects of the test compounds were assessed according to the following protocol. Six male Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg) from saline using a two-lever choice methodology. Food was available as a reinforcer under a fixed ratio 10 schedule (FR 10) when responding occurred on the injection appropriate lever. All tests were performed in standard, commercially available chambers (Coulbourn Instruments), using 45 mg food Pellets (Bioserve) as reinforcers.

Training sessions occurred in a double alternating fashion, and tests were conducted between pairs of identical training sessions (i.e., between either two saline or two cocaine training sessions). Tests occurred only if, in the two preceding training sessions, subjects met the criteria of emitting 85% of responses on the injection correct lever for both the first reinforcer (first fixed ratio) and the total session. Test sessions lasted for 20 min, or until twenty reinforcers had been obtained. Doses of the test compound for which fewer than three rats completed the first fixed ratio were not considered in the characterization of discriminative stimulus effects.

2.4. Data analysis

In all spontaneous locomotor activity studies, horizontal activity (interruption of photocell beams) was measured for 1-h within 10-min periods. Testing was conducted with one mouse per activity chamber.

Each dose-effect curve was analyzed by a one-way, repeated measures analysis of variance (ANOVA) and subsequent planned comparisons. When assessing the stimulant effects of TC4 in locomotor activity, data were also analyzed by TableCurve 2D v. 2.03 software (jandel Scientific), by which the mean average horizontal activity counts/10 min for this

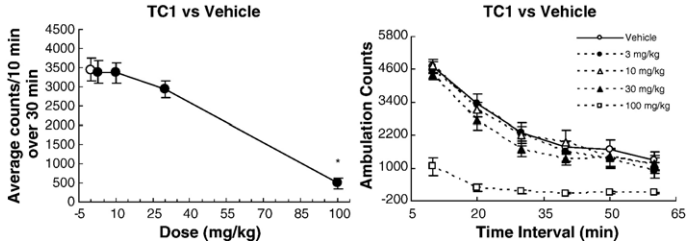

Fig. 2. Effect of TC1 on horizontal activity counts/10 min. Left: Time course of effect. Right: dose response 0–30 min after 20 min pretreatment. Each point represents the average effect determined in eight mice. *$P<0.05$ compared with 0 dose.

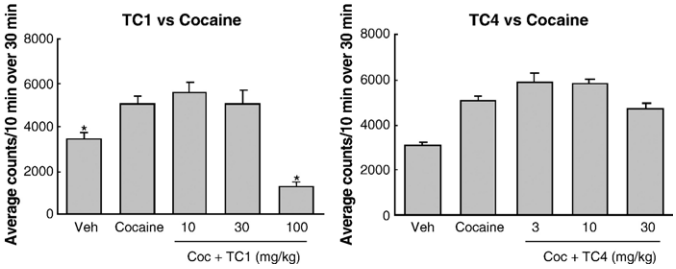

Fig. 4. Interaction between test compounds and cocaine (20 mg/kg) on LMA. Left: Dose response during first 30 min after 20 min pretreatment with TC1. Right: Dose response during first 30 min after 20 min pretreatment with TC4. Each point represents the average effect determined in eight mice. *$P<0.05$ compared with 0 dose.

period were fit to a 3-parameter logistic peak function of $\log_{10}$ dose (with the constant set to 3061, the mean of the vehicle-treated group), and the maximum was estimated from the resulting curve (maximum=4321 counts/10 min at 3.6 mg/kg). The ED_{50} (dose producing 1/2 maximal stimulant activity, where maximal stimulant activity=maximum−mean control counts/10 min) was estimated at 0.94 mg/kg from a linear regression against $\log_{10}$ dose of the ascending portion of the dose-effect curve (0.3–3 mg/kg).

3. Results

3.1. Locomotor activity

Compound TC1 displayed a dose-related decrease in ambulatory activity with an ID_{50} (dose producing 1/2 maximal depressant activity where maximal depression=0 counts/30 min) calculated as 47.6 mg/kg. Fig. 2 displays the average horizontal activity counts/10 min as a function of time (left graph) and dose (right graph), 20 min following TC1 pre-treatment. The period 0–30 min was selected for analysis of dose-response data because this is the time period in which cocaine produced maximal effects. The mean average horizontal activity counts/10 min for this 30-min period were fit to a linear function of $\log_{10}$ dose of the descending portion of the dose-effect curve (10–100 mg/kg dose range).

In contrast to the effect of TC1, TC4 produced a stimulant effect in locomotor activity (Fig. 3). The maximum was estimated from the resulting curve (maximum=4321 counts/10 min at 3.6 mg/kg). The ED_{50} was estimated at 0.94 mg/kg from a linear regression against $\log_{10}$ dose of the ascending portion of the dose-effect curve (0.3–3 mg/kg).

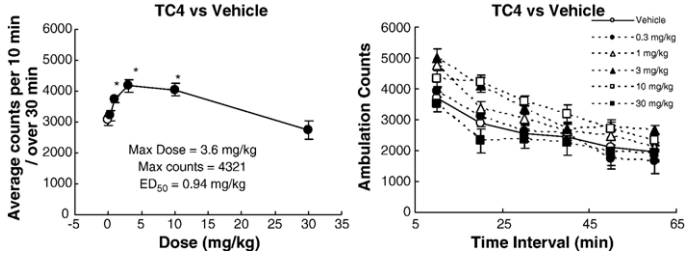

Fig. 3. Effect of TC4 on horizontal activity counts/10 min. Left: Time course of effect. Right: dose response 0–30 min after 20 min pre-treatment. Each point represents the average effect determined in eight mice. *$P<0.05$ compared with 0 dose.

The interaction study of test compounds and cocaine showed that TC1 attenuated locomotor activity induced by 20 mg/kg cocaine with an AD_{50} of 38.6 mg/kg (the ordinate value for the AD_{50} was calculated using the mean of the vehicle plus 0.9% saline (vehicle) group as the minimum value, and the mean of the vehicle plus 20 mg/kg cocaine (cocaine) group as the maximum value), whereas TC4 failed to inhibit the cocaine-stimulated effect (Fig. 4).

3.2. Cocaine discrimination study

All subjects were trained to discriminate cocaine (10 mg/kg) from saline using two-lever choice methodology. After cocaine

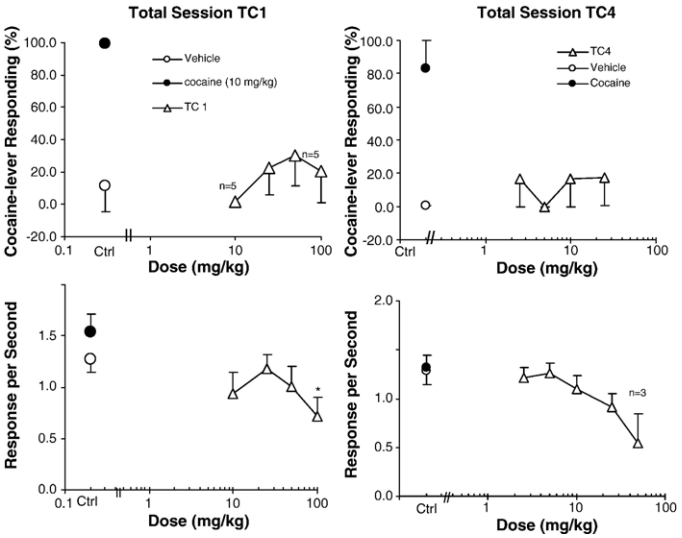

Fig. 5. Test of substitution for the discriminative stimulus effects of cocaine (total session). Upper: Mean (±S.E.M.) percentage of responses emitted on the cocaine-appropriate lever as a function of dose in mg/kg (log scale), for dosed with three or more rats completing the first fixed ratio. Lower: Mean response rate (±S.E.M.) as a function of dose in mg/kg (log scale) for all subjects tested. The sample size is equal to six at all data points except where noted. To the left of the axis break, control (Ctrl) data are shown for the vehicle (2% methylcellulose) and for the training dose of cocaine (10 mg/kg). Data for the substitution study of TC1 or TC4 for the training dose of cocaine are shown to the fight of the axis break. *$P<0.05$ compared with vehicle control.

injection, 99.3% of the responses of subjects were on the cocaine-appropriate lever. After cocaine injection, only 0.25% of the responses were emitted on the cocaine-appropriate lever.

As shown in Fig. 5, total session showed that TC1 partially substituted for the discriminative stimulus effects produced by 10 mg/kg of cocaine. The partial substitution occurred in the dose range of 25 to 100 mg/kg, with maximal 31% substitution following a dose of 50 mg/kg. Response rate was reduced to 56% of vehicle control following 100 mg/kg of TC1. A one-way, repeated measures analysis of variance conducted on response rate for the total session failed to indicate a significant overall effect $F(4, 20)=2.15$, $P=0.112$; planned comparisons (a priori contrast) against the vehicle control indicated a significant difference for the 100 mg/kg dose (all $ps<0.05$ denoted in Fig. 5 with an asterisk). The results for the first reinforcer measurement were in general accordance with the total session data for TC1. The partial substitution of TC1 produced a maximum 36% substitution at a dose of 50 mg/kg and response rate dropped to 36% of vehicle control following 100 mg/kg of TC1.

Within a dose range of 2.5 to 50 mg/kg, TC4 failed to produce a discriminative stimulus similar to that of 10 mg/kg cocaine. Response rate also showed no significant change from vehicle control following all doses. Furthermore, studies into antagonist activity of both compounds failed to generate linear, dose-dependent suppression of the discriminative stimulus effects produced by 10 mg/kg cocaine (data not shown).

Table 1
Receptor binding data comparison for TC1, TC4 and cocaine

Binding sites	TC1	TC4	Cocaine
σ_1			(−) cocaine
Ki	10 nM	152 nM	2.3 μM*
Hill coefficient	0.98±0.00		
σ_2			(−) cocaine
Ki	370 nM	20 nM	~30 μM*
Hill coefficient			
DAT			
Ki	>10 μM	>10 μM	432±29 nM
Hill coefficient			−1.07±0.05
SERT			
Ki	>10 μM	>10 μM	358±24 nM
Hill coefficient			−1.15±0.07
NET			
Ki	>10 μM	>10 μM	2150±190 nM
Hill coefficient			−0.9±0.06
D2			
Ki	1226.68±231.43 nM	1413.86±501.05 nM	NT
Hill coefficient	N/A	N/A	

*From Matsumoto et al., 2002.

4. Discussion

Trishomocubane analogues TC1 and TC4 are novel σ receptor ligands which displayed high affinity and moderate to high selectivity over the two σ receptor subtypes (Liu et al., 2001a; Nguyen et al., 1996). In the current study, TC1 and TC4 were examined for their behavioural effects on locomotor activity and their interactions with cocaine-induced actions. The mechanism of cocaine addiction involves primarily the blockage of dopamine reuptake by inhibiting the DAT, thereby increasing dopamine neurotransmission (Kuhar, 1992). A number of σ receptor ligands, for example rimcazole and its several analogues, have been reported to decrease cocaine-stimulated activity in mice. With 4-fold higher affinity for the DAT (Ki=224 nM) as compared to σ receptors (Ki=908 nM), the action of rimcazole was suggested to be mediated by DAT and/or σ receptors (Katz et al., 2003). As shown in Table 1, TC1 showed high affinity for the σ_1 subtype whereas TC4 was a moderately selective σ_2 ligand. Both compounds displayed low affinity (>10 μM) for all three monoamine transporters DAT, SERT and NET and low affinity (1.2–1.5 μM) for D2 receptors. As a result, the behavioural effects of test compounds were unlikely to result from interaction with the DAT.

Sharkey was the first to report that cocaine binds to σ receptor at micromolar concentrations that can be achieved *in vivo,* suggesting a role for σ receptors in the action of cocaine (Sharkey et al., 1988). More recently, Matsumoto et al., 2002 demonstrated that cocaine exhibits a 10 fold preference for the σ_1 receptor subtype (2 μM), as compared to the σ_2 subtype (31 μM), suggesting that of the two σ receptor subtypes, cocaine's action occurs mainly through σ_1 receptors at *in vivo* concentrations. In comparison, cocaine inhibits dopamine uptake with Ki values reported in the 0.2–0.6 μM range (Debler et al., 1988; Reith et al., 1986). The involvement of σ_1 receptors in the acute stimulant effects of cocaine was confirmed by employing σ_1 receptor antagonists and antisense oligodeoxynucleotides in the antagonism study of cocaine-induced locomotor activity (Matsumoto et al., 2002). In the present study, the high affinity and selective σ_1 receptor ligand TC1 appeared to produce the anti-cocaine actions via interacting, at least partly, with σ_1 receptors. The negative results in the antagonism test for cocaine-induced discriminative stimulus indicated that the interaction between cocaine and σ receptor ligands may not be simple competitive antagonism as has been previously proposed (Matsumoto et al., 2001).

So far, most σ receptor agonists tested in the behavioural study of cocaine had mixed interactions at both σ_1 and σ_2 subtypes. For example, 1,3-di(2-tolyl)guanidine has been shown to enhance the locomotor stimulatory effects of cocaine in rats presumably through interaction with σ_1 receptors (Skuza, 1999). It was also reported that like σ_1, antagonism of the σ_2 subtype proved to be effective in reducing the convulsive effects of cocaine (Matsumoto et al., 2003). However, since no highly selective σ_2 receptor agonists/antagonists are available, the role of σ_2 receptors in cocaine-induced actions has been largely unexplored. In one of our previous studies, TC4 together with three other trishomocubane analogues were examined and identified as σ_2 receptor agonists in modulating amphetamine-stimulated dopamine release in striatum *in vitro* (Liu et al., 2001a,b). TC4 possesses a relatively

good affinity and moderate selectivity for the σ_2 receptor subtype (Ki=20 nM, σ_1/σ_2=7.6). It was noteworthy that when administered alone, TC4 significantly increased locomotor activity at a relatively low dose (Max Dose=3.6 mg/kg, ED_{50}=0.94 mg/kg) with a maximal effect/cocaine maximal effects ratio (ME/CME) of 0.69. The stimulant effect of TC4 in locomotor activity appeared to be related to its high affinity at σ_2 receptors. When the dose was increased in the range of 30 to 100 mg/kg, the stimulation was reduced, presumably through interaction with σ_1 receptors. As a result, it may be postulated that at low dose TC4 acted as an indirect dopamine agonist by interacting with σ_2 receptors, for which cocaine had markedly lower affinity as compared to that for the σ_1 receptor subtype. This may also account for the lack of activity of TC4 when co-administered with cocaine, as well as the abolished effect in the substitution and antagonism study for discriminative stimulus produced by cocaine.

More recently, there has been evidence indicating that σ_1 receptors at the endoplasmic reticulum are intracellular targets for psychotropic drugs whose ultimate action may involve the regulation of endoplasmic reticulum lipid transport and plasma membrane reconstitution (Hayashi and Su, 2005). In addition, recent findings have revealed that cocaine up-regulated Fra-2 and σ_1 receptor genes and protein expression in brain regions involved in addiction and reward, suggesting that they may contribute to the enduring changes that underlie the cellular basis of drug abuse (Liu et al., 2005b).

Although the mechanism of cocaine addiction entails complex processes, it has been demonstrated that some σ receptor ligands, particularly σ_1 ligands, are able to modulate the behavioural effects of cocaine. In the current study, trishomocubane analogue TC1 was shown to attenuate the cocaine-induced stimulant locomotor activity by acting as a selective σ_1 ligand, whereas it lacks affinity for DAT, SERT and NET. Taken together, the trishomocubane analogues of this type may present a novel class of σ ligands which have the advantage of developing potential treatment for cocaine abuse without interacting with DAT, thereby minimizing cocaine-like actions. In addition, further work needs to be conducted to elucidate the interaction between the σ_2 receptor subtype and the actions of cocaine.

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