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(±)-SM 21 attenuates the convulsive and locomotor stimulatory effects of cocaine in mice

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Abstract

Cocaine interacts with σ receptors at physiologically relevant concentrations. While earlier studies demonstrate that antagonism of σ_1 receptors attenuates the behavioral actions of cocaine, the contribution of σ_2 receptors is unclear. Therefore, in the present study, 3α-tropanyl-2-(4-chlorophenoxy)butyrate ((±)-SM 21), a compound with high and preferential affinity for σ_2 receptors, was tested for its ability to attenuate cocaine-induced behaviors. Pre-treatment of Swiss Webster mice with (±)-SM 21 significantly attenuated cocaine-induced convulsions and locomotor activity. © 2001 Published by Elsevier Science B.V.

Keywords: Cocaine; σ Receptor; SM 21

Although the interaction of cocaine with dopamine transporters underlies much of its physiological actions, efforts to develop effective anti-cocaine agents by targeting these sites have been unsuccessful. Cocaine interacts with σ receptors with comparable affinity to dopamine transporters. Furthermore, recent studies have shown that pharmacological antagonists and antisense oligodeoxynucleotides with a high degree of selectivity for σ receptors attenuate a number of cocaine-induced behaviors (Matsumoto and McCracken, 1999; Matsumoto et al., 2001; McCracken et al., 1999a,b; Romieu et al., 2000). Thus, σ receptors may be significant targets for the development of medications to treat cocaine abuse. Of the two most established σ receptor subtypes, the existing data support a role for σ_1 receptors in the protective effects of the antagonists and antisense oligodeoxynucleotides against cocaine-induced behaviors, but the contribution of σ_2 receptors is less clear.

One of the difficulties in evaluating the role of σ_2 receptors in eliciting anti-cocaine actions is the dearth of selective pharmacological antagonists for this subtype and the lack of an amino acid sequence from which antisense oligodeoxynucleotides targeted at σ_2 receptors can be constructed. Recently, 3α-tropanyl-2-(4-chorophenoxy)-butyrate ((±)-SM 21) was reported to possess high and preferential affinity for σ_2 receptors, relative to the σ_1 subtype (Mach et al., 1999). Therefore, in the present study, (±)-SM 21 was evaluated for its ability to attenuate cocaine-induced convulsions and locomotor activity in mice.

For these evaluations, male, Swiss Webster mice ($n = 162$) were injected with a dose of (±)-SM 21 (0–10 mg/kg, i.p.). In some cases, the behavioral assessments were performed immediately following administration of (±)-SM 21. In other evaluations, the (±)-SM 21 served as a pre-treatment, which was then followed 15 min later with an injection of either a convulsive (60 mg/kg, i.p.) or locomotor stimulatory (10 mg/kg, i.p.) dose of cocaine. These doses of cocaine were used because they represent the lowest dose that produced the maximal effect in earlier dose response studies (Brackett et al., 2000; McCracken et al., 1999a,b).

For the convulsion studies, each mouse ($n = 10$ for each treatment group) was placed in a plastic observation box (56×38 cm) after receiving cocaine. The mice were then monitored for the next 30 min for the occurrence of convulsions, which were operationally defined as a loss of righting reflexes for at least 5 s together with the presence of clonic limb movements. For each treatment group, the

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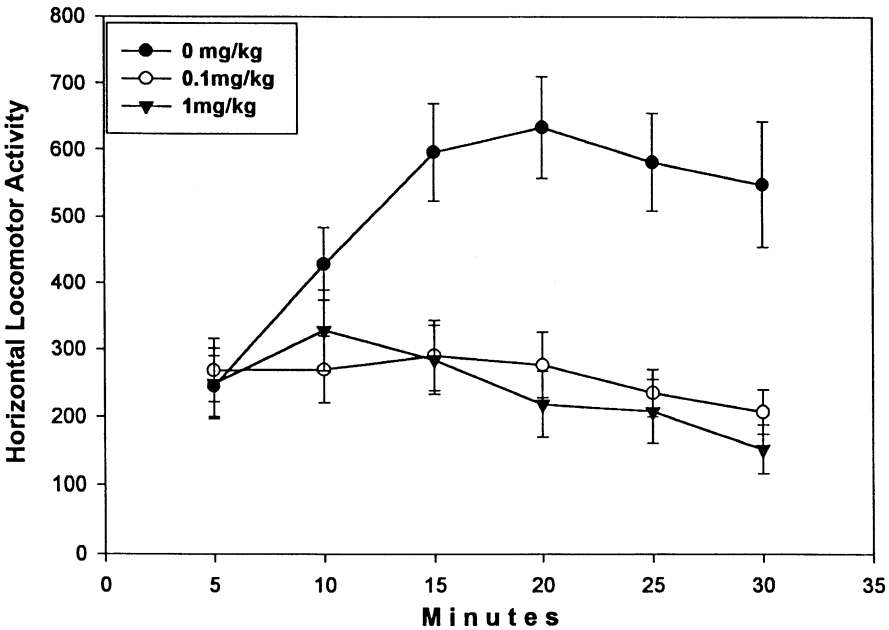

Fig. 1. (±)-SM 21 attenuates the locomotor stimulatory effects of cocaine. Male Swiss Webster mice were injected with vehicle (0 mg/kg, i.p.) or (±)-SM 21 (0.1 or 1 mg/kg, i.p.), followed 15 min later with a locomotor stimulatory dose of cocaine (10 mg/kg, i.p.). There was a significant attenuation of the hyperactivity produced by cocaine in the presence of (±)-SM 21 ($P < 0.01$ for both doses).

number of mice exhibiting convulsions/the total number tested was recorded.

The locomotor studies were conducted as described previously (McCracken et al., 1999a,b). Following a habituation period in the testing chamber of an automated activity monitor (San Diego Instruments, San Diego, CA, USA), each mouse was injected with (±)-SM 21 alone or in combination with cocaine. 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.

Fisher's exact tests confirmed that pre-treatment of mice with the following doses of (±)-SM 21 significantly attenuated the convulsive effects of cocaine ($P < 0.05$): 0.1, 0.5, 1, and 5 mg/kg. At these effective doses, only 40–50% of mice exhibited cocaine-induced convulsions, compared to 100% of mice when pre-treated with vehicle instead of (±)-SM 21. In addition, analysis of variance revealed that doses of (±)-SM 21 (0.1 and 1 mg/kg, i.p.) that alone produced no significant effects on locomotor behavior ($F[3,23] = 2.38$, n.s.) significantly attenuated the hyperactivity normally elicited by cocaine ($F[2,17] = 15.22$, $P < 0.0005$). The ability of (±)-SM 21 to attenuate the cocaine-induced locomotor stimulatory effects is illustrated in Fig. 1. Although the mechanism of action of (±)-SM 21 has yet to be fully characterized, when considered with earlier reports, the present data suggest that this compound may act as a functional antagonist at σ_2 receptors to attenuate the actions of cocaine.

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