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Rapid communication

The NK_1 receptor antagonist WIN51708 reduces sensitization after chronic cocaine

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Abstract

We tested the tachykinin NK_1 receptor antagonist WIN51708 (17βhydroxy17αethynyl5αandrostanol[3,2*b*]pyrimido[1,2-*a*]benzimidazole) in a behavioral sensitization model. Rats were given 7 days of cocaine then 7 days of withdrawal to induce sensitization. Thereafter, another 7 days of cocaine with WIN51708 (2 mg/kg i.p.) given 3.5 h after each cocaine injection was given. WIN51708 reversed sensitization but had no effect on controls. NK_1 receptor antagonists may have use in stimulant abuse and schizophrenia treatment.

Keywords: Cocaine; Sensitization; NK_1

WIN51708 (17-β-hydroxy-17-α-ethynyl-5α-androstanol[3,2-*b*]pyrimido[1,2-*a*]benzimidazole) is a selective NK_1 receptor antagonist which is active in rat (Appell et al., 1992). Chronic cocaine leads to dopamine-dependent increases in brain substance P concentrations (Alburges et al., 2000), which may lead to further dopamine release via NK_1 activation (Kalivas, 1985). Dopamine hyperfunction has also been implicated in the positive symptomatology in schizophrenia, and psychostimulant-induced stereotypies in animals may model aspects of schizophrenia (Ellinwood et al., 1998). We examined the effect of WIN51708 in our behavioral sensitization model (Davidson et al., 2002) to test its therapeutic potential in stimulant abuse and schizophrenia.

Rats were treated in accordance with the Duke University Institutional Animal Care and Use Committee. Male Sprague–Dawley rats were treated with saline or high-dose cocaine (40 mg/kg s.c.) for 7 days and withdrawn for 7 days, followed by the identical saline or cocaine injection regimens for another 7 days. During the second dosing regimen, WIN51708 (2 mg/kg i.p.) or saline was given 3.5 h after the saline or cocaine injection (during the acute cocaine withdrawal phase). There were thus four experimental groups: (1) saline in week 1, then saline+saline in week 3 (S–S/S); (2) saline, then saline+WIN51708 (S–S/W); (3) cocaine, then cocaine+saline (C–C/S); and (4) cocaine, then cocaine+WIN51708 (C–C/W). On day 10 of withdrawal from the second regimen, rats were challenged with 7.5 mg/kg i.p. cocaine. All injections, including the test for sensitization, were performed in the home cage, albeit in a different room. After 60 min of acclimatization in the test room, behavioral ratings were taken every 5 min. Three baseline ratings were followed by another 60 min of ratings after the cocaine challenge. The rating scale was based on that of Ellinwood and Balster (1974). Data were analyzed by Kruskal–Wallis one-way analysis of variance on ranks with post hoc Dunn's test. The C–C/S group exhibited significantly greater cocaine sensitivity, and this sensitization was reversed by WIN51708 treatment (C–C/W). WIN51708 was without significant effect in the saline controls (S–S/W), thus its effect was specific to sensitized rats (Fig. 1).

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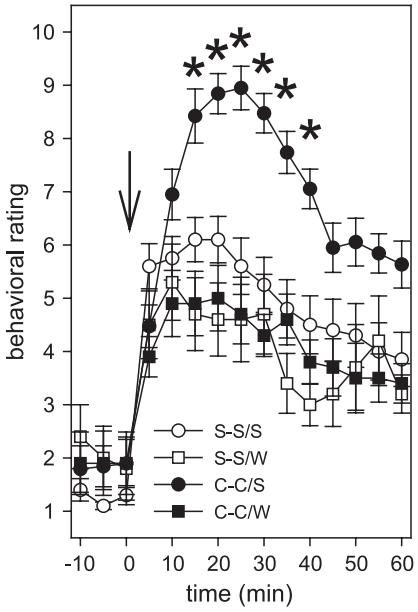

Fig. 1. WIN51708 reverses behavioral sensitization. Behavioral ratings were recorded every 5 min for 60 min after acute cocaine injection at t=0 (arrow). The C–C/S group exhibited behavioral sensitization and WIN51708 reversed this. The behavioral ratings were as follows: 1—asleep; 2—almost asleep; 3—inactive; 4—frozen; 5—grooming; 6—normal active movement; 7—hyperactive; 8—slow patterned movement; 9—fast patterned movement; 10—stereotypy; 11—hyper-reactivity. *P<0.05 vs. control (S–S/S) group. Values are means±S.E.M., n=10–20.

The behavioral sensitization model has been used extensively in drug abuse research but also as an assay for antipsychotics. Stimulant-induced grooming stereotypies have been suggested to be analogous to the stereotypical picking behavior seen in stimulant abuse and some schizophrenics while the hyper-reactivity seen in rodents may be analogous to the hyper-reactivity and/or hallucinations found clinically (Ellinwood et al., 1998). Putative pharmacotherapies are typically tested by dosing the animals shortly before the behavioral challenge (e.g., acute cocaine). However, we have recently shown that 5-HT_2 receptor antagonists can reverse behavioral sensitization when given 3.5 h after the cocaine injections during the sensitization regimen (Davidson et al., 2002). The acute cocaine withdrawal period is associated with anxiety in humans and similar anxiety-like behaviors have been shown in rats (Mutschler and Miczek, 1998). Thus these drugs may reverse cocaine sensitization by reducing withdrawal-associated anxiety/stress, which plays an important role in long term behavioral sensitization. 5-HT_2 receptor antagonists may be disrupting withdrawal stress-induced neurochemical changes critical to the consolidation and/or maintenance of sensitization. More specifically, these drugs could be blocking the activation of protein kinase C (PKC), which phosphorylates limbic *N*-methyl-D-aspartic acid (NMDA) NR2B and GluR1 α-amino-3-hydroxyl-5-methyl-4-isoxazoleprropionic acid (AMPA) subunits, suggested to be markers of cocaine sensitization (Loftis and Janowsky, 2002).

NK_1 receptors are found in abundance in the striatum and their activation increases PKC function (Khawaja and Rogers, 1996). Therefore antagonists at the NK_1 site may act in a similar fashion to 5-HT_2 receptor antagonists (reducing PKC function) in our behavioral sensitization model. Regardless of the mechanism of action of WIN51708, the present data suggest potential uses of NK_1 receptor antagonists in drug abuse and schizophrenia treatment, in addition to pain and anxiety disorders for which these drugs were initially developed.

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