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Research report

Evidence that the 5-HT_{1A} autoreceptor is an important pharmacological target for the modulation of cocaine behavioral stimulant effects

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Abstract

The psychostimulant effects of cocaine critically depend on the serotonergic (5-HT) system, of which the 5-HT_{1A} receptor is an essential component. We recently showed divergent contributions of various pre- and postsynaptic 5-HT_{1A} receptor populations to the behavioral effects of cocaine. Here, we further investigate the role of 5-HT_{1A} autoreceptors in the acute and chronic stimulant effects of cocaine using 5-HT_{1A} receptor ligands in autoreceptor preferring doses. In experiment 1, four groups of rats (N = 10) received either saline or the 5-HT_{1A} agonist, 8-OHDPAT (0.05 mg/kg) 20 min prior to a saline or cocaine (10 mg/kg) injection on 9 consecutive days. In experiment 2, six groups (N = 10) were given either saline, the 5-HT_{1A} antagonist, WAY 100635 (0.05 mg/kg) or 8-OHDPAT (0.05 mg/kg) plus WAY 100635 (0.05 mg/kg) 20 min before a saline or cocaine (10.0 mg/kg) treatment on 9 consecutive days. Initially, both the 8-OHDPAT and WAY 100635 pretreatments completely blocked the locomotor stimulant effects of cocaine whereas the combined 8-OHDPAT plus WAY 100635 pretreatment had no effect. In saline treated groups, neither the WAY 100635 nor the 8-OHDPAT plus WAY 100635 pretreatment influenced spontaneous activity levels, whereas the 8-OHDPAT alone severely reduced spontaneous activity. These effects persisted over the course of the 9 test sessions. A different pattern of results was obtained for the cocaine treatment groups. With repeated treatments, the WAY 100635 treatment always blocked the locomotor activation effect of cocaine, whereas the effects of 8-OHDPAT were transformed from an inhibition to an enhancement of cocaine locomotor stimulation. The combined 8-OHDPAT plus WAY 100635 pretreatment did not affect the stimulant effect of cocaine. These findings demonstrate that low dose autoreceptor preferring treatments with a 5-HT_{1A} agonist and antagonist can strongly modify the behavioral stimulant effects of cocaine and suggest that the 5-HT_{1A} autoreceptor may be an important pharmacological target for the development of treatments for cocaine addiction.
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1. Introduction

A substantial literature has accumulated which implicates the serotonergic (5-HT) system in providing an important contributory role in the behavioral effects of cocaine [10,24,35,37,39,41,49,62,64]. 5-HT involvement in cocaine effects is not surprising in that cocaine binds with a high affinity to the 5-HT transporter (SERT) and thereby increases extracellular 5-HT dialysate levels in 5-HT projection areas [1,46,52]. An important pharmacological target for the study of 5-HT effects upon behavior and on its interaction with cocaine is the 5-HT_{1A} receptor. 5-HT_{1A} receptors are located in the somato-dendritic areas of the 5-

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HT cell body and on postsynaptic cell bodies [21,48,60,63]. The somato-dendritic autoreceptor sites are considered to have a higher sensitivity to pharmacological stimulation than postsynaptic 5-HT_{1A} receptors [4,5,17]. Pharmacological activation of the 5-HT_{1A} autoreceptor inhibits 5-HT neuronal activity whereas activation of the 5-HT_{1A} postsynaptic receptor site has pro-serotonergic effects. Consistent with these different sites, behavioral studies have indicated that low dose (0.01–0.05 mg/kg) treatments with the 5-HT_{1A} agonist, ±8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT) which preferentially stimulates 5-HT_{1A} autoreceptors [15,25,59] can profoundly suppress locomotion with maximal effect at 0.05 mg/kg [13,14]. On the other hand, treatments which also activate postsynaptic 5-HT_{1A} receptors enhance locomotor activation [17,29,34]. In view of the marked differences in the effects of 5-HT_{1A} treatments upon spontaneous activity, it is not unexpected that the effects of selective 5-HT_{1A} agonists (8-OHDPAT) and antagonists (WAY 100635) upon cocaine-induced locomotor activation have been variable. Studies in which dose levels (e.g., ≥ 0.2 mg/kg) of these drug treatments are used, which seemingly activate/block 5-HT_{1A} autoreceptors as well as postsynaptic receptors, have reported that the full 5-HT_{1A} agonist, 8-OHDPAT enhances [10,14,20,38] whereas the 5-HT_{1A} antagonist, WAY 100635 decreases [10,36] the locomotor stimulant effects of cocaine. In contrast, low dose levels of 8-OHDPAT (0.05 mg/kg) can reduce the locomotor stimulant effect of cocaine [13]. Since both 5-HT_{1A} agonism and antagonism can apparently blunt the locomotor stimulant effects of cocaine depending upon dose level, the role of the 5-HT_{1A} receptor in the modulation of cocaine stimulant effects appears puzzling. One obvious consideration is that pharmacological modulation of the 5-HT_{1A} receptor site can alter the behavioral baseline (increase or decrease) and, as a consequence, the effects upon cocaine-induced behavioral responses (increase/decrease) are secondary to the altered behavioral baseline. In addition, most studies have assessed acute cocaine treatment effects so that the initial effects by 5-HT_{1A} pharmacological treatments may not be sustained with repeated cocaine treatments. To develop an improved understanding of the contribution of the 5-HT_{1A} autoreceptor to cocaine behavioral responses, the present report details several experiments in which low (0.05 mg/kg) autoreceptor preferring dose levels of the selective 5-HT_{1A} full agonist, 8-OHDPAT and the selective 5-HT_{1A} antagonist, WAY 100635 [43] were administered as pretreatments and effects upon spontaneous and cocaine-induced locomotor activity were assessed in chronic treatment protocols. An extensive literature involving pharmacological and genetic manipulations designed to induce anxiolytic/anxiogenic effects has demonstrated that anxiety related behavioral changes are manifested in open-field behavior by changes in central zone penetrations and grooming [2,51,61]. Importantly, pharmacological manipulations of the serotonergic system can modulate grooming and central zone penetrations in the open-field [3,22,31,44]. Accordingly, the present investigation includes measurements of these aspects of open-field behavior. The findings obtained in this investigation are supportive of an important contributory role for the 5-HT_{1A} autoreceptor site in the expression of cocaine-induced open-field behavioral responses.

2. Methods

2.1. Animals

Naive male Sprague–Dawley rats from Taconic Farms (Germantown, NY), 4 months old and weighing approximately 400 g at the start of the experiments were used. 40 rats were used in experiment 1 and 60 rats in experiment 2. Upon arrival, the animals were housed in individual 48 × 27 × 20 cm clear polycarbonate cages in a climate-controlled room at 22–24 °C with a 12 h dark and 12 h light cycle. During the 1st week after arrival, all animals were handled and weighed daily for 7 days. During the second week, the animals received three injections (i.p.) of 0.9% saline (1.0 ml/kg) to acclimate the animals to the injection procedure. All experiments occurred during the 12-h light cycle (6 AM–6 PM). This protocol (IACUC 4-B) was approved by the Veterans Administration Medical Center's Subcommittee for Animal Studies.

2.2. Drugs

Cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in sterile distilled H_2O to a concentration of 10 mg/ml. Cocaine injections were administered i.p. ±8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT, Sigma Chemical Co., St. Louis, MO) was dissolved in sterile distilled H_2O to a concentration of 0.1 mg/ml. *N*-{2-[4-2-methoxyphenyl)-1-piperazinyl}ethyl}-*N*-(2-pyridinyl)-cyclohexane carboxamide trihydrochloride (WAY 100635, Sigma Chemical Co., St. Louis, MO) was dissolved in sterile distilled H_2O to a concentration 0.1 mg/ml. 8-OHDPAT and WAY 100635 injections were administered s.c. in a volume of 0.05 ml/kg.

2.3. Apparatus

All of the behavioral tests were conducted in square 60 × 60 × 40 cm and round (68 cm diameter × 40 cm height) open-field compartments of approximately equal area. Testing was conducted in two similar subsections of the testing room with a circular and square chamber in each subsection. While we had previously found that there were no differences in activity levels related to chamber shape or room section, we always equated these factors across treatments to eliminate any possibility that chamber shape or room section could be potential uncontrolled variables. In