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Effects of $GABA_B$ receptor antagonist, agonists and allosteric positive modulator on the cocaine-induced self-administration and drug discrimination

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Abstract

Preclinical and clinical findings indicate that a $GABA_B$ receptor agonist baclofen decreases cocaine use. The present study investigated the effects of the $GABA_B$ receptor antagonist (2*S*)-(+)-5,5-dimethyl-2-morpholineacetic acid (SCH 50911), the agonists baclofen and 3-aminopropyl (methyl)phoshinic acid (SKF 97541) and the allosteric positive modulator 3,5-*bis*(1,1-dimethylethyl-4-hydroxy-β,β-dimethylbenzenepropanol (CGP 7930) in cocaine-and food-maintained responding under a fixed ratio 5 schedule of reinforcement in male Wistar rats. The effects of the $GABA_B$ receptor ligands on cocaine (10 mg/kg)-induced discriminative stimulus in a two-lever, water-reinforced fixed ratio 20 task and on basal locomotor activity were also assessed. Baclofen (2.5–5 mg/kg), SKF 97541 (0.1–0.3 mg/kg) and CGP 7930 (30–100 mg/kg) decreased the cocaine (0.5 mg/kg/injection)-maintained responding; SCH 50911 (3–10 mg/kg) was inactive in this respect. Baclofen (5 mg/kg) and SKF 97541 (0.3 mg/kg), but not CGP 7930 or SCH 50911 attenuated the food-maintained responding. The inhibitory effects of the $GABA_B$ receptor agonists and the modulator were blocked by SCH 50911. SKF 97541 (0.1 mg/kg) or CGP 9730 (30–100 mg/kg) did not produce a significant shift in the cocaine (1.25–10 mg/kg) dose–response curve in a drug discrimination procedure, while baclofen (1.5 mg/kg) or SCH 50911 (10 mg/kg) attenuated the effects of separate doses of cocaine. Baclofen (5 mg/kg) and CGP 7930 (100 mg/kg) significantly reduced basal horizontal activity. We found that pharmacological stimulation of $GABA_B$ receptors by direct agonists or allosteric positive modulation reduces cocaine reinforcement while this property of cocaine is not related to tonic activation of $GABA_B$ receptors. The $GABA_B$ receptor stimulation-induced reduction of cocaine reinforcement was separated from its discriminative stimulus effects. Moreover, a dissociation between effects of direct $GABA_B$ receptor agonists and a $GABA_B$ allosteric positive modulator on cocaine vs. food-maintained responding was demonstrated.

Keywords: $GABA_B$ receptors; Cocaine discrimination; Cocaine self-administration; Food self-administration; Locomotor activity; (Rats)

1. Introduction

The major inhibitory neurotransmitter in the central nervous system, γ-aminobutyric acid (GABA), activates three classes of receptors: ligand-gated chloride channels $GABA_A$ and $GABA_C$ receptors, and G-protein-coupled metabotropic $GABA_B$ receptors. Recent attention has been given to $GABA_B$ receptors since drugs that activate those receptors maybe useful as putative "anti-additive" therapies. The functional $GABA_B$ receptors are formation of heterodimeric assemblies between $GABA_{B(1)}$ and $GABA_{B(2)}$ proteins (e.g. Jones et al., 1998; Kaupmann et al., 1998). It has been proposed two binding sites within $GABA_B$ receptors, both agonist and antagonist sites that differ in binding affinity (nanomolar and micromolar, respectively). $GABA_B$ receptors are directly activated by GABA, (R)-(−)-baclofen, or their derivatives. By presynaptic increase in potassium and decrease in calcium conductances, and by the adenylate cyclase inhibition in postsynaptic systems, these agonists inhibit neurotransmitters release and neuronal excitability, respectively. Antagonists of $GABA_B$ receptors being analogues of GABA interact with receptors located either presynaptically, to enhance

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the release of several neurotransmitters, or postsynaptically to block late inhibitory postsynaptic potentials. Apart from direct regulation, an allosteric modulation of $GABA_B$ receptors has been recently demonstrated (Galvez et al. 2000; Urwyler et al. 2001). Such allosteric positive modulators have no intrinsic efficacy on their own and act only in the presence of the endogenous agonist GABA (Urwyler et al. 2001).

As mentioned above, growing evidence suggests that $GABA_B$ receptor agonists could be promising pharmacotherapies for cocaine addiction. In fact, baclofen, a $GABA_B$ receptor agonist licensed as an anti-spastic drug, has yielded positive findings in clinical trials where it reduced cocaine use in heavy cocaine addicts (Shoptaw et al., 2003) and decreased limbic activation during cue-induced cocaine craving (Brebner et al., 2002). In contrast, baclofen does not alter subjective (i.e. "high", "stimulated") effects of cocaine (Haney et al., 2006). In laboratory animals, acute pretreatment with baclofen decreases the acquisition (Campbell et al., 1999), maintenance (Barrett et al., 2005; Brebner et al., 2000a; Di Ciano and Everitt, 2003; Roberts et al., 1996) and reinstatement of cocaine-reinforced responding (Campbell et al., 1999; Di Ciano and Everitt, 2003) as well as attenuates cocaine lowering brain reward thresholds, using the intracranial self-stimulation paradigm (Slattery et al., 2005). The inhibitory properties of baclofen on cocaine-maintained responding have also been noted following repeated (3 days) administrated (Shoaib et al., 1998). Another $GABA_B$ receptor agonist 3-amino-2[S]-hydroxypropyl)-methylphosphinic acid (CGP 44532) and $GABA_B$ positive allosteric modulators also inhibits the maintenance of cocaine self-administration in rats (Brebner et al., 1999; Smith et al., 2004) and baboons (Weerts et al., 2005). Interestingly, recent studies raise the question whether the $GABA_B$ receptor agonist-induced decrease in cocaine self-injection might be a pharmacologically non-specific effect since they also induced the depression of food-maintained responding in rats (Barrett et al., 2005; Munzar et al., 2000) and baboons (Weerts et al., 2005). However, other studies in rats separate the lower vs. higher doses of $GABA_B$ receptor agonists to reduce responding for cocaine and for food, respectively (Brebner et al., 1999; Roberts and Andrews, 1997; Shoaib et al., 1998). Similarly to clinical reports in which baclofen did not alter the subjective effects of cocaine, baclofen does not produce changes in discriminative stimulus effects of cocaine in rats (Barrett et al., 2005; Munzar et al., 2000) or rhesus monkeys (Negus et al., 2000) trained in a two-lever, food-reinforced task.

To extend knowledge on the $GABA_B$ receptor ligands and modulators in the behavioral effects of cocaine and support the hypothesis that direct or indirect $GABA_B$ receptor stimulation may alter the behavioral effects of cocaine, in the current study we investigated the effects of the new selective and highly potent $GABA_B$ receptor antagonist (2*S*)-(+)-5,5-dimethyl-2-morpholineacetic acid (SCH 50911; Froestl et al., 1995b) and the agonist 3-aminopropyl(methyl)phoshinic acid (SKF 97541; Froestl et al., 1995a) and as well as the $GABA_B$ receptor allosteric positive modulator 3,5-*bis*(1,1-dimethylethyl-4-hydroxy-β,β-dimethylbenzenepropanol (CGP 7930; Urwyler et al., 2001) in the self-administration and drug discrimination procedures. Baclofen (a $GABA_B$ receptor agonist) was also used as a positive control. The above drugs were administered during the maintenance of cocaine or food self-administration or in substitution/combination studies in a cocaine discrimination paradigm. Finally, we also examined the effects of the above $GABA_B$ receptor agents on spontaneous locomotor activity.

2. Materials and methods

2.1. Animals

Male Wistar rats (280–300 g) delivered by a licensed breeder (T. Górzkowska, Warsaw, Poland) were housed individually (self-administration procedures), or 2/cage (drug discrimination), or 8/cage (locomotor activity studies) in standard plastic rodent cages in a colony room maintained at 20±1 °C and at 40–50% humidity under a 12-h light-dark cycle (lights on at 06:00). Animals had free access to food (Labofeed pellets) and water during the 7-day habituation period. Then, rats used in locomotor activity studies had free access to water, while those used in the cocaine self-administration procedures were maintained on limited water during initial training sessions (see below), or the amount of water that an animal received was restricted to that given during daily training sessions (5–6 ml/rat/session), after test sessions (15 min) and on weekends (36 h) in drug discrimination procedures (see below) while animals used in the food self-administration procedures were maintained on limited food intake (see below). All experiments were conducted during the light phase of the light-dark cycle (between 08:00–15:00) and were carried out in accordance with the National Institutes of *Health Guide for the Care and Use of Laboratory Animals* and with approval of the Bioethics Commission as compliant with the Polish Law (21 August 1997). The animals were experimentally naïve.

2.2. Drugs

3-Aminopropyl(methyl)phoshinic acid (SKF 97541; Tocris, UK), (*R*)-baclofen (Tocris, UK), cocaine hydrochloride (National Institute on Drug Abuse, RTI International, USA), (2*S*)-(+)-5,5-dimethyl-2-morpholineacetic acid (SCH 50911; Tocris, UK) and 3,5-*bis*(1,1-dimethylethyl-4-hydroxy-β,β-dimethylbenzenepropanol (CGP 7930; Tocris, UK) were used. Baclofen, cocaine, SCH 50911 and SKF 97541 were dissolved in sterile 0.9% NaCl, while CGP 7930 was diluted in 2 drops (20 μl/drop) of ethanol and then in 1% Tween (Sigma Aldrich, USA). Cocaine was given either i.v. (0.05 ml/injection) or i.p. (1 ml/kg); other drugs were injected i.p. in a volume of 1 ml/kg, except from 100 mg/kg of CGP 7930 which was administered in a volume of 3 ml/kg. Baclofen, CGP 7930, SCH 50911 or SKF 97541 were administered 30, 30, 45 or 30 min, respectively, before cocaine or saline. The dose-range and pretreatment intervals of the $GABA_B$ receptor ligands were chosen based on their functional *in vivo* activity at $GABA_B$ receptors (Carai et al., 2004a,b; Froestl et al., 1995a,b; Slattery et al., 2005; Smith et al., 2004).