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Research report

Effect of GBR12909 on affective behavior: Distinguishing motivational behavior from antidepressant-like and addiction-like behavior using the runway model of intracranial self-stimulation

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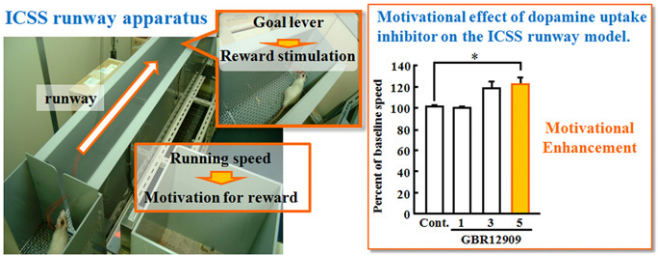
HIGHLIGHTS

- GBR12909 increased running speed in the runway model of ICSS.
- SKF38393 and quinpirole decreased running speed in the runway model of ICSS.
- Imipramine decreased running speed in the runway model of ICSS.
- Imipramine and GBR12909 decreased immobility time in the forced swimming test.
- GBR12909 did not produce significant place conditioning behavior.

GRAPHICAL ABSTRACT



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ABSTRACT

Rationale: It was recently demonstrated that the priming stimulation effect (PSE) in the runway model of intracranial self-stimulation (ICSS) can be used as a model system to study the motivational effects of drugs. However, the characteristics of this novel experimental model have not been fully clarified.
Objective: To elucidate the involvement of dopamine uptake inhibition in motivated behavior and the difference in experimental characteristics between closely related experimental models, we investigated the effects of the dopamine uptake inhibitor GBR12909 in the runway ICSS model, in the forced swimming test (FST), and on conditioned place preference (CPP). In addition, the role of dopamine receptor signaling in the runway model was evaluated using dopamine receptor agonists and antagonists.
Results: GBR12909 dose-dependently increased running speed on the runway and decreased immobility time in the FST without affecting the time spent in the drug-associated compartment in CPP tests. The effect of GBR12909 in the runway model was inhibited by pre-treatment with the dopamine receptor antagonists haloperidol and raclopride. The dopamine receptor agonists SKF38393 and quinpirole dose-dependently decreased running speed.
Conclusions: These results demonstrate that GBR12909 displays motivation-enhancing and antidepressant-like effects without place conditioning effects. In addition, the mechanisms of PSE enhancement in the runway ICSS model are different from those underlying closely associated experimental models and are mediated by increases in dopamine signaling.

1. Introduction

Recent studies reported that certain dopaminergic agents display antidepressant activity in patients with Parkinsonism as well

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as in patients that are resistant to SSRI treatment [1]. In addition, dopaminergic agents such as pramipexole and bupropion produced decreases in immobility time in the forced swimming test (FST) in an experimental model of treatment-resistant depression. Thus, it is hypothesized that dopamine plays a role in certain symptoms underlying depression.

A motivational deficit is one of the more common symptoms of depression. It is also well established that dopamine is involved in some affective behaviors such as motivation for reward. According to the incentive salience hypothesis, dopamine levels in the nucleus accumbens (NAc) are significantly elevated upon presentation of rewarding stimuli, while dopamine becomes more responsive to reward prediction compared to reward acquisition after learning the relationship between reward and predictive cues [2,3]. Since motivation for reward arises from the certainty of getting rewards, we hypothesized that these changes in dopamine responses represent alterations in reward responsiveness, or motivation. Taken together with the efficacy of dopamine receptor agonists for depression in clinical and pre-clinical studies [1,4–7] and the contribution of dopamine systems to motivation, it is hypothesized that dopaminergic agents may exhibit antidepressant-like effects by affecting motivational circuitry. Experimental procedures separately evaluating motivational and antidepressant-like effects of drugs may help to reveal the involvement of neurotransmission in motivation. However, the evaluation of this hypothesis has been somewhat restricted since there have only been a few studies investigating the simultaneous motivational and anti-depressive properties of putative therapeutic drugs.

Runway procedures incorporating reward stimulation, such as intracranial self-stimulation (ICSS) of the medial forebrain bundle (MFB) or self-administration of addictive drugs, have been suggested as a useful experimental tool to separately study the reward acquisition process and motivational properties typically associated with ICSS behavior [8–10]. Moreover, our previous study suggested that priming stimulation may regulate motivated behavior in the runway model of ICSS [11]. Since ICSS measures have been proposed as experimental models for evaluating altered interest or pleasure/hedonia, ICSS has been recognized as a valid measure of motivational state [12]. Indeed, our previous studies demonstrated that both nicotine and methamphetamine enhanced motivated behavior as observed in the runway model of ICSS [13–15]. However, it is not clear whether these behavioral alterations reflect a motivational enhancement for receiving ICSS reward or a reinforcing effect of these addictive drugs. Reward circuitry is reported to be involved in drug addiction as well as motivation for natural rewards [16]. Unfortunately, few studies have simultaneously evaluated motivation and addiction-related behaviors, such as conditioned place preference (CPP) and drug-seeking behavior. Therefore, behavioral experiments discriminating between motivated behavior and addiction-related behavior may facilitate the understanding of precise mechanisms underlying motivation.

In the present study, we evaluated the motivational effect of the dopamine re-uptake inhibitor GBR12909 and the dopamine receptor agonists SKF38393 and quinpirole in the runway model of ICSS to determine the role of dopamine neurotransmission in this animal model. Moreover, we investigated the comparative effects of GBR12909 in the runway ICSS model, FST, and CPP tests to elucidate behavioral and pharmacological differences between the runway model of ICSS and these other traditional animal models of affective behavior.

2. Materials and methods

2.1. Animals

In the runway model, male Wistar rats (Charles River, Japan) weighing 250–300 g at the time of surgery were used. Two animals were housed in individual plastic cages (26 cm × 36 cm × 25 cm). For FST experiments, male Wistar rats (Charles River, Japan), weighing 180–200 g at the time of testing were used. Three animals were housed in individual plastic cages. In the CPP experiment, male Sprague-Dawley rats (Charles River, Japan) were used and weighed 330–400 g at the start of drug conditioning. Two animals were housed in individual plastic cages. The housing room was maintained at 22 ± 2 °C with an alternating 12-h light/dark cycle (lights on at 19:00). Food and water were provided ad libitum. Another animal group was used in each treatment group in the experiments. The experimental protocol was conducted according to the Guidelines of the Ethics Review Committee for Animal Experimentation of Okayama University Medical School.

2.2. Drugs

Imipramine hydrochloride, GBR12909 dihydrochloride, (±)-SKF38393 hydrochloride, (−)-quinpirole hydrochloride, haloperidol, S(−)-raclopride (+)-tartrate salt, and (−)-nicotine were used. All drugs were purchased from Sigma Chemical (St. Louis, MO, USA). Imipramine, SKF38393, quinpirole, and raclopride were dissolved in saline (0.9% sodium chloride). Nicotine was dissolved in saline and the pH was adjusted to 7.0 with NaOH. GBR12909 and haloperidol were suspended in 0.5% carboxymethylcellulose. Imipramine, GBR12909, SKF38393, quinpirole, haloperidol, and raclopride were administered intraperitoneally (i.p.) and nicotine was administered subcutaneously (s.c.) with an injection volume of 0.1 ml per 100 g body weight. Administered nicotine dose is expressed in terms of the free base.

2.3. Experiment 1: assessment of the motivational effect of drugs in the ICSS runway model and involvement of dopamine receptor transmission in this behavior

2.3.1. Surgery

Animals were anesthetized with an i.p. injection of 50 mg/kg sodium pentobarbital (Somnopentyl®, Kyoritsu Seiyaku, Tokyo, Japan), and stainless steel electrodes comprised of a twisted pair of stainless steel wires (tip diameter: 0.2 mm, insulated except for the top 0.5 mm of the tips) were stereotaxically implanted (SR-5; Narishige, Tokyo, Japan) into the MFB at the level of the posterior hypothalamus of the rat according to The Rat Brain in Stereotaxic Coordinates, 4th ed. (flat skull coordinates: 2.8 mm posterior to bregma, 1.8 mm lateral to the sagittal suture, and 8.5–9.0 mm below the skull surface) [17,18]. After the electrodes were inserted into the MFB, they were connected to the pins of a small socket (13.95 mm × 14.5 mm × 13 mm), which was fixed to the skull using dental cement and two screws driven into the skull. At least 7 days of recovery were allowed before the onset of training for intracranial self-stimulation behavior in a Skinner box.

2.3.2. Apparatus

A Skinner box (30.8 cm in width, 25.4 cm in length, and 27.7 cm in height) and a runway apparatus (Neuroscience, Tokyo, Japan) were used. The runway apparatus was made from 5 mm acrylic board and consisted of a start box (26.5 cm in width, 26 cm in length, and 30 cm in height) with a controlled start door that opened downward, a runway (18 cm in width, 180 cm in length, and 30 cm in height), and a priming box (30 cm in width, length, and height). A retractable lever (the goal lever) was placed at the end of the runway, 7 cm above the floor. Constant current stimulation in the form of 0.2-ms pulses of 60 Hz alternating current was used for the stimulation. The stimulation current was individually adjusted for each rat.

2.3.3. Experimental procedures

The experiments were performed as previously described [13]. One week after surgery the rats were tested for self-stimulation in the Skinner box. The rats that pressed the lever at a stable rate for three consecutive days in the Skinner box (50 presses/min) were used for the runway experiment. Each rat was trained in the runway apparatus until its running speed stabilized. Upon reaching the goal end and pressing the lever, they received a reward stimulation (single train of 0.2-ms pulses of 60 Hz alternating current). In a trial, the rat was removed from the runway as soon as it received reward stimulation and was placed in the priming box that stood beside the runway, where 25 s later it received 10 priming stimulations (1 stimulation/s with the same parameters as the reward). When priming stimulation ceased, the rat was immediately transferred from the priming box to the start box of the runway. Five seconds after cessation of the priming stimulation, the start box door opened. If the rat ran to the goal lever and pressed it, the rat received a reward stimulation. The current was set at 50–200 μA to produce a maximal priming stimulation effect (PSE; a maximal difference between the running speeds on primed versus unprimed trials). The running time from the opening of the start door to pressing the goal lever was analyzed via microcomputer on a 0.1-s time scale.

2.3.4. Technique for estimating the motivational effect of drugs in the runway model

This experimental procedure involved 30 trials and consisted of Pretest sessions, Baseline sessions, and Test sessions (Fig. 1a). Each session was comprised of 10 trials. In the Pretest session, the rat received 10 priming stimulations and 1 reward stimulation for pressing the goal lever. In the Baseline session, the rats received 5 priming stimulations and 1 reward stimulation for pressing the goal lever. In the Test session,