Neuroscience Letters 556 (2013) 210–215

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Acute and subchronic effects of buspirone on attention and impulsivity in the five-choice serial reaction time task in rats

Chao-Lin Lu[a], Yu-Chi Ku[a], Shih-Mao Lo[a], Chia-Ho Peng[a], Che-Se Tung[b], You-Wei Lin[b], Yia-Ping Liu[b,c,*]

[a] Department of Psychiatry, Tri-Service General Hospital Beitou Branch, Taipei, Taiwan, ROC
[b] Department of Physiology and Biophysics, National Defense Medical Center, Taipei, Taiwan, ROC
[c] Department of Psychiatry, Tri-Service General Hospital, Taipei, Taiwan, ROC

HIGHLIGHTS

- Acute buspirone treatment affected the attentional accuracy.
- Subchronic buspirone treatment augmented the impulsivity.
- Central serotonin may time-dependently regulate impulsivity.

ARTICLE INFO

Article history:
Received 6 May 2013
Received in revised form
29 September 2013
Accepted 4 October 2013

Keywords:
5-CSRTT
Attention
Buspirone
Impulsivity
Serotonin

ABSTRACT

Serotonin (5-HT)-related drugs are extensively employed in the treatment of mental disorders. However, the roles of the central serotonergic system in impulse control over environmental stimuli remain to be elucidated. The present study demonstrated acute and subchronic effects of a 5-HT_{1A} receptor partial agonist, buspirone, on the performance of rats in response control indexed by the attentional accuracy and impulsive reactivity in the five-choice serial reaction time task (5-CSRTT). Acute buspirone (0.5 mg/kg) affected accuracy, whereas subchronic buspirone treatment augmented impulsivity. Moreover, a subchronic buspirone regimen potentiated the acute buspirone-induced reduction in motor impulsivity. Our data suggested that a time-dependent mechanism was involved in the serotonin-associated behavioral control of response accuracy and motoric impulsivity.

1. Introduction

The central serotonin (5-HT) system has been implicated in the expression of behavioral impulsivity [13,33]. Clinically, a lower level of central 5-HT has been found to be highly relevant to impulsive activities [14,25], and 5-HT-related anxiolytics or antidepressants are effective in treating patients with poor impulse control [32]. The latter observation has been supported by preclinical evidence in which rats become more impulsive if their central 5-HT system is impaired [18,19]. It has been shown that 5-HT regulation over behavioral impulsivity may undergo a time-dependent process, as evidenced by a change in impulsiveness following long-term 5-HT_{1A} manipulation [22].

Buspirone is a partial agonist of 5-HT_{1A} postsynaptic receptors and a full agonist of 5-HT_{1A} presynaptic receptors [20,26]. The drug has been used extensively as a nonbenzodiazepine anxiolytic [31], an antidepressant [16,30], and in adjunct pharmacotherapy to augment the effects of selective serotonin reuptake inhibitors (SSRIs) [21]. In fact, with its delayed onset of action, buspirone appears more reminiscent of SSRIs rather than a typical anxiolytic. An examination of the role of buspirone in the regulation of behavioral impulsivity should therefore consider the short- versus long-term activations of 5-HT_{1A} receptors.

Previously, we have demonstrated that acute buspirone-induced impulsive choice in a delayed reinforcement (DR) task is reversed following chronic buspirone treatment and that this phenomenon can be blocked by 5-HT_{1A} antagonism [22]. In contrast to the impulsive choice, the present study aimed to explore the effects of buspirone on behavior in the five-choice serial reaction time task (5-CSRTT), which is used to examine the motor

* Corresponding author at: Department of Physiology and Biophysics, National Defense Medical Center, 161 Minchuan East Rd., Sec. 6, Taipei 114, Taiwan, ROC. Tel.: +886 2 87923100x18614; fax: +886 2 87923153.
E-mail addresses: yiaping@ms75.hinet.net, yiaping@ndmctsgh.edu.tw (Y.-P. Liu).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.10.013

characteristic of behavioral impulsivity. During the 5-CSRTT, the rats must be able to pay attention to the array of openings in a specially designed apparatus in order to detect the discriminative visual stimulus and respond correctly. The responses that occur before the appearance of the stimulus are considered a premature action in indexing the animals' impulsivity [29]. The 5-CSRTT therefore provides a reliable index of rats with respect to their response accuracy, speed, and motor impulsivity [5]. The task exhibits a satisfactory sensitivity in evaluating the behavioral effects of 5-HT related drugs [34]. In the present study, we investigated the role of the 5-HT_{1A} receptor in motoric response control under acute and subchronic buspirone regimens by analyzing the drug effects on behavioral performance in the 5-CSRTT.

2. Materials and methods

2.1. Animals

A total of 20 male Sprague-Dawley rats (BioLASCO Taiwan Co., Ltd., Taipei, Taiwan, R.O.C.) with body weight of 300–350 g at the start of the experiment, were used. All rats were housed in groups of three and in a temperature- and humidity-controlled holding facility with 12-h light/dark cycles (light on from 07:00 to 19:00). Water was available ad libitum, but the food was restricted to that earned during the test [maximum of 100 × 45 mg purified rodent pellets (Labdiet, St. Louis, MO, USA)] and 20 g per rat of standard rodent chow (BioLASCO Taiwan Co., Ltd.) given at the end of the test. Behavioral testing took place between 08:00 and 12:00 with all rats being tested at the same time every day when possible. All experimental procedures were evaluated and approved by the animal care committee of the National Defense Medical Center.

2.2. 5-CSRTT

The 5-CSRTT program was identical to that of a previously described procedure [23,24]. Each session began with illumination of the 5-CSRTT chamber (25 cm × 31 cm × 33 cm, TSE Systems GmbH, Bad Homburg, Germany) by the house light. The rats had to nose poke the magazine in order to initiate a trial. After a fixed intertrial interval (ITI) of 5 s, the light at the rear of one of the response apertures was briefly illuminated for 1 s (stimulus duration). A nose poke in this aperture within 5 s after illumination of the hole (limited hold period) was recorded as a correct response and was rewarded with delivery of a food pellet to the magazine. Response in a nonilluminated hole was recorded as an incorrect response and was punished by a 5-s house light-extinguished timeout. Accuracy was measured by the % correct [correct responses/(correct responses + incorrect responses) × 100]. The % omission was calculated by the formula [(times that the rat failed to respond within the 5-s limited hold/the total trial number) × 100]. Responses in any one of the apertures prior to the illumination were recorded as an ITI response and were not punished by a timeout. The correct latency was the time that elapsed between the occurrence of the visual stimulus and a nose poke in the correct hole. The magazine latency was the time that elapsed between a nose poke in the correct hole and retrieval of the reward from the magazine. A session was either terminated after a maximum of 100 completed trials or after 30 min depending on which one came first.

2.3. Experimental design

Twenty 5-CSRTT-trained rats were entered into a 15-day treatment protocol and were assigned in a baseline-matched manner to one of the two groups (saline vehicle or buspirone, 10 rats in each group). In order to assess the acute drug effects prior to and after the subchronic regimen, rats received intraperitoneal (i.p.) injections of saline vehicle or buspirone 40 min before the 5-CSRTT testing on Days 1 and 15. During the subchronic regimen, the 5-CSRTT performance was observed on Days 3, 5, 7, 9, 11, and 13, and the daily injections were conducted after the behavioral tests in order to ensure that the observed performance was not due to any acute drug effect.

2.4. Drug

All rats were drug naïve before beginning the buspirone regimen. Buspirone was purchased from Sigma–Aldrich Co. LLC (St. Louis, MO, USA). It was dissolved in 0.9% saline vehicle and was freshly prepared before the experiments to produce a total injection volume of 1.0 mL/kg body weight. The chosen dose of buspirone was 0.5 mg/kg because at a larger dose (i.e., 1 mg/kg, which was effective in a cognitive impulsive choice behavior, see [22]), a higher omission rate (more than 30%) was observed in our pilot study.

2.5. Data analysis

The acute drug effects were analyzed with a Student's *t*-test. In order to analyze the subchronic drug effects, a two-way ANOVA was conducted with one between-subject factor, DRUG, and one within-subject factor, TIME. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Acute buspirone effects (Fig. 1 and Table 1)

Before entering the acute buspirone regimen, rats that were to be assigned to the saline vehicle group or buspirone group were baseline-matched in all of the 5-CSRTT variables (% correct, 72 ± 6 and 74 ± 4; ITI responses, 26 ± 4 and 27 ± 5; correct latency in ms, 1025 ± 84 and 982 ± 90; magazine latency in ms, 3242 ± 158 and 3387 ± 298; and % omission, 8.1 ± 1.4 and 8.4 ± 1.8, for the rats assigned to the groups of saline vehicle or buspirone, respectively).

The two groups of rats then entered the acute treatment regimen. Compared to the saline vehicle, buspirone significantly reduced the % correct [$t(18) = 2.23$, $P < 0.05$] and the ITI responses [$t(18) = 1.92$, $P < 0.05$] but increased the correct latency [$t(18) = 3.44$, $P < 0.01$], the magazine latency [$t(18) = 3.26$, $P < 0.01$], and the omission rate [$t(18) = 4.08$, $P < 0.01$].

3.2. Subchronic buspirone effects (Fig. 2 and Table 1)

The results showed that for the ITI responses, significant effects were found for DRUG [$F(1,18) = 9.52$, $P < 0.01$], TIME [$F(5,90) = 2.38$,

Table 1
Drug effects on the percentage of omission in the 5-CSRTT during different experimental stages.

	Saline	Buspirone
Acute, before subchronic Rx	8.6 (1.7)	23.5 (6.3) **
Subchronic Rx (day 3)	7.8 (2.4)	18.4 (7.7) *
Subchronic Rx (day 5)	7.9 (2.3)	11.5 (3.3)
Subchronic Rx (day 7)	7.3 (1.7)	10.9 (3.5)
Subchronic Rx (day 9)	10.9 (1.9)	6.4 (1.5)
Subchronic Rx (day 11)	7.8 (1.8)	7.7 (2.8)
Subchronic Rx (day 13)	9.5 (2.3)	7.9 (3.1)
Acute, after subchronic Rx	6.9 (1.3)	22.3 (4.6) **

Acute (Day 1), subchronic (Days 3–13), and acute after chronic (Day 15) effects of saline vehicle and buspirone (0.5 mg/kg) was examined. The percentage of omission was calculated by the formulation [(the times of the rat failed to respond sufficiently soon after stimulus onset/the total trial number) × 100]. Values are presented as the mean (standard error). *$p < 0.05$, ** $p < 0.01$, for the comparisons between the buspirone group and the saline vehicle group.