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Original Article

Motivational Effects of Nicotine as Measured by the Runway Method Using Priming Stimulation of Intracranial Self-stimulation Behavior

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It is well known that priming stimulation promotes the motivational effects of intracranial self-stimulation (ICSS) behavior. An experimental methodology using the runway method could separately study the reward and motivational effects of ICSS behavior. In the present study, we examined the motivational effect of nicotine as measured by the runway method using priming stimulation of ICSS behavior. Electrodes were implanted chronically into the medial forebrain bundle (MFB) in rats. A lever for stimulation of the MFB was set on the opposite side of the start box in the apparatus, and rats were trained to get a reward stimulation (50–200 μA, 0.2 ms, 60 Hz) of MFB when the goal lever was pressed. After the rats were trained to press the lever, a priming stimulation of the MFB was performed. After receiving the priming stimulation, rats were placed at the start box of the runway apparatus, and the running time duration until the goal lever was pressed was measured. Subcutaneous injection of nicotine at a dose of 0.2 mg/kg produced an increase in running speed to obtain the reward stimulation, and priming stimulation facilitated the motivational effect to obtain the electrical brain stimulation reward in the rats. These results suggest that nicotine significantly enhanced the motivational effect on ICSS behavior as determined using the runway method. The runway method using priming stimulation of ICSS behavior may become the new experimental methodology with which to measure the motivational effect of some drugs.

Key words: intracranial self-stimulation, runway, nicotine, priming stimulation, motivational effect

Tobacco smoking is a leading avoidable cause of morbidity and mortality worldwide [1]. Chronic smoking behavior is assumed to result from the highly addictive state associated with the consumption of nicotine, the main psychoactive ingredient in tobacco products [2]. The motivational effect of nicotine is based on psychobiological mechanisms underlying reinforcement and dependence, and elucidation of these psychobiological mechanisms has been the focus of a great deal of research [3–6]. A recent study reported that the motivational effect of nicotine could be measured using a runway model of drug self-administration [7]. Moreover, operant runway procedures have been successfully used to study the motivating proper-

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ties of a wide variety of reinforcers such as food [8], water [9], sex [10], intravenous (i.v.) heroin injection [11, 12], amphetamine [13], and cocaine [14]. These reports indicated that operant running behavior with reinforcement reflects the animal's motivation.

Individual studies to determine the reinforcement/reward and motivational effects on intracranial self-stimulation (ICSS) behavior have been conducted using the runway method [15, 16]. Moreover, it is well known that priming stimulation promotes the motivational effects of ICSS behavior [7], and Gallistel *et al.* reported a runway method using priming stimulation of ICSS behavior [15]. In the present study, we examined whether the runway method using priming stimulation of ICSS behavior could estimate the motivational effect of nicotine. First, we ascertained that priming stimulation elevated the motivational effect of receiving the reward stimulation for pressing the goal lever. The goal lever was used as an indicator of the animal's motivation to seek the reward stimulation. Next, we evaluated the running speed and the time it took the animal to run from the start box until the goal lever was pushed. Finally, we assessed the motivational enhancement effect of nicotine in the runway method using priming stimulation of ICSS behavior. It was hypothesized that progressive increases in running speed during the trials would reflect the facilitating effect of the drug on the motivation to obtain the reward stimulation.

Materials and Methods

Subjects. Male Wistar rats (Charles River Laboratories, Yokohama, Japan) weighing 250–300 g at the time of surgery were used. Three animals were housed per cage (26 × 36 × 25 cm) in a room maintained at 22 ± 2°C with an alternating 12-h light/dark cycle (lights were switched on at 19:00 hours). Food and water were provided ad libitum. The experimental protocol was conducted according to the Guidelines of the Ethics Review Committee for Animal Experimentation of Okayama University Medical School.

Surgery. Animals were anesthetized by intraperitoneal injection of sodium pentobarbital (Nembutal, 50 mg/kg). Stainless steel electrodes consisting of a twisted pair of stainless steel wires (tip diameter: 0.2 mm), which were insulated except at the top 0.5 mm of the tips, were stereotaxically implanted (SR-5; Narishige Scientific Instrument Lab, Tokyo, Japan) into the medial forebrain bundle (MFB) at the level of the posterior hypothalamus (flat skull coordinates: 2.8 mm posterior to the bregma; 1.8 mm lateral to the sagittal suture; and 8.5–9.0 mm below the skull surface) [17]. After the electrodes were inserted into the MFB, they were connected to the pins of a small socket fixed to the skull using dental cement, and 2 screws were driven into the skull. At least 7 days were allowed for the rats to recover before beginning training for ICSS behavior in a Skinner box.

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 in this experiment (Fig. 1). The runway apparatus was fabricated from a 5-mm-thick acrylic board and consisted of a start box (26.5 cm in width, 26 cm in length, and 30 cm in height), a controlled start door that opened by dropping down (26.5 cm in width and 30 cm in height), 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 stimulators in the form of 0.2 ms pulses of 60 Hz alternating current were used for the stimulation. The stimulation current was individually adjusted for each rat.

Drug. (−) Nicotine (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in physiological saline (0.9% sodium chloride), the pH adjusted to 7.0 with NaOH, and the solution administered by subcutaneous (s.c.) injection at a volume of 0.1 ml per 100 g body weight. Drug doses were expressed in terms of the free base.

Experimental procedures.

Training of ICSS behavior for the runway method.

For ICSS, rats were trained to press a lever using the Skinner box. Rats that pushed the lever at a stable rate for 3 days in the Skinner box (more than 50 times/minute) were used for the runway experiment. Upon reaching the end of the runway apparatus and pressing the goal lever, rats could receive 1 train of reward stimulation of 0.2 msec pulses of 60 Hz alternating current [18]. The current setting for each individual rat was between 50–200 μA in order to produce a maximal difference between the running

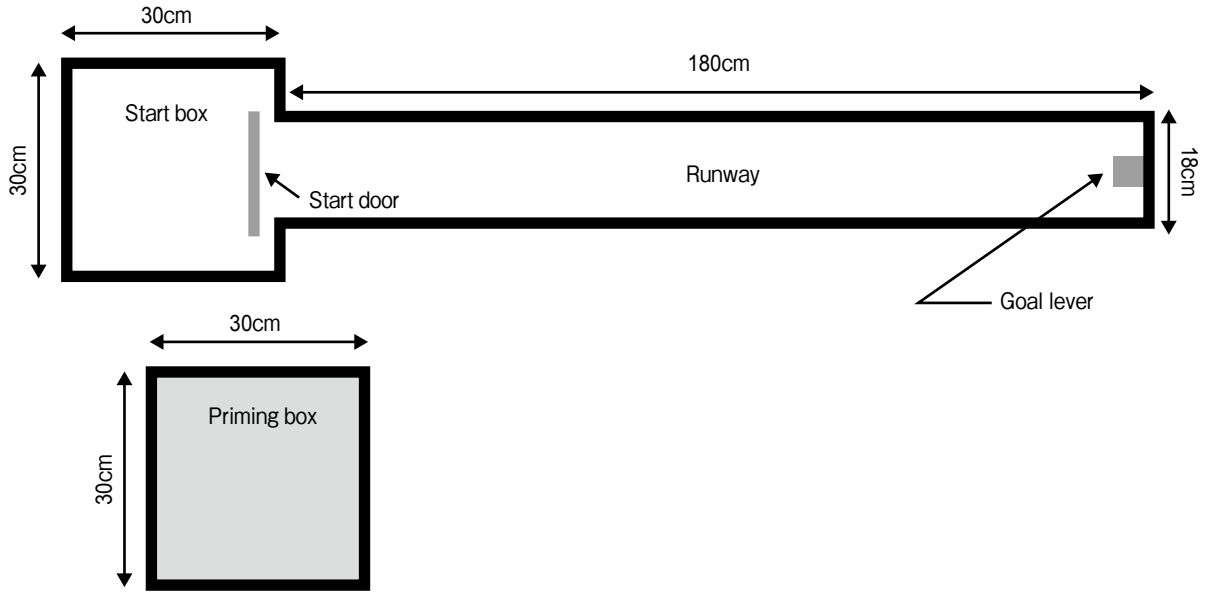

Fig. 1 The experimental apparatus in the runway method of ICSS behavior.

speeds in primed versus unprimed trials; the current value was different for each rat. Each rat was then trained on the runway apparatus until its running speed was stabilized without priming stimulation. When the running speed was stable, the rat was challenged in the next experiment.

Experiment 1.

Effect of priming stimulation on running speed.

In this experiment, the rat was removed from the runway apparatus as soon as it received a reward stimulation for pressing the goal lever, and 25 sec later it received 10 trains of priming stimulation (1 train per second, same parameters as the reward) at the priming box that stood beside the runway apparatus. When the priming stimulation ceased, the rat was moved to the start box of the runway apparatus, and 5 sec after being moved to the start box, the door was opened. This experiment assessed the effect of priming stimulation on running speed and consisted of 20 consecutive trials. Rats received 10 trains of priming stimulation (1 train per second, same parameters as the reward) or non-priming stimulation, and one reward stimulation for pushing the goal lever. Each rat's running speed value was computed as the mean of 10 trials. The running time from door opening to lever depression was recorded by a microcomputer.

Experiment 2.

Measurement technique for determining the motivational effect of nicotine on ICSS in the runway method.

This experimental procedure involved 30 trials and consisted of pre-sessions, baseline sessions, and test sessions. Each session comprised 10 trials. In the pre-session, the rat received 10 trains of priming stimulation and a reward stimulation for pushing the goal lever. In the baseline session, rats received 5 trains of priming stimulation and a reward stimulation for pushing the goal lever. In the test session, after the administration of saline or nicotine, rats received 5 trains of priming stimulation and a reward stimulation for pushing the goal lever. Saline and nicotine were administered 30 min before the baseline or test session. The motivational effect of the nicotine was determined as the ratio of the baseline running speed to the test-session running speed. When the value of the test session increased more significantly than the value of the baseline session, it was determined that the motivational effect of nicotine was positive.

Experiment 3.

Measurement of spontaneous locomotor activity.

Spontaneous locomotor activity was measured using

an Animex apparatus (Muromachi Kikai Inc., Tokyo, Japan). The level of spontaneous activity in a novel environment was measured for 10 min after each rat was individually placed in a cage (40 cm in width, 35 cm in length, and 38 cm in height). The level of activity was estimated as the number of interruptions in the magnetic field caused by horizontal movements of the animal.

Data analysis. The effect of priming stimulation on running speed was statistically evaluated using Student's *t*-test. Locomotor activity and motivational effect on the runway method were statistically evaluated using one-way analysis of variance (ANOVA) followed by the Scheffé test. The significance level was set at $p < 0.05$.

Results

The effect of priming stimulation on running speed is shown in Fig. 2. Running speed increased significantly when a priming stimulation of 10 trains was given ($p < 0.05$). Measurement of spontaneous locomotor activity is shown in Fig. 3. Nicotine doses of 0.05, 0.2, and 0.5 mg/kg did not show any effect on locomotor activity [F (3, 20) = 0.912, not significant].

The experimental design for measuring motivational effect in the runway method is shown in Fig. 4A. The running speed in the pre-session was significantly higher than that seen during the baseline or test sessions [F (2, 15) = 42.577, $p < 0.01$]. There were no significant differences in the running speeds of the baseline and test sessions (Fig. 4B). The motivational effect of nicotine is shown in Fig. 5. Each column represents the mean value of the running speed plus the S.E.M. Nicotine in doses of 0.05 and 0.5 mg/kg did not increase running speed in the runway method. However, 0.2 mg/kg nicotine induced a 112–156% (mean 129%) increase in running speed in the runway method [F (3, 20) = 4.8, $p < 0.05$]. One-way ANOVA followed by the Scheffé test showed that this effect was significant at the saline per side.

Discussion

In this study, we employed a runway self-stimulation method in an attempt to model the motivation of subjects seeking electrical reward stimulation. Rats were trained to run along a straight alley toward a

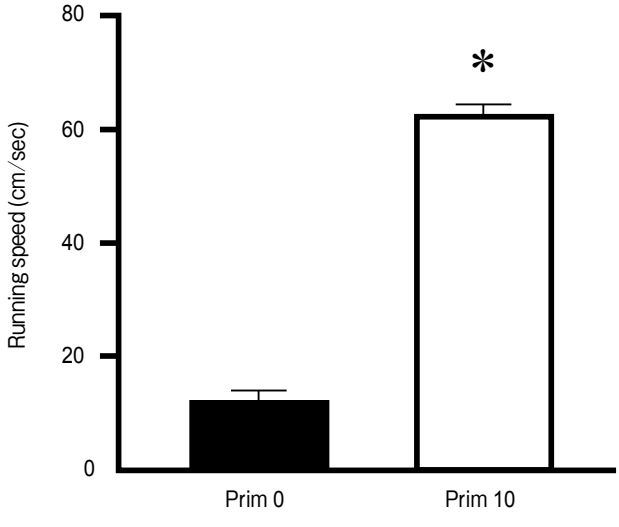

Fig. 2 Priming stimulation effect in the runway method of ICSS. Rats received 0 or 10 trains of priming stimulation (1 train per second, same parameters as reward) and one reward stimulation for pushing the goal lever. Data represent the mean ± S.E.M. of 10 running speed trials (n = 4). Data were analyzed by Student's *t*-test. Prim 10 was significantly different from Prim 0. *$p < 0.05$. Prim: priming stimulation.

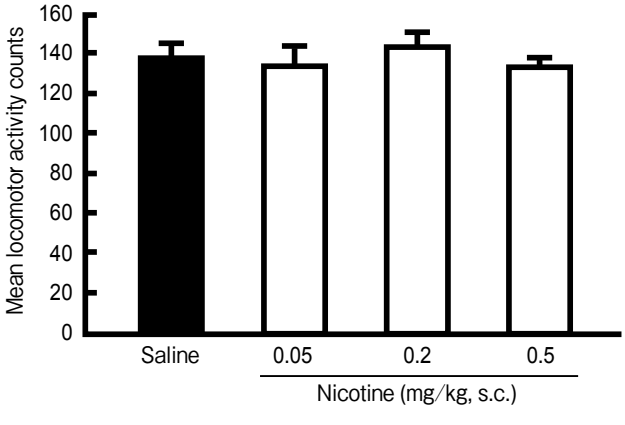

Fig. 3 Effect of nicotine on locomotor activity in rats. Each column shows locomotor activity counts over 10 min. Saline and nicotine (0.05, 0.2, 0.5 mg/kg) were administered by subcutaneous injection (s.c.) 30 min before the test. Data represent the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Scheffé test. Nicotine caused no significant difference compared to saline.

goal box where they then received an electrical reward stimulation. The running speed of the rats en route to obtaining the reward stimulation by pushing the goal lever in the runway method significantly increased after they received priming stimulation ($p < 0.05$) (Fig. 2). Using the runway method, we demonstrated that priming stimulation was appropriate for facilitating running speed. Waraczynski *et al.* reported that running speed increased with the current strength of the administered priming stimulation [19]. Moreover, Reid *et al.* reported that the occurrence of a change in the running speed through priming stimulation indicated a motivational effect in the runway method [16]. Our results also suggest that priming stimulation facilitates the motivational effect in the runway method.

Next, we measured the enhancement effect of nicotine on motivation in the runway method using priming stimulation of ICSS behavior. The motivational effect was evaluated by comparing the running speed of the baseline session with that of the test session (Fig. 4A). In this experimental design, the running speed of the pre-session was significantly higher than that of the baseline and test sessions [$F(2, 15) = 42.577$, $p < 0.01$]. On the other hand, there were no significant differences between the running speeds of the baseline and test sessions (Fig. 4B). In other words, this experimental design was able to evaluate both an increase and decrease of the drug effect. Therefore, we determined the priming stimulation frequency and reward necessary to confirm the efficacy of increasing and decreasing the drug dosage.

In this experiment, we demonstrated that running speed was significantly enhanced when nicotine (0.2 mg/kg) was administered [$F(3, 20) = 4.756$, $p < 0.05$]. However, when nicotine (0.05 mg/kg) was administered, the running speed remained unchanged. The effect of nicotine on ICSS behavior in the runway method showed a U-shaped dose-response curve (Fig. 5). This inverted U-shaped dose response is consistent

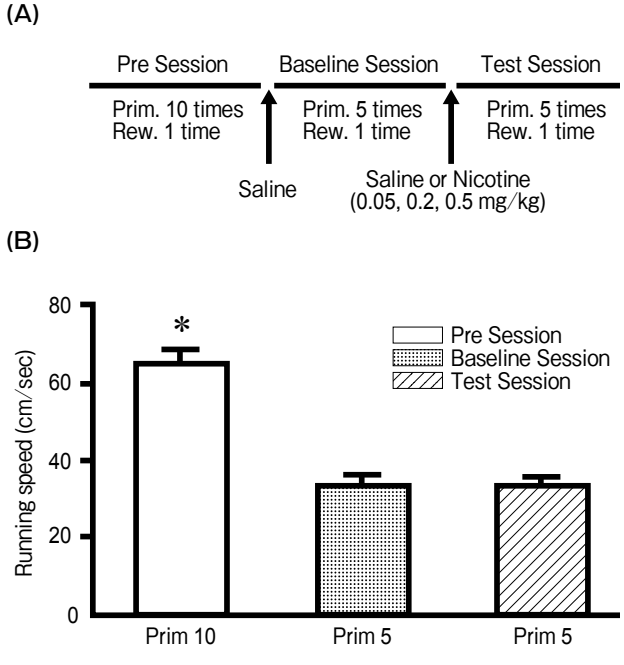

Fig. 4 Experimental design for the measurement of motivational effect and running speed.
(A) Each session consisted of 10 trials. The measurement value was the mean value of 10 trials for each session. The motivational effect of nicotine was positive when the value of the test session was significantly greater than the value of the baseline session.
(B) Running speed for the pre-session, baseline, and test session. The results of saline administration represent the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Scheffé test. The pre-session was significantly different from the baseline or test sessions. *$p < 0.05$. Prim: priming stimulation; Rew: reward stimulation.

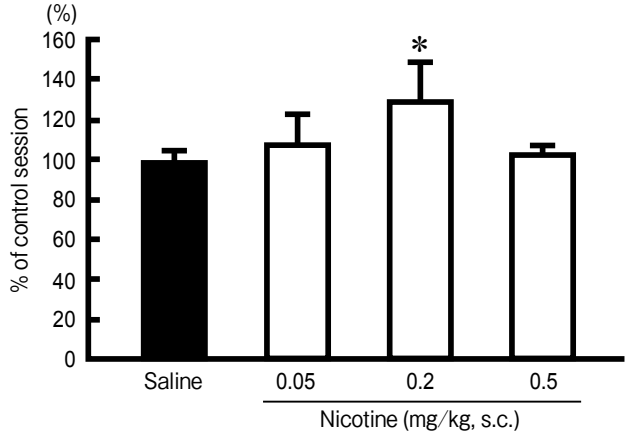

Fig. 5 The motivational effect of nicotine on the runway method using priming stimulation on ICSS behavior.
Each column shows the ratio of the baseline running speed to the test-session running speed. Saline and nicotine (0.05, 0.2, 0.5 mg/kg) were administered by subcutaneous injection (s.c.) 30 min prior to the measurement. Data represent the mean ± S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Scheffé test. Administration of 0.2 mg/kg nicotine showed a significant difference from saline. *$p < 0.05$.

with the results of other nicotine self-administration studies in rodents, where an intravenous injection dose of 0.03 mg/kg has been shown to reliably support operant responses in animals [20–26]. Cohen *et al.* reported that the motivational effect of nicotine induced a U-shaped dose-response curve using a runway model of drug self-administration [7]. Furthermore, the effect on the nicotine U-shaped dose-response curve in forced swimming tests has been used as a screening method for antidepressants. Nicotine at a s.c. injection dose of only 0.2 mg/kg has been shown to significantly decrease the duration of immobility in a forced swimming test with an experimental dose range of 0.01–1.0 mg/kg [27]. In addition, s.c. injection of nicotine at a dose of 0.2 mg/kg significantly inhibited the attenuating effect of naloxone-induced place aversion [28–30]. These findings indicated that the s.c. injection dose of 0.2 mg/kg nicotine was suitable for normalizing schizophrenia and the aversive motivational state. Therefore, s.c. injection of 0.2 mg/kg nicotine was the optimal dose for enhancing running speed and motivational effect in the present study.

We also found that nicotine (0.2–0.5 mg/kg, s.c.) did not increase locomotor activity [$F(3, 20) = 0.912$, not significant] (Fig. 3). This result clearly showed that the enhanced running speed obtained with nicotine (0.2 mg/kg) was not the result of hyperactivity alone. In other words, the increased running speed with nicotine indicated an enhancement of the motivational effect to get the reward stimulation by pushing the goal lever in the runway method. Therefore, this method can be used to measure the motivational effect of nicotine. Moreover, it has been reported that the motivational effect of psychostimulants such as nicotine is related to the mesolimbic dopaminergic system via nicotine receptors [31–35]. It is conceivable that this mesoaccumbens dopaminergic system is deeply concerned with the motivational nerve system [36–39]. Thus, one of the factors in the increase of the running speed in the present study might be the effect of nicotine on the mesoaccumbens dopaminergic system.

In the present study, priming stimulation facilitated a motivational effect on rats to obtain an electrical brain stimulation reward. Moreover, nicotine significantly enhanced the motivational effect in the runway method. These results suggest that the runway method using priming stimulation of ICSS behavior is an effective methodology for evaluating the nicotine enhancement effect on motivation, and may be considered a new experimental methodology for measuring the motivational effect of some drugs.

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