*Current Perspective***A New Method for Evaluation of Motivational Effects of Drugs**Hidenori Sagara¹, Hiroaki Araki^{2,*}, and Yutaka Gomita³¹Department of Pharmaceutical Information Sciences, Matsuyama University, 4-2 Bunkyo-cho, Ehime 790-8578, Japan²Division of Pharmacy, Ehime University Hospital, 454 Shitsukawa, Toon, Ehime 791-0295, Japan³Shujitsu University, 1-6-1, Nishigawara, Okayama 703-8516, Japan

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Abstract. Motivation is a process that continuously changes behavior to achieve a goal and can be conceptualized as a series of steps relating to that process. Intracranial self-stimulation (ICSS) behavior is considered to consist of reward and motivational effects. Moreover, priming stimulation of ICSS behavior is known to promote motivational effects. Using the runway method and priming stimulation, rewards and motivational effects of ICSS behavior can be differentiated. We investigated whether the runway method and priming stimulation of ICSS behavior could be used to evaluate motivational effects of a drug. In the ICSS runway model, running speed was considered as a reference of motivational effect. An assessment of pharmacological drugs known to influence motivational states was also undertaken. Using our experimental methods, prominent changes were observed in running speed when animals were administered methamphetamine and nicotine. Based on our results, we conclude that the runway method may be useful for the evaluation of substances that affect motivation. This review introduces 4 types of neuronal processes involved in motivation, reward mechanisms, outlines evaluation methods, and describes motivational properties of psychoactive drugs.

Keywords: intracranial self-stimulation behavior, rewards effect, motivational effect, runway method, priming stimulation

1. Introduction

Intracranial self-stimulation (ICSS) behavior was discovered by Olds and Milner (1) and is believed to be an effective experimental methodology for understanding reward and motivation systems in animals and humans (2). According to the “constancy theory” (3), reward and motivation systems exist contiguously in the brain, and ICSS behavior occurs by simultaneous activation of both systems. However, Reid et al. successfully developed a runway method employing ICSS behavior (4), which allowed the differentiation of reward and motivation system components responsible for ICSS behavior. By modifying Gallistel’s runway method, we have devised an experimental methodology that can be used to evalu-

ate the efficacy of drugs influencing motivational states.

Motivation is an important neural function that forms the basis for several critical undertakings in our life. The expression of motivation requires a series of affective processes that underlie reward (feeling of pleasure). Neuronal signaling in the mesolimbic dopamine system in the brain has been recognized to play a significant role in the relationship between motivation and reward. This review introduces experimental methods for the evaluation of motivational effects.

2. Motivation and reward processes

We introduce and discuss 4 types of neuronal processes involved in motivation and reward mechanisms.

Process of drive (expectation of reward): When food reward is considered, visceral cues signaling hunger are transferred to the hunger center of the lateral hypothalamus. Memories of food are relayed from memory centers such as the medial temporal lobe, and information conditioned by food and affective responses associated with

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such information are transferred from the limbic system (including the hippocampus and amygdala) to the nucleus accumbens.

Conversion from drive to action: The nucleus accumbens functions as an interface that converts visceral and emotional information to the action of searching for food. In order for the nucleus accumbens to fulfill this function, decision-making signals from the prefrontal cortex are required (5). Before the search action begins, dopamine levels decrease, and then increase only during the actual expression of the search action. Dynamic changes in dopamine nerve firing are necessary to convert drive to action.

Search action: In the search process, information from the nucleus accumbens passes through neural connections to the ventral pallidum, mediodorsal thalamic nucleus, and brainstem motor area; all of which are related to goal-directed motion. This results in the search action.

Reward experience (feeling of pleasure): This is a process where food is consumed and satisfaction is experienced. Furthermore, this process involves μ -opiate receptors, which mainly exist in the ventral tegmental area; *N*-methyl-D-aspartic acid excitatory amino acid (glutamate) receptors; and D_2 dopamine receptors (6). Dynamic changes in dopamine in the nucleus accumbens are necessary to express motivation (will), and activation of the endogenous opiate or dopamine systems in the ventral tegmental area is necessary to experience reward.

3. Experimental methods for evaluation of motivational effects

Chronic electrodes were implanted at a specific brain site along the medial forebrain bundle (MFB), and current from the electrode flowed to that brain site activating the entire MFB. Rats could elicit brain stimulation by pressing the lever in a Skinner box ("self-stimulation behavior"). MFB passes through the lateral hypothalamus, which is considered the most active brain reward site (7). A week after surgery, rats were trained for ICSS in the Skinner box (30.8-cm-wide, 25.4-cm-long, and 27.7-cm-high). Rats that pressed the lever at a stable rate for 3 days in the Skinner box (50 presses per min are used for the runway method).

The runway method of Gallistel et al. was used in this experiment (7, 8). The runway apparatus (Neuroscience, Tokyo) was made from 5-mm acrylic sections and consisted of a start box (26.5-cm-wide, 26-cm-long, and 30-cm-high), a controlled start door (26.5-cm-wide and 30-cm-high) that opened by dropping down, a runway (18-cm-wide, 180-cm-long, and 30-cm-high), and a priming box (30-cm-wide, 30-cm-long, and 30-cm-high).

A retractable lever was set at the end of the runway 7 cm above the floor (the goal lever). Each rat was trained in the runway until its running speed stabilized. Upon reaching the goal end and pressing the lever, rats received a reward stimulation of 0.2-ms pulses of 60-Hz alternating current. The current was set at 50 – 200 μ A to produce a maximal priming stimulation effect (the maximal difference between running speeds on priming stimulation trials vs. unpriming stimulation trials). The stimulation current was individually adjusted for each rat. In a trial, the rat was removed from the runway as soon as it received reward stimulation and placed in the priming box beside the runway, where 25 s later it receives 10 priming stimulations (1 stimulation per second, the same parameters as the reward). When priming stimulation terminated, the rat was transferred from the priming box to the start box of the runway. Five seconds after termination of priming stimulation, the start box door was opened. If the rat ran to the goal lever and pressed it, the rat received reward stimulation. The running time from the opening of the door to the pressing of the goal lever was recorded by a microcomputer.

This experimental procedure for ICSS using the runway method involved 30 trials and consisted of pre-, baseline, and test sessions (Fig. 1A). Each session comprised 10 trials. In the pre-session, rats received 10 priming stimulations and 1 reward stimulation for pressing the goal lever. In the baseline session, rats received 5 priming stimulations and 1 reward stimulation for pressing the goal lever. In the test session, after the administration of vehicle or drugs, rats received 5 priming stimulations and 1 reward stimulation for pressing the goal lever. Vehicle and drugs were administered before the baseline or test session. The running speed in the pre-session was significantly high compared to those of baseline and test sessions [$F(2,15) = 42.577$, $P < 0.05$]. There were no significant differences in the running speeds of the baseline and test sessions (Fig. 1B). The motivational effect of the drugs was calculated as the ratio of the running time in the baseline session to that in the test session. When the running time in the test session is significantly lower than that in the baseline session, the motivational effect of the tested drug was considered to be positive (9 – 11).

4. Characteristics of priming stimulation

Each rat was trained on the runway until its running speed stabilized without priming stimulation. Studies on the effect of priming stimulation frequency on running speed consisted of 50 consecutive trials, with 5 stages of 10 trials each. Rats received 0, 1, 3, 5, and 10 priming stimulations (1 per second, the same parameters as for

Fig. 1. Experimental design for the measurement of motivation and running speed. A: Each session consisted of 10 trials, and the value assigned for each rat was the mean of the 10 trials. When the value for the test session was significantly higher than that for the baseline session, the test drug was considered to have a motivational effect. B: Running speed in the pre-, baseline, and test sessions. Saline was administered during the baseline and test sessions. Each column indicates the mean $\pm$ S.E.M. of 6 rats. Data were analyzed by one-way ANOVA followed by the Sheffé test. * $P < 0.05$, significantly different from baseline and test sessions. Prim., priming stimulation; Rew., reward stimulation. Modified from Reference 9 with permission.

reward) in stages and 1 reward stimulation upon pressing the goal lever. The running time calculated from the door opening to the pressing of the goal lever was recorded using a microcomputer.

The priming stimulation frequency significantly and positively correlated with running speed ($r = 0.897$, $P < 0.05$) (Fig. 2). Furthermore, running speed increased with an increase in current strength of priming stimulation (12, 13). These results indicate that in the runway method employing ICSS, priming stimulation enhances running speed to obtain reward stimulation. In addition, Reid et al. hypothesized that a change in running speed with regard to priming stimulation indicates a motivational effect in the runway method (4). Thus, priming stimulation may enhance motivation to obtain reward stimulation.

5. Motivational effects of reward drugs

We measured the motivational effects of methamphetamine, a psychostimulant well known for clinically en-

Fig. 2. Correlation of priming stimulation frequency and running speed of rats. Running speed increased with priming stimulation frequency. Each point represents the mean $\pm$ S.E.M. of running speed in 10 trials ($n = 4$). Reproduced from Reference 11 (Copyright 2008 The Pharmaceutical Society of Japan) with permission.

hancing motivation. Administration of 1 and 3 mg/kg of methamphetamine increases running speed (11). Motivational and rewarding effects are indispensable for completion of target-oriented behavior, and such complex behavior is not simply regulated by locomotor activity. However, the effect of methamphetamine-induced hyperactivity on goal-directed behavior should be much less than its motivational effect.

In addition, running speed has been demonstrated to significantly increase with a moderate dose of nicotine (0.2 mg/kg) (Fig. 3) (9). A subcutaneous injection of 0.2 mg/kg nicotine significantly decreases the duration of immobility in forced swimming tests with an experimental dose range of 0.01 – 1.0 mg/kg (14). In addition, a subcutaneous injection of 0.2 mg/kg nicotine significantly inhibits the effect of naloxone-induced place aversion (15). These findings indicate that a subcutaneous injection of 0.2 mg/kg nicotine is suitable for alleviating both depression-like behavior and aversive motivational states. These results may explain why 0.2 mg/kg of nicotine is considered the optimal subcutaneous dose for enhancing running speed and motivation.

Psychostimulants such as methamphetamine and nicotine affect the mesoaccumbens dopamine system (16). This system is closely associated with the motivational nervous system (17 – 19) and may be one of the neural substrates influenced by methamphetamine and nicotine. At the level of the posterior hypothalamus, MFB intersects with the mesoaccumbens dopaminergic system. Thus, it is conceivable that methamphetamine and nicotine activate the mesoaccumbens dopamine system and facilitate priming stimulation due to MFB stimulation. On the other hand, it is known that the inhibitory reward-

Fig. 3. Motivational effect of nicotine in the runway method using priming stimulation for ICSS behavior. Each bar indicates the ratio of running speed in the baseline session to that in the test session. Saline and nicotine (0.2 mg/kg) were administered subcutaneously 30 min before measurement. Data represent the mean $\pm$ S.E.M. of 6 rats and were analyzed by Student's *t*-test. Administration of 0.2 mg/kg nicotine increased running speed. * $P < 0.05$. Reproduced from Reference 9 with permission.

ing drugs such as morphine operates to the mesoaccumbens dopaminergic system and shows the rewarding effect. Therefore, when the inhibitory rewarding drugs such as opioids is discussed by our method of experiment, the enhancing of motivational effect might be perceived.

6. Motivational effects induced by the opportunity for ICSS

“Motivation” is a process that continuously changes behavior to achieve a goal and can be conceptualized as a series of steps relating to that process. Thus, motivation can be defined as either a factor that regulates goal-oriented behavior or complete interaction of various factors involved in such a goal.

Motivation in psychology is divided into physiological motivation and other motivations. Physiological motivation relates to behaviors involving drinking, eating, thermoregulation, sex, and emotions. In contrast, other motivations include intrinsic motivations, such as personal interests and curiosity, and social motivations, which relates to interpersonal behavior. In humans, dysfunctions primarily in intrinsic and social motivations lead to social problems. Thus, animal models targeting intrinsic motivations, not physiological motivations, may be more suitable for evaluation of drugs that influence human motivation. We used ICSS behavior in animals to evaluate the efficacy of drugs that influence motivation since this animal model is considered to have high face and predictive validity in modeling psychiatric disorders

of intrinsic motivation.

Traditional operant ICSS behavior comprises reward and motivational effects. Priming stimulation is known to promote the motivational effects of ICSS behavior (20). Using the runway method and priming stimulation, the reward and motivational effects of ICSS behavior can be differentiated. The operant runway procedure has been successfully used to study the motivational properties of a wide variety of reinforcers, including food (21), water (22), and sex (23), and intravenous heroin (24), amphetamine (25), nicotine (26), and cocaine (27). These reports indicate that the operant running speed indicates the animal's motivation.

Using a runway method of experimentation and the opportunity for ICSS as reward, we have shown that running speed substantially increased as the number of priming stimulations increased. We believe that priming stimulation given before the animals are put in the start box increased the drive of seeking the goal lever, which in turn increased running speed. Waraczynski et al. reported similar results (28) and also reported that under priming stimulation conditions, running speed also increased with increases in the stimulation frequency (without changing the current of the reward stimulation). Our study results complement the results of Waraczynski et al. in that motivation increases when the number of stimulations is changed versus a change in frequency used in their study. The effect of priming stimulations in the runway method can be interpreted as behavioral changes resulting from activation of neuronal substrates in the brain subserving motivation.

Using the experimental methods that we created, prominent changes were observed in running speed after exposure to methamphetamine and nicotine, corresponding to their well-known effects on motivation. Since these substances serve as positive controls, our results suggest that the runway method of ICSS behavior can be used to evaluate drugs that influence motivation. In addition, it is of note that certain anxiolytic agents (29), antidepressant drugs (30), and drugs to treat Parkinson's disease also modify the effects of priming stimulation by this method.

The decrement of volition is a symptom of the neuropsychiatric disorders such as melancholia, schizophrenia, and Parkinson diseases. A new method for evaluation of motivational effects of drugs that we proposed might be able to be used as an application for screening development of novel central nervous system drugs. Moreover, the development of the hypobulia remedy contributes to psychonosema patient's rehabilitation. In the future, we expect that our experimental method will be used to evaluate the effects of therapeutic drugs on motivation.

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