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Review

Characteristics of the Runway Model of Intracranial Self-stimulation Behavior and Comparison with Other Motivated Behaviors

Satoru Esumi[§], Yoichi Kawasaki, Yutaka Gomita, Yoshihisa Kitamura[*], and Toshiaki Sendo

Department of Pharmacy, Okayama University Hospital, Okayama 700–8558, Japan

Motivation incorporates several psychological aspects that produce reward-related and learning behaviors. Although reward-related behavior is reported to be mediated by the dopaminergic reward pathway, the involvement of dopaminergic systems in motivated behavior has not been fully clarified. Several experimental methodologies for motivational behavior have been reported, but pharmacological characteristics seem to vary among these methodologies. In this review, we attempt to summarize three main concepts: (1) the relationship of dopamine neuron physiology with motivated behavior, (2) the pharmacological characteristics of the runway intracranial self-stimulation model, and (3) the behavioral distinction of disparate motivated behaviors.

Key words: motivation, reward, dopamine, operant behavior, intracranial self-stimulation

Motivation is a set of psychological characteristics that elicits, controls, and sustains certain goal-directed behaviors. A motivational deficit is a symptom often related to several mental disorders such as major depression, Parkinsonian syndrome, and schizophrenia. Many cases have been reported in which motivational deficits are not improved even though the mental disorder has been treated appropriately [1, 2]. Therefore, we hypothesized that neural mechanisms underlying motivation may be distinct from the neural systems impaired in mental diseases. That is, we believe that previously undescribed central nervous system mechanisms are participating in motivation.

Motivational mechanisms are often recruited during reward-related learning behaviors. As dopamine is well known as the main neurotransmitter that mediates reward-related behavior [3–5], dopamine may participate in motivational behaviors. However, the participation of dopamine neural transmission in motivational behavior is not fully clarified. Although numerous experimental models for motivation have been described, the participation of dopamine signaling varies among these reports.

We previously demonstrated the feasibility of using a runway model that incorporates intracranial self-stimulation (ICSS) behavior to evaluate the motivational effects of drugs [6]. Specifically, this runway ICSS model is able to study the reward- and motivation-based properties of operant behavior separately. For example, motivated behavior in the runway ICSS model reflects distinct pharmacological aspects com-

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*Corresponding author. Phone:+81–86–235–7641; Fax:+81–86–235–7974
E-mail:kitamu-y@cc.okayama-u.ac.jp (Y. Kitamura)
[§]The winner of the 2012 Incentive Award of the Okayama Medical Association in Neuroscience.

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pared with forced swimming tests and conditioned place preference tests [7].

In this article, we review the participation of dopamine neurotransmission in reward-related behavior and the effects of pharmacological manipulations in the runway model of ICSS, which is a methodology developed in our laboratory to evaluate the motivational property of drugs. In addition, we discuss the characteristics of the runway model of ICSS as compared with other methods of evaluating motivation.

Involvement of Dopamine Neural Activity in Motivated Behavior

It is well known that dopamine is one of the key neurotransmitters mediating affect and reward. Natural rewards such as palatable food and water or copulation are reported to increase extracellular dopamine in the nucleus accumbens (NAc) [8–10]. Similarly, self-administration of abused drugs increases extracellular dopamine within the NAc [11–13]. In contrast, changes in dopamine during ICSS behavior are equivocal across studies. Some studies found that dopamine levels in the NAc are increased during ICSS [14–17], but other research has demonstrated that rats continue to press the operant ICSS lever without increases in dopamine in the NAc [18, 19]. Since electrical brain stimulation directly activates reward-related pathways, it is considered that ICSS procedures would be adequate to assess the relationship between reward and dopamine neural activity. However, the role of dopamine in reward-related behavior is controversial. Recent studies have suggested that dopamine contributes to reward prediction or motivational properties rather than reward itself during the reward-related behavior [20, 21]. Dopamine elevations are larger during reward prediction compared to reward acquisition. Dopamine elevations during reward acquisition are reduced along with learning about the relevance between reward and cue prediction [22, 23]. Therefore, it is considered that dopamine mainly contributes to reward prediction or the motivational properties of reward-related cues. Motivational states in these studies may vary and differences in dopamine elevations would reflect these motivational differences.

Extrasynaptic dopamine is released as a consequence of neural firing and consists of 2 different modalities: phasic and tonic dopamine firing [24, 25]. Phasic and tonic release is related to particular behavioral states. For instance, phasic dopamine activity facilitates cue-reward association and acquisition of incentive salience, whereas tonic activity is involved in response inhibition and behavioral flexibility [26–28]. Thus, motivational behavior may be regulated by phasic dopamine firing. In addition, it has been considered that activation of neural systems regulated by dopamine receptors may be controlled by a combination of phasic and tonic firing. It was estimated that phasic and tonic firing would differently affect dopamine D1 and D2 receptor occupancy in a computer simulation study [29]. Furthermore, dopamine D1 and D2 receptors were reported to be differentially involved in negative conditioned behavior after acute nicotine exposure or nicotine withdrawal [30]. Phasic dopamine firing is specifically associated with acute nicotine exposure rather than withdrawal from chronic nicotine. Thus, it is believed that the reaction of dopamine receptors to released dopamine is complex and that dopamine receptors are differently activated depending on the pattern of dopamine release. Dopamine receptors may respond differently to rewarding stimulation, non-rewarding stimulation, and/or reward prediction (motivation). Additionally, a unique pattern of stimulation of dopamine receptors may be required to facilitate motivation.

The Runway Model of ICSS

The runway ICSS model is a methodology that incorporates the ICSS procedure in a runway apparatus (Fig. 1). Once rats have established ICSS behavior at the goal lever, subjects strive to maintain the ICSS behavior even if they are moved away from the lever by the experimenter. After learning the essence of the runway apparatus, rats will run toward the goal lever from the start box to obtain a reward. As the running animals desire the goal reward, the running behavior is considered to represent motivated behavior. In our previous research, it was hypothesized that the runway ICSS model would be applicable to the assessment of the motivational effects of drugs [6]. Moreover, our previous research revealed the following behavioral characteristics and dopaminergic involvement in the runway ICSS model.

Two distinct electrical stimulations – prim-

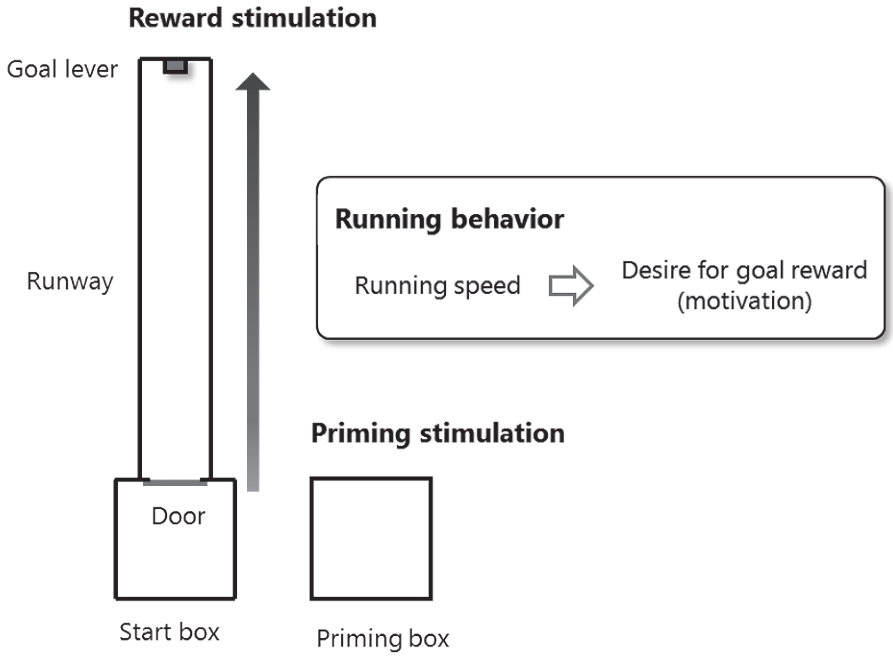

Fig. 1 Schematic diagrams of the runway ICSS apparatus. First, animals receive electrical priming stimulation in the Priming box. After the priming stimulation, animals are placed in the Start box. Animals run to the Goal lever on the other side of the start box through the Runway immediately after the door opens.

ing stimulation and reward stimulation.

In the runway ICSS experiments, animals were provided 2 opportunities for receiving electrical stimulation: a reward stimulation after a lever press and a priming stimulation. Electrical properties of these stimulation are the same (single train of 0.2–ms pulses of 60 Hz alternating current). Before each running trial, priming stimulations are supplied at the priming box, which is a distinct place unrelated to the running behavior. After reaching the goal end and pressing the lever, rats receive a reward stimulation.

The most significant characteristic here is that running speed varies according to the frequency of the priming stimulation. The running speed would presumably reflect the motivation for getting the reward at the goal lever. Interestingly, running behavior is not performed in a no-reward situation, even if sufficient priming stimulation is provided (Fig. 2). Thus, the runway model of ICSS measures motivated behavior based on the goal reward, although the priming stimulation could still modulate the motivated behavior.

Postulated relationship between the runway model of ICSS and dopamine-mediated salience.

Phasic dopamine release is considered to be involved in the reward prediction error, learning, and motivation [31]. Cue-evoked dopamine release should increase in the context of motivation, since cue-evoked dopamine release is reported to become larger after animals learn the relationship between reward and predictive cue stimulation [23]. In the runway model of ICSS, the priming stimulation is an electrical stimulation of dopamine neurons that would temporarily release dopamine. In addition, the priming stimulation enhances running speed in a frequency-dependent manner. Thus, the dopamine release caused by priming stimulation is classified as a phasic dopamine release and motivation might be enhanced depending on the degree or frequency of this phasic dopamine release. However, priming stimulations do not act as rewards, although priming stimulation and reward stimulation are the same in terms of dopamine release. It is unclear how rats distinguish the priming stimulation from reward, but this might be explained by differences in the associations between stimulations and operant tasks in the runway model of ICSS. There is a need to more precisely study the differences between the neural activity when rats are given only a reward and that when rats are provided both

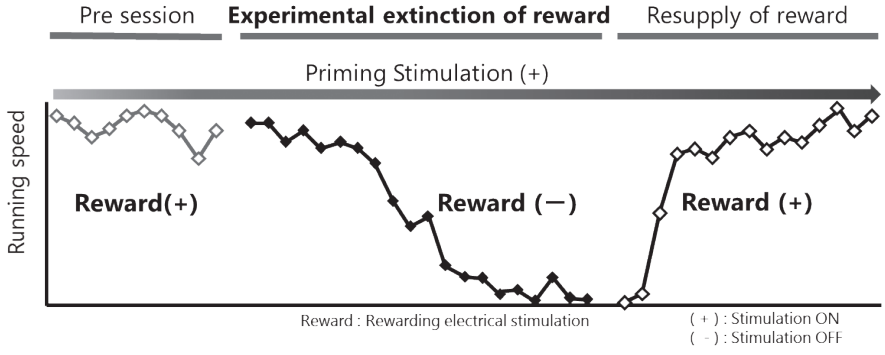

Fig. 2 Representative examples of the effects of the priming stimulation and reward stimulation in the runway ICSS model. In the experimental extinction of reward, rats gradually run slower despite the provision of priming stimulation and this speed reduction is reversed by the resupply of reward. For more information about the experimental extinction of ICSS, see: Sagara *et al*., Biol Pharm Bull (2008) 31(4): 541–545.

motivational stimulation and reward.

Effects of dopaminergic agents in the runway model of ICSS.

The runway ICSS model is based on ICSS behavior produced by intracranial stimulation through an indwelling electrode at the level of the medial forebrain bundle (MFB). Since the MFB is one of the dopaminergic fascicles from the ventral tegmental area to the NAc [32], dopaminergic agents would be expected to affect motivated behavior in this paradigm. Thus, we have primarily focused on the effects of dopaminergic agents in the runway ICSS model. The selective dopamine uptake inhibitor GBR12909 and dopamine-noradrenaline uptake inhibitor nomifensine dose-dependently elevated running speed (*i.e.*, motivation for reward). Facilitation of the priming stimulation effect should be caused by effects on dopamine uptake since GBR12909 and nomifensine are reported to elevate NAc dopamine levels and we have also reported that the enhancing effects of these drugs were inhibited by pretreatment with dopamine antagonists [33, 34]. It is well known that NAc dopamine levels are involved in reward and motivation and that the NAc is a terminal of dopamine neurons expressing dopamine transporters [35, 36]. Thus, dopamine uptake inhibition in the NAc should be involved in the enhancement of running behavior in the runway method of ICSS behavior.

On the other hand, the effects of dopamine receptor agonists on this motivated behavior have been shown to be different from those produced by dopamine uptake inhibitors. The dopamine D1-like agonist SKF38393 or the D2-like agonist quinpirole both suppressed motivated behavior. In addition, simultaneous administration of SKF38393 and quinpirole exhibited additive or synergistic effects compared with single administrations. Thus, the direct stimulation of either D1-like and/or D2-like receptors using dopamine agonists failed to enhance motivated behavior in the ICSS runway model. Additional research is required to reveal a more precise role of dopamine receptors in motivated behavior. Quinpirole has been reported to enhance reward-related operant behaviors such as addictive drug-related behavior, quinpirole self-administration, and ICSS lever press behavior [37–40]. However, in our previous research, quinpirole and SKF38393 suppressed runway-motivated behavior. Therefore, it is believed that dopamine receptor function may differ between the motivated behavior in our runway model and the reward-acquisition behavior in previous reports. Direct receptor stimulation with agonists and indirect stimulation with uptake inhibitors seem to produce different effects in these operant behaviors.

For this distinction, we propose 2 hypotheses. First, differences in the distribution of the dopamine transporter and dopamine receptors may be responsible for differences in runway behavior. Dopamine transporters are reported to be localized within the NAc, striatum, substantia nigra, and ventral tegmental area [41]. In comparison, dopamine receptors seem to be present across a variety of brain regions [42]. A specific activation pattern of dopamine receptors is likely required for the production of motivated

behavior. Simultaneous stimulation of dopamine receptors in various brain regions (produced by systemic administration of dopamine receptor agonists) may result in a depressant effect on motivated behavior. Second, there might exist significant differences in terms of NAc neurotransmission between the indirect activation of dopamine neurons caused by enhancement of intrinsic dopamine transmission by dopamine uptake inhibitors and the direct activation of dopamine receptors using dopamine receptor agonists. The activity of neurons projecting from the NAc may also be differently regulated by these 2 different forms of activation, and it may be necessary to evaluate the neural activity downstream from the NAc to better understand motivational pathways. Most neurons in the NAc are GABAergic. Thus, under the influence of drug treatment, measuring the effects of MFB electrical stimulation on GABA concentrations in nerve terminals projecting from the NAc may be particularly helpful in understanding the activation of motivational circuitry.

The Distinction of the Runway Model of ICSS: Comparison with Other Motivational Behaviors

The runway model of drug self-administration and progressive ratio schedules using various rewards are commonly used methods to evaluate motivation. In this section, we compare the behavioral characteristics of these models with those of the runway model of ICSS.

Runway model of drug self-administration.

In the runway model of drug self-administration, animals are provided an intravenous injection of addictive drugs instead of electrical stimulation as the reward for running behavior. That is, the runway model of drug self-administration is a methodology to assess the animal's motivation for getting a drug reward. In a previous study, Ettenberg *et al.* reported that trained animals would run to a goal box to seek a drug reward, such as cocaine and heroin [43]. Dopamine receptors were found to be involved in the runway task to receive heroin reward, at least partially [44, 45]. However, the drug-seeking, motivational behavior seems to vary depending on the type of rewarding drug. Although the reinforcing effects of cocaine and heroin are equivalent in the conditioned place preference test, cocaine induced "retreat behavior", which is approach-avoidance conflict behavior, whereas heroin exhibited purely facilitative effects for running behavior [46]. Thus, it is considered that the motivational effects of reinforcement on runway operant behavior may differ depending on the reward (type of drug, natural reward, or rewarding electrical brain stimulation). Many addictive factors (such as drugs, gambling, and sex) are known for activating dopamine neurons in brain reward centers [47]. It is suggested that addictive drugs would affect motivation through the dopaminergic pathway. However, it is difficult to determine the precise receptors underlying the motivational mechanisms in the runway model of drug self-administration since addictive drugs act on various receptors. The runway model of ICSS may be more suitable for research focusing on the function of the dopaminergic system on motivation. In other words, the runway model of drug self-administration would be useful to evaluate motivational effects, considering the complex reinforcing properties of addictive drugs.

Progressive ratio operant paradigm using self-administration of reinforcers.

The progressive-ratio paradigm of reinforcement was developed by Hodos (1961) [48] to study the "relative reward strength of stimulation" and has been employed in many studies using rats [49], monkeys [50], dogs [51], pigeons [52], and pigs [53]. Diverse reinforcers, including intravenous injection of psychostimulants [54, 55], food pellets [56], liquids [57], and intracranial electrical stimulation [58] have been used in this paradigm. The relative responsiveness to reinforcements is reported to be different among reinforcers [59–61]. For example, electrical stimulation may be more responsive than natural rewards, such as sucrose reinforcement [62]. A progressive-ratio procedure measures the performance of an increasing amount of work (progressively increasing number of required operant responses) as the effectiveness of reinforcement. As animals execute the operant task, the magnitude of the task (such as lever pressing) required for obtaining a reward increases. When the expense of the ever-increasing operant task exceeds the value or attraction of the offered reward, animals will give up reward acquisition and no longer perform the task. This "breaking point" is one endpoint measure in the progressive ratio procedure. The breaking point is defined as the number of rewards acquired during an operant session before the subjects cease the operant behavior. The breaking point is

considered to reflect the efficacy of the reward and the motivation for acquisition of the reward [62].

Progressive ratio studies during withdrawal from addictive drugs have been reported throughout the literature [59, 62]. Under a withdrawal condition for d-amphetamine or nicotine, the breaking point on a progressive ratio schedule for sucrose reward exhibits a transitory decrease without changing the total sucrose consumption. The decrease in the breaking point suggests that the reward value of sucrose or the motivation for sucrose is decreased. However, this decrease in motivation in the progressive ratio seems to be slightly different from the decrease in the priming stimulation effect (the main motivation-regulating factor) in the runway ICSS model. The reduced breaking point in the progressive ratio strategy is improved by antidepressants [63, 64] whereas the priming stimulation effect is reduced by antidepressants. Therefore, these two experimental strategies may evaluate completely different neurobiological functions.

Conclusion

In this review, we discussed the involvement of dopamine in various experimental methods to evaluate motivation. The involvement of dopamine in motivated behavior appears to be somewhat different from its role in reward-acquisition behavior. Appropriate drug treatments affecting the dopaminergic system might modulate motivation without altering reward processing. In addition, assessment methods for motivated behavior seem to be pharmacologically distinct. Additional research will help reveal more detailed characteristics of these experimental models and the pharmacological characteristics of motivated behavior that are shared across these experimental models.

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