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利用跑爬跑行為工具探討中腦多巴胺系統的神經行為機制

(1/3)

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Progress Report for NSC 94-2413-H-004-014 grant project: Investigation of neurobehavioral mechanisms of mesocorticolimbic dopamine system by the use of a run-climb-run behavioral task (1/3), 利用跑爬跑行爲工具探討中腦多巴胺系統的神經行爲機制(1/3)

By Ruey-Ming Liao (June, 2006)

The mesocorticolimbic dopamine (DA) system is known as the best candidate for the common neural substrate for mediating the subjective rewarding action of natural rewards and drug of abuse, and also for playing a critical role in the maintenance of reinforcement process. However, how exactly the DA exerts its functions in this brain system for reward-motivated behavior remains uncertain and in debate. Despite considerable evidence showing behavioral impairment under DA antagonism or lesion, it is important to be more precise on parsing the relationship between behavior and brain on this issue. This project will set up a sensitive and newly developed measure so-called run-climb-run (RCR) behavioral task to encounter this challenge. It is reasonably presumed the different DA subtype receptors (D1 vs. D2) located in three major terminal areas of this DA system are differentially involved in distinct requirements on RCR behavioral task. As focusing on such a theme, this project aims to investigate the neurobehavioral mechanisms of mesocorticolimbic DA system by the use of RCR behavioral task. Proposed to complete in three years, this project is designed to reveal the effects of DA antagonism on several different behavioral components of the RCR task. The behavioral components will be measured by manipulating 1) solely on the rope length to determine the response cost required for completing behavior, 2) solely on the reward value of reinforcer to judge the earned benefit, and 3) the interaction between cost and benefit by holding one factor in consistent and varying the other. In addition, reinforcers with different values will be conditioned with neutral visual stimuli and then determine the effects of conditioned reinforcement. Another behavioral manipulation will be focused on establishing the concurrent choice paradigms based on selecting either high/cost to get high/benefit or low/cost to get low/benefit. Following the establishment of these different tasks on RCR behavior, the systemic administration and microinjection of selective DA D1 and D2 receptor antagonists into the striatum, the NAcc, and mPFC will be conducted to determine the role of DA receptor subtypes involved. In considering the heterogeneity for these three area, and also the experimental control for anatomical site of microinjection, each area will further divided by two subregions: the dorsomedial and vetrolateral parts for the striatum, the core and shell areas for the NAcc, and the dorsal and ventral parts for the mPFC. Moreover, in order to determine the neuronal activation correlated with different requirements on RCR

behavior, Fos-like immunoreactivity in six neural regions within the mesocorticolimbic DA system will be assayed for each of aforementioned RCR tasks. The aforementioned is the general profile for this 3-year project. The work have been done in the past 10 months of the first year will be described below, which is the main part of this progress report.

The first experiment was designed to investigate the lesion effects of striatal subareas on the RCR task, which study can be assumed as a follow-up work from a previous study from this laboratory reported behavioral deficits induced by systemic injection of DA receptor antagonists (Liao et al., 2001). It is assumed that these DA agents exert their receptor blockade in the terminal areas of mesolimbic DA systems. Accordingly, the present study investigated how lesions in two striatal subareas, the NAcc and the ventolateral striatum, would affect the RCR behavior. Food-deprived rats were trained to traverse an uncovered floor alleyway (150 cm), climb a vertical rope (70 cm), and run across an upper board (100 cm) to access a piece of chocolate for the reinforcement. Following baseline training, ibotenic acid was used to produce excitotoxic lesions in the NAcc and the ventrolateral striatum. Subsequent to the recovery from surgery, post-lesion test was conducted on the RCR task over 3 consecutive days. Extended tests by manipulating the reinforcement increment (as 3 pieces of chocolate provided) and the climbing rope length shorten (from 70 cm to 30 cm) were conducted thereafter. The NAcc lesion significantly disrupted the RCR behavioral performance as revealed by the increased time to complete the task. Although the time to complete the task was increased by the lesion in the ventrolateral striatum, such effect was not statistically confirmed. Behavioral impairment of the NAcc lesioned subjects was reversed by the climbing rope length shorten treatment, but not by the reinforcement increment. In summary, these data indicate that the NAcc was an important brain area for driving the motivation of RCR behavior. The reduced demanding effort or cost to complete task is able to reverse the behavioral deficits on current task induced by lesion in the nucleus accumbens.

Based on the aforementioned findings about the critical involvement of the NAcc, the second experiment was conducted to further delineate the role of D1 and D2 recepters within it. The training procedures of RCR were identical with those described in the preceding. Following the behavioral baseline established, the subjects received the cannulae implantation localized in the NAcc. The subjects were then assigned to receive either SCH23390 (D1 receptor antagonist) or raclopride (D2 receptor antagonist). The doses for either drug were kept constantly in molarity (0, 2, 4, 8 nmole), given in a counterbalanced order. The results showed that both SCH23390 and raclopride could significantly affect the performance of RCR, which was dose dependently. Furthermore, the subject was tested on RCR with a shorter

rope when given with the effective dose of DA receptor antagonist. The preliminary results showed the drug influence of RCR behavioral impairment was diminished under this behavioral manipulation with the shorten rope presented. In summary, these data confirm the DA receptors of the NAcc are critically involved in the mediation of RCR behavioral performance. Moreover, the NAcc related neural mechanisms can be altered by behavioral intervention, indicating the dynamic relationship between brain and behavior.

All together, these findings described above are very informative for charactering the neuro-behavioral mechanism for the motivated behavior as measured by RCR task in this proposed project. The project is actively and productively executed in terms of the progress for this 3-year project.

Reference cited

Liao R.-M., Lin J.-Y., Cheng R.-K., & Liao J.-J. (2001) Effects of SCH23390 and raclopride on a run-climb-run behavioral task in rats. Chinese Journal of Physiology, 44(4), 151-160.