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Research report

Involvement of cannabinoid system in the nucleus accumbens on delay-based decision making in the rat

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ABSTRACT

The nucleus accumbens (NAc) plays a fundamental role in decision making and anticipation of reward. In addition, exogenous cannabinoids affect the behavior of humans and animals including disruption of short-term memory and cognitive impairments. Therefore, in this study, cannabinoid agonist and antagonist were administrated into the NAc to determine the effect of cannabinoid activation in the entire NAc on delay-based decision making. Rats were trained on a cost-benefit T-maze decision making task in which the animals were well-trained to choose between a small/immediate reward and a large/delay reward. After training, the animals were implanted with guide cannulae in the NAc. On test day, they received cannabinoid agonist (Win 55,212-2; 10, 50 and 100 μM) and/or antagonist (AM251; 45 μM) into the NAc. Percentage of high reward choice and latency of reward achievement were evaluated. Results showed that cannabinoid agonist administration caused a decrease in high reward choice such that rats selected small/immediate reward instead of large/delay reward. Moreover, in agonist-treated animals latency of reward achievement increased. Effects of cannabinoid activation on delay-based decision making with equivalent delays demonstrated that if the delay was equated on both arm goals, animals still had a preference for the high/delay reward, showing the results was not caused by an impairment of spatial preference or memory. These finding clarified that cannabinoid system activation in the entire NAc plays a critical role in the regulation of delay-based decision making.

1. Introduction

A common form of decision making is cost-benefit choice, in which an individual needs to evaluate different options (such as costs) in terms of their outcome value (benefits) and weigh them against each other [1]. Delay discounting tasks used as a measure of impulsive decision making, where response costs are varied by imposing a delay before delivery of a larger reward versus obtaining an immediate, smaller reward [2]. The nucleus accumbens (NAc) is an important anatomical substrate for motivation and reward and dysfunction of this region could account for anhedonia, social withdrawal, and other symptoms of depression [3]. Dopamine projection to the NAc core has been implicated in allowing animals to choose to exert effort to receive greater reward [4]. Recent evidence suggests that the NAc is part of a distributed neural circuit that regulates cost-based decision making and is essential for animals to overcome heavy cost burdens [5,6]. This area plays also a more fundamental role in helping an organism overcome different costs to get better rewards and is implicated in goal-directed instrumental action, decision-making and anticipation of reward [7,8]. To make appropriate choices, organisms should weigh the costs and benefits of potential valuable outcomes, a process well known to involve the NAc and its dopaminergic input [9]. Recent evidence establishes that the excitotoxic lesions of the core region of the NAc increase delay discounting and cause a preference for a smaller immediate reward [5].

Cannabinoid receptors play a role in the regulation of a variety of physiological processes such as energy homeostasis, food intake [10,11], body temperature, learning and memory, synaptic plasticity and locomotion [1,12,13]. The cannabinoids influence the behavior of animals that include disruption of short-term memory, cognitive impairments, mood alterations and a reduced ability to focus attention [14]. Cannabinoid receptors type 1 (CB1R) are predominantly localized in the brain and are highly expressed in the NAc, cerebral cortex, limbic areas, and reward circuitry [15] whereas cannabinoid receptors type 2 (CB2R) are mainly expressed in peripheral cells [16,17]. It was reported that CB1R negatively controls the release of several neurotransmitters [13,18]. Neurochemical experiments demonstrated that the cannabinoid agonists raise dopamine levels in the NAc [19] and drugs that

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interfere with dopamine availability produce an increase in impulsive choice [20,21]. Besides, there is evidence that cannabinoid influences cost-benefit decision making. For example, Grant et al. reported that cannabis users showed less rational decision making on the Gamble task than controls [22]. Moreover, previous experiment in our laboratory showed that cannabinoid system plays a critical role in regulating cost-benefit decision making in the anterior cingulated cortex and orbitofrontal cortex [23]. Therefore, in this study, we administrated cannabinoid agonist and antagonist into the entire NAc to estimate the involvement of exogenous cannabinoid in the NAc on delay-based decision making.

2. Materials and methods

2.1. Animal

Male Wistar rats (Pasteur Institute, Tehran, Iran; weighing 230–270 g) were used in this study. The animals were maintained under the standard laboratory conditions (22 ˚C, 12-h light/12-h dark cycle) and grouped three per cage. The animals were handled on a daily basis and food was adjusted for initial body weights of about 85–90% of the free feeding weight during the beginning of the behavioral experiment and after this a controlled weight gain of about 6–12 g per week and water was available ad libitum. All investigations and procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996) and were approved by the local ethical committee, Shahid Beheshti University of Medical Sciences.

2.2. Drugs

In this study, the drugs used were as follows: Win 55,212-2 (Tocris Bioscience, Bristol, UK), as a cannabinoid receptor agonist, was dissolved in12% dimethyl sulfoxide (DMSO; Sigma Aldrich, Germany). AM251 (Tocris Bioscience, Bristol, UK), as a cannabinoid receptor inverse agonist, was diluted in 12% DMSO. Control animals received 12% DMSO as a vehicle.

2.3. Apparatus

A T-maze task involving delay-based decision making was used [24,25]. The gray color Plexiglas mazes had three arms (one start arm and two goal arms) each 60 cm long, 10 cm wide and 40 cm high. Food wells, 3 cm in diameter, were placed at the end of the goal arms. For delay-based decision making protocol, four retractable doors were built in the goal arms of the maze. One door was placed just before the food well at each arm, 5 cm from the end of the arm and the other after the entrance into each arm, 12.5 cm from the entrance point (Fig. 1A). These doors were used to delay the access of the animals to rewards in delay-based decision making task. Furthermore, on “forced” trials, a 30 cm tall and 10 cm wide block was used to force the animal to go to one of the goal arms.

2.4. Behavioral training

Rats were trained to perform T-maze decision-making tasks with a differential cost (short vs. long waiting time) and reward (small vs. large reward amount) in the two arms of the maze. The experimental procedure corresponds to the schedule described by previous study [23,25]. Before the start of training, the rats were handled every day for one week to familiarize them with human contact and were put on a restricted feeding schedule. When they reached 85–90% of their free-feeding weight, the rats were introduced to the T-maze.

2.4.1. Habituation phase

At first, for three days the animals were placed in the start arm of T-maze in groups of two and were allowed to explore the maze for 20 min. For the next three days, plentiful food was left in both feeding wells in the goal arms (45 mg food-reinforcement pellets, Formula A/I; P. J. Noyes, Lancaster, NH) and each animal investigated the maze individually. At the end of this phase, all of the rats were eating the pellets in the food wells.

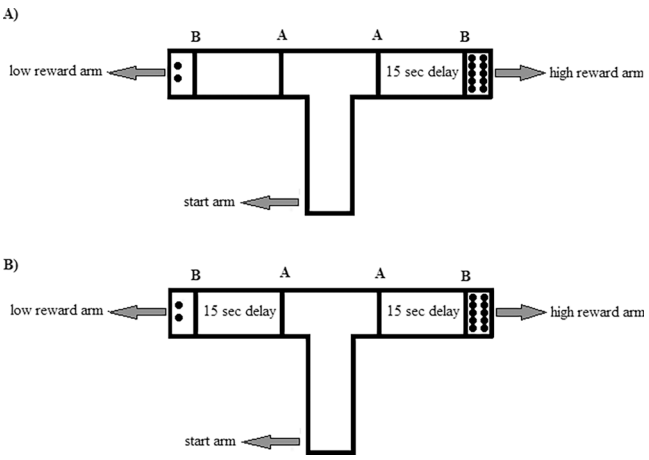

Fig. 1. Schematic illustration of the apparatus. A) Delay-based T-maze decision-making task (main task). The apparatus has three arms including start, high reward and low reward arms. The animals could choose to wait (15 s) in order to obtain a higher reward (10 pellets) and/or choose to receive low reward (2 pellets) immediately. (B) Equal delay control task. 15 s delay was introduced to both goals arms and the animals should wait (15 s) to gain reward in high or low reward arms.

2.4.2. Discrimination phase

After habituation to the maze, animals learned to discriminate a high-rewarded goal arm containing four food pellets from a low-rewarded goal arm containing two food pellets. Discrimination training was run in three stages. At the first stage of discrimination training, we put ten pellets in the feeding well of high reward arm (HRA) and two pellets in the feeding well of low reward arm (LRA). For half of the rats, the HRA arm was to the left, and, for the others, it was to the right. The animals were placed individually in the start arm and were allowed to receive the pellets from both sides without a barrier in any of the goal arms. There were three days of first stage and each rat ran 5 trials per day. At the second stage, the animals were given access to one of the goal arms, thus forcing the animal to sample pellets for a particular arm on each trial. The LRA/HRA order of the forced trials was determined pseudo randomly so that the animal never had more than two consecutive turns to either side. Rats ran 10 trials per day for three days, to complete the second phase. At the third stage, animals were allowed to sample food from only one of the goal arms. Each day, the animals performed two “forced” trials and ten “choice” trials with an interval of 2 min. During this phase, the animals had to choose one of the goal arms and they were removed from the maze following the consumption of the reward in the chosen arm well.

2.4.3. Delay phase

At this stage, door B was closed in both goal arms and once the rat entered a goal arm, door A was closed and door B was opened and the animal had access to the chosen food well. During this phase, the animals had to choose one of the goal arms and they received an immediate reward in both arms. Once the animals had reached an average high reward choice (HRC) of 80% or more, a delay of 5 s was introduced to the HRA. Similarly, after a few days of training in this phase and exceeding the average HRC of 80%, the delay was increased to 10 and then 15 s. One rat was not able to perform the task and follow the training and was excluded from the experiment. The animals needed 4–6 days to complete each of these phases of the decision training, and