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Activation of the cannabinoid system in the nucleus accumbens affects effort-based decision making

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ABSTRACT

Effort-based decision making addresses how we make an action choice based on an integration of action and goal values. The nucleus accumbens (NAc) is implicated in allowing an animal to overcome effort constraints to obtain greater benefits, and it has been previously shown that cannabis derivatives may affect such processes. Therefore, in this study, we intend to evaluate the involvement of the cannabinoid system in the entire NAc on effort-based decision making. Rats were trained in a T-maze cost-benefit decision making the task in which they could choose either to climb a barrier to obtain a large reward in one arm or run into the other arm without a barrier to obtaining a small reward. Following training, the animals were bilaterally implanted with guide cannulae in the NAc. On test day, rats received cannabinoid agonist (Win 55,212-2; 2, 10 and 50 μM) and/or antagonist (AM251; 45 μM), afterward percentage of large reward choice and latency of reward attainment were investigated. Results revealed that the administration of cannabinoid agonist led to decrease of large reward choice percentage such that the animals preferred to receive a small reward with low effort instead of receiving a large reward with high effort. The administration of antagonist solely did not affect effort-based decision making, but did attenuate the Win 55,212-2-induced impairments in effort allocation. In agonist-treated animals, the latency of reward collection increased. Moreover, when the effort was equated on both arms, the animals returned to choosing large reward showing that obtained results were not caused by spatial memory impairment. Our finding suggested that activation of the cannabinoid system in the NAc impaired effort-based decision making and led to rats were less willing to invest the physical effort to gain large reward.

1. Introduction

Decision making involves weighing costs against benefits, for instance, in terms of the effort that is required to obtain a reward of a given magnitude (Schouppe et al., 2014). In the other words, organisms frequently make effort-related decisions based on the evaluations of reinforcement value and response costs (Randall et al., 2014). In normal situations, animals show a strong preference for the large reward/high effort option while having the choice to obtain a small reward with little effort (Endepols et al., 2010). Effort-related choice behavior is mediated by cortical-limbic-striatal network, including the anterior cingulate cortex (Schweimer et al., 2005; Walton et al., 2003), and the nucleus accumbens (NAc) (Hauber and Sommer, 2009; Ghods-sharifi and Floresco, 2010; Endepols et al., 2010). Rats with excitotoxic anterior cingulate cortex lesions select the low cost/low reward option in a T-maze cost-benefit task when given the choice between climbing a barrier to obtain a large reward in one arm or running for a small reward into the other arm with no barrier present (Rudebeck et al., 2006; Schweimer et al., 2005; Walton et al., 2003), and similar results are observed following inactivation or lesions of the NAc (Hauber and Sommer, 2009; Ghods-sharifi and Floresco, 2010). Indeed, there are robust projections from the anterior cingulate cortex to the NAc (McGeorge and Faull, 1989) and it is established that the NAc receives and integrates information from the anterior cingulate cortex that is used to guide effort-based decision making (Hauber and Sommer, 2009). Human imaging studies suggest that activity in dorsal prefrontal cortical areas encompassing the anterior cingulate correlate with the subjective value of options discounted by physical effort (Chong et al., 2017).

Notably, it is increasingly recognized that cannabinoid transmission may regulate effort-based valuations occurring in cortico-striatal networks. The cannabinoid system plays a role in the regulation of a variety of physiological processes such as pain modulation, feeding, locomotion, and cognition (Robson, 2014). Systemic administration of cannabinoid agonists has been reported to increase the NAc dopamine levels, which contribute to reward-related processing and positive

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reinforcement (Fattore et al., 2010). Indeed, studies show that the endocannabinoid signaling in the brain affects the motivation for natural rewards such as palatable food (Parsons and Hurd, 2015). Cannabinoid CB1 receptors (CB1R) are richly expressed in the brain, whereas cannabinoid CB2 receptors are mainly expressed in the immune system and periphery (Fatahi et al., 2015; Kano, 2014). CB1R coupling to the G protein signal transduction pathways in the presynaptic nerve terminals inhibits adenylyl cyclase, thus attenuating the production of cAMP (Svizenska et al., 2008). There is evidence to suggest that the administration of a CB1R agonist to rats impairs decision making processes that involve cognitive effort costs (Silveira et al., 2016). The cannabinoid CB1 receptor has a role in the regulation of impulsive action and impulsive choice, whereby CB1 receptor agonism decreases impulsive choice (Wiskerke et al., 2011). In addition, the previous study in our laboratory established that the cannabinoid system plays a critical role in regulating cost-benefit decision making in the anterior cingulate cortex and in the orbitofrontal cortex (Khani et al., 2015). Specifically, CB1 agonism in the anterior cingulate cortex, but not orbitofrontal cortex, decreased willingness to exert physical effort for the larger reward. However, how cannabinoid modulation in the striatum affects this process is unknown. Therefore, in the current study, we aimed to investigate the role of the cannabinoid system in the entire NAc with respect to effort-based decision making.

2. Materials and methods

2.1. Animal

One hundred fifteen male Wistar rats (Pasture Institute, Tehran, Iran) were used, weighing between 230 and 270 g. They were housed in standard cages under controlled temperature (22 ± 2 °C) and light conditions (lights on at 07:00, lights off at 19:00). 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 the current study, the following drugs were used: Win 55,212-2 (Tocris Bioscience, Bristol, UK), as a cannabinoid receptor agonist, was dissolved in12% dimethyl sulfoxide (DMSO; Sigma Aldrich, Germany; was diluted in saline). AM251 (Tocris Bioscience, Bristol, UK), as a cannabinoid receptor antagonist, was diluted in 12% DMSO. Control animals received 12% DMSO as a vehicle.

2.3. Apparatus

A T-maze task involving effort-based decision making was used (Salamone et al., 1994; Walton et al., 2002). The T-maze consisted of a start arm (which joined on to two goal arms) and two goal arms (each 60 cm long, 10 cm wide and 40 cm high) made of gray color Plexiglas. Food wells, 3 cm in diameter, were placed at the end of the goal arms and food rewards were placed on it. 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. Three-dimensional triangular barriers with different heights (10, 20 and 30 cm) made of mesh wire were used in the midpoint of the high-reward goal arm to introduce different levels of physical effort cost in different stages of training. In order to obtain a reward, the animals had to climb over a barrier (Fig. 1A).

2.4. Behavioral training

Rats were trained to perform T-maze decision making tasks with differential costs (low vs. high effort) and rewards (small vs. large reward amount) in the two arms of the maze. With some slight differences, the experimental procedure corresponded to the schedule described in previous work (Denk et al., 2005; Walton et al., 2002). In brief, before the start of the training process, the rats were handled by the experimenter every day for one week in order to familiarize them with the human contact; they 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 three and they were allowed to explore the maze for 20 min. For the next three days, the plentiful food was left in both feeding wells of the goal arms (45 mg popcorn, Formula A/I; P. J. Noyes, Lancaster, NH) and each animal investigated the maze individually. At the end of this phase, all the rats were eating the reward found in the food wells.

2.4.2. Discrimination phase

After the rats were habituated to the maze, the animals learned to discriminate between the high-rewarded goal arm containing six food rewards and the low-rewarded goal arm containing two food rewards. Discrimination training was run in three stages. In the first stage of discrimination training, we put six pieces of reward in the feeding well of the large reward arm (LRA) and two pieces of reward in the feeding well of the small reward arm (SRA). For half of the rats, the LRA arm was to the left; for the others, it was to the right. The animals were placed individually in the starting arm and were allowed to receive the reward from both sides without a barrier in any of the goal arms. There were three days in the first stage and each rat ran five trials per day.

At the second stage, in each trial, one of the goal arms was closed and the animals accessed to one of the goal arms. Rats ran 10 trials per day for three days in order to complete the second phase. In the other words, in 5 trials the animals accessed just to SRA and in the other 5 trials, they just accessed to LRA to test both goal arms. Subsequently, in the third stage, the 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. There was a 2-min interval between each trial and each rat ran consecutive trials. 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 well situated in the chosen arm. The animals were trained until they choose the LRA in 80% of the trials for three consecutive days.

2.4.3. Barrier phase

Once the animals had reached an average large-reward choice (LRC) of 80% or more, a barrier 10 cm high made of wire mesh was placed at the midpoint of the LRA to increase the physical effort cost of the large reward. Similarly, after a few days of training in this phase and exceeding the average LRC of 80% for three consecutive days, the barrier height was increased in 10 cm steps until the maximum height of 30 cm was reached at the end of the training period.

2.5. Stereotaxic surgery and drug administration

Rats were anesthetized by intraperitoneal microinjection of xylazine (10 mg/kg) and ketamine (100 mg/kg) and placed into a stereotaxic device (Stoelting Co., USA). An incision was made along the midline, the scalp was removed and the area surrounding bregma was cleaned and dried. Additionally, lidocaine with epinephrine (0.2 ml) was injected in different locations around the incision. Stainless steel guide cannulae (23 gauge) were bilaterally implanted 1 mm above the target