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ORIGINAL ARTICLE

The Study of Interaction Effects of Dopamine Receptors Antagonist and Ritalin on Cost-benefit decision making in male Healthy adult rats

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ABSTRACT
Understanding the mechanisms of decision making is one of the most controversial topics in neuroscience. Some studies reported that Ritalin increased dopamine concentration, primarily in the prefrontal cortex. However, the interaction effects of Ritalin and dopamine receptor inhibition in healthy rats on cost-benefit decision making is unknown. Therefore, we aimed to investigate the interaction effects of haloperidol (dopamine D2 receptors antagonist) and Ritalin on cost-benefit decision making, using two distinct T-maze tasks: the ability of animals to adjust their effort with the height of an obstacle in a T-maze, or to process reward quantity information. We found that exposure to Ritalin has increased and haloperidol application significantly decreased the cost-benefit decision making in male adult intact rats. Additionally, application of haloperidol in Ritalin-treated rats has increasing effect on the cost-benefit decision making as compared with the haloperidol group in all behavioral experiments. These data suggest that dopamine mediates cost-benefit decision making. Moreover, dopamine effect on decision making is Ritalin dependent.
Key words: *Ritalin, dopamine, T-maze, cost-benefit decision making*

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INTRODUCTION

Cost-benefit decisions comprise of the relative attempt associated with a particular choice among a set of options [1]. Understanding the mechanism that how different factors are mediated an appropriate decision, is one of the important topics of cognitive neuroscience. There are some evidences to suggest that mesolimbic dopamine (DA) fibers projecting to the nucleus accumbens are necessary for effort-based decision making [2]. However, the role of dopamine D1 and D2 receptors in effort-based decision making is far from clear. It is well accepted that Ritalin improved attention and decision-making in attention deficit/hyperactivity disorder (ADHD), and also in healthy animals and humans [3, 4, 5]. Some studies reported that Ritalin increased DA and noradrenaline concentration, mostly in the prefrontal cortex [6, 7]. However, the interaction effects of Ritalin and haloperidol on adult brain are far from clear. Effort-based decision making is mediated by DA transmission. Administration of DA receptor antagonists induces impulsive choice in rats, reducing the preference for larger, delayed rewards [8, 9, 10, 11]. Conversely, increasing DA transmission with psychostimulants (eg amphetamine, methylphenidate, nomifensine) has the opposite effect, making animals more tolerant of delays imposed before delivery of larger rewards [9, 11, 12]. The aim of current study was to investigate the interaction effects of haloperidol (dopamine D2 receptors antagonist) and Ritalin on cost-benefit decision making, using two distinct T-maze tasks: the ability of animals to adjust their effort with the height of an obstacle in a T-maze, or to process reward quantity information. In these tasks, animals could either choose to climb a barrier (20, 40, 30 cm) to obtain a high reward (eight pellets) in one arm or a small reward (two pellets) in the other arm without a barrier. Moreover, animals choose either a small reward after a nominal amount of physical effort, or

obtaining a larger reward after considerably more work (climbing a 30 cm barrier) in discount 4:2 and 2:2 tasks.

MATERIAL AND METHODS

Animals

Five groups of eight, male Wistar rats (250-300 g) purchased from Pasteur institute (Tehran, Iran) in current experiment. The rats were divided in three per cage with free access to food and water except the times that their amounts of food were changed according to our experiment. Lightening in the animal colony was maintained on a 12 hour light/dark schedule with light on at 7:00. All procedures were performed in accordance with the National Institute of Health (NIH) Guidelines for the Care and Use of Laboratory Animals, and were approved by Ethical Committee of Iran University of Medical Sciences (Tehran, Iran).

T-maze apparatus

The rats were tested on a T-maze cost/benefit task that developed by Salamone et al. [13]. The elevated apparatus consisted of a start arm and two goal arms (each 60 cm length, 10 cm width, and 30 cm height). A food well was placed at the end of each goal arm. On forced trials, a block was placed to prevent the animal from entering one goal arm. The barriers that the rat had to climb were made of wire mesh with a right-angled triangle. The animals had to climb the vertical side of the triangle and down the 45º angle to attain the reward. The height of the barriers was increased during training from 20 cm to 40 cm.

Habituation

Rats were habituated to the T-maze on 4 days. On these days, the animals were placed in start arm and were allowed to explore the maze for 20 min. plentiful food was left in both feeding wells in the goal arms (50 mg food pellets).

Discrimination training

Discrimination training consisted of three phases. The first phase of training animals learned to discriminate a low-rewarded arm (LR) containing two pellets from high-rewarded arm (HR) containing eight pallets in the feeding well. For one-half of the animals, the HR arm was on the left and for the other half on the right. This side destination was maintained throughout the remaining training and test trial. In this phase, each rat received five trials per day for 2 days. The trial ended when the rat had eaten from both food cups or 150 second elapsed before a 20-cm barrier was introduced into the HR. In phase two of discrimination training, each rat received 10 trials per day for 2 days and also access to one of the goal arms was prevented by placing a wooden block at the entrance (forced trials), thus forcing the rat sample a particular arm on each trial. Rats were forced into the HR or LR arm five times. They were not forced into the same arm more than two times in a line. The experiment finished after the rats ate from the food cup or 150 seconds over and done. The third phase, each rat received 10 trials per day for 3 days and on trial 5 and 10, admission to the previously selected arm was blocked with the box in order to avoid rats from adopting a side bias. The experiment lasts immediately after the rat ate the food from the cup or 150 second over. Rats were investigated in this phase for three days (see table 1 for a time line). The final day of this phase, all of animals selected the HR arm on more than 90% of the occasion during the training session.

Barrier training

During barrier training, the first barrier (20 cm) was placed in the HR arm. Thereafter, the height of the barrier was increased to the 40 cm. Then, the height of the barrier was decreased to the 30 cm. Animals received five trials every day. On the first trial of experiments, the trial last only after the rat had climbed the barrier and eaten the pellets or 300 seconds over. On the last four trials, the experiment ended immediately after the rat selected one of the arms and consumed the pellets or 150 seconds elapsed.

Drug treatment

Ritalin was obtained from Novartis (England). Current study was performed in five groups (eight animals in each group): control, sham, Ritalin, haloperidol, Ritalin +haloperidol. Ritalin was gavaged (10 mg/kg) twice a day over 14 consecutive days and then ceased. The dose of Ritalin administration was based on prior studies [4]. Behavioral study started the day after cessation of Ritalin. Haloperidol was administrated (0.1 mg/kg, i.p.) 50 min before beginning of behavioral experiments. There was no manipulation in control group. All drugs were mixed in saline 0.9% and injected at a volume of (0.5 ml). Sham animals received saline 0.9% (0.5 ml) instead of Ritalin twice a day for 14 days or instead of haloperidol, 50 min before beginning of behavioral experiments.

Experimental design

Six behavioral experiments were designed to evaluate the effect of Ritalin and haloperidol on the sensitivity of animals to differences of the height of barriers and also to the quantity of reward. In all experiments, Ritalin and haloperidol were applied according to the part 2.3.

In the first experiment, behavioral experiment started without barrier. In the experiment two, barrier in height of 20 cm was placed in HR arm for the evaluation of effort-based decision making of rats to obtain high reward with the 20 cm barrier. In the experiment 3, the height of barrier increased to 40 cm. This test was performed to evaluate that whether incising of height of barrier would increase the effort of animal to gain high reward. In the experiment four, the 40 cm barrier was replaced with 30 cm one to evaluate whether decreasing of height of barrier would decrease the effort of animal to gain high reward. Experiment five was designed to evaluate that whether decreasing of the award would have effects or not. Therefore, the ratio of reward was then changed and four pellets were placed in HR arm and two in LR one, and also barrier in height of 30 cm was placed in HR arm. In the experiment six, two pellets were placed in the HR arm and two in the LR one and also barrier in height of 30 cm was placed in HR arm. Each experiment was conducted only in one day.

Statistics

All data were analyzed by SPSS software using one-way analysis of variance (ANOVA) and Tukey's test as post test. Results were expressed as the mean±standard error and considered significant for $P<0.05$.

RESULTS

Experiment 1

As is shown in Fig. 1A, chronic administration of Ritalin significantly increased the number of HR selection in experiment of without barrier ($p<0.05$) as compared with the control group. Moreover, administration of haloperidol significantly decreased the number of HR selection in this experiment ($p<0.05$) as compared with the control group. Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin, significantly decreased the number of HR selection ($p<0.05$) as compared with the haloperidol group. There were no significant differences between Ritalin +haloperidol and control groups.

Experiment 2

As is shown in Fig. 1B, barrier (20 cm) that placed in HR arm significantly shift the animals choices for the HR selection in the group Ritalin ($p<0.05$) as compared with the control group. Additionally, administration of haloperidol significantly decreased the number of HR selection in this experiment ($p<0.05$) as compared with the control group. Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin, significantly decreased the number of HR selection ($p<0.05$) as compared with the haloperidol group. There were no significant differences between Ritalin +haloperidol and control groups.

Experiment 3

The replacement of the 20 cm barrier with a 40 cm one in the HR arm produced the significant effort in the animals that received Ritalin for 14 days ($p<0.05$) to gain high reward compared with the control (Fig. 1C). Additionally, the administration of haloperidol significantly decreased effective effort in the animals that only received haloperidol ($p<0.05$) to gain high reward compared with the control (Fig. 1C). Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin, significantly decreased the number of HR selection ($p<0.05$) as compared with the haloperidol group.

Experiment 4

The replacement of the 40 cm barrier with a 30 cm one in the HR arm significantly increased the number of HR selection in in the animals that received Ritalin ($p<0.05$) as compared with the control group. Additionally, administration of haloperidol significantly decreased the number of HR selection in this experiment ($p<0.05$) as compared with the control group. Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin, significantly decreased the number of HR selection ($p<0.05$) as compared with the haloperidol group. There were no significant differences between Ritalin+haloperidol and control groups.

Experiment 5

When the ratio of food pellets were changed from 8:2 to 4:2 as can be observed in Fig. 2A, Ritalin application caused the significant increase ($p<0.05$) in the number of HR selection in the Ritalin group as compared with the control group (Fig. 2A). Additionally, haloperidol significantly decreased the number of HR selection in the haloperidol group as compared with the control group. Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin, significantly decreased the number of HR selection ($p<0.05$) as compared with the haloperidol group. There were no significant differences between Ritalin +haloperidol and control groups.

Experiment 6

When the ratio of food pellets were changed from 4:2 to 2:2 as can be observed in Fig. 2B, Ritalin application caused the significant decrease ($p<0.05$) in the number of HR selection in the Ritalin group as compared with the control group (Fig. 2B). Additionally, haloperidol decrease the number of HR selection in the haloperidol group as compared with the control group. Also, administration of haloperidol (50 min before beginning of experiments) in animals that received Ritalin did not induce any significant effect on the number of HR selection as compared with the haloperidol group.

Table 1: Time lines of behavioral study

Habituation	Discrimination training	Barrier training			Ritalin treatment	Halopridole treatment
4 days	7 days	3 days	3 days	3 days	14 Consecutive days	The day after ritalin cessation 50 min before begining of experiments; i.p.

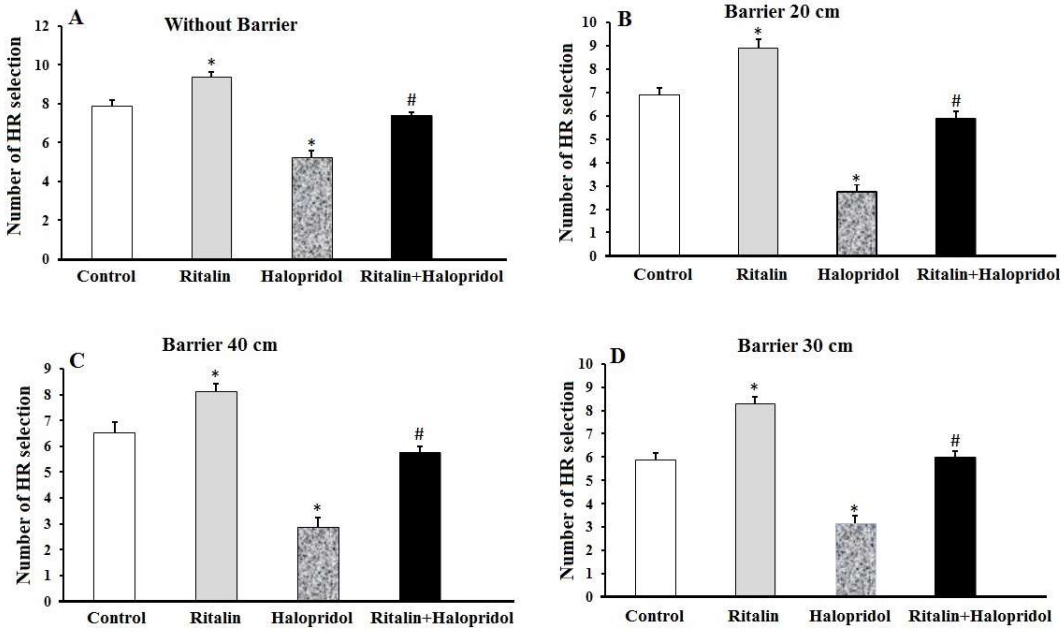

Figure 1: Effect of MPH on the number of high-reward (HR) arm selection with different size of barriers in experiment 1 to 4 (A-D). Each point represents the mean±SEM (9 rats per group). *p<0.05 indicates a significant difference with control animals. #p<0.05, indicates a significant difference with Ritalin group.

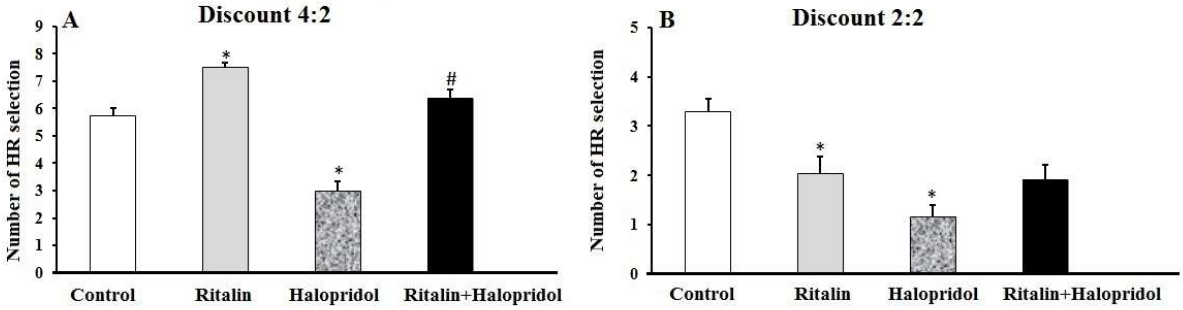

Figure 2: Effect of MPH on the number of high-reward (HR) arm selection with different ratio of rewards in experiment 5 and 6 (A-B). Each point represents the mean±SEM (9 rats per group). *p<0.05 indicates a significant difference with control animals. #p<0.05, indicates a significant difference with Ritalin group.

DISCUSSION

The main finding of present study was that exposure to Ritalin has increasing effect on the cost-benefit decision making in male adult intact rats. Moreover, haloperidol application significantly decreased effort-based decision making. Additionally, application of haloperidol in Ritalin-treated rats has increasing effect on the cost-benefit decision making as compared with the haloperidol group in all behavioral experiments. Ritalin is a psycho-stimulant and abused by adolescents and students when they have exams or need to stay awake for long time [14]. The role of Ritalin on decision making has been studied before [15], however, the consequences of chronic Ritalin intake and its interaction with haloperidol on cost-benefit decision making, especially in mature brain, are not clear. It is highly likely that prefrontal cortex has an important contribution on the behavioral tasks and also decision making [16, 17]. Developing of prefrontal cortex in humans continues until young adulthood [18]. Although, several of studies evaluated the effects of Ritalin on attention in ADHD humans and rats [5, 19, 20], but in the current study, we investigated the effects of inhibition of D2 dopamine receptors (haloperidol) on response selection in a cost-benefit T-maze tasks. Additionally, we examined the interaction of Ritalin and Haloperidol on the effort-based decision making, using a T-maze cost-benefit procedure. In this task, animals could either choose to climb a barrier (20, 40, 30 cm) to obtain a high reward (eight pellets) in one arm or a small reward (two pellets) in the other arm without a barrier. Here, we administrated high dose of Ritalin (10 mg/kg) in healthy adult rats over 14 days and then stop the treatment of animals with that. Then, we evaluated the effect of Ritalin on the cost-benefit decision making one day after cessation of that. We showed that Ritalin-treated rats significantly adjust their attempt with the height of barrier and chose HR arm more than control animals. Moreover, haloperidol-treated rats cannot adjust their attempt with the height of barrier. However, haloperidol application in Ritalin-treated rats significantly reversed HR selection as compared with the haloperidol group. Our findings that dopamine receptor blockade with haloperidol reduced the ability of animals to work harder to obtain a larger reward complement previous studies that reporting similar results in decision making [10, 13, 21]. However, the specific dopamine receptors that mediate cost-benefit decision making may differ between brain regions. Some evidences revealed that distinct forms of cost-benefit decision making mediated by different neuroanatomical profiles of increased cortical and striatal dopamine activity [22, 23]. Additionally, our behavioral study demonstrated that Ritalin had increasing effect on the number of HR selection when the ratio of food pellets changed from 8:2 to 4:2 (Fig. 2A). However, when the ratio of food pellets changed from 4:2 to 2:2, Ritalin had depressing effect on the number of HR selection as compare with the control rats (Fig. 2B). Some studies reported the enhancing effects of Ritalin on the healthy brain. For example, Berridge et al. showed that application of Ritalin (5-10 mg/kg i.p.) enhanced locomotor activity and impaired attention and performance on prefrontal cortex dependent cognitive skills in rats; however, administration of low dose Ritalin (0.25-1 mg/kg, i.p.) in normal adult rats increased performance on attention tasks [6]. Controversially, our behavioral study revealed that the orally application of high doses of Ritalin (10 mg/kg) in normal adult rats enhanced performance and attention such as attention on the height of barriers in the HR arm or quantity of reward. Additionally, there are some evidences that chronic treatment of Ritalin (3 and 9 mg/kg) lead to depression of prefrontal neurons that lasting for 10 weeks [24]. But, our behavioral showed that chronic treatment with Ritalin (10 mg/kg) increased attention in healthy adult rats. In conclusion, the present study suggests that dopamine mediates cost-benefit decision making. Moreover, dopamine effect on decision making is Ritalin dependent.

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