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Research report

Noradrenergic signaling in the medial prefrontal cortex and amygdala differentially regulates vicarious trial-and-error in a spatial decision-making task

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HIGHLIGHTS

- Effects of the noradrenergic drug clonidine in the mPFC and AMY on VTE were tested.
- Clonidine injection into either the mPFC or AMY impaired spatial choice performance.
- Clonidine injection into the mPFC suppressed VTE in the early phase of the task.
- Clonidine injection into the AMY hindered the decrease in VTE in the later phase of the task.

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ABSTRACT

In uncertain choice situations, we deliberately search and evaluate possible options before taking an action. Once we form a preference regarding the current situation, we take an action more automatically and with less deliberation. In rats, the deliberation process can be seen in vicarious trial-and-error behavior (VTE), which is a head-orienting behavior toward options at a choice point. Recent neurophysiological findings suggest that VTE reflects the rat's thinking about future options as deliberation, expectation, and planning when rats feel conflict. VTE occurs depending on the demand: an increase occurs during initial learning, and a decrease occurs with progression in learning. However, the brain circuit underlying the regulation of VTE has not been thoroughly examined. In situations in which VTE often appears, the medial prefrontal cortex (mPFC) and the amygdala (AMY) are crucial for learning and decision making. Our previous study reported that noradrenaline regulates VTE. Here, to investigate whether the mPFC and AMY are involved in regulation of VTE, we examined the effects of local injection of clonidine, an alpha2 adrenergic autoreceptor agonist, into either region in rats during VTE and choice behavior during a T-maze choice task. Injection of clonidine into either region impaired selection of the advantageous choice in the task. Furthermore, clonidine injection into the mPFC suppressed occurrence of VTE in the early phase of the task, whereas injection into the AMY inhibited the decrease in VTE in the later phase and thus maintained a high level of VTE throughout the task. These results suggest that the mPFC and AMY play a role in the increase and decrease in VTE, respectively, and that noradrenergic mechanisms mediate the dynamic regulation of VTE over experiences.

1. Introduction

In uncertain choice situations, we deliberately search and evaluate the possible options before taking an action, whereas once we form a preference about the current situation, we take an action more automatically and with less deliberation. In rats, the deliberation process can be seen in vicarious trial-and-error behavior (VTE), which is characterized as a head-orienting behavior directed toward options at a choice point [1,2]. Traditionally, VTE is thought to be a behavioral expression of the rat's reference to a mental map

Abbreviations: AMY, amygdala; HR, high-reward arm; LR, low-reward arm; mPFC, medial prefrontal cortex; NA, noradrenaline; VTE, vicarious trial-and-error behavior.

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of the environment or a 'cognitive map' for solving the task [3]. With methodological advances, recent studies have shown that VTE reflects a mental search of future options as deliberation, expectation, and planning for learning and decision making when rats feel conflicted by finding that VTE is associated with a neural representation of possible options and the value of those outcomes [4,5].

VTE is demand dependent. This behavior increases in response to the uncertainty associated with initial learning, changes in task rules, difficult choices, and multi-dimensional decision making before taking an action [6–10]. Once a preference in the current situation is formed, VTE decreases along with more automated action selection [6–10]. A nonoptimal amount of VTE appears to be associated with impaired performance in maze tasks [8,11–15]. These studies suggest that VTE is likely controlled depending on demands about the current situation and the cognitive state. However, few studies have focused on the brain circuits that control VTE.

Our previous study found that the noradrenaline (NA) system facilitates generation of VTE depending on uncertainty of choice [8], suggesting that brain regions that are modulated by NA in learning and decision making are involved in VTE. In uncertain and complex choice situations in which VTE typically increases, the medial prefrontal cortex (mPFC) and amygdala (AMY) have been considered to be crucial [16–21]. Both regions are innervated by noradrenergic (NAergic) neurons, and NA modulates the cognitive functions of the mPFC and AMY, such as attention, memory, and decision making [22–24].

The mPFC is critically involved in behavioral flexibility for resolving uncertainty and conflicting responses [25–27]. When the optimal choice or task rule is unknown, NA is released in the mPFC and allows adaptation of choice behavior [28–30]. Impairment of behavioral flexibility and new learning by lesions of the mPFC [26] is mimicked by lesions of NAergic neurons in the mPFC [31,32]. NA in the mPFC signals uncertainty and the onset of exploratory choices for searching and forming the optimal choice [27,33]. From these studies, the mPFC is thought to be involved in induction of VTE in response to exploratory situations.

The AMY is crucial for determining the advantageous choice during complex decision making [16–20]. During choice tasks, AMY neurons encode the expected value of options [34] and the association with the expected reward following a correct action [35]. NA in the AMY facilitates associative learning [36] and is important for taking an action based on the already established association [37–39]. Thus, the AMY can contribute to the evaluation process during VTE and may be related to deciding the optimal option and thus suppression of VTE.

Taken together, we hypothesize that the mPFC and AMY are crucial sites in the brain circuit that is involved in the regulation of VTE. To test this hypothesis, we evaluated the effects of local injection of clonidine, which is an alpha2-adrenergic autoreceptor agonist that suppresses NA release [40,41], into either the mPFC or AMY on VTE in a T-maze spatial decision-making task in rats.

2. Materials and methods

2.1. Animals

Twenty-eight male Wistar rats (Sankyo Labo Service Corporation Inc., Tokyo, Japan), approximately 10 weeks old at the start of the experiment, were used. The rats were housed in groups of three at a room temperature of 24 °C and a 12 h light:12 h dark cycle (lights on at 08:00 am) with ad libitum access to water. Throughout the experiment, the rats were food restricted to maintain 85% of their free-feeding body weight. Animals were handled for several days before starting the pretest training to habituate them to the experimenter. All experimental procedures were carried out in accordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC) and were approved by the Animal Experimentation Ethics Committee of Tokyo Metropolitan University. Every effort was made to minimize animal suffering and the number of animals used.

2.2. Apparatus

The apparatus was a black-painted wooden continuous T-maze, 90 × 90 × 1 cm, with five acrylic doors. The maze had feeders at the corner of the return rails (Fig. 1A). The maze was placed in a dimly lit test room at a height of 75 cm from the floor, surrounded by a black curtain. Rats could use information about objects above the maze, such as frames of the curtain and mounted video camera, as environmental cues.

2.3. Maze training

The behavioral procedures were performed as described in our previous study [8]. During the first few days of maze training, the rats were habituated to the T-maze. For habituation, all doors were opened, with food pellets (45 mg/pellet, F0021-J, Bio-serv, Frenchtown, NJ, USA) placed along the entire T-maze, and the rat was allowed to freely explore and eat during a 30-min period. In the days following the free exploration on the maze, a rat was placed at the start area and allowed to run the maze when both the center door and one of the front doors at the T-shaped point were opened. When the rat reached a reward site and acquired a pellet, the back door on that side was opened, and the rat returned to the start area spontaneously and also obtained a pellet in the start area. The running was alternately repeated (i.e., opening the left runway was followed by opening the right runway) and continued for 30 min or until the rat had reached the criterion of 40 runs in 30 min per day. After a rat ran the alternate training for about 2–4 weeks and achieved the criterion on two consecutive days, the rat underwent surgery for implantation of cannulae. After recovery from surgery, each rat underwent the maze training procedure again. The re-training continued until the same criterion (40 runs in 30 min) was reached in two successive days in which rats did not show clear VTE at the choice point and were more likely to run automatically. Then, the maze test started on the following day.

2.4. Surgery

The surgery was performed the day after completion of the maze training. Rats were randomly assigned to two groups: one group underwent implantation of cannulae into the bilateral mPFC, and the other group underwent implantation of cannulae into the bilateral AMY. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic frame (NARISHIGE, Tokyo, Japan) with ear bars. An incision was made to expose the skull surface, and adjustment was made to place bregma and lambda in the same horizontal plane. Then, small holes were drilled in the skull above the target sites. Rats were bilaterally implanted with 22-gauge Teflon guide cannulae (Plastic One Inc., Roanoke, VA, USA) into the mPFC at an angle of 10° from the vertical line (AP: +3.2 mm, ML: ±0.6 mm from bregma, and DV = 2.6 mm from the dura) or into the AMY vertically (AP: –3.1 mm, ML: ±5.0 mm from bregma, and DV: 6.3 mm from the dura) [42]. Implanted cannulae were fixed with dental cement and anchored onto the skull with screws. Each rat was allowed to recover from surgery for at least 7 days prior to maze training.