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Reversible inactivation of the lateral hypothalamus reversed high reward choices in cost-benefit decision-making in rats

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ABSTRACT

The Lateral hypothalamus (LH) is an important component of the networks underlying the control of feeding and other motivated behaviors. Cost-benefit decision-making is mediated largely by the prefrontal cortex (PFC) which strongly innervates the LH. Therefore, in the current study, we conducted a series of experiments to elucidate the role of the perifornical area of the lateral hypothalamus (PeF-LH) in effort and/or delay-based decision-making. We trained different groups of rats in a delay-based and/or an effort-based form of cost-benefit T-maze decision- making task in which they could either choose to pay the cost to obtain a high reward in one arm or could obtain a low reward in the other arm with no cost. During test days, the rats received local injections of either vehicle or lidocaine4% (0.5 µl/side), in the PeF-LH.

In an effort-based decision task, PeF-LH inactivation led to decrease in high reward choice. Similarly, in a delay-based decision task animals' preference changed to a low but immediately available reward. This was not caused by a spatial memory or motor deficit. PeF-LH inactivation modified decision behavior. The results imply that PeF-LH is important for allowing the animal to pay a cost to acquire greater rewards.

1. Introduction

The central nervous system generates motivational states to promote the seeking and ingestion of substances in the environment. These motivated states are accompanied by central nervous system processes that energize behavior (i.e., produce a state of psychological arousal and encourage locomotor behavior) and promote goal-directed behavior (Bindra, 1959; Bolles, 1975). In a classic paper, Stellar (1954) proposed a hypothalamus-centered theory of motivation and he theorized that the hypothalamus contained anatomically dissociable "centers" and each center played a critical role in the promotion of specific motivated behaviors (Stellar, 1954). In the 1951 Anand and Brobeck described the importance of the lateral hypothalamus (LH) in feeding and drinking behaviors in rat (Anand & Brobeck, 1951). After that, other studies demonstrated that the LH is involved in motivation and reward processes (Olds & Milner, 1954). It is likely that the motivational and rewarding properties of the LH stimulation are the result of the activation of neurons in the LH that project to the mesolimbic dopaminergic (DAergic) system (Geisler & Zahm, 2005; Phillipson, 1979).

The role of the hypothalamus in promoting motivated behavior comes from studies examining orexin. Orexin neurons can be putatively organized into three cell-clusters in the hypothalamus: a cluster in the dorsomedial hypothalamus (DMH), the perifornical area of lateral hypothalamus (PeF-LH), and the lateral of lateral hypothalamus (Aston-Jones et al., 2010).

The PeF-LH is a major wake-promoting structure (Hu, Yang, Qiao, Hu, & Zhang, 2015). It predominantly contains neurons that are activated during cortical activations (Kostin, McGinty, Szymusiak, & Alam, 2012). The PeF-LH has been implicated in the regulation of several physiological functions, including arousal, locomotor activity and cognition (Hurley & Johnson, 2014). Stimulation of the PeF-LH evokes locomotor activity, electroencephalogram activation, and behavioral arousal (Alam & Mallick, 2008; Sinnamon, Karvosky, & Ilch, 1999; Stock, Rupprecht, Stumpf, & Schlor, 1981). Neurochemically, the PeF-LH is heterogeneous and includes neuronal groups expressing

Abbreviations: LH, lateral hypothalamus; OXA, Orexin A; DAergic, dopaminergic; DMH, dorsomedial hypothalamus; PeF-LH, perifornical area of lateral hypothalamus; OX_1R_s, orexinergic receptor 1; VTA, ventral tegmentum area; HRA, high food arm; LRA, low food arm; HRCs', high reward choices; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; AMY, amygdale; DA, dopamine; BLA, basolateral amygdala; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; NS, no significant

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glutamate, orexin and GABA (Abrahamson, Leak, & Moore, 2001; Bittencourt et al., 1992; Gerashchenko & Shiromani, 2004; Ohno & Sakurai, 2008; Peyron et al., 1998).

Orexin neurons receive different signals related to emotional stimuli, physiological and environmental, and project broadly to the whole CNS. Orexin neurons are "multi-tasking" neurons regulating a set of vital body functions, including sleep/wake states, feeding behavior, energy homeostasis, reward systems, cognition and mood (Chieffi et al., 2017).

Recent evidence links the orexin system with reward and reinforcement (Aston-Jones, Smith, Moorman, & Richardson, 2009). The previous report showed that orexin A (OXA) as an orexinergic receptor type 1(OX_1R_s) agonist enhanced excitatory synaptic transmission in the ventral tegmentum area (VTA) and also enabled plasticity associated with cocaine (Borgland, Taha, Sarti, Fields, & Bonci, 2006), suggesting an underlying mechanism for the proposed reinforcing effects of OxA.

"Decision-making is an adaptive behavior that takes into account several internal and external input variables and leads to the choice of a course of action over other available and often competing alternatives" (Khani & Rainer, 2016).

Each activity has its advantages and disadvantages. "For example, action A may lead to a larger reward than action B, but it may do so only after a longer time has elapsed or after more effort has been invested" (Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006). These costs and benefits must be weighed before deciding which course of action to choose and the recent research have been shown the relation between some brain regions and calculating the cost of actions.

There are several reasons to believe that the PeF-LH might also be important in motivating cost–benefit decisions. Borgland and his collogues showed that blocking OX_1R_s signaling could reduce the effort rats are willing to exert for drug and palatable food reinforcers (Borgland et al., 2009).

However, it is uncertain what, if any, role PeF-LH plays in cost–-benefit decisions. Because the LH is known to mediate both arousal and reward via orexin and this region can drive motivated behavior, we aimed to determine the reversible inactivation of the PeF-LH could affect the effort- and /or delayed based decision- making of rats and change their preference for high reward.

2. Material and methods

2.1. Animals

Thirty-six male Wistar rats (Pasteur Institute, Iran) were used as subjects. Rats were 8 weeks old at their arrival to the animal facility. Rats were housed in groups of three per cage under standard conditions in a temperature-controlled room and maintained on a standard 12/12 h light/dark cycle (lights on at 07:00 am). Water was available ad libitum. The animals were handled on a daily basis and food was adjusted for initial body weights of about 85% of the free feeding weight during the beginning of the behavioral experiment (190–220 g) and after this a controlled weight gain of about 6–12 g per week. All animals were naïve to the current tests and had no experience in any behavioral experiments.

2.2. Apparatus

T-mazes were used adopted with parameters from the study by Denk et al. (2005). The Plexiglas mazes had three arms each 60 cm long, 10 cm wide and 40 cm high. For experiment 1, 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 (Fig. 1a). For experiment 2, four retractable doors were built in the goal arms of the maze. One door was placed just before the food 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. The doors were used in delay-based decision-making task to delay the access of the animals to rewards (Fig. 1b). Furthermore, there were grooves at the beginning of the entrance to each goal arm in both mazes, where a door of 10 cm width and 40 cm height could be placed on certain trials to force the animal to go to one of the goal arms ("forced" trials).

2.3. Experimental design

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% of their free-feeding weight, the rats were introduced to the T-maze. On the tow days, the animals were placed in the start arm in cages of three and were allowed to explore the maze for 10 min. The plentiful food was left in both feeding wells in the goal arms.

The third and fourth days of habituation were identical except for the fact that each animal investigated the maze individually. At the end of these 2 days, all of the rats were eating the pellets in the food wells.

The first phase of discrimination training involved putting ten pellets in the feeding well of one goal arm [high reward arm (HRA)] and two pellets in the other goal arm [low reward arm (LRA)]. For half of the rats, the HRA was to the left, and, for the others, it was to the right. Initially, each rat was placed in the start arm and was allowed to choose both food arms on each trial. Five trials ran each day over 2 d. For the next 2 d, the rats were moved onto the second phase in which access to one of the goal arms was prevented by placing a door at its entrance (forced trials), thus forcing the rat to sample a particular arm on each trial. The order of the forced trials was determined pseudo-randomly so that they never had more than two consecutive turns to either side. There were 10 trials run per day for each animal. On each day, at first each rat received two forced trials, one to each goal arm, then 8 choice trials, with an inter-trial interval of approximately 5 min. The rats were removed from the maze after eating the food in the selected arm without being able to sample from the other arm. This protocol was used throughout all experiments.

2.3.1. Effort-based decision-making task

After the rats had learned the unequal size of the reward, they then underwent barrier training. When 80% of choices were HRA with the 10-cm barrier for each rat the barrier height was increased to 20 cm. Rats were given three training days with a 20-cm barrier and 3 days with a 30-cm barrier. In experiment 1a (n = 10) the barrier introduced just for high reward arm but for experiment 1b (n = 6) the barriers introduced for both arms. The high reward choice was calculated.

2.3.2. Delay-based decision-making task

After the rats had learned the different size of reward, a delay of 5 s was introduced into the HRA, meaning that in the LRA the rat received it immediately a tow food pellet, whereas in the HRA it had to wait 5 s, confined in the arm by the movable gates, before receiving ten food pellets. Each day rats received ten trials, two forced and eight choice trials. Once rats chose the HRA on at least 80% of trials in 3 days, the delay was increased to 10 s, and then to 15 s after the same criteria were met. In experiment 2a (n = 7), the delay introduced for high reward arm and in experiment 2b (n = 6) both delays introduced for both arm.

2.3.3. Total latency time

For all trials in both experiments, a latency period is calculated. Total Latency time is a time from a start point till the animal made a decision and chose an arm. When the ears of the rats passed the entrance of the arm (place of the door A) the chronometer was stopped.

2.4. Surgery

Anesthesia was achieved using a mixture of ketamine (100 mg/kg)