Neuropharmacology 139 (2018) 205–216

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Contributions of medial prefrontal cortex to decision making involving risk of punishment

Caitlin A. Orsini [a], Sara C. Heshmati [a], Tyler S. Garman [b], Shannon C. Wall [b], Jennifer L. Bizon [a, b, c], Barry Setlow [a, b, c, d, *]

[a] Department of Psychiatry, University of Florida, Gainesville, FL, 32610, USA
[b] Department of Neuroscience, University of Florida, Gainesville, FL, 32610, USA
[c] Center for Addiction Research and Education, University of Florida, Gainesville, FL, 32610, USA
[d] Department of Psychology, University of Florida, Gainesville, FL, 32610, USA

ARTICLE INFO

Article history:
Received 25 January 2018
Received in revised form
10 July 2018
Accepted 12 July 2018

Keywords:
Medial prefrontal cortex
Decision making
Risk
Punishment
Monoamine

ABSTRACT

The prefrontal cortex (PFC) plays an important role in several forms of cost-benefit decision making. Its contributions to decision making under risk of explicit punishment, however, are not well understood. A rat model was used to investigate the role of the medial PFC (mPFC) and its monoaminergic innervation in a Risky Decision-making Task (RDT), in which rats chose between a small, "safe" food reward and a large, "risky" food reward accompanied by varying probabilities of mild footshock punishment. Inactivation of mPFC increased choice of the large, risky reward when the punishment probability increased across the session ("ascending RDT"), but decreased choice of the large, risky reward when the punishment probability decreased across the session ("descending RDT"). In contrast, enhancement of monoamine availability via intra-mPFC amphetamine reduced choice of the large, risky reward only in the descending RDT. Systemic administration of amphetamine reduced choice of the large, risky reward in both the ascending and descending RDT; however, this reduction was not attenuated by concurrent mPFC inactivation, indicating that mPFC is not a critical locus of amphetamine's effects on risk taking. These findings suggest that mPFC plays an important role in adapting choice behavior in response to shifting risk contingencies, but not necessarily in risk-taking behavior *per se*.

1. Introduction

Adaptive decision making requires weighing the relative costs and benefits associated with available options and arriving at a choice that is beneficial in the long term. Perturbations in decision making involving risks of adverse consequences are characteristic of several psychiatric disorders (Crowley et al., 2010; Ernst et al., 2003; Gowin et al., 2013; Linnet et al., 2011). For example, individuals with substance use disorder (SUD) display exaggerated risk taking, tending to prefer more immediately rewarding options even though they may be accompanied by adverse consequences (Gowin et al., 2013). In contrast, individuals with anorexia nervosa display pathological risk aversion and may fail to take even low or moderate risks to obtain desirable outcomes (Kaye et al., 2013). Given the central role of decision-making deficits in these and other psychiatric disorders, it is important to understand their underlying neural mechanisms.

Human neuroimaging experiments and studies of patients with focal brain damage have provided considerable insight into the neural correlates of risk-based decision making. The majority of these studies have used the Iowa Gambling Task (IGT) or similar simulated gambling tasks to assess risky decision making. In the IGT, subjects choose between four decks of cards, two of which yield large payoffs but even larger losses, and two of which yield small payoffs but even smaller losses (Brand et al., 2007). As subjects learn the task, they develop a strategy in which "risky" decks are avoided in favor of the smaller, but "safer" decks. Patients with lesions of either the ventromedial prefrontal cortex (vmPFC) (Bechara et al., 1994) or dorsolateral prefrontal cortex (dlPFC) consistently choose the risky decks (Clark et al., 2003; Fellows and Farah, 2005; Manes et al., 2002). Neuroimaging studies support these findings and show that the PFC is recruited during the IGT and

* Corresponding author. Department of Psychiatry, University of Florida College of Medicine, P.O. Box 100256, Gainesville, FL, 32610-0256, USA.
E-mail address: setlow@ufl.edu (B. Setlow).

https://doi.org/10.1016/j.neuropharm.2018.07.018
0028-3908/

similar tasks (Ernst et al., 2002; Fukui et al., 2005; Lawrence et al., 2009; Lin et al., 2008). Together, these studies suggest that the PFC is critical for maintaining optimal decision-making behavior.

Experiments in animal models corroborate findings from human lesion and imaging studies. For example, lesions or inactivation of the medial PFC [mPFC, the rodent homologue of human dlPFC (Uylings et al., 2003)] cause rats to make fewer advantageous choices in several tasks that model the human IGT (de Visser et al., 2011; Paine et al., 2015; Zeeb et al., 2015). Notably, however, findings from a different rodent risky decision-making task suggest that the mPFC may not necessarily influence risk taking *per se*. St. Onge and Floresco (2010) employed a task in which rats chose between a small, certain reward and a large, uncertain reward, the probability of which changed across blocks of trials within a test session. In this task, mPFC inactivation increased choice of the large reward when the probability of large reward delivery decreased across a test session, but decreased choice of the large reward when the order of probability changes was reversed (St Onge and Floresco, 2010). These findings suggest that mPFC inactivation interfered with the ability to update reward value representations as the contingencies changed across the session, rather than directly influencing risk preferences. This conclusion is consistent with the well-documented role of the mPFC in cognitive flexibility (Birrell and Brown, 2000; Floresco et al., 2006, 2008; Ragozzino, 2007; Ragozzino et al., 1999a, 1999b, 2003).

Monoamine signaling in the mPFC has been implicated in both risky decision making and cognitive flexibility (Dalley et al., 2001; Fitoussi et al., 2015; Floresco and Magyar, 2006; Floresco et al., 2006; McGaughy et al., 2008; St Onge et al., 2011; St Onge and Floresco, 2010). Both dopamine (DA) and norepinephrine (NE) are elevated in the mPFC in the presence of stimuli that predict aversive outcomes such as footshock (Feenstra et al., 1999). This increase in monoamine signaling may indicate a role for NE and DA in ascribing salience to stimuli predictive of aversive outcomes, as NE depletion in the mPFC blocks aversive place conditioning (Ventura et al., 2007, 2008) and DA receptor blockade impairs the ability to use conditioned punishers to guide instrumental behavior (Floresco and Magyar, 2006). Several studies have also implicated mPFC monoamine neurotransmission in other types of decision making and cognitive flexibility. For example, both DA and serotonin (5-HT) in the mPFC contribute to intertemporal decision making, which involves choices between a small, more immediate reward and a large, delayed reward (Loos et al., 2010; Winstanley et al., 2006; Yates et al., 2014). With respect to cognitive flexibility, DA and NE in the mPFC contribute to the ability to shift behavior when choice contingencies change (Dalley et al., 2001; Mingote et al., 2004; van der Meulen et al., 2007). For instance, depletion of mPFC NE impairs performance on an attentional set shifting task (McGaughy et al., 2008) and DA D2 receptor (D2R) mRNA expression in the mPFC is associated with greater flexibility in shifting choice behavior during risky decision making (Simon et al., 2011). Considered together, these data suggest that during decision making involving risk of punishment, the mPFC, and specifically mPFC monoamine transmission, could be important not only for signaling the motivational value of risky choices, but also for adjusting the salience attributed to these choices as task contingencies change.

Most of the aforementioned studies (both human and rodent) used decision-making tasks in which the "costs" associated with the large reward or net gain consisted of reward omission or a timeout period during which rewards were unavailable. Many real-world decisions, however, involve the possibility of actual harmful consequences. As the neural mechanisms of risky decision making can differ depending on the type of "cost" involved (Orsini et al., 2015a), it is important to determine how the mPFC contributes to decision making under risk of explicit punishment. Previous work from our lab employed correlational approaches to address this issue by evaluating relationships between expression of several neurobiological markers in mPFC and performance on a decision making task that incorporates both rewards (food) and risks of adverse consequences (footshock punishment) (Deng et al., 2018; Simon et al., 2011). Because the results of these studies were correlational in nature, however, the current experiments employed behavioral pharmacological manipulations to more directly address the role of mPFC in this form of decision making. The first goal was to use a pharmacological inactivation approach to determine how the mPFC is involved in decision making involving risk of explicit punishment (Simon et al., 2009; Simon and Setlow, 2012). The second goal was to use a combination of behavioral pharmacological approaches to assess the involvement of mPFC monoamine transmission.

2. Materials and methods

2.1. Subjects

Male Long Evans rats (60 days of age upon arrival from Charles River Laboratories; n = 71) were housed individually and maintained on a 12 h light/dark cycle (lights on at 0700) throughout all experiments. Rats were allowed *ad libitum* access to water, but during behavioral testing, were food restricted to 85% of their free feeding weight, with target weights adjusted upward by 5 g every week to account for growth. All procedures were conducted in accordance with the University of Florida Institutional Animal Care and Use Committee and adhered to the guidelines of the National Institutes of Health.

2.2. Apparatus

For all behavioral sessions, rats were tested in twelve computer-controlled operant test chambers (Coulbourn Instruments), each of which was housed in an individual sound-attenuating cabinet. Every chamber was equipped with a recessed food delivery trough with a photobeam to detect nosepokes and a 1.12-W lamp to illuminate the trough. Each trough was connected to a food hopper, from which 45 mg grain-based food pellets (Test Diet; 5TUM) were delivered into the trough. The food trough was located 2 cm above the floor in the center of the front wall of the chamber and was flanked by two retractable levers. The floor of each test chamber was comprised of stainless steel rods connected to a shock generator (Coulbourn Instruments), which delivered scrambled footshocks. An activity monitor was mounted on the ceiling of each chamber to record locomotor activity during behavioral sessions. The activity monitor used an array of infrared detectors focused over the test chamber to measure movement, which was defined as a relative change in infrared energy falling on the different detectors in the array. Finally, a 1.12 W houselight was affixed to the rear wall of the sound-attenuating cabinet. Test chambers were connected to a computer running Graphic State 3.0 software (Coulbourn Instruments), which simultaneously controlled task events and collected behavioral data.

2.3. Surgical procedures

Upon arrival, rats were given one week to acclimate to the vivarium on a free feeding regimen before undergoing stereotaxic surgery. Rats were anesthetized with isoflurane gas (1–5% in O_2) and were given subcutaneous injections of buprenorphine (0.05 mg/kg), Meloxicam (1 mg/kg) and sterile saline (10 mL). After being placed in a stereotaxic frame (David Kopf), the scalp was disinfected with a chlorohexidine/isopropyl alcohol swab and an