Behavioural Brain Research 268 (2014) 229–238

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

# Effects of dopamine D1 receptor blockade in the prelimbic prefrontal cortex or lateral dorsal striatum on frontostriatal function in Wistar and Spontaneously Hypertensive Rats

Jamie M. Gauthier[a], David H. Tassin[a], Linda P. Dwoskin[b], Kathleen M. Kantak[a,*]

[a] Department of Psychological and Brain Sciences, 64 Cummington Mall, Boston University, Boston, MA 02215, USA
[b] Department of Pharmaceutical Sciences, 789 South Limestone, University of Kentucky, Lexington, KY 40536, USA

## HIGHLIGHTS

- Frontostriatal cognitive functions were disrupted in SHR compared to WIS.
- SCH23390 infusions in prelimbic PFC worsened executive function in SHR.
- SCH23390 infusions in prelimbic PFC impaired executive function in WIS.
- SCH23390 infusions in lateral DST did not alter executive function in SHR or WIS.
- SCH 23390 infusions in both sites produced relatively less habitual responding in WIS.

## ARTICLE INFO

*Article history:*
Received 30 December 2013
Received in revised form 7 April 2014
Accepted 11 April 2014
Available online 19 April 2014

*Keywords:*
Attention Deficit Hyperactivity Disorder
Behavioral flexibility
Dorsal striatum
Dopamine D1 receptors
Executive function
Prefrontal cortex
Reward devaluation

## ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is associated with dysfunctional prefrontal and striatal circuitry and dysregulated dopamine neurotransmission. Spontaneously Hypertensive Rats (SHR), a heuristically useful animal model of ADHD, were evaluated against normotensive Wistar (WIS) controls to determine whether dopamine D1 receptor blockade of either prelimbic prefrontal cortex (plPFC) or lateral dorsal striatum (lDST) altered learning functions of both interconnected sites. A strategy set shifting task measured plPFC function (behavioral flexibility/executive function) and a reward devaluation task measured lDST function (habitual responding). Prior to tests, rats received bilateral infusions of SCH 23390 (1.0 μg/side) or vehicle into plPFC or lDST. Following vehicle, SHR exhibited longer lever press reaction times, more trial omissions, and fewer completed trials during the set shift test compared to WIS, indicating slower decision-making and attentional/motivational impairment in SHR. After reward devaluation, vehicle-treated SHR responded less than WIS, indicating relatively less habitual responding in SHR. After SCH 23390 infusions into plPFC, WIS expressed the same behavioral phenotype as vehicle-treated SHR during set shift and reward devaluation tests. In SHR, SCH 23390 infusions into plPFC exacerbated behavioral deficits in the set shift test and maintained the lower rate of responding in the reward devaluation test. SCH 23390 infusions into lDST did not modify set shifting in either strain, but produced lower rates of responding than vehicle infusions after reward devaluation in WIS. This research provides pharmacological evidence for unidirectional interactions between prefrontal and striatal brain regions, which has implications for the neurological basis of ADHD and its treatment.



## 1. Introduction

The prelimbic prefrontal cortex (plPFC) in rats is critical for executive functions such as working memory, decision-making and behavioral flexibility [1]. Strategy set shifting is a common procedure for evaluating behavioral flexibility and other executive functions. Animals are required to attend to relevant stimuli, ignore irrelevant stimuli and shift the allocation of attention between strategy sets. Furthermore, this procedure is useful for evaluating many aspects of learning requiring behavioral flexibility, such as discrimination and reversal learning as well as intra-dimensional and extra-dimensional shifts [1]. Lesions and dopamine D1 receptor blockade of plPFC impair set shifting [2–4].

Among its connections, the plPFC projects focally to medial (mDST) and diffusely to lateral (lDST) dorsal striatum [5]. The DST is thought to be important for the development and maintenance

* Corresponding author. Tel.: +1 617 353 9201.
*E-mail address:* kkantak@bu.edu (K.M. Kantak).

http://dx.doi.org/10.1016/j.bbr.2014.04.018
0166-4328/

of incentive-based learning and mediates performance of instrumental actions during reward-related tasks by two distinct learning processes [6]. The first process, goal-directed learning, is where actions are performed with regard to their consequences and behavior is flexible. The second process, habit learning, is attained after extensive training, with behavior now inflexible and actions no longer dependent on outcome. Goal-directed and habitual behaviors are measured with reward devaluation procedures (e.g., through aversion or satiation), depending on whether rats are tested during early stages of training or are over-trained, respectively. Such procedures provide important evidence that rats form detailed representations of reinforcement and that altering those representations changes the incentive value of the reinforcement. Lesions of the mDST disrupt acquisition and expression of goal-directed behavior [7,8], whereas lesions of the lDST disrupt habitual control of behavior [8,9]. Information on whether PFC mediates habitual responding (e.g., [7]) or whether DST mediates set shifting (e.g., [10]) is incomplete.

Given that in rats direct plPFC projections are widespread in DST [5] and DST input feedbacks indirectly to its cortical origins [11], we manipulated these two interconnected brain sites to assess frontostriatal function in Spontaneously Hypertensive Rats (SHR) and the normotensive Wistar (WIS) control strain. SHR exhibit an ADHD phenotype characterized by hyperactivity, inattention and impulsivity [12,13] and by deficits in working memory, set shifting, and habit learning [14–16]. In the current study, we determined whether dopamine D1 receptor blockade in either plPFC or lDST of WIS and SHR altered learning functions of both sites in which the D1 receptor plays a critical role in mediating effects of dopamine on synaptic plasticity and cognitive functioning [2,17].

## 2. Materials and methods

### 2.1. Subjects

Experimentally naïve male rats of the WIS (Crl(WI)BR) and SHR (Crl(SHR)BR) strains were approximately 60 days old (276–300 g for WIS and 205–240 g for SHR) upon arrival from Charles River Laboratories (Wilmington MA, USA for WIS and Portage MI, USA for SHR). Rats were housed individually in wedge-shaped clear plastic cages in a temperature- (21–23 °C) and light- (08:00 h on, 20.00 h off) controlled vivarium. After arrival, rats were accustomed for 72 h to the vivarium, where they had ad libitum access to food and water. Rats began mild food restriction at least 5 days before starting the experiment to establish motivation to lever press for food pellets. Rats received 16 g of food per day to maintain body weight at ~90% of the free-feeding body weight that was adjusted over the course of the experiment. Rats were maintained in accordance with the NIH Guide for Care and Use of Laboratory Animals. The Boston University Institutional Animal Care and Use Committee approved research protocols.

### 2.2. Apparatus

Experimental chambers (ENV-008CT Med Associates, St. Albans VT, USA) were used for all behavioral sessions. Each chamber was outfitted with two retractable levers, a stimulus light above each lever, a house light and a food receptacle. Connected to the food receptacle was a pellet dispenser, which delivered 45 mg food pellets. A sound-attenuating cubicle (Med Associates), with an exhaust fan to provide ventilation, enclosed each chamber. A PC-compatible computer programmed in Medstate Notation and connected to an interface (Med Associates) controlled experimental events.

### 2.3. Surgery and histology

For implantation of guide cannulae, rats received 0.05 mg/kg subcutaneous buprenorphine as a preoperative analgesic and then were anesthetized with an intraperitoneal injection of 80 mg/kg ketamine plus 8 mg/kg xylazine. Guide cannulae (22 gauge; Plastics One, Roanoke VA, USA) were bilaterally implanted into the plPFC (anteroposterior [AP] + 3.2 mm, lateral [L] ± 1.4 mm at a 15° angle, dorsoventral [DV] −2.9 mm) or lDST (AP −0.8 mm, L ±4.0 mm, DV −3.5 mm). Guide cannulae were positioned 1 mm above the intended site and placements were measured from bregma. Guide cannulae and four stainless steel anchoring screws were attached to the skull and permanently embedded in dental acrylic. Two 28-gauge obturators (Plastics One) were used to occlude guide cannulae between infusions. Rats were allowed at least 7 days of recovery from surgery before initiation of the study. Upon completion of each experiment, rats were given an overdose of sodium pentobarbital, and then perfused intracardially with 0.9% saline and 10% formalin solutions. Brains were removed, post-fixed in 10% formalin for 4 h, and then stored in 30% sucrose at 4 °C for 3 days. Forty-μm coronal sections were collected using a cryostat. Sections were mounted on gelatin-coated slides and stained to verify guide cannulae placements.

### 2.4. Microinfusion procedure

Rats received bilateral infusions of the dopamine D1 receptor antagonist SCH 23390 (1.0 μg/0.5 μl/side) or 0.9% saline vehicle (0.5 μl/side) into the plPFC or lDST 5 min before the set shift and reward devaluation test session. This dose of SCH 23390 is behaviorally active and does not decrease lever press responding nonspecifically [18]. The infusion cannula extended 1 mm beyond the guide cannula tip and was left in place for 1 min following each infusion to allow adequate diffusion of drug into surrounding brain tissue.

### 2.5. Strategy set shifting task procedures

To determine plPFC function, the operant version of the strategy set shifting task [3] was adapted for use in the present study. A 15-sec delay, rather than 0-sec delay, version of the task was used, as it better reveals performance differences between SHR and control strains. With a 0-sec delay, SHR do not exhibit behavioral deficits during various task phases relative to WIS or Wistar-Kyoto controls, whereas with a 15-sec delay, behavioral deficits are observed in SHR [16]. The task was divided into three phases: habituation, initial set formation and set shift. Habituation procedures were used to train rats to lever press within 10 sec of lever insertion into the chamber to earn a chocolate-flavored food pellet (BioServ, Frenchtown NJ, USA) on each of 100 discrete trials and to establish a lever position bias.

For the initial set formation phase, rats were required to press the lever opposite its lever position bias (left or right), regardless of which stimulus light was illuminated to earn a food pellet (egocentric spatial response discrimination). Each trial began with both levers retracted and the chamber in darkness for 20 sec. One stimulus light (selected pseudorandomly) then was illuminated, and 3 sec later the houselight was turned on and both levers were inserted into the chamber. Correct lever presses resulted in food pellet delivery after a 15 sec delay. Levers were retracted after a lever was pressed (correct or incorrect) or if 10 sec elapsed without a lever press (trial omission). Following a correct lever press, the stimulus light remained illuminated for 4 sec, and the house light remained illuminated until 4 sec following food pellet delivery. After an incorrect lever press or an omitted trial, the stimulus light and house light were extinguished immediately. Trials