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Research report

Dissociable roles of dopamine and serotonin transporter function in a rat model of negative urgency

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HIGHLIGHTS

- Rats increased lever responding for food following omission of expected reward.
- DAT function in NAc positively correlated with negative urgency scores.
- SERT function in OFC positively correlated with negative urgency scores.

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ABSTRACT

Negative urgency is a facet of impulsivity that reflects mood-based rash action and is associated with various maladaptive behaviors in humans. However, the underlying neural mechanisms of negative urgency are not fully understood. Several brain regions within the mesocorticolimbic pathway, as well as the neurotransmitters dopamine (DA) and serotonin (5-HT), have been implicated in impulsivity. Extracellular DA and 5-HT concentrations are regulated by DA transporters (DAT) and 5-HT transporters (SERT); thus, these transporters may be important molecular mechanisms underlying individual differences in negative urgency. The current study employed a reward omission task to model negative urgency in rats. During reward trials, a cue light signaled the non-contingent delivery of one sucrose pellet; immediately following the non-contingent reward, rats responded on a lever to earn sucrose pellets (operant phase). Omission trials were similar to reward trials, except that non-contingent sucrose was omitted following the cue light prior to the operant phase. As expected, contingent responding was higher following omission of expected reward than following delivery of expected reward, thus reflecting negative urgency. Upon completion of behavioral training, V_{max} and K_m were obtained from kinetic analysis of [^{3}H]DA and [^{3}H]5-HT uptake using synaptosomes prepared from nucleus accumbens (NAc), dorsal striatum (Str), medial prefrontal cortex (mPFC), and orbitofrontal cortex (OFC) isolated from individual rats. V_{max} for DAT in NAc and for SERT in OFC were positively correlated with negative urgency scores. The current findings suggest that mood-based impulsivity (negative urgency) is associated with enhanced DAT function in NAc and SERT function in OFC.

1. Introduction

Impulsivity is often fractioned into two broad categories, impulsive choice (i.e., inability to delay gratification) and impulsive action (i.e., inability to inhibit a prepotent response) [1]. In addition to these facets of impulsivity, negative urgency has received considerable consideration in clinical research. Negative urgency is the tendency to act rashly during a negative mood state and is one of four measures of impulsivity included in the UPPS personality

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questionnaire [2]. Similar to other facets of impulsivity, negative urgency is a predictor of several maladaptive behaviors, including drug abuse, binge eating, pathological gambling, risky sex, and problematic alcohol use ([3–5]; see [6] for a full review).

Currently, animal models of negative urgency are lacking, thus limiting exploration of the neurobiological mechanisms involved in this facet of impulsivity. In one study, a reward omission test was used to model negative urgency in rats [7]. In this paradigm, rats learned to associate a stimulus light with delivery of one sucrose pellet and then responded on a lever to earn sucrose pellets. When expected food delivery was omitted, rats showed increased lever responding on the lever associated with food delivery. This finding translated to human participants who showed a similar increase in response rate following omission of expected monetary reward, with the increase in response rate being associated with negative urgency scores on the UPPS [7]. These findings suggest that a reward omission procedure may be useful model of negative urgency in both humans and laboratory animals.

One advantage of using animal models is the ability to elucidate the underlying neural mechanisms of negative urgency. Understanding the neurobiological mechanisms involved in negative urgency may help explain why these individuals are more likely to engage in maladaptive behaviors. Several brain regions within the mesocorticolimbic pathway, including nucleus accumbens (NAc), dorsal striatum (Str), medial prefrontal cortex (mPFC), and orbitofrontal cortex (OFC), have been implicated in various facets of impulsivity [8,9]. Furthermore, dopamine (DA) and serotonin (5-HT) systems are important mediators of impulsive behavior [8–10]. Extracellular DA and 5-HT concentrations are regulated by DA transporters (DAT) and 5-HT transporters (SERT). Polymorphisms in genes encoding DAT and SERT are associated with impulsivity, as well as neuropsychiatric conditions associated with increased impulsivity, such as attention deficit hyperactivity disorder (ADHD) and substance use disorders [11–16]. The role of DAT and SERT in impulsivity is further supported by pharmacological evidence showing that DAT and SERT inhibitors alter impulsive behavior in humans [17–19] and rats [20–23]. However, it is unclear if DAT and SERT mediate negative urgency behavior. Thus, the goal of the present study was to determine the role of mesocorticolimbic DAT and SERT function in negative urgency behavior in rats using a reward omission task as previously described [7].

2. Materials and methods

2.1. Materials

[^{3}H]5-HT (5-[1,2-^{3}H(N)-hydroxytryptamine creatinine sulfate; specific activity, 27.1 Ci/mmol) and [^{3}H]DA (3,4-ethyl-2 [*N*-^{3}H] dihydroxyphenylethylamine; specific activity, 31 Ci/mmol) were purchased from Perkin Elmer Life Sciences (Boston, MA). 5-Hydroxytryptamine creatinine sulfate (5-HT), dopamine HCl, desipramine HCl, nomifensine maleate,1-(2-*bis*(4-fluorphenyl)-methoxy)-ethyl-4-(3-phenyl-propyl) piperazine HCl (GBR 12909), fluoxetine HCl, pargyline HCl, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), catechol, L-ascorbic acid and D-glucose were purchased from Sigma–Aldrich (St. Louis, MO). Paroxetine HCl was provided generously by Beecham Pharmaceuticals (Surrey, UK). All other chemicals were purchased from Fisher Scientific Co. (Pittsburgh, PA).

2.2. Animals

Forty-seven male, experimentally-naïve Sprague–Dawley rats (250–275 g at the beginning of operant training) were obtained from Harlan Laboratories (Indianapolis, IN) and were housed individually upon arrival. Rats were acclimated in a colony room held at constant temperature and handled for 7 days before operant training. Light and dark phases were on a 12:12 h cycle, and all procedures occurred during the light phase. Rats were food restricted (approximately 85% of free feed body weight) during behavioral studies. All procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals" [24] and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

2.3. Behavioral apparatus

Operant conditioning chambers (28 cm × 21 cm × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound-attenuating chambers (ENV-018 M; MED Associates) were used. The front and back walls of the experimental chambers were made of aluminum, while the side walls were made of Plexiglas. A recessed food tray (5 cm × 4.2 cm) was located 2 cm above the floor in the bottom-center of the front wall. A 28-V white cue light was located 6 cm above each response lever. A white house light was mounted in the center of the back wall of the chamber. All responses and scheduled consequences were recorded and controlled by a computer interface using Med-IV software.

2.4. Procedure

2.4.1. Reward omission task

The reward omission task employed has been previously described [7]. Rats were given 10 sessions consisting of 32 light-sucrose Pavlovian associations/session. During these sessions, either the left or right stimulus light (counterbalanced across rats) was illuminated for 5 s, followed by delivery of one sucrose pellet (F0021 dustless precision pellet, Bio-Serve, Frenchtown, NJ). Following a 2-s delay in the dark, the house light was illuminated for 10 s (intertrial interval; ITI).

Rats then were given 8 sessions of operant conditioning training consisting of 32 2-min trials/session. Each trial was separated by a 10-s ITI. During these sessions, both levers were extended into the chamber. One lever was designated as active, in which responses resulted in delivery of one sucrose pellet. The other lever was designated as inactive, in which responses were recorded, but had no programmed consequence. The response requirement increased every 2 sessions (FR-1, 3, 5, and 10). Levers designated as active and inactive were counterbalanced across rats.

Following operant training, rats were given 30 baseline training sessions for the reward omission task. Each baseline session consisted of 32 trials separated into 2 components. Each trial began with a light-sucrose Pavlovian association component. Following delivery of the sucrose pellet, a 2-s delay in the dark was imposed, followed immediately by the extension of both levers. Each lever was presented for 2 min. Rats completed a FR-10 schedule of reinforcement on the active lever to receive one sucrose pellet. No time-out period was imposed following reinforcement. After 2 min, a 10-s ITI occurred, signaled by illumination of the house light.

Following the baseline training sessions, rats received an alternating schedule of training and test sessions, such that 4 training sessions separated each of 3 test sessions. During a test session, rats were given 24 reward trials and 8 omission trials, randomly intermixed. Reward trials were identical to those presented during baseline training sessions. Omission trials were similar to reward trials, except that rats did not receive a sucrose pellet following presentation of the stimulus light during the Pavlovian component of the trial. Negative urgency scores were calculated using the equation $U = [(O - R)/R] \times 100\%$, where U is the negative urgency score, O the average number of responses during omission trials, and R is the average number of responses during reward trials. Increasing