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Research report

Role of serotonin transporter function in rat orbitofrontal cortex in impulsive choice

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HIGHLIGHTS

- OFC SERT function is negatively correlated with delay discounting behavior.
- Fluoxetine microinjection into OFC decreased impulsivity in high impulsive rats.
- Enhanced SERT function in OFC underlies high impulsive choice.

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ABSTRACT

Impulsivity is a multi-faceted personality construct that plays a prominent role in drug abuse vulnerability. Dysregulation of 5-hydroxytryptamine (serotonin, 5-HT) systems in subregions of the prefrontal cortex has been implicated in impulsivity. Extracellular 5-HT concentrations are regulated by 5-HT transporters (SERTs), indicating that these transporters may be important molecular targets underlying individual differences in impulsivity and drug abuse vulnerability. The present study evaluated the role of SERT in mediating individual differences in impulsivity. Rats were tested for both impulsive action using the cued go/no-go task and for impulsive choice using a delay discounting task in a counterbalanced design. Following behavioral evaluation, K_m and V_{max} were obtained from kinetic analysis of [^{3}H]5-HT uptake by SERT using synaptosomes prepared from both orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) obtained from each individual rat. V_{max} for SERT in OFC, but not mPFC, was negatively correlated with mean adjusted delay scores in the delay discounting task. In contrast, V_{max} for SERT in OFC and mPFC was not correlated with performance in the cued go/no-go task. To further evaluate the relationship between SERT function and impulsive choice, a selective SERT inhibitor, fluoxetine (0, 15, 50 and 150 pmol/side) was microinjected bilaterally into OFC and effects on the delay discounting task determined. Following stabilization of behavior, fluoxetine increased mean adjusted delay scores (decreased impulsivity) in high impulsive rats compared to saline microinjection, but had no effect in low impulsive rats. These ex vivo and in vivo results suggest that enhanced SERT function in OFC underlies high impulsive choice behavior.

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1. Introduction

The majority of individuals who experiment with drugs do not develop a substance abuse disorder [1]. An important goal is to identify factors underlying individual differences in drug abuse vulnerability. One factor known to play a prominent role is impulsivity. Increased levels of impulsivity have been implicated in alcohol, cocaine, methamphetamine, opioid and nicotine abuse [2]. Personality and behavioral tests have been developed to measure different

Abbreviations: mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; 5-HT, 5-hydroxytryptamine (serotonin); SERT, serotonin transporter; 5-CSRTT, five-choice serial reaction time task; K_m, affinity; V_{max}, maximal transport velocity.

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components of impulsivity, including the Five Factor Model of personality, which identifies different facets of impulsivity [3]. Two commonly used behavioral tasks employing human subjects and measuring distinct components of impulsivity include the cued go/no-go task, a measure of impulsive action, and the delay discounting task, a measure of impulsive choice [4]. In the cued go/no-go task, responding during a go cue is reinforced, but not reinforced during a no-go cue [5]. Individuals who fail to extinguish responding during the no-go cue are considered to have greater levels of impulsive action. In the delay discounting task, individuals choose between a small, immediate reward and a larger, delayed reward [6]. Individuals who consistently choose the small immediate reward over the large delayed reward are considered to exhibit greater impulsive choice. As indicated by personality traits and behavioral measurements in the cued go/no-go and delay-discounting tasks, individuals with high impulsivity have been reported to consume greater amounts of alcohol, tobacco and marijuana [7,8], and have a high liability for substance abuse.

Although a positive relationship between impulsivity and drug abuse has been reported, whether impulsivity is an antecedent condition or an outcome of drug use is not known and difficult to evaluate in human subjects [2]. Preclinical models are well-suited to address this question due to the ability to evaluate pre-existing individual differences in impulsivity in drug naive subjects followed by subsequent evaluation of drug abuse liability using established behavioral models. In this respect, rats exhibiting high impulsivity in the delay discounting task self-administer greater amounts of cocaine, methylphenidate, and nicotine relative to low impulsive rats [9], consistent with findings from human studies.

Importantly, neurobehavioral mechanisms underlying vulnerability to drug abuse also may be evaluated in animal models to establish causal links. Several studies have shown that the serotonin (5-HT) system in the prefrontal cortex (PFC) plays a major role in the neurochemical effects of drugs of abuse, specifically psychostimulants which increase extracellular 5-HT in a number of brain regions and contribute to the development and maintenance of addiction [10]. In addition to the role of 5-HT in addiction, 5-HT in orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) is involved in modulating different aspects of impulsivity [10]. For instance, lesions in OFC and mPFC alter delay discounting behavior [11–14, but see 15,16]. Further, 5-HT in OFC and mPFC mediate behavior in the delay discounting task, as indicated by results from a number of experimental approaches, e.g., microinjection, lesion and microdialysis [17]. In addition, both acute dietary tryptophan depletion in humans and forebrain 5-HT depletion induced by infusion of 5,7-dihydroxytryptamine into rat dorsal raphe increase impulsive choice in the delay discounting task [18–20]. With respect to impulsive action, 5-HT in the mPFC has been linked to the rate of acquisition of behavior in the cued go/no-go task [21]. In addition, injection of 5,7-dihydroxytryptamine into median raphe increases impulsive action [16,22–24]. However, neurochemical mechanisms in mPFC and OFC that underlie impulsive behavior in the cued go/no-go task have not been evaluated in depth using preclinical models, which is surprising considering the established relationship between impulsivity and drug abuse vulnerability in humans when employing this task [7].

Extracellular 5-HT concentrations are regulated primarily by plasma membrane transporters, i.e., the 5-HT transporter (SERT; [25]). Polymorphisms in genes encoding SERT are associated with impulsivity in both normal individuals and in neuropsychiatric conditions associated with high impulsivity (e.g., attention deficit hyperactivity disorder) [26,27]. A role for SERT in impulsivity is supported also by pharmacological evidence in which citalopram, a SERT inhibitor, decreased impulsive choice in the delay discounting task in rats [28]. However, relationships between basal SERT function specifically in prefrontal cortical subregions and impulsive behavior have not been investigated.

The present study determined whether individual differences in SERT function in the OFC and/or mPFC have a role in the expression of individual differences in impulsive action and choice. Kinetic parameters, affinity (K_m) and maximal transport velocity (V_{max}), for [^{3}H]5-HT uptake were determined in OFC and mPFC synaptosomes obtained from individual rats that were trained in both cued go/no-go and delay discounting tasks using a counterbalanced design. In addition to these ex vivo studies, effects of fluoxetine microinjection, a selective SERT inhibitor, on impulsive choice were determined to directly evaluate the relationship between basal SERT function and impulsivity.

2. Materials and methods

2.1. Materials

5-[1,2-^{3}H(N)]-Hydroxytryptamine creatinine sulfate ([^{3}H]5-HT; specific activity, 27.1 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, MA). 5-HT, desipramine HCl, 1-(2-*bis*(4-fluorphenyl)-methoxy)-ethyl-4-(3-phenyl-propyl) piperazine HCl (GBR 12909), fluoxetine HCl, pargyline HCl, catechol, and L-ascorbic acid were purchased from Sigma–Aldrich (St. Louis, MO). D-Glucose was purchased from Aldrich Chemical Co. (Milwaukee, WI). Xylazine was purchased from Lloyd Laboratories Inc. (Metro Manila, Philippines). Ketamine was purchased from Putney Inc. (Portland, ME). Acepromazine was purchased from Vedco Inc. (St. Joseph, MO). Carprofen was purchased from Pfizer Animal Health (New York, NY). All other chemicals were purchased from Fisher Scientific (Pittsburgh, PA).

2.2. Subjects

Thirty two male Sprague–Dawley rats (250–275 g, 59–63 days old; Harlan Laboratories, Indianapolis, IN) were housed individually in a temperature- and humidity-controlled colony with a 12/12 h light/dark cycle. Rats were food restricted (85% of free feeding body weight), and had free access to water in their home cages. Experiments were conducted during the light phase. Rats were cared for in accordance with the 2011 edition of the "Guide for the Care and Use of Laboratory Animals" and procedures were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

2.3. Behavioral apparatus

Operant chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) with aluminum front and back walls and Plexiglas sides were located inside sound-attenuating chambers (ENV-018M; MED Associates). A recessed food tray (5 × 4.2 cm) was 2 cm above the floor in the bottom-center of the front wall. Retractable levers (4.5 cm) were 6 cm above the floor on each side of the food tray. A 28-V white cue light was 6 cm above each lever. A white house light was mounted in the center of the back wall. All responses and scheduled consequences were recorded and controlled by a computer interface using Med-IV software.

2.4. Experimental design

Rats (n = 20) were tested in both the cued go/no-go and delay discounting tasks, with order of testing counterbalanced. Following the last behavioral test day (rats were ~88 days old), synaptosomes were prepared from OFC and mPFC obtained from each rat to determine kinetic parameters of SERT function. In a separate experiment,

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