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Regional differences in dopamine receptor blockade affect timing impulsivity that is altered by d-amphetamine on differential reinforcement of low-rate responding (DRL) behavior in rats

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ABSTRACT

The ability to control when to start an action and when to stop is crucial in human and animal behavior. A failure to suppress premature behavior or to carry out an action in a timely manner is commonly seen in several neuropsychological disorders. Despite the phenomenon, the exact neural mechanisms underlying this timing impulsivity remain to be elucidated. Systemic injection of D-amphetamine (AMP) has been shown to disrupt rat's performance in the differential reinforcement of low-rate (DRL) task that requires both optimal timing and proper impulsive control as measured by peak time and non-reinforced responses, respectively. By directly infusing selective D1 or D2 receptor antagonists (SCH23390 and raclopride, respectively) into three brain areas, we aimed to uncover which brain regions and which dopamine receptor subtypes are involved in counteracting the rat's deficit of DRL performance induced by the systemic injection of AMP. We found that D1, but not D2 receptors in the dorsal hippocampus (dHIP) and nucleus accumbens (NAC) played an important role in impulsive control as well as in timing. In the medial prefrontal cortex (mPFC), both D1 and D2 receptors played an equal role in impulsive control, but only mPFC D1 was critical in the control of timing. Together, our data revealed a regional-dependent and dopamine receptor subtype specific effect across each region tested in the mesocorticolimbic circuits on the deleterious effect of AMP in the DRL task. The current findings further advance our understanding of the neurobehavioral mechanisms involved in timing impulsivity.

1. Introduction

The ability to control when to start an action and when to stop is crucial in human and animal behavior. A failure to suppress premature behavior or to carry out an action in a timely manner is a common behavioral phenotype; such lack of impulsive-control and/or failure to inhibit urge, in contrast to functional impulsivity, can be seen in neuropsychiatric disorders such as attentional deficit hyperactivity disorder (ADHD), drug addiction, and pathological gambling or shopping. Impulse-control, as a multifaceted construct, can be separated into impulsive action and impulsive choice. In the domain of impulsive action, with respect to inhibitory dysfunction, "failing to wait" can be measured in experimental rodents using the 5-choice serial reaction time (5-CSRT) task and differential reinforcement of low-rate responding (DRL) schedule controlled behavior [1–4]. Research findings have mainly involved 5-CSRT when investigating the neurobiology and psychopharmacology of impulsive action. Surprisingly, little is known about DRL behavior used to address the neuropharmacology of impulsive action. It is noted that the behavioral performances characterized in these two tasks are discrepant. For example, the DRL behavior does not provide an external cue like the 5-CSRT does. In the 5-CSRT task, animals are trained to execute a correct choice behavior based on visually attending an external cue. In contrast, the DRL procedure does not provide such an external cue; rather, the subject relies on the internal representation of the passage of time since a prior response. Based on this external vs. internal difference, the DRL behavior is thought to be a more accurate measure of "wait" in time as compared to the 5-CSRT [1,2,4]. It is then important to examine the potentially distinct component of impulsive action involved in the DRL behavior.

Operant behavior maintained during the DRL schedule has been characterized as showing temporal regulation [5–10] as well as

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behavioral inhibition [11–15]. Rats trained in the DRL schedule are required to inhibit or withhold lever press for a minimum specified period of time (usually 5 s to 72 s) in order to obtain a reinforcer. An early/premature response before the criterion time will reset the program clock and then the subject has to wait again for the specific set of time, starting from the time the non-reinforced response was made. This reset or "penalty" distinguishes the DRL procedure from other schedules of reinforcement such as the fixed-ratio (FR) schedule and the fixed-interval (FI) schedule, both of which generate a relatively high rate of responding. In addition, the DRL task is also distinct from other temporal discrimination tasks, such as the discrete-trial temporal bisection task, and from temporal differentiation tasks, such as the peak procedure; this is because these tasks do not involve a program clock reset following a premature response [16–18]. In considering the timing process that has been proposed to be involved in the impulsive control [1,19], the DRL behavioral task is suitable for the study of timing impulsivity. It should also be noted that the exact neural basis underlying the timing and impulsive action of DRL behavior so far remains largely unknown.

Substantial evidence has shown that DRL behavioral responses are profoundly affected by the systemic administration of d-amphetamine (AMP) and other psychostimulants [20]. While a considerable number of studies have shown that the level of extrasynaptic dopamine (DA) in the brain is significantly increased by AMP [21], whether DA-dependent mechanisms underlie the AMP in affecting DRL behavior remains unclear. Based on previous findings that the mesocorticolimbic circuits are involved in behavioral inhibition or impulsive action [2,22,23], we hypothesized that behavioral inhibition and temporal processing involving DRL behavior may be mediated by various anatomical areas within the mesocorticolimbic DA systems, as well as by a variety of pharmacological substrates. Thus, this study investigated the possible brain region-specific and receptor-specific dopaminergic modulation of AMP-altered DRL behavior by directly infusing a selective D1 or D2 receptor antagonist (SCH23390 or raclopride, respectively) into three DA terminal areas of the brain in rats: the medial prefrontal cortex (mPFC), the nucleus accumbens (NAC), and the dorsal hippocampus (dHIP).

2. Materials and methods

2.1. Subjects

Sixty male Wistar rats, averaged approximately 250 g of body weight upon receipt, were purchased from the Breeding Center of Experimental Animals in National Taiwan University Hospital, Taipei, Taiwan. The rats were housed individually. After 10 days of adaptation with food and water provided ad libitum, the rats were maintained on a water-restriction regimen such that there was 5 min access to tap water in the home cage occurring no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85% of their pre-restriction body weight during the entire experiment. Food pellets were continuously available in each home cage. All procedures were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by an institutional review committee.

2.2. Apparatus

The interior dimensions of each operant chamber were 20 × 25 × 30 cm (MED Associated, St. Albans, VT, USA). Aluminum panels formed the front and back walls, and clear Plexiglas comprised the remaining sides and the top. Stainless steel rods (with a diameter of 5 mm) were set 11 mm apart to provide flooring. Each chamber was equipped with a lever positioned 7.3 cm above the floor and 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front panel of the chamber. The reinforcer delivery mechanism gave 0.04 ml of tap water at each presentation. The water was delivered into a receiving dish (25 mm diameter) located at the center of the front panel and 2 cm above the floor. The chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. Each chamber was enclosed in a plywood box with a fan to provide necessary ventilation and to mask any outside noise. A set of four operant chambers was connected with a PC to control the operant variables and data collection via an in-house designed program [9,10,24].

2.3. Surgery

Under sodium pentobarbital (40 mg/kg; IP) anesthesia, each rat was placed in the stereotaxic instrument (David Kopf Instruments) for the bilateral implantation of stainless steel cannulae. As determined by Paxinos and Watson [25], the coordinates for the final injection sites were: AP = +3.7 mm, L = ± 0.7 mm, D = −4.5 mm for the mPFC; AP = +1.7 mm, L = ± 1.8 mm, D = −6.5 mm for the NAC and AP = −3.2 mm, L = ± 2.2 mm, D = −3.2 mm for the dHIP. Stainless steel stylets were inserted into the guide cannulae to keep the guides patent until the microinjections were conducted. At the end of surgery, penicillin (50000 I.U.) was administered intramuscularly to prevent infection. Subjects were allowed 7 days to recover from surgery.

2.4. Drugs and microinjection

D-amphetamine sulfate (Sigma Chemical Co.; St. Louis, MO, USA), SCH23390 HCl (Tocris Cookson; Bristol, UK), and raclopride L-tartrate (RBI; Natick, MA, USA) were dissolved in 0.9% physiological saline (SAL). The vehicle solution was 0.9% physiological saline. At the time of microinjection of SCH2330 (SCH) or raclopride (RAC), the stylets were replaced by 28 gauge injection needles connected by PE20 tubing to 2 μl Hamilton micro-syringes. Each drug or vehicle solution was locally infused in a volume of 0.25 μl over 1 min per site for a total duration of 2 min. The injector needles were extended from the bottom of the guide cannulae for 1.0 mm in the dHIP group and 1.5 mm in both the mPFC and NAC groups. After injection, the needles were left in place for an additional minute to enhance diffusion from the injection site and to reduce the possibility of reflux. To ensure an equal binding to the receptors, we chose to deliver the drugs in equal molecular weight (in nmol) for the D1 and D2 antagonists in the entire study.

2.5. Procedures

The rat received DRL–10 s behavior training with procedures described previously [24][e.g. 24]. In brief, after basic lever response training, the DRL–5 s task was introduced for fifteen daily sessions, followed by at least thirty daily sessions for DRL–10 s before the intracranial cannulation surgery was carried out. After post-surgery recovery, the rats received five additional daily sessions of retraining to ensure stable performance before drug tests. All daily training or test sessions lasted for 15 min.

Pharmacological testing was conducted to examine whether the performance regarding DRL–10 s behavior was changed by systemic AMP treatment and whether this could be reversed by local infusion of a selective DA receptor antagonist into the selected brain areas. There were three groups of rats, each prepared with the microinjection cannula aimed at the mPFC, NAC, or dHIP. Half of the rats in each group received SCH treatment while the other half received RAC treatment (n = 10 each). The systemic injection of AMP or saline vehicle was administered intraperitoneally (i.p.) 15 min before the behavioral session commenced and the intra-cranial microinjection of SCH, RAC or vehicle was infused right before the systemic injection. The dose of AMP, 1 mg/kg, was selected based on previous reports [9,20], specifically avoiding a too high dose that can bring down operant responses. In each test, a given rat received two drug injections, one being a systemic administration and one being a microinjection, on