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Research Report

Role of medial prefrontal and orbitofrontal monoamine transporters and receptors in performance in an adjusting delay discounting procedure ☆

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ABSTRACT

Performance in an adjusting delay discounting procedure is predictive of drug abuse vulnerability; however, the shared underlying specific prefrontal neural systems linking delay discounting and increased addiction-like behaviors are unclear. Rats received direct infusions of methylphenidate (MPH; 6.25, 25.0, or 100 μg), amphetamine (AMPH; 0.25, 1.0, or 4.0 μg), or atomoxetine (ATO; 1.0, 4.0, or 16.0 μg) into either medial prefrontal cortex (mPFC) or orbitofrontal cortex (OFC) immediately prior to performance in an adjusting delay task. These drugs were examined because they are efficacious in treating impulse control disorders. Because dopamine (DA) and serotonin (5-HT) receptors are implicated in impulsive behavior, separate groups of rats received microinfusions of the DA receptor-selective drugs SKF 81297 (0.1 or 0.4 μg), SCH 23390 (0.25 or 1.0 μg), quinpirole (1.25 or 5.0 μg), and eticlopride (0.25 or 1.0 μg), or received microinfusions of the 5-HT receptor-selective drugs 8-OH-DPAT (0.025 or 0.1 μg), WAY 100635 (0.01 or 0.04 μg), DOI (2.5 or 10.0 μg), and ketanserin (0.1 or 0.4 μg). Impulsive choice was not altered significantly by MPH, AMPH, or ATO into either mPFC or OFC, indicating that neither of these prefrontal regions alone may mediate the systemic effect of ADHD medications on impulsive choice. However, quinpriole (1.25 μg) and eticlopride infused into mPFC increased

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impulsive choice, whereas 8-OH-DPAT infused into OFC decreased impulsive choice. These latter results demonstrate that blockade of DA D_2 receptors in mPFC or activation of 5-HT_{1A} receptors in OFC increases impulsive choice in the adjusting delay procedure.

1. Introduction

Delay discounting refers to a decrease in subjective value of a reinforcer as the delay to its delivery is increased and can be measured in both humans and laboratory animals. Typically, a subject is allowed to choose between an immediate, small reward and a delayed, larger reward. Subjects are considered more impulsive if they choose the small, immediate reward over the larger, delayed reward (Ainslie, 1975). Delay discounting is associated with substance abuse, as individuals diagnosed with substance use disorders show steeper discounting of monetary rewards relative to controls (e.g., Bickel et al., 1999; Coffey et al., 2003; Hoffman et al., 2006; Madden et al., 1997; Mitchell, 1999; Vuchinich and Simpson, 1998). Preclinical studies also show that increased sensitivity to delay is a predictor of drug abuse vulnerability, as measured in several operant and non-operant paradigms (Anker et al., 2009; Diergaarde et al., 2008; Marusich and Bardo, 2009; Perry et al., 2005, 2008a; Poulos et al., 1995; Yates et al., 2012; but see Diergaarde et al., 2012 for an exception). Thus, elucidating the neural substrates underlying impulsive choice and addiction is important for the development of novel therapies to improve treatment outcomes.

Some lesion studies have implicated different regions of the prefrontal cortex in delay discounting. The prefrontal cortex includes medial prefrontal and orbital frontal cortices (mPFC and OFC, respectively) and is involved in the acquisition and relapse of drug use (see Perry et al., 2011 for a review). Inactivation of mPFC increases sensitivity to delayed reinforcement in a T-maze paradigm (Churchwell et al., 2009), although lesions to this area do not alter delay discounting performance in an operant procedure (Cardinal et al., 2001). Evidence suggests a role for OFC in impulsive decision making, although available results are somewhat inconsistent. Lesions to OFC have been reported to increase (Mobini et al., 2002; Kheramin et al., 2002, 2004; Rudebeck et al., 2006), decrease (Winstanley et al., 2004), or have no effect on discounting (Abela and Chudasama, 2013; Churchwell et al., 2009; Stopper et al., 2014). These inconsistent findings may relate to the extent and anatomical specificity of the lesion site across studies (e.g., Mar et al., 2011).

At the neurochemical level, evidence suggests that dopaminergic (DA) and serotonergic (5-HT) activity within mPFC and OFC are involved in discounting behavior. Animals high in impulsive choice show reduced electrically-evoked DA release in mPFC relative to low impulsive animals (Diergaarde et al., 2008), and an elevation of intra-mPFC 5-HT efflux is observed in animals performing a progressive delay discounting procedure (Winstanley et al., 2006). Furthermore, decreasing DA levels in mPFC increases preference for a small, immediate reinforcer (Loos et al., 2010; Pardey et al., 2013). Similarly, antagonism of 5-$HT_{2A/C}$ or DA D_2-like receptors within OFC increases impulsive choice (Pardey et al., 2013; Wischhof et al., 2011; Zeeb et al., 2010), although these effects may be dependent on baseline levels of discounting (e.g., Zeeb et al., 2010). However, none of these studies have examined the role of DA or 5-HT receptors in mPFC or OFC using an adjusting delay discounting procedure.

The goal of the present study was to determine the role of DA and norepinephrine transporters (DAT and NET, respectively), as well as DA and 5-HT receptors in mPFC and OFC, in impulsive choice. In the current experiments, we used an adjusting delay procedure to calculate a mean adjusting delay (MAD) score, a measure of indifference between a small, immediate reinforcer and a large, delayed reinforcer. Lower MAD scores indicate increased impulsive choice, whereas higher MAD scores indicate decreased impulsive choice. We used this procedure because it has been shown to be a predictor of distinct stages of the addiction process (Anker et al., 2009; Marusich and Bardo, 2009; Perry et al., 2005, 2008a; Yates et al., 2012). In Experiment 1, rats received intra-mPFC infusions of the ADHD medications methylphenidate (MPH), amphetamine (AMPH), and atomoxetine (ATO), which exert their therapeutic effects by blocking DAT and/or NET (see Biederman, 2005 for a review). Furthermore, individuals with ADHD show greater discounting of delayed reinforcement relative to controls (Anouk et al., 2013; Demurie et al., 2012; Scheres et al., 2010). In Experiment 2, rats received intra-mPFC infusions of the DA receptor-selective drugs SKF 81297 (D_1-like agonist), SCH 23390 (D_1-like antagonist), quinpirole (D_2-like agonist), and eticlopride (D_2-like antagonist). In Experiment 3, rats received intra-mPFC infusions of the 5-HT receptor-selective drugs 8-OH-DPAT (5-HT_{1A} agonist), WAY 100635 (5-HT_{1A} antagonist), DOI (5-HT_{2A} agonist), and ketanserin (5-HT_{2A} antagonist). Experiments 4–6 were similar to Experiments 1–3, except that rats received intra-OFC infusions.

2. Results

2.1. Baseline MAD scores

Fig. 1 shows MAD scores during the final three sessions before guide cannulae implantation and during the final three sessions before receiving the first microinfusion. A $2 \times 3 \times 2 \times 3$ ANOVA showed that rats that received bilateral cannulae into OFC had higher baseline MAD scores relative to rats that received cannulae into mPFC ($F(1, 36) = 10.40$, $p < 0.05$), perhaps due to a difference in the type of pellet reward used across these experiments (see Procedures). However, there were no main effects of surgery, experiment, or session. Therefore, data for each experiment were collapsed in the statistical analyses. Overall, MAD scores were stable for rats receiving inta-mPFC and intra-OFC infusions.

2.2. ADHD medications

There were trends for MPH to increase MAD scores in mPFC and OFC (mPFC: $t(10) = 2.18$, $p = 0.06$, effect size = 0.90; OFC: $t(10) = 1.98$, $p = 0.08$, effect size = 0.75; Fig. 2a), which suggests a