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Research report

Dopaminergic modulation of the orbitofrontal cortex affects attention, motivation and impulsive responding in rats performing the five-choice serial reaction time task

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ABSTRACT

Understanding the neurobiological factors underlying individual differences in impulsivity may provide valuable insight into vulnerability to impulse control disorders. Recent data implicate both the orbitofrontal cortex (OFC) and the dopaminergic system in psychiatric disorders associated with high levels of impulsivity, including substance abuse, mania and obsessive–compulsive disorder. However, the consequences of modulating dopaminergic activity within the OFC on impulsive behaviour are largely unknown. The effects of direct intra-OFC infusions of agonists and antagonists at the dopamine D_1 and D_2 receptors were therefore assessed in rats performing the five-choice serial reaction time test (5CSRT) of attention and motor impulsivity. Intra-OFC administration of SCH23390, a D_1 receptor antagonist, decreased impulsive responding in highly impulsive (HI) rats, but did not affect behaviour in less impulsive (LI) animals. Furthermore, the D_2 agonist quinpirole caused significant deficits in task performance, impairing accuracy, increasing omissions and decreasing the number of trials completed, which resembled the effects of systemic administration. In contrast, the D_1 agonist SKF 81297 had little effect on behaviour. Neither agonist increased impulsivity. These data provide partial support for the suggestion that high levels of impulsivity are associated with increased dopamine levels within the OFC, but further indicate that simulating dopamine's actions selectively at the D_1 or D_2 receptor cannot reproduce a highly impulsive phenotype. Dopaminergic activity within the OFC may therefore modulate impulsivity indirectly, perhaps in conjunction with other neurotransmitter systems. Furthermore, D_2-mediated neurotransmission within the OFC could make a more fundamental contribution to cognitive behaviour.

1. Introduction

Understanding how changes in orbitofrontal cortex (OFC) function influences reward-related behaviour is becoming a research goal of ever-increasing importance. Dysfunction within this region is thought to critically contribute to both obsessive–compulsive disorder (OCD) and bipolar disorder [1,2], and the observation that the OFC is hypoactive in cocaine addicts has lead to the suggestion that this region likewise plays a key role in mediating substance abuse [3,4]. There is a clear need for improved treatments for such disorders, and important new leads could arise through studying the neurochemical regulation of the OFC.

Patients with OFC damage display a pattern of aberrant social behaviour and maladaptive decision-making which is often described as impulsive, and such patients score highly on questionnaire-based measurements of impulsivity [5]. Deficits in impulse control are manifest in both bipolar disorder, substance abuse disorder and, to some extent, OCD, and it has been hypothesized that these deficits may be attributable to OFC dysfunction [6–8]. Impulsivity can contribute to the making of unwise or poorly reasoned choices, such as the selection of small immediate rewards over larger but more delayed ones [9]. Given the apparent importance of OFC input for reward-related decision-making, it is perhaps unsurprising that data from studies using both humans and rodents implicate the OFC in the making of such delay-discounting judgements [10–13].

However, impulsivity can also reflect deficits in response inhibition, as exemplified by difficulties in inhibiting a prepotent motor response either in anticipation of a reward signal ("waiting") or in cancelling a motor act once it has been engaged ("stopping") [14]. Although the OFC is not considered a primary area in the regulation of inhibitory processes, a growing body of evidence suggests that

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this region does contribute to these aspects of behaviour, perhaps due to its more general role in processing negative feedback [15]. For example, reductions in OFC grey matter are correlated with poor performance on the stop-signal reaction time test of motor impulsivity observed in OCD patients and their relatives [16,17]. Damage to the OFC in rats likewise slowed stop-signal reaction time, indicative of an impairment in stopping ability, and transiently increased premature responding on the five-choice serial reaction time task (5CSRT), suggestive of a deficit in waiting for the appropriate signal before emitting a response [18,19]. Recent work in rats also suggests that high levels of premature responding are predictive of future cocaine dependency, and that changes in gene transcription within the OFC can exacerbate withdrawal-induced increases in this form of motor impulsivity [20,21].

Abnormalities in dopaminergic neurotransmission are thought to contribute to bipolar disorder [22], OCD [23] and substance abuse [24]. It is therefore possible that changes in dopamine (DA) signaling within the OFC may contribute to the impulsive symptoms associated with these illnesses. In terms of impulsive-decision-making, it has been observed using *in vivo* microdialysis that DA selectively increases within the OFC while rats are performing a delay-discounting task [25]. In addition, local inhibition of dopaminergic neurotransmission leads to decreases in impulsive choice [26], further suggesting that DA could be a key modulator of impulsive decision-making of this kind. However, whether DA within the OFC contributes to the regulation of more motor aspects of impulse control has yet to be determined. Systemic administration of the DA D_1 receptor antagonist SCH23390 decreases premature responding on the 5CSRT, whereas the D_2 receptor antagonist eticlopride has no effect on this measure of impulsivity [27,28]. A similar pattern of behaviour is observed when these drugs are infused directly into the nucleus accumbens [29]. However, both receptor antagonists have been found to reduce the increase in impulsive responding observed in this task after administration of the psychostimulant d-amphetamine [28].

In terms of cortical function, DA's effects could be baseline-dependent in keeping with the prevailing hypothesis that the relationship between DA levels and behavioural performance follows an inverted U-shaped curve [30]. Although infusion of dopaminergic agents into the medial prefrontal cortex (mPFC) did not affect impulsive responding on the 5CSRT, compounds active at the D_1 receptor differentially affected animals ability to accurately detect the location of the light stimulus: poor performers showed an improvement after infusions of the D_1 receptor agonist while highly accurate rats became worse after infusions of the D_1 receptor antagonist [31]. The aim of the current experiment was therefore to determine whether modulating DA signaling within the OFC through local infusions of DA agonists and antagonists would affect performance of the 5CSRT, and whether any effects were dependent on baseline levels of impulsivity.

2. Materials and methods

2.1. Subjects

Subjects were 41 male Long-Evans rats (Charles River Laboratories, St. Constant, Canada). Rats weighed 275–300 g at the start of the experiments and were food-restricted to 85% of their free-feeding weight and maintained on 14 g rat chow per day. Water was available *ad libitum*. All animals were pair-housed in a colony room under a reverse 12 h light–dark cycle (lights off at 8:00 a.m.) maintained at a temperature of 21 °C. Testing and housing was in accordance with the Canadian Council of Animal Care, and all experimental protocols were approved by the Animal Care Committee of the University of British Columbia.

2.2. Behavioural apparatus

Behavioural testing took place in eight standard five-hole operant chambers, each enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc., Vermont, USA). Each chamber was fitted with an array of five response holes positioned 2 cm above a bar floor. A stimulus light was set at the back of each hole. Nosepoke responses into these apertures was detected by a horizontal infrared beam. A food magazine, also equipped with an infrared beam and a traylight, was located in the middle of the opposite wall, and sucrose pellets (45 mg; Bioserv, New Jersey, USA) could be delivered into it from an external pellet dispenser. Chambers could be illuminated by a houselight, and were controlled by software written in Med PC by CAW running on an IBM compatible computer.

2.3. Behavioural training: the five-choice serial reaction time task (5CSRT)

Animals were first habituated to the operant chambers over two daily 30 min sessions during which sucrose pellets were placed in the response holes and food magazine. As described in detail in previous publications [32,33], animals were trained to respond in one of the five holes when the stimulus light located in the back of the response aperture was briefly illuminated (0.5 s). The stimulus light could appear in any of the five holes, and the spatial location of the target was varied randomly from trial to trial. Each session consisted of 100 trials and lasted approximately 30 min. Animals initiated each trial by making a nosepoke response at the food tray. There was then a 5 s ITI during which animals had to withhold from making a response at the array before the stimulus light was presented in one of the holes. Premature or impulsive responses made at the array during this time period were punished by a 5 s time-out period during which the houselight was turned on and no further trials could be initiated. A correct response at the illuminated hole was rewarded with delivery of one food pellet in the food tray. Food delivery was signaled by onset of the traylight which remained on until the animal collected its reward. An incorrect or lack of response (omission) was not rewarded and punished in the same manner as premature responses. Repeated responding at the correct hole was classified as perseverative responding and, whilst monitored, was not punished. Animals received 5–6 sessions per week until a high level of stable performance was reached (group mean of $\geq$80% accuracy, $\leq$20% omissions, no statistically significant variation between sessions for any variable as determined by ANOVA, see data analysis section below). This took between 49–53 sessions for the different groups.

2.4. Surgery

Rats were anesthetized with ketamine (Ketaset, 100 mg/kg i.m.; Vetoquinol, Lavaltrie, Canada) and xylazine (Rompun 10 mg/kg i.m.; UBC Animal Care Centre, Vancouver, Canada) and secured in a stereotaxic frame with the incisor bar set at −3.3 for a flat skull position. Bilateral 22-gauge, stainless-steel guide cannulae (Plastics One, Roanoke, USA) were implanted into the OFC according to the following stereotaxic coordinates [34]: anteroposterior +3.8 (from bregma), mediolateral ±2.6, and dorsoventral −2.9 from dura. The cannulae were secured to the skull using three bone screws and dental cement. Twenty-nine gauge obdurators, flush with the end of the guide cannulae, joined to plastic dust caps (Plastics One, Roanoke, USA) were then inserted to protect the head assembly. After surgery, animals were housed individually and food was provided *ad libitum* for 1 week. For the first 48 h after surgery, animals were housed on corn-cob bedding to minimize the risk of any infection caused by sawdust bedding particles adhering to the surgical site. Following this recovery period, animals were re-trained on the 5CSRT.

2.5. Microinfusion procedure

The infusion procedure was adapted from Winstanley et al. [32]. Once a stable post-operative baseline had been established over 5–7 sessions, rats were habituated to the microinfusion procedure with two mock infusions. Infusions were given on a 3-day cycle, starting initially with a baseline session. The following day, rats received a drug or saline infusion prior to testing. On the third day, animals were not tested and remained in their home cages.

During infusions, rats were gently restrained whilst obdurators were removed and a 29-gauge injector extending 1 mm beyond the length of the guide cannulae was inserted into each guide (Plastics One, Roanoke, USA). A volume of 0.5 μl of solution was infused at a rate of 0.25 μl/min, after which the injector was left in place for 1 min to allow the drug to diffuse in the local vicinity of the injector tip. The injectors were then removed and the obdurators replaced. Rats were then placed in cages similar to their home cages in a quiet holding area for 10 min before being placed into the operant chambers, and the 5CSRT started. All infusions were administered in a behavioural testing room separate from the operant testing room.

2.6. Experiment 1: effect of intra-OFC infusions of the D_1 receptor antagonist SCH23390 or the D_2 receptor antagonist eticlopride on 5CSRT performance

One group of rats (n = 9) received infusions of saline or SCH23390 (0.1, 0.3 and 1.0 μg/side), while the second group (n = 10) received infusions of saline or eticlopride (0.1, 0.3 and 1.0 μg/side). The order in which all doses were given was counter-balanced using a Latin square drug design.