Behavioural Brain Research 328 (2017) 19–27

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Dissociable effects of systemic and orbitofrontal administration of adrenoceptor antagonists on yohimbine-induced motor impulsivity

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ARTICLE INFO

Article history:
Received 10 January 2017
Received in revised form 14 March 2017
Accepted 21 March 2017
Available online 23 March 2017

Keywords:
Impulsivity
5-Choice serial reaction time task
Prazosin
Propranolol
Noradrenaline
Dopamine

ABSTRACT

The α_2-adrenoceptor antagonist, yohimbine, is commonly used as a pharmacological stressor. Its behavioural effects are typically attributed to elevated noradrenaline release via blockade of central, inhibitory autoreceptors. We have previously reported that yohimbine increases motor impulsivity in rats on the five-choice serial reaction time task (5CSRTT), a cognitive behavioural assessment which measures motor impulsivity and visuospatial attention. Furthermore, this effect depended on cyclic adenomonophosphate (cAMP) signalling via cAMP response element binding (CREB) protein in the orbitofrontal cortex (OFC). However, the role of specific adrenoceptors in this effect is not well-characterised. We therefore investigated whether the pro-impulsive effects of systemic yohimbine could be reproduced by direct administration into the OFC, or attenuated by intra-OFC or systemic administration of prazosin and propranolol—antagonists at the α_1- and β-adrenoceptor, respectively. Male Long-Evans rats were trained on the 5CSRTT and implanted with guide cannulae aimed at the OFC. Systemically administered α_1- or β-adrenoceptor antagonists attenuated yohimbine-induced increases in premature responding. In contrast, local infusion of yohimbine into the OFC reduced such impulsive responding, while blockade of α_1- or β-adrenoceptors within the OFC had no effect on either basal or yohimbine-stimulated motor impulsivity. Direct administration of selective antagonists at the α_1-, α_2- or β-adrenoceptor into the OFC therefore produce clearly dissociable effects from systemic administration. Collectively, these data suggest that the pro-impulsivity effect of yohimbine can be modulated by adrenergic signalling in brain areas outside of the OFC, in addition to non-adrenergic signalling pathways within the OFC.

1. Introduction

A loss of impulse control is a key symptom in a number of mental illnesses, such as bipolar disorder and attention-deficit hyperactivity disorder (ADHD), and also confers significant vulnerability to addiction disorders and suicidality [1–3]. As with nearly all psychiatric conditions, stress can markedly exacerbate impulse control deficits, a finding that could be attributed to the general decrease in prefrontal cortex functioning caused by activation of the stress response [4,5]. However, psychopharmacology studies suggest that similar neurobiological factors may influence the expression of impulsivity and the response to stress, potentially through the monoaminergic neurotransmitter noradrenaline (NA) that critically mediates the impact of arousal on cognitive function [6–8].

The α_2-adrenoceptor antagonist yohimbine has been used as a "pharmacological stressor" in that it can simulate the stress response in neuropsychological experiments. Yohimbine increases NA release via blockade of inhibitory autoreceptors on noradrenergic neurons [9], and can lead to harmless sensations of heightened arousal and mild anxiety while also increasing impulsive responding in healthy volunteers [10,11]. However, yohimbine can also significantly exacerbate psychiatric symptoms, triggering manic episodes in bipolar patients, panic attacks in those with post-traumatic stress, and withdrawal symptoms, craving and drug-seeking in opioid-dependent patients [12–15]. Similar effects have been observed in animal models of these cognitive processes, in that yohimbine increases impulsivity, and at higher doses, anxiety in rats [16–19], and exacerbates reinstatement in models of relapse to addiction (e.g. [20–22]). Such data support the hypothesis that elevated NA may contribute to these psychopathologies,

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http://dx.doi.org/10.1016/j.bbr.2017.03.034
0166-4328/

and may even mediate the deleterious effects of stress on the manifestation of psychiatric conditions. Certainly, a central role for potentiated NA release has been suggested to underlie both the switch to mania in bipolar disorder and in the addictive power of certain drugs of abuse [6,23–25].

However, drugs such as atomoxetine also increase NA levels through blockade of the NA transporter, yet have beneficial effects in reducing impulsivity in ADHD [26,27]. Yohimbine is also a notoriously "dirty" drug, and has appreciable affinity for other monoaminergic receptors. For example, yohimbine can act as an agonist at serotonin 5-$HT_{1/7}$ receptors and an antagonist at dopamine D_2 receptors [28,29]. However, yohimbine-induced reinstatement of drug-seeking after extinction can be blocked by antagonists at adrenergic receptors, suggesting yohimbine is acting at least in part through noradrenergic mechanisms [30,31]. In contrast, recent data suggest that noradrenergic mechanisms are not primarily responsible for yohimbine's effects on motor impulsivity [32]. One aim of the current study was therefore to reproduce these important null findings.

With regards to the neural mechanism responsible for the pro-impulsivity effect of yohimbine, the original report of this behavioural effect in rats focused on cyclic adenomonophosphate (cAMP) signalling within the orbitofrontal cortex (OFC) [18]. The cAMP intra-cellular signalling cascade is one of the primary pathways through which ligand-binding at G-protein coupled receptors impacts neuronal function, and its activation or inhibition is a common step in monoaminergic signal transduction [33,34]. Increasing levels of the cAMP response element binding protein (CREB) within the OFC through viral mediated gene transfer potentiated yohimbine's ability to increase impulsive (premature) responses on a simplified version of the five-choice serial reaction time task (5CSRTT) in rats, whereas over-expression of the dominant negative protein mCREB had the opposite effect, blocking yohimbine's pro-impulsivity effects [18]. Hence, the OFC appears to be one important site at which yohimbine's effects can be modulated, but the receptors at which ligand-binding may trigger such synergistic or antagonistic effects to that of systemically-administered yohimbine have yet to be determined.

Adrenergic α_1-, α_2- and β-receptors are expressed throughout the frontal cortices [35–39], with a particularly strong β-receptor density in the medial and ventrolateral OFC [40]. The OFC also receives moderately strong innervation by noradrenergic fibers from the locus coeruleus, with a comparable density of noradrenergic varicosities observed across orbitofrontal subregions [41]. We therefore compared the effects of systemic versus intra-OFC administration of the α_1-receptor antagonist prazosin and the β-receptor antagonist propranolol on 5CSRTT performance, both in isolation and in tandem with systemic injection of yohimbine, in order to further test the role of noradrenergic signalling in the ability of yohimbine to modulate impulsivity.

2. Methods

2.1. Subjects

Subjects were three cohorts of male Long–Evans rats (cohort 1: n = 8; cohorts 2 and 3: n = 16; total n = 40; Charles River Laboratories, Saint-Constant, QC, Canada) weighing 275–300 g upon arrival at the animal facility. Animals were food restricted to 85–90% of free-feeding weight and maintained on a diet of 14 g of standard rat chow per day. Water was available *ad libitum* in home cages. Animals were housed in pairs and maintained in a climate-controlled colony room on a 12 h reverse light cycle (lights off at 8:00 A.M.). All experimental work was approved by the University of British Columbia's Animal Care Committee and husbandry was performed in accordance with the standards set forth by the Canadian Council of Animal Care.

2.2. Behavioural apparatus

Testing took place in 16 standard Med Associates five-hole operant chambers housed in ventilated sound-attenuating cabinets. Each chamber featured a food tray outfitted with both a stimulus light and an infrared beam for detecting nose-poke inputs. Sucrose pellets (45 mg; Bio-Serv, Frenchtown, NJ, USA) could be delivered to this tray from an external food hopper and a house light was positioned on the chamber wall above. An array of five response apertures was located on the opposite wall, each equipped with stimulus lights and infrared beams for detecting input. The operant chambers ran according to MedPC programs written by CAW, and controlled by an IBM-compatible computer.

2.2.1. 5CSRTT

Training and testing procedures were conducted as per previous studies [42,43]. Animals were initially habituated to the operant chambers over the course of two 30 min exposures during which sucrose pellets were placed in each of the apertures and animals were allowed to explore the apparatus. Animals were then trained to make nose-poke responses into the response apertures upon brief illumination (0.5 s) of the light located therein. The stimulus light could appear in any of the five apertures, 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 a trial by making a nose-poke response at the food tray, which was immediately followed by an intertrial interval (ITI) during which animals had to withhold from making a response. Following the ITI, the stimulus light was presented in one of the apertures. A correct response at the illuminated aperture was rewarded with delivery of a sucrose pellet to the food tray. Food delivery was signalled by onset of the tray light, which remained on until the animal collected its reward. An incorrect or lack of response (omission) was not rewarded and instead punished by a 5 s timeout period during which the house light was illuminated and no further trials could be initiated. Repeated responding at the correct aperture was classified as perseverative responding and was monitored but not punished. A response during the ITI was classed as a premature response and punished in the same manner as incorrect and omitted responses.

Training took place over 12 stages. For the first stage, the task was run with the following parameters: 30 s stimulus duration, 30 s limited hold period (the amount of time which rats had to make a nose-poke response in the illuminated hole), and 2 s ITI. These parameters were gradually adjusted as training progressed to final parameters of 0.5 s stimulus duration, 5 s limited hold period, and 5 s ITI. Animals performed five daily sessions per week and were tested until statistically stable performance was observed across all variables over five sessions (sessions to stability: 51, 52, and 64 sessions for cohorts 1–3, respectively). All animals were able to perform the 5CSRTT with ≥80% discriminative accuracy and <20% omissions.

2.3. Surgery

Once a statistically stable behavioural baseline had been established (see Data analysis Section), animals were implanted with bilateral guide cannulae targeting the OFC using standard aseptic stereotaxic techniques. Animals were anesthetised with either ketamine/xylazine (cohort 1, n = 8) or 2% isoflurane in oxygen (cohorts 2 and 3, n = 32) and then secured in a stereotaxic frame with the incisor bar set to −3.3 mm. Once anesthetised, animals were given 5 mg/kg ketoprofen subcutaneously. Sterile bilateral 22-