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Effects of the dopamine stabilizer, OSU-6162, on brain stimulation reward and on quinpirole-induced changes in reward and locomotion

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Abstract

Dysregulation of limbic dopamine (DA) neurotransmission results in abnormal positive or negative emotional states that characterize several mental disorders. Drugs that restore DA homeostasis are most likely to constitute effective treatments for such emotional disturbances. In this study, we investigated the effects of several doses of OSU-6162, a drug that belongs to a new class named "DA stabilizers", on brain stimulation reward. Because quinpirole produces, depending on the dose, a pre-synaptic depressant and a post-synaptic stimulatory effect on reward and locomotor activity, we also compared the ability of OSU-6162 and haloperidol to prevent these effects of the full DA agonist. Results show that OSU-6162 produced a dose-orderly reduction of reward with no change in the capacity of the animals to produce the operant response, and prevented, like haloperidol, both stimulatory and depressant effects of quinpirole on locomotor activity but only its reward stimulatory effect. The observed functional antagonism of OSU-6162 on these DA-dependent behaviors suggests that it may constitute an effective treatment for abnormal positive emotional state, and that it would be exempt of motor side-effects.

1. Introduction

Dysfunctions in homeostatic control of limbic dopamine (DA) neurotransmission result in abnormal states that characterize several neuropsychiatric and neurological disorders (Galvan and Wichmann, 2008; Goto et al., 2007; Marsden,

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2006). Drugs of abuse, for instance, generate a strong rewarding effect that contrasts with anhedonia occurring following withdrawal from their chronic use, affective states associated with a respective increase and decrease in limbic DA (see Koob and Le Moal, 2001). Similarly, in schizophrenia, positive symptoms (e.g. hallucinations and delusions) are associated with an enhancement in DA neurotransmission (see Hietala et al., 1995; Laruelle et al., 1996; Lindström et al., 1999), whereas a reduction in DA neurotransmission has been proposed to underlie negative (e.g. social withdrawal, blunted affect) symptoms (see Goto et al., 2007). Motor abnormalities that characterize Parkinson's disease result from a dramatic reduction in striatal DA due to degeneration of the mesostriatal DA pathway. With the progression of the disease, treatment-induced uncontrolled dyskinetic movements and psychotic symptoms appear, perhaps due to the development of supersensitive DA receptors (Blanchet et al., 1995; Fénelon et al., 2000; Obeso et al., 2000). Most of the current medications used to control, or reduce, symptoms associated with these disorders target DA receptors. Drugs acting at DA D2-like receptors, for instance, constitute a first choice for treatment of psychosis. While some are more effective than others on a particular set of symptoms, none to date are effective at improving both those associated with reduced (i.e. cognition, anhedonia) and enhanced (i.e. positive symptoms) DA neurotransmission (Agid et al., 2008). OSU-6162 and ACR-16 belong to a new generation of drugs that seem to stabilize DA-dependent behaviours. They appear to increase DA neurotransmission when its endogenous tone is low and reduce it when it is high. In animals exposed to novel environment, a situation associated with increased spontaneous locomotion and ventral striatal DA release (Legault and Wise, 2001), OSU-6162 reduces locomotion (Natesan et al., 2006; Rung et al., 2008). Similarly, OSU-6162 is effective at attenuating behavioral effects of amphetamine, a psychostimulant that increases ventral striatal DA release (Brandt-Christensen et al., 2006; Natesan et al., 2006). On the other hand, OSU-6162, at a similar range of doses, stimulates locomotion in animals that are well habituated to the testing environment and that display a low level of spontaneous locomotion (Natesan et al., 2006; Rung et al., 2008). It reduced L-Dopa-induced dyskinesia in parkinsonian primates with minimal interference with its antiparkinsonian effects (Hadj Tahar et al., 2001). Although the exact mechanisms by which OSU-6162 alters DA-dependent behaviors remain to be fully understood, current data suggest that it interacts selectively with DA receptors. OSU-6162 displays a low but specific affinity for D2 receptors, and in vitro studies showed that it acts as a partial agonist at this receptor and increases, at low concentration, D2 receptor activation via allosteric site (Sonesson et al., 1994, Natesan et al., 2006; Lahti et al., 2007; Seeman and Guan, 2007). It was also suggested that OSU-6162 acts preferentially at presynaptic autoreceptors (Carlsson et al., 2004). These functional effects at the D2 receptor may account for the DA-dependent behavioral stabilization property of OSU-6162 in as much as they apply in vivo. The behavioral stabilization has been limited to locomotor response and it is not clear how this drug will act on other behaviors mediated by limbic DA pathways. Thus the main objectives of this study were to determine whether OSU-6162 causes uni- or bidirectional changes on operant responding for electrical brain stimulation (brain stimulation reward, BSR), and can alter the reduction and the amplification of reward induced by quinpirole, a DA D2-like agonist.

In a first study, we compared the effects of several doses of OSU-6162 and of quinpirole, on BSR. Then, we tested whether OSU-6162 can prevent the effects of quinpirole on reward and on spontaneous locomotion measured in a novel environment, and compared it to that of haloperidol, a DA antagonist. Since manipulations of DA neurotransmission by systemic drug injections often result in motor side effects, we used the curve-shift method to measure BSR and quantify changes in reward and operant responding (Miliaressis et al., 1986b).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, St-Constant, Quebec) weighing between 300 and 350 g at the surgery time were used. They were initially housed two per cage, and one per cage after the surgery, in a temperature and humidity-controlled room (21 ± 1 °C; 53 ± 2%) with a 12 h light-dark cycle (lights on at 06:30 am). They were allowed to habituate to the new housing environment for 7 days before the surgery and had access to food and water *ad libitum*. All procedures were in accordance with guidelines of the Canadian Council on Animal Care and all efforts were made to minimize suffering and number of animals used.

2.2. Surgery

Rats were anaesthetized with isoflurane (2.5–3.5%, O_2 0.6 L/min) and mounted on a stereotaxic apparatus. A 0.2 ml solution of the local anaesthetic marcaine (0.25%) was injected subcutaneously at the site of incision. Two stainless steel wires of 0.27 mm in diameter insulated with Epoxy, except for the round tip, were implanted within each hemisphere into the lateral hypothalamus using the following flat skull coordinates: 2.8 mm posterior to bregma, 1.7 mm lateral to the saggital suture and 8.6 mm below the surface of the skull (Paxinos and Watson, 1986). An uninsulated wire serving as the inactive electrode (anode) was wrapped around four stainless steel screws threaded into the cranium and the whole assembly was fixed with dental acrylic. A 0.1 ml (im) solution of Duplocillin LA containing 300,000 I.U. of penicillin was administered to prevent infections.

2.3. Brain stimulation reward

2.3.1. Apparatus and procedure

One week after surgery, rats were placed in a test cage (25 × 25 cm) made from three opaque polymer walls and one front Plexiglas wall that allowed observation. Each cage was equipped with an infrared photocell located inside a hole (3 cm diameter × 3 cm deep) 2 cm above a wire-mesh floor. To minimize disturbance due to external noise test cages were encased in ventilated wooden boxes insulated with Styrofoam. Rats were trained to produce a nose-poke response to trigger a constant-current pulse generator (Mundl, 1980) that delivered a single 500 ms train of 0.1 ms cathodal rectangular pulses. Each stimulation train was followed by an inter-train interval (500 ms) during which the pulse generator could not be triggered; the animal could not self-administer more than one train per sec (see Boye and Rompre, 1996). The effects of the stimulation on the behaviour were initially evaluated on each of the electrodes at different current intensities (200–500 μA); the site at which the