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The effect of striatal dopamine depletion and the adenosine A_{2A} antagonist KW-6002 on reversal learning in rats

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Abstract

This study assessed whether dopamine in the dorsomedial striatum is necessary for flexible adaptation to changes in stimulus–response contingencies. As KW-6002 (Istradefylline), an adenosine A_{2A} antagonist, improves motor deficits resulting from striatal dopamine depletion, we also tested for potential ameliorative effects of KW-6002 on dopamine depletion-induced cognitive deficits. Male Lister hooded rats were presented with two bowls, discriminable by either a textured covering on the outer surface, their scent or the bowl contents (digging media) in which bait was buried. Once they had learned in which bowl food was buried, the stimulus–response contingencies were reversed. In both phases (acquisition and reversal), the criterion for learning was defined *a priori* as six consecutive correct trials. Following depletion of dopamine in the dorsomedial striatum, acquisition of the discriminations was intact but there was an increase in the number of trials to attain criterion performance in the reversal phases, indicating an impairment in reversal learning. KW-6002 (1 mg/kg bidaily for 10 days) non-specifically increased the number of trials to criterion at all stages of the test and in both controls (sham-operated) and dopamine-depleted rats. Chronic KW-6002 treatment did not improve the reversal deficits in dopamine-depleted rats. These findings suggest that dopamine transmission in the dorsomedial striatum is critical for the flexible shifting of response patterns and the ameliorative effects of KW-6002 following depletion of dopamine in the striatum may be restricted to motor functions without relieving deficits in response-shifting flexibility.
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1. Introduction

Accumulating evidence suggests that animals with lesions of the dorsolateral striatum are impaired in learning tasks that require formation of stimulus–response associations (Adams, Kesner, & Ragozzino, 2001; Featherstone & McDonald, 2004a, 2004b, 2005; Kantak, Green-Jordan, Valencia, Kremin, & Eichenbaum, 2001; McDonald & Hong, 2004; McDonald & White, 1993, 1994; Reading, Dunnett, & Robbins, 1991; White, 1989; White & McDonald, 2002). In contrast to the dorsolateral striatum, the dorsomedial striatum does not appear to play a critical role in the initial formation of stimulus–response associations. Inactivation of the dorsomedial striatum does however impair the ability of animals to flexibly adapt their response patterns when stimulus–response contingencies change (Kirkby, 1969; Kolb, 1977; Pisa & Cyr, 1990; Ragozzino & Choi, 2004; Ragozzino, Ragozzino, Mizumori, & Kesner, 2002).

Recent studies have investigated the neurochemicals in the dorsomedial striatum involved in the learning that underlies adaptive shifts in response patterns. These studies have shown that NMDA receptors and acetylcholine in the dorsomedial striatum play an important role in rule reversal learning (Palencia & Ragozzino, 2004, 2006; Ragozzino

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& Choi, 2004; Ragozzino, Jih, & Tzavos, 2002). However, the role of dopamine in the dorsomedial striatum has yet to be investigated.

An earlier study showed that amphetamine, which increases dopamine release in the striatum, impaired reversal learning without affecting initial acquisition of stimulus discriminations (Weiner & Feldon, 1986). However a more recent study has shown an effect of amphetamine on both acquisition and reversal of stimulus–response rules (Idris, Repeto, Neill, & Large, 2005). Genetic knockout mice lacking the dopamine D_2 receptor show deficiencies in both initial learning and reversal learning, with a more considerable deficit in reversal learning (Izquierdo et al., 2006; Kruzich & Grandy, 2004). Additionally, drugs specifically targeting dopamine receptor subtypes D_2 and D_3 have been shown to affect reversal learning without affecting acquisition learning (Lee, London, & Jentsch, 2005). Taken together, these studies suggest that dopamine is important for stimulus–response learning. It is the aim of this study to investigate the role of dopamine in the dorsomedial striatum in stimulus–response association formation and rule reversal learning.

In addition, to widen the scope of our understanding of the neurochemicals involved in stimulus–response learning we also examined the effects of the adenosine A_{2A} antagonist KW-6002 (clinically known as Istradefylline). KW-6002 is a likely candidate as an adjunctive drug therapy to dopamine replacement in the treatment of Parkinson's disease (Bara-Jimenez et al., 2003; Hauser, Hubble, & Truong, 2003). KW-6002 has been shown to ameliorate the motor symptoms in animals with striatal dopamine depletion (Coccurello, Breysse, & Amalric, 2004; Grondin et al., 1999; Kanda et al., 2000; Lundblad, Vaudano, & Cenci, 2003; Shiozaki et al., 1999) yet the influence of the compound on 'cognitive' functions, in both intact rats and rats with striatal dopamine depletion, remains untested. This is surprising considering that, in addition to motor complications, impairments of cognitive flexibility are both a consequence of Parkinson's disease and a complication of dopamine replacement therapy (Cools, 2006). KW-6002 exerts its effects by blocking the adenosine A_{2A} receptor, which is structurally coupled with dopamine D_2 receptors in the striatum (Alexander & Reddington, 1989; Ferre, O'Connor, Fuxe, & Ungerstedt, 1993; Franco et al., 2000; Svenningsson, Le Moine, Fisone, & Fredholm, 1999). It has been suggested that KW-6002 acts by indirectly enhancing the efficacy of striatal D_2 receptors for dopamine (Ferre, Fredholm, Morelli, Popoli, & Fuxe, 1997).

The present study was designed to examine the role of dopamine in the dorsomedial striatum and its interaction with KW-6002 in a test of simple discriminations and reversal learning. Rats are able to learn to retrieve food bait from digging bowls according to a texture on the outer-surface of the bowl, the digging medium within the bowl or an odour added to the bowl. The present study took advantage of the rapidity of acquisition of these discriminations to examine the effect of striatal dopamine depletion and any possible restorative effect of KW-6002 administered chronically over 10 days.

2. Materials and methods

2.1. Subjects

Thirty-six male Lister hooded rats (Harlan, UK), weighing between 310 and 590 g at the start of testing, were individually housed on a 12-h light/dark cycle (lights on at 7am). Most of the testing was carried out in the light phase however, due to the unconstrained nature on the timing of the behavioural task, testing of some rats did continue beyond the onset of the dark phase (7pm). Rats were maintained on a restricted diet of 15–20 g of lab chow per day, with water freely available in the home cage. "Honey Loops" (Kellogg's, UK), were used as reinforcement during testing, but the quantity consumed was not subtracted from the daily food ration. All practices were performed under UK Home Office License in accordance with the guidelines laid out in the Handbook of Laboratory Animal Management and Welfare (Wolfensohn & Lloyd, 1998) and the requirements of the United Kingdom Animals (Scientific Procedures) Act 1986.

2.2. Surgery

Rats were pretreated with the monoamine oxidase inhibitor pargyline (50 mg/kg; Sigma–Aldrich, Dorset, UK) intraperitoneally 30 min prior to surgery and carprofen (Rimadyl™, 0.1 ml/kg; 5% w/v; Pfizer Ltd., Kent, UK) subcutaneously. Anaesthesia was induced with Sagatal (60 mg/kg pentobarbitone sodium BP; Rhône Mérieux Ltd., Essex, UK) intraperitoneally. Dopamine was bilaterally depleted from the medial portion of the dorsal striatum by injection of 8 μg of 6-hydroxydopamine base in 2 μl of 0.002% ascorbate saline (6-OHDA; Sigma–Aldrich, Dorset, UK) 2.5 mm anterior to Bregma, 1.8 mm lateral to the midline and 4.0 mm below skull surface, with the nosebar set at +5.0 mm, using a cone-tipped 5.0 μl Hamilton (SGE) syringe. 6-OHDA was administered at a rate of 0.1 μl/10 s and left *in situ* for a further 3 min. Control rats (intact group) received equivalent injections of sterile saline only, at the same co-ordinates. Skin incisions were cleaned and closed using sterile metal clips. Three days were allowed for post-operative recovery before proceeding with drug administration.

Of the original 36 rats, 2 were excluded as a result of post-surgical complications. Following histology, a further seven were excluded because the dopamine depletion was asymmetric in placement or size. The 25 rats in the final analysis comprised 11 sham-operated (intact) and 14 with bilateral dopamine depletion. Within these groups, five intact and eight dopamine-depleted rats received vehicle and six intact and six dopamine-depleted rats received KW-6002. One intact rat that received vehicle did not complete the task rendering this group one rat fewer in the analysis.

2.3. Drug administration

Intact and dopamine-depleted rats were assigned to groups to receive either vehicle (1 ml/kg of 1% methylcellulose) or drug (KW-6002, 1 mg/kg in vehicle; Vernalis Research Ltd., Winnersh, UK), which were administered twice daily (morning and late afternoon) for a total of 10 days plus one dose on the 11th day prior to the final testing. This dose of KW-6002 has been shown to have an intermediate effect on behavioural performance (O'Neill & Brown, 2006). Moreover, chronic administration of equivalent doses of KW-6002 significantly reduced the cellular changes in mRNA expression in rats with a 6-OHDA lesion (Aoyama et al., 2002). As the task was self-paced by the rat and only one rat could be tested at a time, it was not possible to determine the precise time any given rat would complete (hence the next rat would start) the task. Therefore, the dosing times

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