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The H_3 receptor agonist immepip does not affect L-dopa-induced abnormal involuntary movements in 6-OHDA-lesioned rats

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ABSTRACT

The treatment of dyskinesia in Parkinson's disease remains poor but H_3 receptor agonists have been suggested as a novel pharmacological approach. We examined the effects of the H_3 agonist, immepip, in 6-OHDA-lesioned rats exhibiting AIMs (abnormal involuntary movements), a rat analogue of dyskinesia, in response to L-dopa compared to the known anti-dyskinetic agents amantadine, MK-801 and 8-OHDPAT. We then attempted to extend these studies in to dyskinetic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated common marmosets.

Amantadine, MK-801 and 8-OHDPAT all dose-dependently reduced L-dopa-induced axial, lingual and oral (ALO) AIMs in 6-OHDA-lesioned animals accompanied by a reduction in contralateral rotation with higher doses of amantadine and MK-801. By contrast, immepip had no effect on AIMs expression or contralateral rotation. In the MPTP-treated common marmoset exhibiting dyskinesia to L-dopa, immepip alone induced retching and in combination with L-dopa administered subcutaneously or orally induced the rapid onset of retching and vomiting which was not controlled by pretreatment with domperidone. Administration of the unrelated H_3 agonist, imetit had the same effect. Despite causing negative side-effects, it appears that both agonists reduced the antiparkinsonian response to L-dopa resulting in reduced dyskinesia.

H_3 agonists appear unlikely candidates for the treatment of dyskinesia in PD based on lack of evidence of efficacy and potential adverse effects.

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1. Introduction

Chronic treatment with L-dopa in Parkinson's disease (PD) can induce involuntary movements (dyskinesia) that are expressed following each drug dose and that may become treatment limiting (Jankovic, 2005). Administration of the weak NMDA receptor antagonist amantadine can suppress dyskinesia (Metman et al., 1999), but it is often poorly tolerated and accompanied by tolerance; as a consequence, novel approaches to treatment are required (Kalia et al., 2013). A range of non-dopaminergic approaches have been uncovered using the two most predictive animal models of dyskinesia in PD currently available, the L-dopa-treated 6-OHDA-lesioned rat exhibiting abnormal involuntary movements (AIMs) and the L-dopa-treated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned primate showing dyskinesia (Jenner, 2003; Lundblad et al., 2002). However to date no medications have shown inhibition of dyskinesia in PD without causing a worsening of motor symptoms.

The use of histamine H_3 agonists has been suggested as a novel approach. H_3 receptors are located presynaptically on various types of nerve terminals thereby controlling the release of a range of neurotransmitters including histamine, dopamine, serotonin, acetylcholine, glutamate and GABA (Arias-Montano et al., 2001; Arrang et al., 1983; Doreulee et al., 2001; Molina-Hernandez et al., 2000, 2001; Prast et al., 1999; Sanchez-Lemus and Arias-Montano, 2004). There is a high density of H_3 receptors in both striatum and substantia nigra (Cumming et al., 1991; Lovenberg et al., 1999; Pillot et al., 2002a; Ryu et al., 1994, 1996) and there is evidence for alterations in the levels of histamine, the density of histaminergic innervation and the density of H_3 receptors in the basal ganglia in PD and 6-OHDA-lesioned rats (Anichtchik et al., 2000, 2001; Nowak et al., 2009; Rinne et al., 2002; Ryu et al., 1994, 1996; Shan et al., 2012). Importantly, histamine and H_3 receptors have been implicated in the control of motor activity (Chiavegatto et al.,

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1998; Nistico et al., 1980; Pillot et al., 2002b; Sakai et al., 1991; Tuomisto and Eriksson, 1980) and they may function to decrease excessive GABA and glutamate release in the basal ganglia thought to underlie dyskinesia (Gomez-Ramirez et al., 2006).

In normal rats, H_3 agonists can induce ipsilateral rotation when injected unilaterally into the substantia nigra. However, in 6-OHDA-lesioned rats, the intra-cerebroventricular (icv) or intra-nigral application of an H_3 agonist inhibits the contralateral rotational response to apomorphine suggesting a potential adverse effect on motor function (Garcia-Ramirez et al., 2004; Liu et al., 2008). However, so far only a single study has examined the systemic administration of H_3 agonists relevant to PD in either 6-OHDA-lesioned rats or MPTP-treated primates. In 6-OHDA-lesioned rats, low doses of the H_3 agonist, R-α-methylhistamine administered subcutaneously had no significant effect on contralateral rotation to L-dopa plus carbidopa but a reduction occurred at the highest dose used; there was no reduction in ipsilateral rotation induced by amphetamine (Huotari et al., 2000). This might again suggest a potential adverse effect on motor function relevant to PD but the effect on AIMs was not investigated. In the only previous study testing H_3 agonists in L-dopa-treated dyskinetic common marmosets, equivocal results were obtained (Gomez-Ramirez et al., 2006). The H_3 agonist immepip did inhibit L-dopa induced dyskinesia but only at a single dose level – other lower and higher doses were ineffective – and did not worsen parkinsonian disability. By contrast, the H_3 agonist imetit had no significant effect on dyskinesia or motor disability.

In an attempt to clarify the potential role of H_3 agonists in controlling dyskinesia, we have initially assessed changes in L-dopa-induced AIMs in the 6-OHDA-lesioned rat produced by a range of doses of immepip and then extended these studies into L-dopa-treated dyskinetic marmosets. In the rat, we have compared the effects of immepip with those of amantadine, MK-801 and 8-OHDPAT as compounds previously shown to be effective in suppressing AIMs in this model.

2. Materials and methods

2.1. 6-OHDA-lesioned rats

Adult male Wistar rats (270–285 g; B & K Universal Ltd, Hull) were housed in groups of 3–4 at a temperature of 25 ± 1 °C with 50% relative humidity on a 12-h light-dark cycle. Water and food were available *ad libitum* except during experiments. All experiments were performed in accordance with the Animals (Scientific Procedures) Act 1986 under Project licence no 70/6019, approved by the King's College London Ethical Review Panel. A unilateral 6-OHDA hydrochloride (8 μg free base in 4 μl 0.9% saline containing 0.05% ascorbic acid (Sigma, UK)) lesion of the medial forebrain bundle (MFB) was performed using standard stereotaxic techniques as previously described (Papathanou et al., 2011). Two weeks after surgery, (+)-amphetamine sulphate (2.5 mg/kg i.p., Sigma UK)- and apomorphine hydrochloride (0.5 mg/kg s.c., Sigma, UK)-induced rotational activity was determined using automated rotometers (MedAssociates, UK) on two separate days as previously described. Only those rats exhibiting greater than 6 turns per min at peak activity were used for further study (data not shown).

2.2. AIMs and rotational activity

Animals were treated with L-dopa (6.25 mg/kg plus benserazide, 15 mg/kg, i.p.) daily for 21 days and then twice weekly for further two weeks to induce and maintain stable AIMs as previously described (Papathanou et al., 2011). Only those animals exhibiting moderate to severe AIMs (peak score=3–4) were used for further study. On test days, animals were treated with L-dopa methyl ester (6.25 mg/kg plus benserazide hydrochloride 15 mg/kg i.p.; Sigma, UK) plus either immepip (1, 5 and 10 mg/kg s.c.; Solvay Pharmaceuticals, The Netherlands), amantadine hydrochloride (10, 20, 40 mg/kg i.p.; Sigma, UK), MK-801 (0.06, 0.125, 0.25, and 0.5 mg/kg s.c.; dizocilpine; Sigma, UK), R-(+)-8-OHDPAT (0.06, 0.2, 0.6, 2 mg/kg s.c.; 8-hydroxy-2-(di-*n*-propylamino) tetralin; Tocris, UK.), or vehicle (0.9% saline) in a modified Latin square design spaced over 2–3 weeks with a washout period of 2 days between treatments. Immepip (10 mg/kg sc) was also administered alone. All experiments were performed between 9.00 h and 14.00 h. Animals were placed in Perspex cylinders (D:40 cm × H:30 cm) for 1 h prior to drug administration to allow acclimatisation. Axial, limb and orolingual (ALO) AIMs were scored for 1 min every 20 min from 20 min before and up to 120 min after drug administration or for 5 min every 15 min from 30 min before and up to 210 min after drug administration according to a rating scale as previously described (Papathanou et al., 2011). ALO AIMs scores were combined and taken as an overall index of dyskinesia (Lundblad et al., 2002). Rotational activity was scored separately as an index of locomotor activity as previously described (Papathanou et al., 2011).

2.3. MPTP-treated common marmosets

Adult common marmosets (*Callithrix jacchus*, $n=6$, 3 male and 3 female, Harlan, UK), weighing between 300 g and 450 g were employed in this study. The animals were housed in pairs under standard conditions at a temperature of 24 ± 2 °C and relative humidity of 50%, employing a 12 h light-dark cycle. All animals were given fresh fruit once daily and had *ad libitum* access to food pellets (Mazuri primate diet, Special Dietary Services) and water. The study was carried out in accordance with the Animals (Scientific Procedures) Act 1986 and with approval of the King's College London Ethical Review Panel under Project licence number 70/6345.The animals were treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) (2 mg/kg, s.c.) over 5 days to induce stable motor deficits as previously described (Smith et al., 2000; Tayarani-Binazir et al., 2010). Prior to the start of the study, the animals were primed with L-dopa (12.5 mg/kg) for up to 30 days to induce dyskinesia and expressed moderate to severe dyskinesia when challenged with L-dopa (12.5 mg/kg, p.o.).

2.4. Dyskinesia and motor disability

On the day of behavioural testing, the animals were placed into behavioural study cages and allowed to acclimatise for 1 h, during which the last 10 min period was used to determine baseline motor disability and dyskinesia as previously described. Animals were treated with L-dopa methyl ester (12.5 mg/kg plus carbidopa 12.5 mg/kg p.o. in 10% sucrose; Sigma, UK) or L-dopa methyl ester (8.0 mg/kg plus benserazide hydrochloride 10.0 mg/kg s.c. in 0.9% saline; Sigma, UK) plus either immepip dihydrobromide (1, 5 and 10 mg/kg s.c.; Solvay Pharmaceuticals, The Netherlands) or imetit dihydrobromide (1, 5 and 10 mg/kg s.c.; Solvay Pharmaceuticals, The Netherlands) or 0.9% sterile saline in a modified Latin square design over 2–3 weeks with a washout period of 2 days between treatments. Immepip (10 mg/kg s.c.) and imetit (10 mg/kg s.c.) were also administered alone. Domperidone hydrochloride (2 mg/kg, p,o. in 10% sucrose; Sigma, UK) was used in an attempt to reduce the incidence of vomiting. Locomotor activity, motor disability and dyskinesia were monitored by a blinded observer over the following 6 h as previously described.

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