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Continuous cerebroventricular administration of dopamine: A new treatment for severe dyskinesia in Parkinson's disease?

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ABSTRACT

In Parkinson's disease (PD) depletion of dopamine in the nigro-striatal pathway is a main pathological hallmark that requires continuous and focal restoration. Current predominant treatment with intermittent oral administration of its precursor, Levodopa (L-dopa), remains the gold standard but pharmacological drawbacks trigger motor fluctuations and dyskinesia. Continuous intracerebroventricular (i.c.v.) administration of dopamine previously failed as a therapy because of an inability to resolve the accelerated dopamine oxidation and tachyphylaxia. We aim to overcome prior challenges by demonstrating treatment feasibility and efficacy of continuous i.c.v. of dopamine close to the striatum. Dopamine prepared either anaerobically (A-dopamine) or aerobically (O-dopamine) in the presence or absence of a conservator (sodium metabisulfite, SMBS) was assessed upon acute MPTP and chronic 6-OHDA lesioning and compared to peripheral L-dopa treatment. A-dopamine restored motor function and induced a dose dependent increase of nigro-striatal tyrosine hydroxylase positive neurons in mice after 7 days of MPTP insult that was not evident with either O-dopamine or L-dopa. In the 6-OHDA rat model, continuous circadian i.c.v. injection of A-dopamine over 30 days also improved motor activity without occurrence of tachyphylaxia. This safety profile was highly favorable as A-dopamine did not induce dyskinesia or behavioral sensitization as observed with peripheral L-dopa treatment. Indicative of a new therapeutic strategy for patients suffering from L-dopa related complications with dyskinesia, continuous i.c.v. of A-dopamine has greater efficacy in mediating motor impairment over a large therapeutic index without inducing dyskinesia and tachyphylaxia.

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide. The loss of dopamine through denervation in the striatum as a result of progressive neuronal degeneration in the substantia nigra pars compacta (SNpc), is the primary neurotransmitter marker of the disease (De Lau and Breteler, 2006). Since dopamine does not cross the digestive mucosa or the blood brain barrier, its lipophilic precursor L-dopa has been employed and remains the pivotal oral medication (Chaudhuri and Schapira, 2009). However, after persistent use over several years, many pharmacokinetic drawbacks contribute to the occurrence of motor fluctuations and dyskinesia (Fahn and Parkinson study group, 2005). Indeed L-dopa has a short half-life, limittped and variable reabsorption through the digestive and blood brain barriers and potentially harmful peripheral distribution. Moreover, L-dopa requires the aromatic L-amino acid decarboxylase for the synthesis of dopamine, which declines in the striatum with disease progression (Ciesielska et al., 2015).

Under normal conditions, dopaminergic neurons of the SNpc generate a short phasic discharge firing pattern. The frequency and duration of this pattern embeds them in the tonic low-frequency background range and maintains the striatal dopamine concentration at a relatively constant level (Paladini and Roeper, 2014). However, in the dopamine-depleted state relevant to PD, intermittent oral doses of L-dopa can

Abbreviations: DA, dopamine; i.c.v, intra-cerebro-ventricular; L-dopa, levodopa; MPTP, 1 méthyl-4-phenyl-1,2,3,6 terahydropyridine; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; SMBS, sodium metabisulfite; SN*pc*, substantia nigra *pars compacta*.

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induce discontinuous stimulation of striatal dopamine receptors that in turn contribute to dysfunctional dopaminergic pathways. Thus, continuous dopamine administration is considered more physiologically appropriate by preventing oscillations in neurotransmitter concentration (Olanow et al., 2006; Gershanik and Jenner, 2012). De Yebenes et al. (1987) previously demonstrated that intracerebroventricular (i.c.v.) administered dopamine with an anti-oxidant adjuvant (sodium metabisulfite; SMBS) transiently improved motor handicap and increased dopamine in rat brains with unilateral neurotoxin 6-hydroxydopamine (6-OHDA)-induced damage as well as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxicated monkeys. The clinical feasibility of this administrative route has been supported by two PD patient case reports of dopamine infusion to the frontal ventricle, whereby a reduction in motor handicap was observed (Venna et al., 1984; Horne et al., 1989). However, both preclinical and clinical reports also highlight two overriding problems that prevented further development; (i) occurrence of tachyphylaxia and (ii) oxidation of dopamine causing enhanced dopamine metabolism and oxidative stress.

Dopamine oxidation can be limited by preparing, storing and administering dopamine in very low oxygen conditions. In addition, greater advances in programmable pumps now minimize tachyphylaxia by allowing administration of a lower effective dopamine dose in accordance with the circadian cycle. The purpose of this study is to demonstrate that continuous circadian i.c.v. administration of dopamine close to the striatum is feasible, efficient and safe in mouse and rat models of PD, supporting clinical development of this strategy to be revisited in PD patients with L-dopa related complications with dyskinesia.

2. Material and methods

2.1. LUHMES cells

Lund human mesencephalic (LUHMES) cells (gift from Pr. Marcel Leist; CAAT, University of Konstanz, Germany) were grown for 2 days in differentiation medium (advanced DMEM/F12, 1 × N2 supplement, 2 mM L-glutamine, 1 mM cAMP, 1 μg/ml tetracycline and 2 ng/ml recombinant GDNF) before seeding in 6 or 24 well plates and grown for a further 3 days before treatment. See supplementary material for details.

After 5 days of differentiation, LUHMES cells were treated with 1-methyl-4-phenylpyridinium (MPP+; 5 μM) for 24 h (h) before exposure to dopamine or L-3,4-dihydroxyphenylalanine (L-dopa) (Sigma Aldrich, St Louis, MO, USA) for a further 24 h. Viability was measured on 10,000 cells by flow cytometry (CANTO II) using propidium iodide (0.5 μM) and analysed with DIVA software (BD Biosciences, Le pont de Claix, France).

2.2. Rodent neurotoxic models

All experiments were carried out in accordance with the recommendations for the care and use of laboratory animals (FELASA) as well as European Directive 86/609-2010/63/UE guidelines for animal experimentation. Protocols were approved by an Ethical Committee (Nord-Pas-de-Calais; CEEA75) to induce MPTP neurotoxicity on 5 month old C57Bl/6 J mice (Ethical permit number: CEEA102012) or 6-OHDA neurotoxicity in 5 month old Wistar rats (Ethical permit number: CEEA 262011 and CEEA2016020911207601). Animals were group-housed (10 mice or 5 rats per cage) and a habituation period of 7 days after transportation was respected before any experimental manipulation was carried out. All surgery was performed under anesthesia and all efforts were made to minimize suffering.

Experimental procedures for obtaining the MPTP mice and 6-OHDA rat models have been previously described (Laloux et al., 2012). Briefly, mice received four intraperitoneal injections (with 2 h intervals) of either saline solution only or 20 mg/kg MPTP (Sigma Aldrich, St Louis, MO, USA). The rats received one cerebral unilateral injection of vehicle or 8 μg 6-OHDA (Sigma Aldrich, St Louis, MO, USA) through stereotaxic surgery to the right medial forebrain bundle.

2.3. Treatment parameters for rodent models

L-dopa methyl ester hydrochloride (Sigma Aldrich, St Louis, MO, USA) was extemporaneously prepared in saline with 12 mg/kg Benserazide, independent of L-dopa dose (Cenci and Lundblad, 2007). During the treatment regime L-dopa was administered intraperitoneally (i.p.) twice a day at doses previously reported for mice and rats (Espadas et al., 2012; Fornai et al., 2000). Anaerobia-dopamine (A-dopamine, Patent #WO2015173258 A1) was prepared by dissolving in saline (0.9% NaCl, pH 7.4) before the osmotic pump was filled and connected to a brain infusion cannula under an atmosphere that contained 5% hydrogen, 5% carbon dioxide and 90% nitrogen (BACTRON anaerobic/environmental chamber). Before stereotaxic surgery, osmotic pumps were primed under anaerobia for over 4 h at 37 °C. The stability of the A-dopamine solution in osmotic pump at 37 °C was checked for up to 30 days using an HPLC assay for dopamine (data not shown).

Treatment over 7 days began one week post MPTP or saline injections in mice. Mice were divided into 13 experimental groups; Saline only, MPTP only, MPTP + A-dopamine (3 to 5 different doses), MPTP + O-dopamine (3 different doses), and MPTP + L-dopa (3 different doses). A- or O-dopamine was administered continuously by i.c.v. (1 μl/h; 24 h/24 h) after surgical cannula-pump (ALZET 2001) implantation in the right lateral ventricle (see supplemental material for details). L-dopa was administered by i.p. twice a day over the same treatment period.

Chronic dopamine treatments (30 days) on rats began 3 weeks after unilateral 6-OHDA or saline cerebral injection. Only 6-OHDA rats displaying >5 turns/min in the Apomorphine-induced rotation test were used in the study (75% of the rats). Rats were divided into 6 experimental groups; saline only, 6-OHDA only, 6-OHDA + A-dopamine (3 different doses) and 6-OHDA + L-dopa. After surgical cannula-pump (programmable IPRECIO® SMP200 pumps) implantation on the 6-OHDA lesion side (see supplemental material for details) A-dopamine was administered to the right lateral ventricle by i.c.v. at a rate of 3 μl/h for 16 h out of 24 h (Zeitgeber time 13 to 5). Rats were housed in a 12 h light/12 h dark cycle and the implanted pump was set to deliver dopamine over 16 h, predominantly during the active (dark) phase of the rat while it is awake. However this also included part of the resting (light) phase to allow behavioral assessments under treatment (see Supplemental image 1 for the time delivery settings). L-dopa was administered by i.p. twice a day over the same treatment period.

2.4. Behavioral assessment

2.4.1. Actimetry

Spontaneous motor activity in mice and rats was recorded by an actimeter (Panlab, Barcelona, Spain) over 10 min (Laloux et al., 2012). This apparatus and the associated Actitrack software allowed distance travelled, speed and rearing behavior to be measured based on infrared beams obstructions.

2.4.2. Drug-induced rotation test

To assess rotational asymmetry, contralateral rotations over 10 min were counted 30 min after rats were subcutaneously (s.c.) injected with apomorphine (APOKINON®; 0.5 mg/kg). Only nigro-striatal-lesioned animals performing >5 turns/min were included in the experimental cohorts as these have >80% depletion of striatal dopamine terminals (Francardo et al., 2011).

2.4.3. Cylinder test

Rats performed the cylinder test (Schallert et al., 2000) to evaluate spontaneous forelimb lateralization. The number of vertical forepaw