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Imaging DA release in a rat model of L-DOPA-induced dyskinesias: A longitudinal *in vivo* PET investigation of the antidyskinetic effect of MDMA

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ABSTRACT

In the context of Parkinson's disease, motor symptoms result from the degeneration of nigrostriatal neurons. Dopamine (DA) replacement using L-3,4-dihydroxyphenylalanine (L-DOPA) has been the treatment of choice in the early stages of the disease. However, with disease progression, patients suffer from motor complications, which have been suggested to arise from DA released from serotonergic terminals according to the false neurotransmitter hypothesis. The synthetic amphetamine derivative (±) 3,4-methylenedioxymethamphetamine (MDMA) has been shown to significantly inhibit dyskinesia in humans and in animal models of PD. In this study, we examined the effect of MDMA on L-DOPA-induced DA release by using [11C]raclopride kinetic modeling to assess alterations in DA neurotransmission in a rat model of L-DOPA-induced dyskinesia (LID) in a longitudinal *in vivo* PET study. Rats were submitted to 6-OHDA lesions, and the lesions were confirmed to be sufficiently severe based on the performance during stepping tests and [11C]methylphenidate PET scans. The rats underwent two [11C]raclopride PET sessions before (baseline) and after two weeks of chronic L-DOPA treatment (priming). L-DOPA priming led to strong abnormal involuntary movements (AIMs). In group 1, L-DOPA priming reduced L-DOPA-induced DA release in the lesioned striatum with no effect on the healthy side, while the concomitant administration of L-DOPA and MDMA (group 2) increased the DA levels in the lesioned and healthy striatum. In addition, behavioral analysis, which was performed two weeks after the second PET session, confirmed the antidyskinetic effect of MDMA. Our data show that L-DOPA-induced DA release is attenuated in the Parkinsonian striatum after chronic L-DOPA pretreatment and that the antidyskinetic mechanism of MDMA does not depend primarily on dopaminergic neurotransmission.

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% of the population above the age of 60 years (Dehay and Bezard, 2011). The disease is characterized by a progressive loss of predominantly nigrostriatal dopaminergic neurons. Substitution of endogenous dopamine (DA) by the administration of its precursor L-3,4-dihydroxyphenylalanine (L-DOPA) represents the standard therapy in early and late stages of the disease. With disease progression and the associated long-term treatment with L-DOPA, most patients suffer from serious behavioral side effects of the therapy, i.e., dyskinesia that usually develops within 5–10 years of beginning L-DOPA therapy (Poewe et al., 2010). Many attempts have been made to identify the mechanisms underlying these severe motor fluctuations, but they are still not fully understood.

Unilateral 6-hydroxydopamine (6-OHDA) lesion of the medial forebrain bundle (MFB) in rats provides a useful animal model for hemiparkinsonism and L-DOPA-induced dyskinesia (LID), as repeated administration of L-DOPA leads to the development of abnormal involuntary movements (AIMs) on the body side contralateral to the lesion (Lundblad et al., 2002; Taylor et al., 2005). AIMs are divided into four subtypes: locomotor, axial, limb and oro-lingual. In most animal

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models, the severity of the AIMs increases gradually with L-DOPA treatment and reaches a plateau after 10 to 14 days; after this point, the AIMs remain stable (Cenci and Lundblad, 2007). Interestingly, only rats with a dopaminergic denervation of >90% develop AIMs, however, severe damage of the nigrostriatal DA pathway does not necessarily result in AIMs (Winkler et al., 2002).

In late PD, dopaminergic neurons are extensively degenerated, and the conversion of exogenous L-DOPA to DA increases in serotonergic (5-HT) neurons ascending from the dorsal and median raphe nuclei (Carta et al., 2007, 2008b). This contribution to DA-synthesis by the 5-HT neurons forms the basis of the "false-transmitter" hypothesis of L-DOPA (Arai et al., 1995; Carta et al., 2007; Tanaka et al., 1999). Lacking D_2 autoreceptors and DA transporters, 5-HT neurons descending from the raphe nuclei provide extracellular DA to the striatum in non-physiologically high amounts, which stimulates the striatal dopaminergic receptors in an uncontrolled manner (Carta et al., 2007, 2008b; Maeda et al., 2005).

The synthetic amphetamine derivative (±) 3,4-methylenedioxymethamphetamine (MDMA) has been shown to have a combined antiparkinsonian and antidyskinetic effect in humans (a single case report, described by (Margolis, 2001)), nonhuman primates (Iravani et al., 2003) and rats (Bishop et al., 2006; Lebsanft et al., 2003; Schmidt et al., 2002). Based on these reports, therapy for dyskinetic PD patients by means of a powerful serotonergic drug such as MDMA appears promising. Understanding the mechanism will allow for the targeted development of novel therapeutic strategies for PD. MDMA has been shown to have several sites of action (for review see (Battaglia et al., 1988; Baumann et al., 2007; Capela et al., 2009); however, neither its antiparkinsonian nor its antidyskinetic mechanism is fully understood. MDMA is a potent 5-HT releaser, and it also elevates extracellular catecholamine levels, but to a lesser extent (Baumann et al., 2007; Capela et al., 2009; Gudelsky and Yamamoto, 2008; Rothman et al., 2001). Nevertheless, the antidyskinetic property of this drug has been suggested to primarily depend on its effect on the 5-HT system (Bishop et al., 2006; Iravani et al., 2003). Because large oscillations of DA release from serotonergic nerve terminals have been suggested to significantly contribute to LIDs, the antidyskinetic effect of MDMA might possibly arise from a reduction of oscillatory DA release from serotonergic terminals.

Functional positron emission tomography (PET) imaging provides a powerful tool to measure changes of neurotransmitter concentrations indirectly by competition experiments. These experiments are based on the principle that the radioligand and the endogenous neurotransmitter compete for the same receptor sites (*occupancy model*) (Laruelle, 2000). [^{11}C]Raclopride PET has been shown to be a valuable tool for the quantification of changes in DA release *in vivo* (Morris et al., 2008; Normandin and Morris, 2008). DA competes with [^{11}C] raclopride for the same binding site on the D_2/D_3 receptor and displaces the radioligand due to its higher affinity for the receptor. This competition was found to be linearly related to the amount of DA after a pharmacological challenge with amphetamine in simultaneous PET/microdialysis experiments in primates (Breier et al., 1997; Endres et al., 1997; Hartvig et al., 1997; Laruelle, 2000; Morris et al., 2008; Tsukada et al., 1999).

This study was undertaken to test the hypotheses that the antidyskinetic effect of MDMA arises from a reduction of L-DOPA-induced DA release from serotonergic nerve terminals and that chronic L-DOPA treatment alters the L-DOPA-induced DA release in the lesioned striatum.

In order to evaluate the changes of L-DOPA-induced DA release due to MDMA co-treatment in dyskinetic 6-OHDA-lesioned rats we used the double bolus [^{11}C]raclopride scan protocol and performed pixelwise and VOI-based analysis of the dynamic PET data. To select the rats with most pronounced lesions, we performed stepping test and [^{11}C]methylphenidate PET. Axial, limb and oro-lingual AIMs were scored using behavioral analysis. Additionally, *postmortem* high-pressure liquid chromatography (HPLC) was used to determine long term changes in neurotransmitter levels.

Materials and methods

Animals

Thirty-two male Sprague–Dawley rats (Charles River, Sulzfeld, Germany) were used in the experiments. The animals were housed in groups of four per Makrolon Type IV standard cage under a 12/12 h light-dark cycle with restricted access to food (standard rat chow, 15 g per animal per day) and water *ad libitum*. All procedures were conducted in accordance with the German Animal Protection Law and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health and the European Union.

Substances

6-Hydroxydopamine·HBr (6-OHDA) was dissolved in saline containing 0.1% ascorbic acid (6 μg/μL free base). L-3,4-Dihydroxyphenylalanine methyl ester (L-DOPA, 10 mg/mL and 50 mg/mL free base), benserazide·HCl (7.5 mg/mL and 15 mg/mL free base), desipramine·HCl (20 mg/mL), fentanyl (5 μg/mL) and carprofen (5 mg/mL) were diluted in saline (Fresenius Kabi, Bad Homburg, Germany). (±) 3,4-Methylendioxymethamphetamine·HCl (MDMA, 10 mg/mL free base) was dissolved in phosphate-buffered saline (PBS, Biochrom KG, Berlin, Germany). MDMA was generously provided by the Department of Inorganic Chemistry, University of Tuebingen, Germany. Fentanyl was purchased from Ratiopharm (Ulm, Germany). Carprofen (Rimadyl®) was purchased from Pfizer GmbH (Berlin, Germany). All other chemicals were purchased from Sigma-Aldrich (Steinheim, Germany).

All solutions were administered subcutaneously (s.c.) at a volume of 1 mL/kg body weight except for desipramine–HCl, which was administered intraperitoneally (i.p.).

Radiotracer synthesis

D-threo-[^{11}C]methylphenidate, a dopamine transporter ligand, was synthesized by alkylation of *D*-threo-*N*-NPS-ritalinic acid (ABX, Radeberg, Germany) using [^{11}C]methyliodide (CH_3I) (Ding et al., 1994). High specific activity (SA) [^{11}C]CH_3I was prepared in an automated module (PETtrace MeI Microlab, GE Medical Systems, Uppsala, Sweden). The radiolabeling was performed in a PET tracer synthesizer for [^{11}C]-methylations (GE Medical Systems, Münster, Germany). After purification and formulation, the product was obtained with a 45%–65% radiochemical yield. The total synthesis time was 60 min, and the radiochemical purity of the final formulated radiotracer was >95% as determined by HPLC analysis. The SA was determined at the time of injection as 77 ± 38 GBq/μmol.

[^{11}C]Raclopride, a D_2 receptor ligand, was synthesized by alkylation of S-(+)-*O*-demethyl-raclopride (ABX, Radeberg, Germany) using [^{11}C]methyltriflate. Therefore, high SA [^{11}C]CH_3I was prepared using the automated PETtrace MeI Microlab module (GE Medical Systems, Münster, Germany) and converted to [^{11}C]methyltriflate. Radiolabeling was performed in a PET tracer synthesizer for ^{11}C-methylations (GE, Münster, Germany). After purification and formulation, the product was obtained at 25%–30% yield (decay uncorrected from [^{11}C]CH_3I). The total synthesis time from the end of the beam (EOB) was 50 min. The radiochemical purity of the final formulated radiotracer was >95% as determined by HPLC. The SA was determined at the time of injection and ranged between 234 ± 124 GBq/μmol.

Experimental design

The timeline of the experimental design is displayed in Fig. 1. The rats were lesioned with 6-OHDA in the left (ipsilateral) MFB. After three weeks of recovery, dopaminergic denervation was assessed using behavioral analysis (stepping test) from experimental day 22 to 24. Only the 26 rats with the most pronounced stepping deficit

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