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Effect of chronic L-DOPA treatment on 5-HT$_{1A}$ receptors in parkinsonian monkey brain

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ABSTRACT

After chronic use of L-3,4-dihydroxyphenylalanine (L-DOPA), most Parkinson's disease (PD) patients suffer from its side effects, especially motor complications called L-DOPA-induced dyskinesia (LID). 5-HT$_{1A}$ agonists were tested to treat LID but many were reported to worsen parkinsonism. In this study, we evaluated changes in concentration of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and of 5-HT$_{1A}$ receptors in control monkeys, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys, dyskinetic MPTP monkeys treated chronically with L-DOPA, low dyskinetic MPTP monkeys treated with L-DOPA and drugs of various pharmacological activities: Ro 61-8048 (an inhibitor of kynurenine hydroxylase) or docosahexaenoic acid (DHA) and dyskinetic MPTP monkeys treated with L-DOPA + naltrexone (an opioid receptor antagonist). Striatal serotonin concentrations were reduced in MPTP monkeys compared to controls. Higher striatal 5-HIAA/serotonin concentration ratios in L-DOPA-treated monkeys compared to untreated monkeys suggest an intense activity of serotonin axon terminals but this value was similar in dyskinetic and nondyskinetic animals treated with or without adjunct treatment with L-DOPA. As measured by autoradiography with [^{3}H]8-hydroxy-2-(di-*n*-propyl) aminotetralin (8-OH-DPAT), a decrease of 5-HT$_{1A}$ receptor specific binding was observed in the posterior/dorsal region of the anterior cingulate gyrus and posterior/ventral area of the superior frontal gyrus of MPTP monkeys compared to controls. An increase of 5-HT$_{1A}$ receptor specific binding was observed in the hippocampus of MPTP monkeys treated with L-DOPA regardless to their adjunct treatment. Cortical 5-HT$_{1A}$ receptor specific binding was increased in the L-DOPA-treated MPTP monkeys alone or with DHA or naltrexone and this increase was prevented in low dyskinetic MPTP monkeys treated with L-DOPA and Ro 61-8048. These results highlight the importance of 5-HT$_{1A}$ receptor alterations in treatment of PD with L-DOPA.

1. Introduction

Parkinson's disease (PD) affects one percent of the population over the age of sixty and the number of cases is rising due to the increasing life expectancy (Olanow et al., 2001). The dopamine precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), is the gold standard drug treatment of PD. However, after chronic use of L-DOPA, motor complications such as L-DOPA-induced dyskinesia (LID) appear in at least half of PD patients and limit its use (Olanow et al., 2001). The mechanisms involved in LID are not fully understood.

Pharmacological studies in animal models of PD suggest that dopamine released from serotonin (5-hydroxytryptamine, 5-HT) axon terminals acts as a false neurotransmitter and is the main pre-synaptic determinant of LID (Carta et al., 2007; Cenci and Lindgren, 2007). Being devoid of dopamine transporter and autoreceptors, 5-HT axon terminals would release dopamine in a non-physiological manner, leading to excessive swings in extracellular dopamine and to dyskinesia after L-DOPA treatment (Carta et al., 2007). These findings make the 5-HT system a target for

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine (serotonin); 6-OHDA, 6-hydroxydopamine; 8-OH-DPAT, 8-hydroxy-2-(di-n-propyl) aminotetraline; ac, anterior commissure; AcgG, anterior cingulate gyrus; CA, cornu ammonis; DG, dentate gyrus; DHA, docosahexaenoic acid; Hip, hippocampus; L-DOPA, L-3,4-dihydroxyphenylalanine; LID, L-DOPA-induced dyskinesia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; SFG, superior frontal gyrus.

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anti-dyskinetic therapies. Indeed, specific 5-HT receptor drugs were shown to reduce LID in PD (for review see Fox et al., 2009) but changes in 5-HT activity in the brain caused by this neurodegenerative disease and its treatments are not well documented. Up to now, 5-HT_{1A} receptors were investigated more than other 5-HT receptor subtypes in LID treatment. Besides 5-HT_{1A} autoreceptors in the raphe nucleus, there is evidence from immunocytochemistry, *in situ* hybridization, autoradiography and lesion of striatal axonal projections (Francis et al., 1992) of the post-synaptic localization of 5-HT_{1A} receptors in the hippocampus and the cerebral cortex (Kia et al., 1996; Pompeiano et al., 1992; Francis et al., 1992; Hajos et al., 1999).

5-HT_{1A} receptor agonists are believed to reduce LID through different mechanisms: (1) having a higher sensitivity to pharmacological stimulation than other types of 5-HT_{1A} receptors (Eskow et al., 2009), activation of 5-HT_{1A} autoreceptors located on dorsal raphe neurons would decrease their firing rate, reducing dopamine release as a false neurotransmitter by their axon terminals (Kannari et al., 2001; Lindgren et al., 2010) and (2) activation of 5-HT_{1A} heteroreceptors in the motor cortex may reduce glutamate release in the striatum by corticostriatal neurons which are believed to be hyperactive in LID (Antonelli et al., 2005; Dupre et al., 2011). It was shown that injection of a 5-HT_{1A} receptor agonist into the primary motor cortex, alleviates motor complications in dyskinetic rats (Ostock et al., 2011). The presynaptic 5-HT_{1A} autoreceptors located on raphe nucleus are the primary target of pharmacological stimulation that regulates raphestriatal L-DOPA-derived dopamine release involved in LID development (Carey et al., 2004; Eskow et al., 2009). Higher doses of 5-HT_{1A} receptor agonists are needed to stimulate extra-raphe postsynaptic receptors that modulate locomotor and hypothermic responses (Bert et al., 2006; Blanchard et al., 1993).

LID treatments with 5-HT_{1A} agonists were reported to reduce dyskinesia but some of these treatments were shown to worsen PD symptoms, which represent the major problem in their efficacy (Fox et al., 2009). Striatal 5-HT_{1A} stimulation with 8-hydroxy-2-(di-*n*-propyl) aminotetralin (8-OH-DPAT) reduced D_1 agonist-induced dyskinesia while it increased movements in hemiparkinsonian rats (Dupre et al., 2008a; Mignon and Wolf, 2007). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) marmoset monkeys, a decrease of LID by systemic administration of (+) 8-OH-DPAT, a more potent 5-HT_{1A} receptor agonist enantiomer, has been associated with an increase of other motor disabilities that may be related to postsynaptic 5-HT_{1A} receptors stimulation (Iravani et al., 2006). However in another study, administration of the racemic (±)-8-OH-DPAT mixture decreased LID without worsening PD symptoms in MPTP macaques (Munoz et al., 2008). Administration of tandospiron, another 5-HT_{1A} agonist, is known to reduce LID in PD patients but also to worsen PD symptoms (Kannari et al., 2002). An adjunct treatment with a 5-HT_{1A} receptor agent may lead to decreased LID without worsening PD symptoms. For this purpose and to clarify the role of 5-HT_{1A} receptors, the effects of different pharmacological treatments on 5-HT_{1A} receptor levels in L-DOPA-treated monkeys were evaluated in the present study.

In addition to their 5-HT_{1A} agonist properties, the compounds mentioned above are known to exert other pharmacologic activities. Sarizotan, a 5-HT_{1A} receptor agonist effective in the treatment of LID in MPTP monkeys (Grégoire et al., 2009) and PD patients (Bara-Jimenez et al., 2005), acts also as a dopamine antagonist (see Iravani et al., 2006). Tandospirone possesses antagonist activity on adrenergic and dopamine receptors and (±)-8-OH-DPAT, under certain conditions, may have affinity for dopamine and 5-HT_{7A} receptors (see Fox et al., 2009; Iravani et al., 2006). Therefore, the antidyskinetic effect of these drugs as well as worsening of PD symptoms may also be related to their activity on other receptors. Indeed, L-stepholidine, a 5-HT_{1A} receptor agonist and a D_2 receptor antagonist, was shown to reduce LID in rats via both receptors (Mo et al., 2010).

In the present study, we investigated possible alterations of brain 5-HT_{1A} receptors in control and MPTP monkeys that developed or not dyskinesia following chronic L-DOPA administration and adjunct treatments of various pharmacological activities in order to clarify their role in PD and LID expression. 5-HT concentrations and 5-HT_{1A} receptor levels were measured in different brain areas of MPTP monkeys treated with L-DOPA and Ro 61-8048 (a kynurenine hydroxylase inhibitor that inhibits glutamate release and blocks glutamate NMDA receptors), docosahexaenoic acid (DHA, a retinoid X receptor agonist) or naltrexone (a nonselective opiate receptor antagonist). This is the first report showing alterations of 5-HT_{1A} receptors in MPTP monkeys associated with LID as compared to MPTP monkeys treated with L-DOPA and adjunct treatments to inhibit dyskinesias. Chronic treatment with L-DOPA might lead to several changes in the brain, not specifically related to dyskinesias. Animals co-treated with L-DOPA and antidyskinetic drugs compared to animals treated with L-DOPA displaying dyskinesia allow a better assessment of 5-HT_{1A} receptors in LID expression.

2. Materials and methods

2.1. Animals

Thirty-one *de novo* adult female monkeys (*Macaca fascicularis*, 2.5–4.3 kg) were investigated in the present study according to the standards of the National Institute of Health guide for the care and use of laboratory animals (NIH publications Nos. 80–23, revised 1978). They were ovariectomized and used for the present experiment one month after ovariectomy. All procedures were designed to minimize animal suffering and to reduce the number of animals used, and were approved by the Institutional Animal Care Committee of Université Laval.

Of these 31 monkeys, 4 remained untreated and served as controls whereas 27 received MPTP (Sigma–Aldrich Canada Ltd., Oakville, ON, Canada) continuously at a dose 0.5 mg/day in saline solution, via a subcutaneous osmotic mini-pump until stabilization of bilateral PD syndrome (5–6 months). MPTP monkeys were treated for one month and included six groups: MPTP monkeys treated with saline ($n = 4$), MPTP monkeys treated daily with L-DOPA/Benserazide (100 mg/25 mg: Prolopa®: Hoffmann-La Roche, Mississauga, ON, Canada) (termed L-DOPA thereafter) (p.o.) that developed LID and were killed 24 h ($n = 4$) or 4 h ($n = 5$) after their last dose of L-DOPA, MPTP monkeys treated with the same dose of L-DOPA + Ro 61-8048 (50 mg/kg/day: Newron Pharmaceuticals, Italy) (by nasogastric gavage) that developed mild LID and were killed 24 h after their last dose of L-DOPA ($n = 5$) (Grégoire et al., 2008), MPTP monkeys treated with the same dose of L-DOPA + DHA (100 mg/kg/day: Cayman Chemical, Ann Arbor, MI, USA) (p.o.) that developed mild LID ($n = 5$) (Samadi et al., 2006) and finally, a group with L-DOPA + naltrexone (1 mg/kg/day: Sigma, St. Louis, MO, USA) (s.c.) that developed severe LID ($n = 4$) (Samadi et al., 2005); the two latter groups were killed 4 h after their last dose of L-DOPA. Groups of animal brains were analyzed according to their time of euthanasia to consider its possible effect on 5-HT turnover and receptors. Dyskinesias are believed to be associated with long-term changes in the brain. Hence, animals were killed 24 h and 4 h after their last dose of L-DOPA, that is after behavioral activation in order to dissociate long-term changes induced by the drug from acute effects in its presence. Indeed, the L-DOPA behavioral antiparkinsonian activity and dyskinesias returned to baseline within 4 h of treatment as reported in the behavioral description of these