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The preferential nNOS inhibitor 7-nitroindazole and the non-selective one N^G-nitro-L-arginine methyl ester administered alone or jointly with L-DOPA differentially affect motor behavior and monoamine metabolism in sham-operated and 6-OHDA-lesioned rats

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ABSTRACT

Reciprocal interactions between nitrergic and dopaminergic systems play a key role in the control of motor behavior. In the present study, we performed a comparative analysis of motor behavior (locomotor activity, catalepsy, rotational behavior) and monoamine metabolism in the striatum and substantia nigra of unilaterally sham-operated and 6-OHDA-lesioned rats treated with the preferential neuronal nitric oxide synthase (nNOS) inhibitor 7-nitroindazole (7-NI) or the non-selective one N^G-nitro-L-arginine methyl ester (L-NAME), alone or in combination with L-DOPA. Each NOS inhibitor given alone (50 mg/kg) induced a distinct catalepsy 30 min after injection but only 7-NI impaired spontaneous locomotion after 10 min. In 6-OHDA-lesioned rats, chronic L-DOPA (25 mg/kg) induced 2.5-h long contralateral rotations. 7-NI (30 and 50 mg/kg) markedly reduced the intensity of L-DOPA-induced contralateral rotations while extending their duration until 4.5 h whereas L-NAME (50 and 100 mg/kg) only tended to attenuate their intensity without affecting the duration. 7-NI but not L-NAME significantly increased endogenous tissue DA levels in the nigrostriatal system of both sham-operated and 6-OHDA-lesioned rats. In L-DOPA-treated group, 7-NI significantly enhanced the L-DOPA-derived tissue DA content in this system and decreased the level of the intracellular DA metabolite DOPAC produced by monoamine oxidase (MAO). In contrast to 7-NI, L-NAME decreased markedly DA content and did not

Abbreviations: ANOVA, analysis of variance; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HPLC, high-pressure liquid chromatography; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; 6-OHDA, 6-hydroxydopamine hydrochloride; HVA, homovanillic acid; L-NAME, N^G-nitro-L-arginine methyl ester; MAO, monoamine oxidase; 7-NI, 7-nitroindazole; PD, Parkinson's disease; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulate; STR, striatum

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affect DOPAC level in the ipsilateral striatum. It means that the differences in 7-NI and L-NAME-mediated modulation of L-DOPA-induced behavioral and biochemical effects resulted not only from the inhibition of NOS activity but also from differences in their ability to inhibit MAO.

1. Introduction

Alterations in the nitrergic transmission mediated by the atypical gaseous neurotransmitter nitric oxide (NO) observed in Parkinson's disease (PD) and its animal models are an inherent consequence of the dopaminergic deafferentation of the striatum (STR) (Böckelmann et al., 1994; Eve et al., 1998; de Vente et al., 2000; Sancesario et al., 2004; Pierucci et al., 2011). NO is a short-lived bioactive molecule that plays an important role in many different processes in the central nervous system, such as release and reuptake of neurotransmitters (Iravani et al., 1998; Strasser et al., 1994; West and Galloway, 1997a, 1997b), synaptic plasticity (Picconi et al., 2012; Iravani et al., 2012), regulation of gene expression (Johnston and Morris, 1994) and in the control of motor function (Del Bel et al., 2005). In the STR, NO is synthesized in a subpopulation of GABAergic medium-sized aspiny neurons expressing neuronal nitric oxide synthase (nNOS) that is activated following a transient increase in the intracellular Ca^{2+} levels mediated via NMDA receptor stimulation by glutamate (GLU) (Kubota et al., 1993, Garthwaite, 2008). However, besides NMDA receptors, also dopamine (DA) D_1 and D_2 receptor activation regulates nNOS activity in that structure (Sammut et al., 2006, 2007). Consistently, DA via a direct stimulation of DA $D_{1/5}$ receptors co-expressed on striatal nNOS interneurons facilitates NO production while acting indirectly via DA D_2 heteroreceptors localized on other striatal neurons attenuates its synthesis (Sammut et al., 2006, 2007).

Considering the dramatic loss of striatal DA in PD, it seemed reasonable to suppose that NO biosynthesis could be impaired in this disease. In line with this assumption, it has been demonstrated that the expression of nNOS mRNA (Eve et al., 1998) and the number of NO-synthesizing neurons (Böckelmann et al., 1994) were markedly reduced in the caudate-putamen of PD patients. In the DA-deafferented rat STR both the enzymatic activity of nNOS (deVente et al., 2000) and the protein expression of this enzyme were significantly decreased (Sancesario et al., 2004). Degeneration of DA cells in the substantia nigra (SN) also caused a decline in nNOS protein level in that structure (Czarnecka et al., 2013).

However, in other studies, especially those performed in the MPTP model of PD, an over-production of NO has been strongly suggested as an important pathogenic factor (Przedborski et al., 1996; Liberatore et al., 1999). In the support of this view, the pharmacological inhibition of inducible or constitutive isoforms of NOS prevented MPTP- and 6-OHDA-evoked depletion of DA in rodents (Singh et al., 2005; Haik et al., 2008; Di Matteo et al., 2009). Such treatment was also protective against MPTP-induced loss of nigrostriatal DA neurons (Schulz et al., 1995, Watanabe et al., 2008). Moreover, significant increases in nNOS mRNA levels in the medial medullary lamina of globus pallidus and in the subthalamic nucleus of PD patients (Eve et al., 1998) as well as the enhanced number of nNOS expressing neurons in the STR of 6-OHDA-lesioned rats have been reported (Gomes and Del Bel, 2003).

Assuming the hypofunction of the nitrergic system in 6-OHDA-lesioned rats, in our recently published study we have demonstrated that chronic combined administration of a low dose of the NO donor molsidomine (2 mg/kg) jointly with the widely used antiparkinsonian drug L-3,4-dihydroxyphenylalanine (L-DOPA; 25 mg/kg) caused a slight but significant decrease in the number of contralateral rotations and a marked enhancement in a tissue concentrations of L-DOPA-derived DA in the STR and SN when compared to the values of these parameters in rats treated chronically with L-DOPA alone (Lorenc-Koci et al., 2013). The rotational behavior after L-DOPA is commonly used as an indicator of antiparkinsonian function of potential novel drugs but also it is considered to be a measure of dyskinesiogenic liability (Carey, 1991; Henry et al., 1998; Lane et al., 2006). In our study rotational behavior after L-DOPA was slightly reduced in the presence of molsidomine, therefore the obtained result could be interpreted as a modulation of dopaminergic response but also as a potential antidyskinetic effect (Lorenc-Koci et al., 2013). In fact, in the most recent study performed by Solís et al. (2015), antidyskinetic activity of molsidomine has been confirmed by a direct measurement of dyskinesia in the Pitx3¬/¬ aphakia mice, a genetic model of PD.

On the other hand, antidyskinetic activities of nNOS inhibitors, such as 7-nitroindazole (7-NI), N^G-nitro-L-arginine methyl ester (L-NAME) and N(G)-nitro-L-arginine (L-NOARG) have been also directly demonstrated by measurements of axial, limbic, locomotor and orofacial dyskinesia in unilaterally 6-OHDA-lesioned rats treated chronically with L-DOPA (Padovan-Neto et al., 2009, 2011; Takuma et al., 2012). However, so far the exact time course of contralateral rotations measured directly after the combined administration of the preferential nNOS inhibitor 7-NI and L-DOPA or the non-selective one L-NAME and L-DOPA has not been well documented. Therefore, in the present study, we compared the effects of these NOS inhibitors on rotational behavior in 6-OHDA-lesioned rats treated chronically with L-DOPA at a dose of 25 mg/kg, like in our previous study with molsidomine (Lorenc-Koci et al., 2013). Since development of tolerance can be observed after administration of NOS inhibitors (Marras et al., 1995; Del Bel et al., 2005, 2010), in contrast to NO donor molsidomine which does not cause such phenomenon (Reden, 1990; Rosenkranz et al., 1996), NOS inhibitors were given twice i.e. before the penultimate and the last chronic dose of L-DOPA. In general, nNOS inhibitors worsen motor function (Sandi et al., 1995; Starr and Starr, 1995, Del Bel et al., 2002, 2004), therefore, we also studied whether 7-NI and L-NAME affect more