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Anti-dyskinetic effect of the neuronal nitric oxide synthase inhibitor is linked to decrease of FosB/DeltaFosB expression

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HIGHLIGHTS

- 6-OHDA-lesioned rat develops AIMs after receiving chronic L-DOPA treatment.
- FosB/ΔFosB expression increases in the dopamine-depleted striatum induced by L-DOPA.
- Inhibitor of nNOS reduced AIMs simultaneously to FosB/ΔFosB overexpression in the lesioned striatum.

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ABSTRACT

Rodents with lesion of dopaminergic pathway when receiving repeated L-3,4-dihydroxiphenylalanine (L-DOPA) treatment develop abnormal involuntary movements called dyskinesia. We demonstrated that nitric oxide synthase (NOS) inhibitors mitigate L-DOPA-induced dyskinesia in rodents. The aim of the present study was to verify if the in vivo preferential neuronal NOS (nNOS) inhibitor 7-nitroindazole (7-NI) affect the expression of the transcription factor FosB/ΔFosB in the lesioned striatum, an indicator of neuronal activity associated with dyskinesia. Male *Wistar* rats with unilateral microinjection (medial forebrain bundle) of either the neurotoxin 6-hydroxidopamine (6-OHDA; $n = 4$–6/group) or saline (sham; $n = 6$/group) were provided with L-DOPA (30 mg/kg plus benserazide 7.5 mg/kg/day, oral gavage), once a day during 22 days. 6-OHDA-lesioned animals developed abnormal involuntary movements (AIMs) classified as axial, limb, orofacial and locomotive dyskinesia and presented FosB/ΔFosB increase in the dopamine-depleted striatum. Administration of 7-NI (30 mg/kg, i.p.), 30 min prior to L-DOPA reduced the severity of AIMs (≈65% for axial, limb and orofacial and 74% for locomotive AIMs scores), without interfering with the rotarod performance. Simultaneously, 7-NI attenuated the expression of FosB/ΔFosB in dopamine-depleted striatum (≈65% in medial and ≈54% in lateral striatum, bregma 0.48 mm). FosB/ΔFosB expression in lateral striatum was correlated with L-DOPA-induced dyskinesia. The findings described here corroborate a new approach to the management of L-DOPA-therapy in Parkinson's disease (PD) treatment.

L-DOPA therapy remains the gold standard treatment for PD. However, L-DOPA chronic administration does not cure PD. In the contrary, it is related with motor complications including L-DOPA-induced dyskinesia (LID) [6,23]. Once it has been established, dyskinesia will be induced after each L-DOPA administration, limiting the therapeutic benefit over time. Evidence from rodent models of PD and dyskinesia provide information to better understand the molecular mechanisms underlying the development of LID [9,27]. The combined effects of progressive dopamine (DA) cell loss in substantia nigra pars compacta (SNpc) associated with pulsatile stimulation of dopaminergic receptors [34,35] are thought to

Abbreviations: L-DOPA, L-3,4-dihydroxiphenylalanine; PD, Parkinson's disease; LID, L-DOPA-induced dyskinesia; SNpc, Substantia nigra *pars* compacta; NOS, nitric oxide synthase; L-NOARG, NG-nitro-L-Arginine; 7-NI, 7-nitroindazole; L-NAME, NG-nitro-L-Arginine-methyl esther; AIMs, abnormal involuntary movements; DA, Dopamine; 6-OHDA, 6-hydroxydopamine; TH, tyrosine hydroxylase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

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be the major determinant of L-DOPA liability in the induction of dyskinesia.

NOS inhibitors appeared as a potential pharmacological approach for the treatment of LID [14]. The association of L-DOPA and NOS inhibitors (7-NI, NG-nitro-L-Arginine – L-NOARG, NG-nitro-L-Arginine-methyl ester (L-NAME, both nonselective NOS inhibitor), reduced established LID with no observable motor impairment in rodents [36,37,46] and non-human primates [22,50]. Sub chronic administration of 7-NI reduced AIMs indicating that prolonged administration of 7-NI does not produce tolerance [33]. Chronic administration of L-NAME but not aminoguanidine, decreased LID in 6-OHDA-lesioned rats [46].

The transcription factor FosB/ΔFosB is increased in the rodent DA-depleted striatum following L-DOPA treatment [1,8,11,32,36,38]. There is a similar pattern of FosB/ΔFosB expression in patients [28,47] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys [4]. Following chronic L-DOPA exposure, FosB/ΔFosB is selectively expressed in NADPH-d/NOS-positive striatal neurons in parkinsonian rodents [11,38]. FosB/ΔFosB may regulate the expression of genes that induce the pathogenic cascade related to the altered motor responses to L-DOPA [8]. The foremost mechanism of FosB/ΔFosB expression in striatal NOS-expressing neurons during LIDs is not known.

Here we confirm that a single application of 7-NI mitigate pre-established LID in 6-OHDA-lesioned rat.

Experiments were conducted according to the principles and procedures described by the guidelines for the care and use of mammals in neuroscience and behavioral research (ILAR, USA). Male *Wistar* rats (200–250 g) were submitted to stereotaxic surgery for microinjection of 6-OHDA as described before [37]. Control animals received saline microinjections (sham-operated). To assess lesion intensity, rats were tested for apomorphine (Sigma–Aldrich, USA, 0.5 mg/kg, s.c.) induced rotation. 6-OHDA-lesioned rats presenting more than 90 rotations/45 min were included in the study [37]. At the end of experiment, the extension of the lesion was verified by immunohistochemistry for tyrosine hydroxylase (TH) at the SNpc.

6-OHDA-lesioned rats ($n = 10$) received daily administration of L-DOPA (30 mg/kg/day + benserazide 7.5 mg/kg/day, Prolopa dispersive, Hoffman-LaRoche, Brazil) for 22 days. Axial, limb, orofacial and locomotor AIMs were evaluated according to a rat dyskinesia scale [10,29,49] on the 1st, 7th, 14th, 21st and 22nd day of treatment. Each rat was scored on a severity scale from 0 to 4 in each of the four subtypes of AIMs at 1 and 2 h after L-DOPA intake during 1 min [37]. On the 22nd day of treatment 6-OHDA-lesioned rats were divided into equivalent sub-groups according to the AIMs scores obtained on day 21st. Each subgroup received, 30 min before L-DOPA, either 7-NI (Sigma–Aldrich, USA, 30 mg/kg, "7-NI/L-DOPA", $n = 6$) or its vehicle (50% polyethylene glycol-saline solution, "Veh/L-DOPA", $n = 4$). 6-OHDA-lesioned ($n = 6$) and sham-operated ($n = 6$) animals that receive no treatment of any kind were used as controls. 7-NI effects were obtained by between comparisons of AIMs on 22nd. Additionally, motor coordination and balance were tested using a rota-rod (Ugo Basile, Rota-rod 7750, Italy) to exclude any possibility of 7-NI interference in motor behavior. Rotarod tests (speed of the acceleration from 4 to 40 rpm over a 300 s period) were performed 1 and 2 h after L-DOPA intake [15]. Because there was no statistical difference between time measurement ($p > 0.05$, paired "*t*" test) results are expressed as the average latency time spent on the rod.

Two hours after L-DOPA administration on day 22nd rats were perfused transcardiacally with 250 ml of cold saline followed by 400 ml of 4% paraformaldehyde (Sigma–Aldrich, St. Louis, MO, USA) in 0.1 M phosphate buffer (pH 7.4). Brains were postfixed at 4 °C C for 1 h in the above fixative and cryoprotected at 4 °C overnight in 0.1 M phosphate buffer (pH 7.4) with 30% sucrose. Immunohistochemistry was performed in coronal sections (25 μm) through the SNpc and striatum using a standard peroxidase based method [19]. SNpc and striatal sections were incubated, respectively, with primary rabbit polyclonal anti-TH (1:2000, Pel Freez, Rogers, AR, USA) and rabbit polyclonal anti-FosB/ΔFosB (1:1000, Santa Cruz Biotechnology, USA).

Quantifications were carried out using three sections per animal in a light microscope (Leica DMRB) equipped with a video camera (Leica DFC420). Neuroanatomical sites were identified using the atlas of Paxinos and Watson [39] and the analysis was done using the software ImageJ (http://rsb.info.nih.gov). DA-depletion was analyzed [35] in SNpc (AP: −5.8 mm and AP: −6.04 mm, from Bregma) [39]. FosB/ΔFos-B positive cells in the striatum were analyzed at levels AP: 0.48 mm and AP: −0.92 mm (from bregma) [39] corresponding, respectively, to rostro-medial and caudal portions of striatum. Analysis was performed in every fifth section (i.e. separated by 125 μm). In the striatum, quantification were done within two adjacent areas of 286 μm × 214 μm (40X) and the total number of neurons were averaged and expressed in number of cells/0.5 mm^2. At rostro-medial level (AP: 0.48 mm), four quadrants within the dorso-medial, ventro-medial, dorso-lateral and ventro-lateral regions were analyzed. At caudal levels (AP: −0.92 mm) striatum was analyzed at dorso-lateral and ventro-lateral quadrants. Because there was no difference between dorso- and ventro-medial quadrants, as well dorso- and ventro-lateral quadrants, the number of FosB/ΔFos-B positive nuclei in these regions was averaged and data is expressed in terms of "medial" and "lateral" striatum.

AIMs scores collected during chronic L-DOPA treatment were analyzed by Friedman test followed by a Wilcoxon post hoc. Effects of 7-NI on AIMs and rotarod performance were analyzed using Mann–Whitney test. The 7-NI effects in the FosB/ΔFosB expression among the different sites of striatum were analyzed by two-way ANOVA, with repeated measures followed by a Duncan's post hoc. Comparisons were done for treatments (Veh/L-DOPA and 7-NI/L-DOPA) being side (lesioned- and unlesioned side) the repeated measure. Statistical significance level was set at $p < 0.05$.

TH-immunostaining indicated almost complete degeneration (>90%) of the TH-positive cell/fiber in the lesioned SNpc and striatum. The development of axial, limb, orofacial and locomotive AIMs (Fig. 1A and B) increased during chronic L-DOPA treatment ($p < 0.05$). Corroborating our previous results, acute 7-NI (30 mg/kg) attenuated L-DOPA-induced axial, limb and orofacial AIMs (Fig. 1C; $p < 0.05$) as well as locomotive AIMs scores (Fig. 1D; $p < 0.05$). 7-NI prevented L-DOPA-induced motor impairment in the rotarod by increasing animal ability to stay in the rod (Fig. 1D; $p < 0.05$). The ability of the rat stay in the rotarod was inversely correlated with AIMs incidence (Fig. 1E and F).

As described before by Western blot [36] 6-OHDA induced an increase in the FosB/ΔFos-B in the lesioned striatum as compared to sham-operated animals (data not shown).

At the medial portion of the lesioned striatum (bregma 0.48 mm, Fig. 2A), L-DOPA induced a significant increase in the Fos-B/ΔFos-B staining (1.6 fold) when compared to the unlesioned striatum (side: $F(1,8) = 13.79$, $p = 0.005$; compare Fig. 3A and G). 7-NI induced a reduction (≈65%), in the Fos-B/ΔFos-B immunopositive neuron staining in the lesioned striatum (treatment: $F(1,8) = 6.97$, $p = 0.029$; interaction: $F(1,8) = 4.37$, $p = 0.069$). In the lateral part (Fig. 2B), there was also a significant increase (≈43.5 fold) in the Fos-B/ΔFos-B immunolabeling (side: $F(1,8) = 40.50$, $p < 0.001$; compare Fig. 3B and H). The effects of 7-NI inducing a reduction (≈54%) in the Fos-B/ΔFos-B immunopositive neuron expression (compare Fig. 3H and K) were significant (treatment: $F(1,8) = 6.15$, $p = 0.038$) and specific in the lesioned striatum (interaction: $F(1,8) = 6.04$, $p = 0.039$).

At caudal level (bregma −0.92 mm, Fig. 2C) a significant increment (≈1.9 fold) in the Fos-B/ΔFos-B staining was also observed

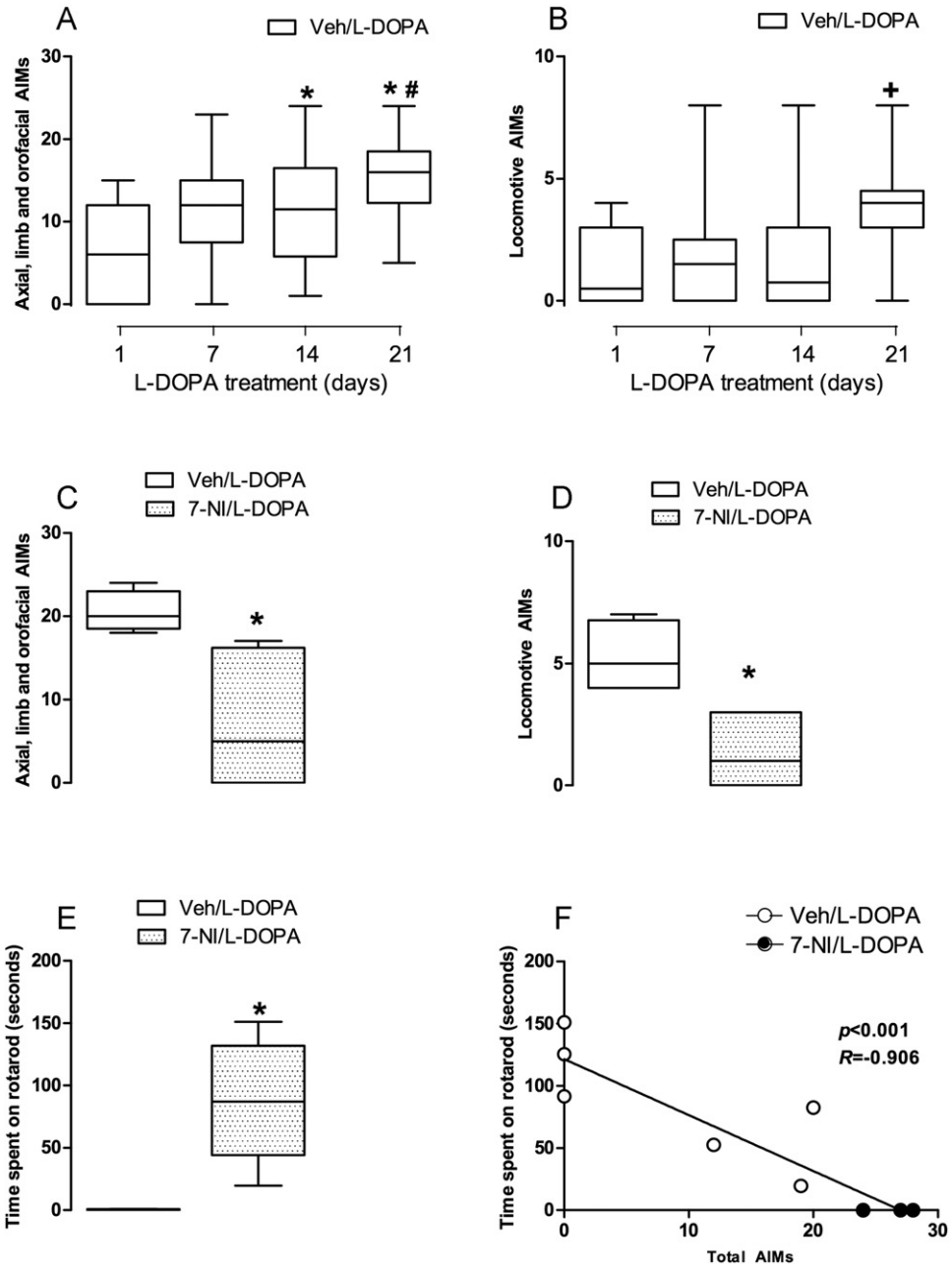

Fig. 1. Chronic treatment with L-DOPA to 6-OHDA-lesioned rats: development of abnormal involuntary movements (AIMs), rotarod performance and effect of 7-nitroindazole (7-NI). L-DOPA increased over the time AIMs affecting (A) axial, limb, orofacial muscles ($\chi^2(3) = 13.36$, $p = 0.004$) as well (B) locomotive behavior ($\chi^2(3) = 13.77$, $p = 0.003$). $^{*}p < 0.05$ vs day 1, $^{\#}p < 0.05$ vs day 14, $^{+}p < 0.05$ vs all other days (Friedman followed by Wilcoxon, $n = 10$). (C) Axial, limb and orofacial AIMs and (D) locomotive AIMs were reduced by previous administration of 7-NI. (E) Rats' performance on rotarod was improved by 7-NI and (F) the time spent on the rod are plotted against the total AIMs (sum of axial, limb, orofacial and locomotive AIM scores). Black and white circles represent Veh/L-DOPA and 7-NI/L-DOPA-treated rats, respectively. The probability value of the regression (p) and the Spearman's correlation coefficient (R) are given in the top left corner. 7-NI (30 mg/kg) or it's vehicle were administered 30 min prior L-DOPA intake on the day 22. $^{*}p < 0.05$ vs Veh/L-DOPA (Mann–Whitney U test; $n = 4$–6 per group).

(side: $F(1,8) = 21.10$, $p = 0.001$; compare Fig. 3C and I) with a marginal effect of 7-NI (treatment: $F(1,8) = 2.51$, $p = 0.151$, interaction: $F(1,8) = 3.07$, $p = 0.117$, see Fig. 3I and L).

Fos-B/ΔFos-B expression intensity correlated with LID in medial ($r = 0.81$, $p = 0.005$, Spearman), lateral ($r = 0.86$, $p = 0.002$, Spearman) and caudal level ($r = 0.72$, $p = 0.02$, Spearman) portion of the dopamine depleted striatum.

The result of this study support that chronic L-DOPA treatment of 6-OHDA-lesioned rats induced an increase in the FosB/ΔFos-B-immunopositive neurons in the dopamine depleted striatum, confirming others and ours previous description [36]. This overexpression was attenuated in lateral portion of striatum by one single injection of 7-NI, 30 min before L-DOPA application (increase of more than 43 fold followed by a 54% reduction).

In addition, it indicates an association between axial, limb and orolingual AIMs with FosB/ΔFos-B labeling in the sensorimotor (lateral) part of the striatum [1]. Other studies demonstrated that lateral striatum influence the orofacial and limb movements [5,7,16,17,24,26,41,42]. In comparison, locomotive AIMs would mainly be linked to medial striatum [1,16]. Therefore, FosB/ΔFos-B-expression and the action of 7-NI in the lesioned striatum are related with neuroanatomical projections.

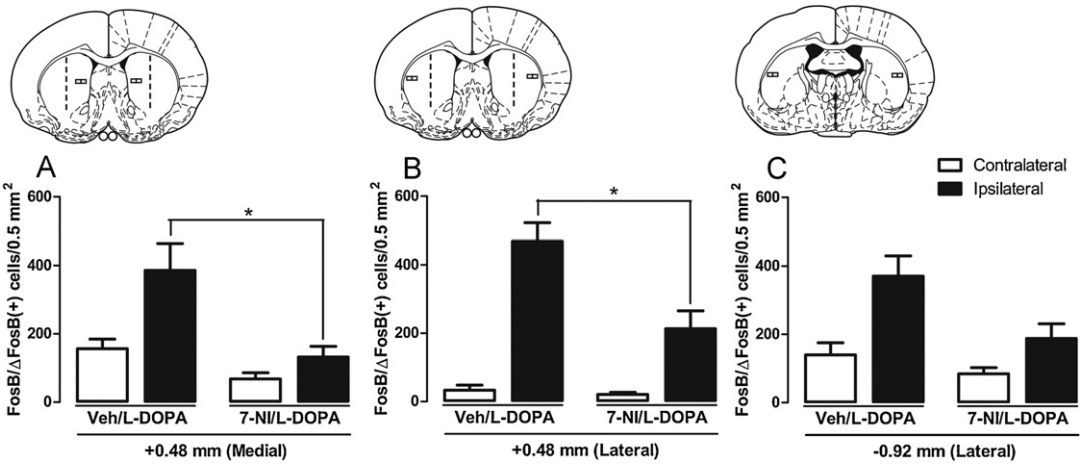

Fig. 2. Effects of 7-nitroindazole (7-NI) in the expression of Fos-B/ΔFos-B in the striatum. Quantification of Fos-B/ΔFos-B was performed in medial and lateral areas of lesioned- and unlesioned striatum of 6-OHDA-lesioned L-DOPA-treated rats. At bregma + 0.48 mm [39], L-DOPA induced an increment on Fos-B/ΔFos-B in medial (A) and lateral (B) portions of lesioned striatum. 7-NI was able to reduce ~34% and ~45% Fos-B/ΔFos-B overexpression in these areas respectively. At bregma −0.92 mm (C), L-DOPA increased Fos-B/ΔFos-B staining in lateral areas of lesioned striatum and this effects was not attenuated by 7-NI. $^{*}p < 0.05$ (two-way ANOVA with repeated measures, $n = 4$–6/group).

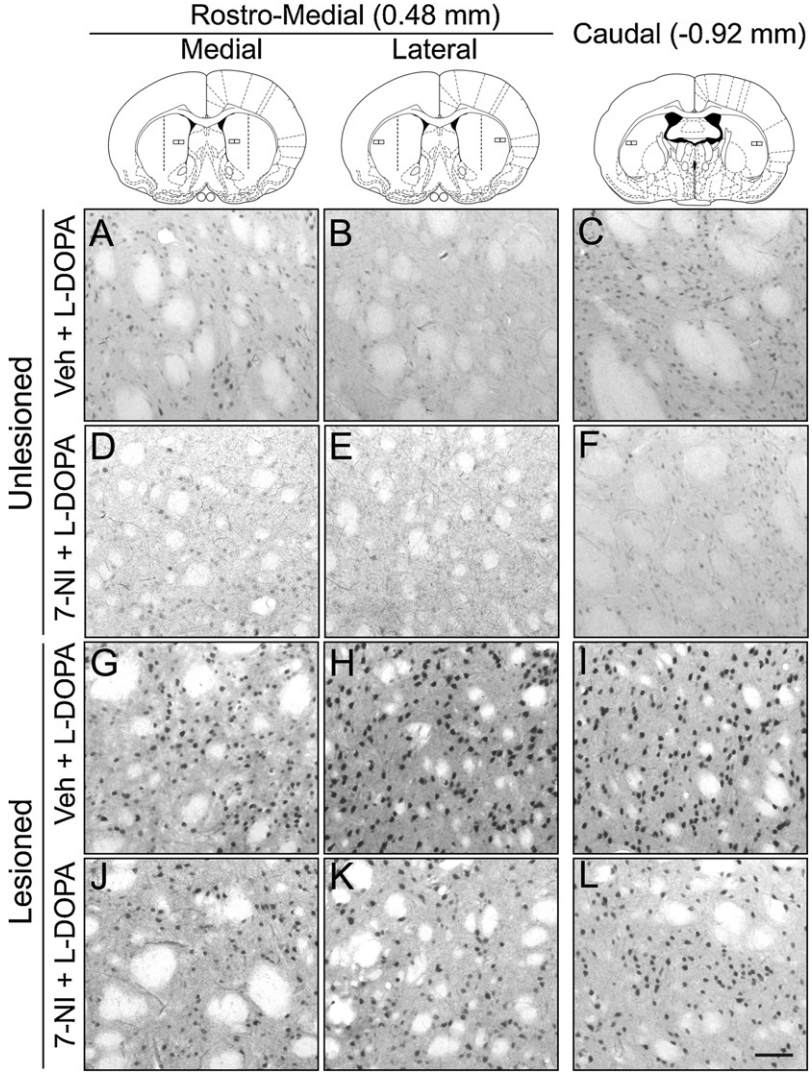

Fig. 3. FosB/ΔFos-B-positive neuron immunolabeled nuclei in the unlesioned (upper panel) and lesioned (dopamine depleted, lower panel) striatum of 6-OHDA-microinjected rats. Images were taken at medial (left panel) and lateral (middle panel) portions of striatum at bregma + 0.48 mm and at lateral regions (right panel) of striatum at bregma −0.92 mm [39]. Increments in Fos-B/ΔFos-B-positive nuclei were observed in lesioned striatum of dyskinetic animals (G–I, "Veh/L-DOPA"). 7-NI was able to reduce Fos-B/ΔFos-B staining (J-L, "Veh/L-DOPA") although statistically significance was observed only for regions analyzed at bregma 0.48 mm. Scale bar: 100 μm.

Nitric oxide (NO) plays a main role in motor control within the central nervous system as shown by pharmacological blockage and knockdown of nNOS enzyme [13,14]. Within the striatum, NO has a needed role in striatal output pathways by interacting with other neurotransmitter systems [48]. Dopamine D1-like receptor activation [44] and electrical stimulation of nigrostriatal neurons increased NO efflux in the striatum [43]. These studies indicate a dopamine modulation of striatal nNOS enzyme/interneuron activity via dopamine D1-like and D2-like receptor dependent mechanism [43–45]. Finally, data from our group [33,36,37,50] and others [22,46] that pharmacological blockage of NOS enzyme was able to attenuate LID without interfering with beneficial L-DOPA motor effects.

Maintenance of dyskinesia implies in plastic changes with long-term modifications of the basal ganglia network. The NO system undergoes plasticity after dopamine depletion but the relation between NO and LID is not understood yet [14,30,40]. Immediate early gene expression is proposed to be a mediator of long-term response of the brain to drugs, stress and other chronic events [21], including L-DOPA administration [2,8,11,32,38]. FosB/ΔFosB-related proteins are proposed to be the main postsynaptic striatal marker for dyskinesia in rodent model of PD [1,8]. The importance of FosB/ΔFosB up regulation as a determinant of LID is supported by the anti-dyskinetic effect of treatment blocking either striatal FosB/ΔFosB induction during chronic L-DOPA administration [1] or dyskinetic effect induced by the exacerbate expression of the protein [8]. Our results suggest that 7-NI attenuation of LID in parkinsonian rodents is, at least in part, through blocking the induction of FosB/ΔFosB expression.

Following dopamine depletion and LID induction, striatal D1-like receptor undergoes redistribution to the postsynaptic membrane and cytoplasmic compartments [3,20,31]. FosB/ΔFosB is expressed in dynorphin-positive striatal neurons [1,25], which express the dopamine D1-like receptor and project into the direct output pathway [18]. LID is blocked in the D1-like but not D2-like receptors knockout mice with striatal DA depletion induced by 6-OHDA [12]. It suggests that D1-like receptor stimulation is essential for the development of LID and the expression of the molecular markers such as FosB/ΔFosB [12]. According to these results, it is possible that the attenuation of LID induced by 7-NI involves preferentially striatal neurons of the direct pathway which express the D1-like dopaminergic receptors. More experiments are needed to reveal the specific type of striatal neurons.

In conclusion, we show the reduction of LID in the 6-OHDA-lesioned rat striatum by nNOS inhibitor, associated with the attenuation of striatal FosB/ΔFosB expression. Taken together, the data supports the evidence that the anti-dyskinetic effect of NO inhibitors is, at least in part, linked to the expression of the transcription factor FosB/ΔFosB.

References

[1] M. Andersson, A. Hilbertson, M.A. Cenci, Striatal fosB expression is causally linked with L-DOPA-induced abnormal involuntary movements and the associated upregulation of striatal prodynorphin mRNA in a rat model of Parkinson's disease, Neurobiol. Dis. 6 (1999) 461–474.

[2] M. Andersson, C. Konradi, M.A. Cenci, cAMP response element-binding protein is required for dopamine-dependent gene expression in the intact but not the dopamine-denervated striatum, J. Neurosci. 21 (2001) 9930–9943.

[3] A. Berthet, G. Porras, E. Doudnikoff, H. Stark, M. Cador, E. Bezard, B. Bloch, Pharmacological analysis demonstrates dramatic alteration of D1 dopamine receptor neuronal distribution in the rat analog of L-DOPA-induced dyskinesia, J. Neurosci. 29 (2009) 4829–4835.

[4] O. Berton, C. Guigoni, Q. Li, B.H. Bioulac, I. Aubert, C.E. Gross, R.J. Dileone, E.J. Nestler, E. Bezard, Striatal overexpression of DeltaJunD resets L-DOPA-induced dyskinesia in a primate model of Parkinson disease, Biol. Psychiatry 66 (2009) 554–561.

[5] L.L. Brown, F.R. Sharp, Metabolic mapping of rat striatum: somatotopic organization of sensorimotor activity, Brain Res. 686 (1995) 207–222.

[6] P. Calabresi, M. Di Filippo, V. Ghiglieri, N. Tambasco, B. Picconi, Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap, Lancet Neurol. 9 (2010) 1106–1117.

[7] J.J. Canales, A.M. Graybiel, A measure of striatal function predicts motor stereotypy, Nat. Neurosci. 3 (2000) 377–383.

[8] X. Cao, T. Yasuda, S. Uthayathas, R.L. Watts, M.M. Mouradian, H. Mochizuki, S.M. Papa, Striatal overexpression of DeltaFosB reproduces chronic levodopa-induced involuntary movements, J. Neurosci. 30 (2010) 7335–7343.

[9] M.A. Cenci, Transcription factors involved in the pathogenesis of L-DOPA-induced dyskinesia in a rat model of Parkinson's disease, Amino Acids 23 (2002) 105–109.

[10] M.A. Cenci, C.S. Lee, A. Björklund, L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA, Eur. J. Neurosci. 10 (1998) 2694–2706.

[11] M.A. Cenci, A. Tranberg, M. Andersson, A. Hilbertson, Changes in the regional and compartmental distribution of FosB- and JunB-like immunoreactivity induced in the dopamine-denervated rat striatum by acute or chronic L-DOPA treatment, Neuroscience 94 (1999) 515–527.

[12] S. Darmopil, A.B. Martín, I.R. De Diego, S. Ares, R. Moratalla, Genetic inactivation of dopamine D1 but not D2 receptors inhibits L-DOPA-induced dyskinesia and histone activation, Biol. Psychiatry 66 (2009) 603–613.

[13] E.A. Del Bel, F.S. Guimarães, M. Bermúdez-Echeverry, M.Z. Gomes, A. Schiaveto-de-souza, F.E. Padovan-Neto, V. Tumas, A.P. Barion-Cavalcanti, M. Lazzarini, L.P. Nucci-da-Silva, D. de Paula-Souza, Role of nitric oxide on motor behavior, Cell. Mol. Neurobiol. 25 (2005) 371–392.

[14] E. Del-Bel, F.E. Padovan-Neto, R. Raisman-Vozari, M. Lazzarini, Role of nitric oxide in motor control: implications for Parkinson's disease pathophysiology and treatment, Curr. Pharm. Des. 17 (2011) 471–488.

[15] A. Dekundy, M. Lundblad, W. Danysz, M.A. Cenci, Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model, Behav. Brain Res. 179 (2007) 76–89.

[16] P.R. Dickson, C.G. Lang, S.C. Hinton, A.E. Kelley, Oral stereotypy induced by amphetamine microinjection into striatum: an anatomical mapping study, Neuroscience 61 (1994) 81–91.

[17] A. Ebrahimi, R. Pochet, M. Roger, Topographical organization of the projections from physiologically identified areas of the motor cortex to the striatum in the rat, Neurosci. Res. 14 (1992) 39–60.

[18] C.R. Gerfen, S. Miyachi, R. Paletzki, P. Brown, D1 dopamine receptor supersensitivity in the dopamine-depleted striatum results from a switch in the regulation of ERK1/2/MAP kinase, J. Neurosci. 22 (2002) 5042–5054.

[19] M.Z. Gomes, R. Raisman-Vozari, E.A. Del Bel, A nitric oxide synthase inhibitor decreases 6-hydroxydopamine effects on tyrosine hydroxylase and neuronal nitric oxide synthase in the rat nigrostriatal pathway, Brain Res. 1203 (2008) 160–169.

[20] C. Guigoni, E. Doudnikoff, Q. Li, B. Bloch, E. Bezard, Altered D(1) dopamine receptor trafficking in parkinsonian and dyskinetic non-human primates, Neurobiol. Dis. 26 (2007) 452–463.

[21] S.E. Hyman, E.J. Nestler, Initiation and adaptation: a paradigm for understanding psychotropic drug action, Am. J. Psychiatry 153 (1996) 151–162.

[22] M.M. Iravani, K.A. Stockwell, K. Tayarani-Binazir, M.J. Jackson, L.A. Smith, S. Rose, P. Jenner, Inhibition of neuronal nitric oxide synthase as a novel target for suppression of levoda-induced dyskinesia in primates, Neurosci. Meeting Planner Soc. Neurosci. (2008), Abstr 139. 15/M6.

[23] P. Jenner, Molecular mechanisms of L-DOPA-induced dyskinesia, Nat. Rev. Neurosci. 9 (2008) 665–677.

[24] A.E. Kelley, C.G. Lang, A.M. Gauthier, Induction of oral stereotypy following amphetamine microinjection into a discrete subregion of the striatum, Psychopharmacology (Berl) 95 (1988) 556–559.

[25] M.B. Kelz, J. Chen, W.A. Carlezon, K. Whisler, L. Gilden, A.M. Beckmann, C. Steffen, Y.J. Zhang, L. Marotti, D.W. Self, T. Tkatch, G. Baranauskas, D.J. Surmeier, R.L. Neve, R.S. Duman, M.R. Picciotto, E.J. Nestler, Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine, Nature 401 (1999) 272–276.

[26] R. Kuczenski, D.S. Segal, Sensitization of amphetamine-induced stereotyped behaviors during the acute response, J. Pharmacol. Exp. Ther. 288 (1999) 699–709.

[27] E. Lane, S. Dunnett, Animal models of Parkinson's disease and L-DOPA induced dyskinesia: how close are we to the clinic? Psychopharmacology (Berl) 199 (2008) 303–312.

[28] H.S. Lindgren, D. Rylander, H. Iderberg, M. Andersson, S.S. O'Sullivan, D.R. Williams, A.J. Lees, M.A. Cenci, Putaminal upregulation of FosB/_FosB-like immunoreactivity in Parkinson's disease patients with dyskinesia, J. Parkinson's Dis. 1 (2011) 347–357.

[29] M. Lundblad, M. Andersson, C. Winkler, D. Kirik, N. Wierup, M.A. Cenci, Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease, Eur. J. Neurosci. 15 (2002) 120–132.

[30] M. Mitkovski, F.E. Padovan-Neto, R. Raisman-Vozari, L. Ginestet, C.A. da-Silva, E.A. Del-Bel, Investigations into potential extrasynaptic communication between the dopaminergic and nitrergic systems, Front Physiol. 3 (2012) 372.

[31] M.P. Muriel, V. Bernard, A.I. Levey, O. Laribi, D.N. Abrous, Y. Agid, B. Bloch, E.C. Hirsch, Levodopa induces a cytoplasmic localization of D1 dopamine receptors in striatal neurons in Parkinson's disease, Ann. Neurol. 46 (1999) 103–111.

[32] A. Muñoz, Q. Li, F. Gardoni, E. Marcello, C. Qin, T. Carlsson, D. Kirik, M. Di Luca, A. Björklund, E. Bezard, M. Carta, Combined 5-HT1A and 5-HT1B receptor agonists for the treatment of L-DOPA-induced dyskinesia, Brain 131 (2008) 3380–3394.

[33] N. Novaretti, F.E. Padovan-Neto, V. Tumas, C.A. da-Silva, E.A. Del Bel, Lack of tolerance for the anti-dyskinetic effects of 7-nitroindazole, a neuronal nitric oxide synthase inhibitor, in rats, Braz. J. Med. Biol. Res. 43 (2010) 1047–1053.
[34] J.A. Obeso, M.C. Rodriguez-Oroz, M. Rodriguez, M.R. DeLong, C.W. Olanow, Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model, Ann. Neurol. 47 (2000) S22–S32, discussion S32-24.
[35] C.W. Olanow, J.A. Obeso, F. Stocchi, Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications, Lancet Neurol. 5 (2006) 677–687.
[36] F.E. Padovan-Neto, M.B. Echeverry, S. Chiavegatto, E. Del-Bel, Nitric oxide synthase inhibitor improves de novo and long-term L-DOPA-induced dyskinesia in hemiparkinsonian rats, Front Syst. Neurosci. 5 (2011) 40.
[37] F.E. Padovan-Neto, M.B. Echeverry, V. Tumas, E.A. Del-Bel, Nitric oxide synthase inhibition attenuates L-DOPA-induced dyskinesias in a rodent model of Parkinson's disease, Neuroscience 159 (2009) 927–935.
[38] N. Pavón, A.B. Martín, A. Mendialdua, R. Moratalla, ERK phosphorylation and FosB expression are associated with L-DOPA-induced dyskinesia in hemiparkinsonian mice, Biol. Psychiatry 59 (2006) 64–74.
[39] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, 4th ed., Academic Press, San Diego, 1998.
[40] M. Pierucci, S. Galati, M. Valentino, V. Di Matteo, A. Benigno, A. Pitruzzella, R. Muscat, G. Di Giovanni, Nitric oxide modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders, CNS Neurol. Disord. Drug Targets 10 (2011) 777–791.
[41] M. Pisa, Regional specialization of motor functions in the rat striatum: implications for the treatment of parkinsonism, Prog. Neuropsychopharmacol. Biol. Psychiatry 12 (1988) 217–224.
[42] J.D. Salamone, K. Mahan, S. Rogers, Ventrolateral striatal dopamine depletions impair feeding and food handling in rats, Pharmacol. Biochem. Behav. 44 (1993) 605–610.
[43] S. Sammut, K.E. Bray, A.R. West, Dopamine D2 receptor-dependent modulation of striatal NO synthase activity, Psychopharmacology (Berl) 191 (2007) 793–803.
[44] S. Sammut, A. Dec, D. Mitchell, J. Linardakis, M. Ortiguela, A.R. West, Phasic dopaminergic transmission increases NO efflux in the rat dorsal striatum via a neuronal NOS and a dopamine D(1/5) receptor-dependent mechanism, Neuropsychopharmacology 31 (2006) 493–505.
[45] S. Sammut, D.J. Park, A.R. West, Frontal cortical afferents facilitate striatal nitric oxide transmission in vivo via a NMDA receptor and neuronal NOS-dependent mechanism, J. Neurochem. 103 (2007) 1145–1156.
[46] K. Takuma, T. Tanaka, T. Takahashi, N. Hiramatsu, Y. Ota, Y. Ago, T. Matsuda, Neuronal nitric oxide synthase inhibition attenuates the development of L-DOPA-induced dyskinesia in hemi-Parkinsonian rats, Eur. J. Pharmacol. 683 (2012) 166–173.
[47] P.K. Tekumalla, F. Calon, Z. Rahman, S. Birdi, A.H. Rajput, O. Hornykiewicz, T. Di Paolo, P.J. Bédard, E.J. Nestler, Elevated levels of DeltaFosB and RGS9 in striatum in Parkinson's disease, Biol. Psychiatry 50 (2001) 813–816.
[48] A.R. West, K.Y. Tseng, Nitric oxide-soluble guanylyl cyclase-cyclic GMP signaling in the striatum: new targets for the treatment of parkinson's disease? Front Syst. Neurosci. 5 (2011) 55.
[49] C. Winkler, D. Kirik, A. Björklund, M.A. Cenci, L-DOPA-induced dyskinesia in the intrastriatal 6-hydroxydopamine model of parkinson's disease: relation to motor and cellular parameters of nigrostriatal function, Neurobiol. Dis. 10 (2002) 165–186.
[50] J.E. Yuste, M. Bermúdez, F.R. Bernal, C. Barcia, J. Martin, E. Del Bel, E.F. Villalba, M.T. Herrero, NOS inhibitors improve L-DOPA-induced dyskinesias in experimental models of Parkinsonism, Mov. Disord. 26 (2011) 257–258.