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Increase in the number of striatal neuronal nitric oxide synthase immunoreactive (nNOS-ir) interneurones in MPTP-treated common marmosets primed for and displaying levodopa-induced dyskinesia

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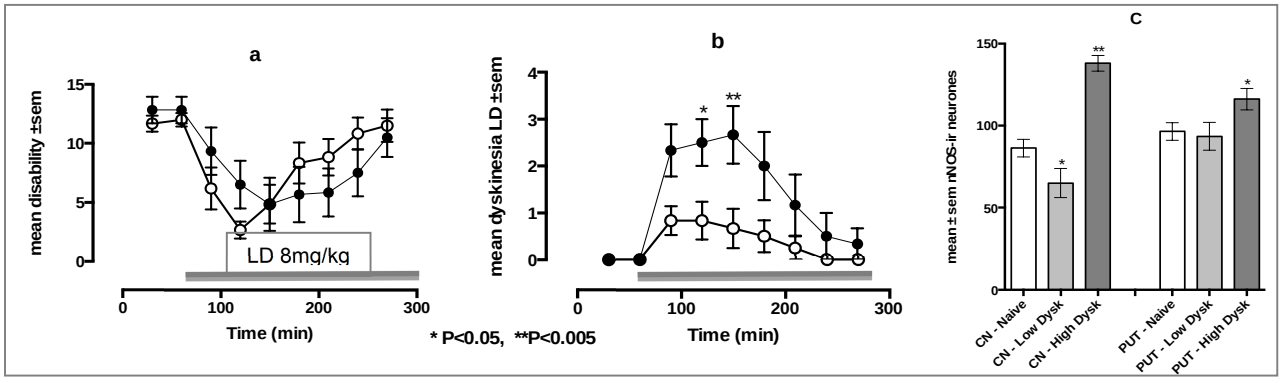
In Parkinson's disease (PD), dyskinesia is a consequence of nigral dopaminergic cell death and chronic levodopa treatment. The cause of levodopa-induced dyskinesia (LID) is unknown but may result from adaptive neuronal changes in the striatum (1). In PD, as well as rodents with an unilateral median forebrain bundle lesion, expression of nNOS mRNA, as well the number of nNOS immunoreactive (-ir) neurones is markedly altered and nNOS inhibitors can reduce levodopa-induced motor abnormalities (2).

We counted the number of neuronal nitric oxide synthase immunoreactive (nNOS-ir) interneurones in the caudate nucleus (CN) and putamen (PUT) in normal, drug naïve, common marmosets (n=6) compared to MPTP-treated animals (0.2mg/kg/day, s.c. for 5 consecutive days) that were chronically treated with levodopa (8 mg/kg levodopa plus 10 mg/kg benserazide) but expressed little dyskinesia (n=6) and those that expressed marked dyskinesia (n=7). In the low dyskinesia group (n=6), peak dyskinesia rarely exceeded score 1 and the high dyskinesia group (n=7) scores were >2. The animals were euthanized by pentobarbital sodium (60 mg/kg), and perfuse fixed with 4% paraformaldehyde. Striatal and nigral sections (30 µm) were processed for immunoperoxidase staining for nNOS-ir and tyrosine hydroxylase immunoreactivity (TH-ir) in substantia nigra (SN) and striatum respectively.

Fig 1: Motor disability (a) and dyskinesia (b) in MPTP-treated, low (open data points) and high dyskinetic (closed data points) marmosets in response to acute dose of levodopa (p.o.). In panel c,.the striatal (CN and PUT) nNOS-ir cell counts in low and high dyskinesia group is compared to drug naïve, normal animals.



The high dyskinesia group expressed more severe LID in response to levodopa (8 mg/kg po) than the low dyskinesia animals (P<0.005; two-way ANOVA) (fig 1b), although the reversal of

motor disability was equally improved (fig 1a) in the two MPTP-treated groups. In the naive group there were 470±23 TH-ir neurones in the substantia nigra, which was reduced significantly ($P<0.001$; one-way ANOVA) to 124±29 and 79±10 in the low and high dyskinetic groups respectively. While there was a small but significant decrease in number of nNOS-ir interneurons in the CN of low dyskinetic group, there were no differences in PUT (Fig 1c). However, in the high dyskinesia group, there was a significant increase in nNOS-ir both CP and PUT (fig 1c). This increase in dyskinesia might reflect adaptive striatal changes involving GABA/neuropeptideY/nNOS containing striatal output neurones.

1- Iravani MM, McCreary A, Jenner P (2012) Parkinsonism Relat. Disord. Suppl 1, S123-125

2- Takuma, K., T. Tanaka, T. Takahashi, et al. (2012). Eur J Pharmacol, 683, 166-73.