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Research Report

Effects of 5-HT1A receptor stimulation on striatal and cortical M1 pERK induction by L-DOPA and a D1 receptor agonist in a rat model of Parkinson's disease

*David Lindenbach, Kristin B. Dupre[1], Karen L. Eskow Jaunarajs[2], Corinne Y. Ostock, Adam A. Goldenberg, Christopher Bishop**

Behavioral Neuroscience Program, Department of Psychology, Binghamton University – State University of New York, Binghamton, NY, USA

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ABSTRACT

Motor symptoms of Parkinson's disease are commonly treated using L-DOPA although long-term treatment usually causes debilitating motor side effects including dyskinesias. A putative source of dyskinesia is abnormally high levels of phosphorylated extracellular-regulated kinase (pERK) within the striatum. In animal models, the serotonin 1A receptor agonist ±8-OH-DPAT reduces dyskinesia, suggesting it may exhibit efficacy through the pERK pathway. The present study investigated the effects of ±8-OH-DPAT on pERK density in rats treated with L-DOPA or the D_1 receptor agonist SKF81297. Rats were given a unilateral dopamine lesion with 6-hydroxydopamine and primed with a chronic regimen of L-DOPA, SKF81297 or their vehicles. On the final test day, rats were given two injections: first with ±8-OH-DPAT, the D_1 receptor antagonist SCH23390 or their vehicles, and second with L-DOPA, SKF81297 or their vehicles. Rats were then transcardially perfused for immunohistological analysis of pERK expression in the striatum and primary motor cortex. Rats showed greater dyskinesia in response to L-DOPA and SKF81297 after repeated injections. Although striatal pERK induction was similar between acute and chronic L-DOPA, SKF81297 caused the largest increase in striatal pERK after the first exposure. Neither compound alone affected motor cortex pERK. Surprisingly, in the ventromedial striatum, ±8-OH-DPAT potentiated L-DOPA-induced pERK; in the motor cortex,

Abbreviations: serotonin, 5-HT; serotonin 1A receptor, 5-HT_{1A}R; 6-hydroxydopamine, 6-OHDA; abnormal involuntary movements, AIMs; D_1 receptor, D_1R; dopamine, DA; ±8-OH-DPAT, DPAT; extracellular-regulated kinase, ERK; L-DOPA-induced dyskinesia, LID; primary motor cortex, M1; median absolute deviation, M.A.D.; Parkinson's disease, PD; phosphorylated extracellular-regulated kinase, pERK; SCH23390, SCH; SKF81297, SKF; standard error of the mean, S.E.M.; vehicle, VEH

*Correspondence to: Department of Psychology, Binghamton University, PO Box 6000, Binghamton 13902-6000, NY, USA. Fax: +1 607 777 4890.
E-mail address: cbishop@binghamton.edu (C. Bishop).
[1]Present address: National Institute of Neurological Disorders and Stroke, Bldg 35 - Porter Bldg, Rm 1C411, 35 Convent Dr., Bethesda, MD, USA.
[2]Present address: Center for Neurodegeneration and Experimental Therapeutics, Department of Neurology, University of Alabama-Birmingham, Birmingham, AL, USA.

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±8-OH-DPAT potentiated pERK with L-DOPA or SKF81297. Our results support previous work that the striatal pERK pathway is dysregulated after dopamine depletion, but call into question the utility of pERK as a biomarker of dyskinesia expression.

1. Introduction

The most effective symptomatic treatment for Parkinson's disease (PD) is the dopamine (DA) precursor L-DOPA (Cenci et al., 2011). However, most PD patients who take L-DOPA will gradually develop motor side effects including L-DOPA-induced dyskinesia (LID) that increase in severity over time and are due, in part, to super-sensitization of striatal DA receptors (Ahlskog and Muenter, 2001; Feyder et al., 2011). Though the molecular mechanisms of LID are only partially understood, DA loss and subsequent DA replacement therapy result in abnormal striatal plasticity via pathological enhancement of synaptic long-term potentiation and reduced long-term depression (Jenner, 2008; Picconi et al., 2003).

Dysregulation of the striatal extracellular-regulated kinase (ERK) signaling pathway is a candidate mechanism for LID since this molecular cascade promotes synaptic plasticity (Thomas and Huganir, 2004). Phosphorylation of ERK (pERK) stimulates its kinase activity and formation of striatal pERK is promoted by at least two distinct pathways, one mediated by Ras proteins and another by D_1 receptors (D_1Rs; Santini et al., 2008; Shiflett and Balleine, 2011). In rodent and primate models of PD, L-DOPA (through D_1R-mediated mechanisms) and D_1R agonists robustly increase striatal pERK, the magnitude of which often correlates with the severity of dyskinesia (Gerfen et al., 2002; Papadeas et al., 2004; Pavon et al., 2006; Santini et al., 2009, 2010; Westin et al., 2007). Moreover, pharmacological inhibition of pERK formation reduces LID without affecting the efficacy of L-DOPA, suggesting a distinct role for pERK in LID (Lindgren et al., 2009; Santini et al., 2007).

Research into the long-term effects of DA replacement on pERK has yielded conflicting results. Some studies have shown that pERK induction by L-DOPA or D_1R agonists is highest after the first drug exposure, implying that pERK is involved in DA receptor sensitization (Santini et al., 2007, 2010; Papadeas et al., 2004). Others have found that pERK is highest after repeated L-DOPA exposure, suggesting pERK may be a biomarker of dyskinesia expression (Pavon et al., 2006). Thus, the precise relationship between the expression of striatal pERK and dyskinesia remains elusive.

In animal models, serotonin 1A receptor (5-HT_{1A}R) agonists reduce both LID and D_1R-mediated dyskinesia (Bibbiani et al., 2001; Dupre et al., 2008, 2011, 2013). Following DA-depletion, the expression of 5-HT_{1A}Rs within the striatum and primary motor cortex (M1) increases, an effect that is sometimes potentiated by L-DOPA treatment (Frechilla et al., 2001; Huot et al., 2012). Although 5-HT_{1A}R stimulation enhances pERK levels via activation of the Ras pathway in vitro (Garnovskaya et al., 1996; Raymond et al., 1999) and may do so in vivo (Buritova et al., 2009) it is currently unknown how 5-HT_{1A}Rs impact pERK within the striatum and M1 of a PD brain. Given that pERK is presently thought of as a marker of dyskinesia, 5-HT_{1A}R agonism would be expected to reduce pERK expression in a PD model.

This study investigated how pERK levels in the corticostriatal circuit are affected by compounds that either stimulate or attenuate dyskinesia in a unilateral rat model of PD. Brains were analyzed following a de novo dose of L-DOPA or a D_1R agonist and after repeated exposures to these drugs. It was expected that administration of a 5-HT_{1A}R agonist would reduce pERK induction by both L-DOPA and a D_1R agonist.

2. Results

2.1. *Experiment 1: effects of 5-HT_{1A}R stimulation on L-DOPA-induced striatal and M1 pERK activation*

2.1.1. *Behavioral testing*

Fig. 1A contains a timeline for experiment 1. Rats were assigned to one of six treatment groups based on scores on the forepaw adjusting steps test, a metric of forelimb akinesia (see Section 4.5.). The average total intact score was 21% and motor ability did not differ between groups ($F_{5,32}$=.13, p=.985). LID development during the 10 days of chronic L-DOPA treatment was monitored using the abnormal involuntary movements (AIMs) scale (see Section 4.4.). Within-subjects comparisons indicated that treatment day had a significant impact on AIMs (χ^2=20.49, p<.001) such that scores were increased on the 10th day relative to the 1st day (Fig. 2A; Z=3.58, p<.001), but not on the 10th day relative to the 6th day (Z=.16, p=.877). These results indicate that rats sensitized to L-DOPA in a typical manner (Cenci and Lundblad, 2007), but reached a stable level of responding by the 10th day. A between-subjects analysis using the Kruskal–Wallis test showed that the treatment groups did not differ in their AIMs scores on day 1, 6 or 10 (Fig. 2B). On day 11, rats were injected with two compounds: the 5-HT_{1A} agonist ±8-OH-DPAT (DPAT), the D_1 antagonist SCH23390 (SCH) or vehicle (VEH) and L-DOPA or VEH. A subset of animals (~1/3) was monitored for AIMs at 10 and 20 min after the final injection (prior to sacrifice). Rats given their 1st dose of L-DOPA did not display visible AIMs at these time points. However, rats on their 11th dose of L-DOPA showed an average summed AIMs score of 1.5, while rats pre-treated with DPAT averaged .5 AIMs and rats given SCH averaged a score of 1 on the AIMs scale.

2.1.2. *Regional changes in striatal pERK expression*

A 3-way mixed model 2 × 4 × 6 ANOVA was utilized to examine effects of lesion, striatal region, and treatment group on pERK. Findings are depicted in Fig. 3. A main effect of lesion revealed a 16-fold greater number of pERK-positive cells in the lesioned than intact hemisphere ($F_{1,34}$=37.93, p<.001). A main effect of striatal region was due to the fact that the two medial areas had more pERK than the lateral areas ($F_{2.3,77.3}$=26.93, p<.001). An effect of treatment group was also seen whereby rats given