Impact of Phosphodiesterase 10A Inhibition on L-DOPA-Induced Dyskinesia

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Introduction

Parkinson’s disease (PD) is a progressive neurological disorder characterized by resting tremor, rigidity and bradykinesia. PD is associated with a preferential loss of the dopamine (DA) producing neurons in the substantia nigra compacta.

L-DOPA is currently the most effective treatment for PD. However, over time chronic L-DOPA treatment loses efficacy and side-effects such as L-Dopa-induced dyskinesias (LIDs) begin to occur (Winkler et al., 2002). Increasing striatal cyclic nucleotide levels via the administration of phosphodiesterase (PDE) inhibitors has emerged as a new potential pharmacological approach to counteract LIDs (Threlfell and West, 2013). PDE regulate the diffusion of cAMP/cGMP in striatal medium spiny neurons (MSNs), which are the primary targets of dopamine neurons (MSNs), which are the primary targets of dopamine regulation the diffusion of cAMP/cGMP in striatal medium spiny neurons (MSNs), which are the primary targets of dopamine

Materials and Methods

DA Lesions

Male adult Sprague-Dawley (Harlan) rats weighting 240-280 g were randomly assigned to groups receiving either a 6-OHDA or sham lesion. Three days prior to surgery, animals were handled twice per day in preparation for behavioral testing. Handling included training rats for a stepping test used to predict the extent of the 6-OHDA lesion. All rats received desipramine (10mg/kg i.p.) 30 min prior to surgery to prevent the lesioning of norepinephrine neurons by 6-OHDA and were anesthetized with isoflurane. A single injection of 6-OHDA (8 µg of 6-OHDA free base in 4µl of 0.1% acetic acid) was delivered into the right medial forebrain bundle (coordinates taken from bregma: -4.3 mm AP, -1.6 mm ML, -8.3 mmDV). The same experimental paradigm was used for the sham-lesioned rats using vehicle (4 µl of 0.1% acetic acid). To confirm the lesion, the stepping test and tyrosine hydroxylase immunohistochemistry were performed. Rats that exhibited a significant decrease in adjusting steps in the forelimb contralateral to the lesion were selected for further study (Figure 2).

Drug Administration

Animals received either a cocktail of: 1) vehicle, 2) L-DOPA, (5 mg/kg, i.p.) and benserazide (12.5 mg/kg, i.p.), or 3) TP-10 (3.2 mg/kg, i.p.) together with L-DOPA/benserazide. TP-10 was administered 30 min prior to L-DOPA.

Behavioral Assessment

Rats were evaluated by a blinded investigator for abnormal involuntary movements (AIMs; dyskinesias) three days per week (Wed-Fri) in a transparent cage every 30 min and up to 180 min after L-DOPA administration. The frequency and intensity of LIDs were recorded for individual dyskinetic behaviors and a total combined LIDs score was determined for each rat (Figure 3).

Results

Figure 1. (a) Model of the effects of striatal dopamine depletion and the resulting parkinsonism on striatal output and basal ganglia-thalamocortical circuits. (b) model of chronic L-DOPA treatment on striatal output and basal ganglia thalamocortical circuits

Figure 2. Immunohistochemical and behavioral assessment of DA depletion. Tyrosine Hydroxylase staining in coronal sections of midbrain (a) and striatum (b). Top: sham operated controls. Bottom: 6-OHDA-lesioned. Evaluation of the unilateral sham or 6-OHDA lesion impact on forelimb use using the stepping test (c). Compared to sham-operated controls, 6-OHDA-lesioned rats exhibited significant impairments in contralateral (**p=0.001, two-way ANOVA, Bonferroni post-hoc test), but not ipsilateral (p=0.05), forelimb adjustment steps.

Figure 3. Gradual induction of abnormal involuntary movements (AIMs) during a chronic treatment with L-DOPA. Left: The abnormal involuntary movements were characterized by scoring the following subtypes of movements as described by (A) axial: lateral flexion and axial rotation of the neck and trunk towards the side contralateral to the lesion; (B) limb: repetitive, rhythmic jerk movements or dystonic posturing of the forelimb; (C) orolingual: abnormal masticatory movements that may include tongue protrusions (D) locomotor: locomotion contralateral to side of lesion, flight: L-DOPA treatment produced development of (A) axial, limb, orolingual and (B) locomotor abnormal involuntary movements (AIMs, dyskinesias), whereas L-DOPA plus TP-10 induced significantly lower levels of dyskinesias (p<0.05, “**” test).

Figure 4. Model of cAMP and cGMP interactions and PDE10A function in L-DOPA-induced dyskinesias. The figure shows the site of action of TP-10 in striatal MSNs (modified from West and Tung, 2011).

Conclusions

These observations demonstrate that robust PDE10A inhibition reduces the incidence and severity of AIMs observed in dyskinetic rats. Thus, selective targeting of PDE10A signaling in striatal MSNs gives promise for a different therapeutic target for the treatment of LID in patients with PD.

Taken together with reports that cyclic nucleotide levels are depressed in dyskinetic animals (Giorgi et al., 2008), it is possible that the therapeutic effects of TP-10 occur via augmentation of striatal-pallidal output. This would be expected to partially restore balance within the direct and indirect striatal output pathways (i.e., reverse L-DOPA-mediated suppression of indirect pathway output). Thus, selective targeting of PDE10A signaling in striatal MSNs may be a promising approach for treating LID-induced dyskinesias in patients with PD.

References


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