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# Chronic SKF83959 induced less severe dyskinesia and attenuated L-DOPA-induced dyskinesia in 6-OHDA-lesioned rat model of Parkinson's disease

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**Abstract**

SKF83959, a recently identified selective agonist of putative phosphoinositide-linked (PI-linked) $D_1$ dopamine (DA) receptor, is found to elicit excellent anti-parkinsonism effects in monkeys and rodents. In the present study, the effects of SKF83959 on L-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia (LID) were assessed in a unilateral 6-hydroxydopamine (6-OHDA) lesioned rat model of Parkinson's disease (PD). The results indicated that chronic L-DOPA (6 mg/kg) induced a progressive dyskinesia-like behavior in PD rats, whereas SKF83959 (0.5 mg/kg) elicited significantly less severe dyskinesia while exerts its anti-parkinsonian action effectively. Application of $D_1$ receptor, but not $D_2$, $\alpha$ or 5-HT receptor antagonist attenuated SKF83959-induced dyskinesia, indicating that a $D_1$ receptor-mediated events, assumedly via PI-linked $D_1$ receptor. Interestingly, chronic co-administration of SKF83959 significantly reduced LID at no expanse of reduction in the anti-parkinsonian potency in PD rats. However, this anti-dyskinesia effect was not observed while SKF83959 was acutely administered in rats with established LID. This implies that chronic SKF83959 attenuated the development of dyskinesia. Immediate early gene FosB is previously reported to positively associate with dyskinesia. However, we found that the anti-dyskinesia effect of chronic SKF83959 was independent of FosB since SKF83959 produced stronger FosB expression in the lesioned striatum than that of L-DOPA while exerting its anti-dyskinesia action. The present data demonstrated that SKF83959 reduces LID by attenuating the development of dyskinesia; the underlying signaling pathway for the anti-dyskinesia action of SKF83959 appears not to depend on FosB.
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*Keywords:* SKF83959; L-dihydroxyphenylalanine (L-DOPA); Dyskinesia; Parkinson's disease; Dopamine receptor; Immediate early gene

## 1. Introduction

The dopamine (DA) precursor, L-dihydroxyphenylalanine (L-DOPA), is the most effective drug for the treatment of Parkinson's disease (PD). However, chronic administration of L-DOPA is associated with the development of uncontrollable movements known as dyskinesia in a vast majority of patients (Nutt, 1990; Olanow et al., 2004; Fahn, 2005). Many patients have to terminate the therapy due to severe dyskinesia. Data from studies of monkeys and PD patients suggest that treatment with DA agonists is less potent at inducing dyskinesia than L-DOPA (Pearce et al., 1999; Rascol et al., 2000).

Recently, a novel DA receptor-coupled second messenger system other than the conventional $G_\alpha$-adenylyl cyclase-cAMP pathway has been reported. This $D_1$-like DA receptor couples to $G_q$ protein and stimulates phospholipase Cβ (PLCβ), resulting in hydrolysis of phosphoinositide (PI) (Undie et al., 1994; Deveney and Waddington, 1995; Pacheco and Jope, 1997; Clifford et al., 1999). SKF83959, a recently identified

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selective agonist for the putative PI-linked DA receptor, also acts as an antagonist of cAMP-coupled $D_1$ receptor (Andringa et al., 1999a; Jin et al., 2003; O'Sullivan et al., 2005; Waddington et al., 2005). It has been documented that SKF83959 has potent anti-parkinsonian effects on non-human primates and rodent models of PD, which may be mediated through activation of PLCβ (Gnanalingham et al., 1995a,b,c,d; Andringa et al., 1999b; Zhen et al., 2005). However, little information is available on the relationship between the atypical D1 DA agonist SKF83959 and dyskinesia (Andringa et al., 1999b). In the present study, we employed an L-DOPA-induced dyskinesia (LID) model to study the role and mechanism of SKF83959 on dyskinesia in unilateral 6-hydroxydopamine (6-OHDA)-lesioned PD rats. The recently developed score system for abnormal involuntary movements (AIMs) was used to monitor the scope of dyskinesia (Cenci et al., 1998; Lee et al., 2000; Lundblad et al., 2002). The results demonstrated that chronic treatment with SKF83959 induced less severe dyskinesia than that of L-DOPA while exerting its powerful anti-parkinsonian action. Chronic administration of SKF83959 also attenuated the severity of LID. We further demonstrated that the SKF83959-mediatedanti-dyskinesia effect is independent of early response gene FosB.

## 2. Methods

### 2.1. Materials

*R*-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine [*R*-(+)-SCH23390] was from Tocris; spiperone was obtained from ICN Biochemicals; 6-hydroxydopamine (6-OHDA) hydrochloride, desipramine hydrochloride, apomorphine hydrochloride, L-dihydroxyphenylalanine (L-DOPA) methyl ester, mesulergine hydrochloride, prazosin hydrochloride and benserazide hydrochloride were from Sigma. 6-Chloro-7,8-dihydroxy-3-methyl-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (SKF83959) was kindly provided by NIMH synthesis program. FosB antibody was purchased from Santa Cruz.

### 2.2. Animal surgeries

Male Sprague–Dawley rats, weighing 200–250 g, were purchased from The Experimental Animal Center of Tongji Medical College, HUST. Surgery was conducted as described before (Zhen et al., 2002). Briefly, Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and received a single stereotactic injection of 8 μg 6-OHDA hydrochloride in 4 μl artificial cerebrospinal fluid containing 0.05% ascorbic acid into the medial forebrain bundle using the following coordinates (in mm, relative to bregma): anteroposterior (AP), −2.5; lateral (L), +2.0; dorsoventral (DV), −8.5. The toxin was infused at the rate of 1 μl/min, and the cannula was left in place for 2 min before being withdrawn. To limit the damage to adrenergic neurons, desipramine hydrochloride (25 mg/kg, i.p.) was administered 30 min before 6-OHDA injection. The experimental protocols were approved and strictly followed by the Institutional Animal Care and Use Committees, and all efforts were made to minimize the animal pain and suffering. Three weeks after surgery, rats were challenged with apomorphine hydrochloride (0.2 mg/kg, s.c.) and contralateral rotation was monitored. Animals showing fewer than 20 rotations per 5 min were excluded from further studies.

### 2.3. Pharmacological treatments

Six weeks after the lesion surgery, rats were divided into four groups randomly and were administered daily (i.p.) either SKF83959 (0.5 mg/kg), or L-DOPA methyl ester (6 mg/kg, i.p.), or SKF83959 (0.5 mg/kg) + L-DOPA, or saline, for 21 days. Benserazide (15 mg/kg) was co-administered with L-DOPA. In the SKF83959 + L-DOPA group, rats received 0.5 mg/kg SKF83959 30 min prior to L-DOPA treatment. AIMs were monitored twice a week using the behavioral score system (see below). Drug-induced rotational behavior was also evaluated as described below. To assess the potential role of other receptors, rats were pretreated with various receptor antagonists such as *R*-(+)-SCH23390 (0.1 mg/kg), spiperone (2 mg/kg), mesulergine HCl (0.1 mg/kg), prazosin HCl (0.1 mg/kg), respectively 20 min prior to application of SKF83959 or L-DOPA.

### 2.4. Behavioral measurements

Rats were monitored for abnormal involuntary movements (AIMs) using a procedure and score system described by Lee and Lundblad with slight modification (Lee et al., 2000; Lundblad et al., 2002). On test days, rats were placed individually in cages of the same style as those used to house the animals. They were assessed every 35 min for total 140 min after injection of the drugs or saline. Each rat was scored for exhibition of the following 3 categories of AIMs: (1) axial, lateral flexion and axial rotation of the neck and trunk towards the side contralateral to the lesion; (2) limb, repetitive, rhythmic jerky movements or dystonic posturing of the forelimb on the side contralateral to the lesion; (3) orolingual, tongue protrusion without the presence of food or other objects. For each observation period of 1 min, a score of 0–4 was assigned for each category based on the following criteria: 0, absent; 1, present for less than half of the observation time; 2, present for more than half of the observation time; 3, present all the time but suppressible by threatening stimuli; 4, present all the time and not suppressible.

For assessing rotational behavior, rats were placed in a 50-cm-diameter bowl and allowed to acclimate to the environment for 10–20 min before injection. Contralateral turns were counted every 5 min for a total of 30 min started at 5 min of injection. For some experiments, the rotation was observed until the turning behavior was stopped.

### 2.5. Immunohistochemistry

Rats were deeply anesthetized with sodium pentobarbital (60 mg/kg) and then rapidly perfused transcardially with 200 ml of cold saline and 400 ml of 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Brains were immediately removed and fixed in 4% paraformaldehyde for 24 h and cryoprotected in 30% sucrose solution. The tissues were cut at 25 μm on a freezing microtome. Sections through the striatum were collected in 0.01 M PBS containing 0.02% sodium azide and stored at 4 °C until use. Immunohistochemistry was performed using a standard peroxidase-based method. The sections were incubated with FosB antibody (1:200) overnight at 4°C followed by biotinylated secondary antibody and HRP-conjugated streptavidin. The sections were developed using diaminobenzidine as the chromogen. FosB immunostainings were digitally captured through an Olympus DP70 camera connected to the microscope, and the immunoreactive cells in a field of 1.02 × 0.78 mm were counted using the image processing and analysis program ImagJ (NIH).

### 2.6. Data analysis

Data are presented as mean ± S.E. AIMs score was evaluated by repeated-measures ANOVA. Rotational behavior was analyzed by Friedman's test followed by the Wilcoxon test. The statistical significance level was set at $p < 0.05$.

## 3. Results

### 3.1. Chronic SKF83959 and L-DOPA elicited different dyskinesia-like behavioral response in PD rat model

Repeated administration of 0.5 mg/kg SKF83959 for 21 days induced dyskinesia-like behavior in 6-OHDA lesioned

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