

## Laboratory Investigation

Yong Sook Park, M.D., Ph.D.<sup>1</sup>  
 Mi Fa Jeon, Ph.D.<sup>3</sup>  
 Bae Hwan Lee, Ph.D.<sup>3</sup>  
 Jin Woo Chang, M.D., Ph.D.<sup>2,3</sup>

Department of Neurosurgery<sup>1</sup>  
 Chung-Ang University  
 College of Medicine  
 Seoul, Korea

Department of Neurosurgery<sup>2</sup>  
 Brain Korea 21 Project  
 for Medical Science &  
 Brain Research Institute<sup>3</sup>  
 Yonsei University  
 College of Medicine  
 Seoul, Korea

# Lesion of Subthalamic Nucleus in Parkinsonian Rats : Effects of Dopamine D<sub>1</sub> and D<sub>2</sub> Receptor Agonists on the Neuronal Activities of the Substantia Nigra Pars Reticulata

**Objective :** It was hypothesized that dopamine agonist administration and subthalamic nucleus (STN) lesion in the rat might have a synergistic effect on the neuronal activities of substantia nigra pars reticulata (SNpr) as observed in patients with Parkinson's disease. The effects of SKF38393 (a D<sub>1</sub> receptor agonist) and Quinpirole (a D<sub>2</sub> receptor agonist) were compared in parkinsonian rat models with 6-hydroxydopamine (6-OHDA) after STN lesion.

**Methods :** SKF38393 and Quinpirole were consecutively injected intrastrially. SNpr was microrecorded to ascertain the activity of the basal ganglia output structure. The effect of SKF38393 or Quinpirole injection on the firing rate and firing patterns of SNpr was investigated in medial forebrain bundle (MFB) lesioned rats and in MFB+STN lesioned rats.

**Results :** The administration of SKF38393 decreased SNpr neuronal firing rates and the percentage of burst neurons in the MFB lesioned rats, but did not alter them in MFB+STN lesioned rats. The administration of Quinpirole significantly decreased the spontaneous firing rate in the MFB lesioned rats. However, after an additional STN lesion, it increased the percentage of burst neurons.

**Conclusion :** This study demonstrated that dopamine agonists and STN lesion decreased the hyperactive firing rate and the percentage of burst neurons of SNpr neurons in 6-OHDA lesioned rats, respectively. Quinpirole with STN lesion increased a percentage of burst neurons. To clear the exact interactive mechanism of D<sub>1</sub> and D<sub>2</sub> agonist and the corresponding location, it should be followed a study using a nonselective dopamine agonist and D<sub>1</sub>, D<sub>2</sub> selective antagonist.

**KEY WORDS :** 6-hydroxydopamine · Substantia nigra pars reticulata · Kainic acid · Subthalamic nucleus · Dopamine agonist · Parkinson's disease.

## INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative movement disorder induced by a progressive loss of dopamine cells in the pars compacta of the substantia nigra (SNpc), leading to dopamine depletion in the striatum<sup>(9)</sup>. Since the discovery of the dopamine precursor, levodopa, it has remained as the most effective medical treatment for PD. However, after several years of exposure to levodopa, the majority of patients develop on-off motor fluctuations, painful dystonia, wearing-off phenomena and levodopa-induced dyskinesia<sup>(10)</sup>. The mechanisms underlying the motor complications in PD remain poorly understood. However, it is now well known that deep brain stimulation (DBS) of the subthalamic nucleus (STN) is reported to decrease motor fluctuations and dyskinesia in patients with PD despite the fact that most patients continue to take levodopa<sup>(14)</sup>. The STN lesion in the rat also normalizes the decreased activity of globus pallidus internus (Gpi) in the rat with a previous medial forebrain bundle (MFB) lesion<sup>(20)</sup>. Thus, both strategies, dopamine agonist administration and STN lesion in the rat, might have a synergistic effect on the neuronal activities of substantia nigra pars reticulata (SNpr) as observed in PD patients treated with bilateral DBS.

In this study, the effects of SKF38393 (a D<sub>1</sub> agonist) and Quinpirole (a D<sub>2</sub> agonist) were compared in parkinsonian rat models with 6-hydroxydopamine (6-OHDA) after STN lesion. To investigate these effects, the changes of the firing rates and firing patterns of SNpr neurons were analyzed.

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 • Address for reprints :  
 Jin Woo Chang, M.D., Ph.D.  
 Department of Neurosurgery  
 Brain Korea 21 Project  
 for Medical Science &  
 Brain Research Institute  
 Yonsei University College of  
 Medicine, 205 Seongsanno  
 Seodaemun-gu  
 Seoul 120-752, Korea  
 Tel : +82-2-2228-2159  
 Fax : +82-2-393-9979  
 E-mail : jchang@yumc.yonsei.ac.kr

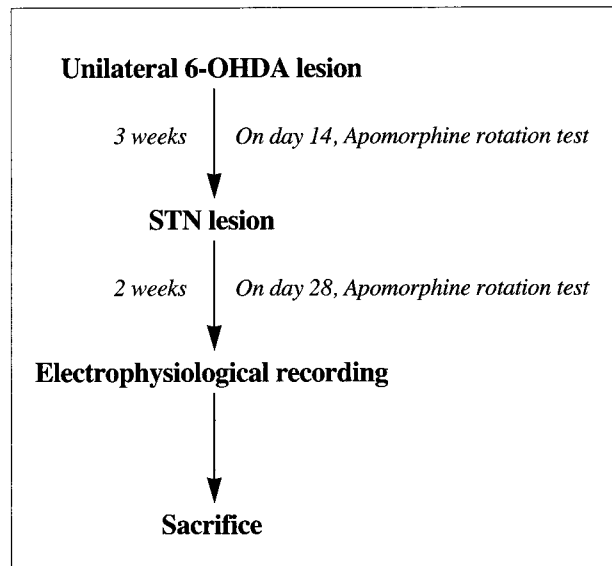
**MATERIALS AND METHODS**

**Surgical procedures for MFB and STN lesions**

Male adult Sprague-Dawley rats weighing 200-250 g were used for the first surgical procedure. Rats were divided into 4 groups: (i) control group, 7 rats without lesions; (ii) 6-OHDA lesioned group, 7 rats that had an MFB lesion induced by 6-OHDA; (iii) 6-OHDA+STN lesioned group, 7 rats with a 6-OHDA lesion of MFB plus a STN lesion, induced by kainic acid; and (iv) 6-OHDA+STN sham group, 7 rats treated with saline instead of kainic acid in STN. Five animals per group were housed in a temperature-controlled room on a 12 hr-light/12 hr-dark schedule with free access to food and water. Rats were anesthetized with a mixture of ketamine (75 mg/kg), acepromazine (0.75 mg/kg) and rompun (4 mg/kg) and mounted in a stereotaxic apparatus. Six-OHDA hydrobromide (Sigma, St Louis, MO, 8 µg free base in 0.2% ascorbic acid) was injected into unilateral MFB according to the following stereotaxic coordinates : AP-4.4 mm, ML 1.2 mm relative to bregma, and DV -7.5 mm from the dura. The injection was made at a rate of 0.5 µl/min using a cannula, and was controlled using a Hamilton microsyringe. A polyethylene tube connected the cannula and the microsyringe. To prevent the noradrenergic neurons being destroyed, desipramine (12.5 mg/kg, i.p.) was administered 30 min prior to the 6-OHDA infusion. The unilateral STN lesion was achieved by injecting 1 µg of kainic acid (Sigma, St Louis, MO) dissolved in 0.5 µl of saline into the right STN (coordinates : AP -3.8 mm, ML 2.5 mm relative to bregma, and DV-8.0 mm from the dura) at the rate of 0.25 µl/min. In the group of rats with combined lesions (6-OHDA+STN lesion), the STN lesion was performed 3 weeks after the 6-OHDA lesion. Sham lesion was performed by using the same protocols as used for the combined lesions, but saline was injected instead of kainic acid. The apomorphine-induced contralateral turning response (0.1 mg/kg i.p.) was performed at 2 weeks after MFB lesioning to select the rats bearing successful lesion.

**Extracellular microrecordings**

The electrophysiological recording was performed 5 weeks after the 6-OHDA lesion in all rats. STN lesions were performed 2 weeks before the recording (Fig. 1). Extracellular, single unit recordings were undertaken in rats anesthetized with urethane (1.3 mg/kg i.p.). A glass microelectrode (impedance, 7-10 Mohm) filled with 2.5% Pontamine sky blue in 0.5 M sodium acetate buffer (pH 7.6) was used to investigate the single recordings. Microelectrodes were stereotaxically guided through a drilled skull burr hole to the target coordinates (SNpr : AP-5.3 mm, ML 2.4 mm relative



**Fig. 1.** Flow chart of the processing. 6-OHDA : 6-hydroxydopamine; STN : subthalamic nucleus.

to bregma, and DV 7.5-8.0 mm from the dura). Electrical signals were amplified using a DAM80 preamplifier (WPI, UK) in bridge mode, displayed on a storage oscilloscope and monitored with an audio amplifier. Single unit activity was isolated with a window discriminator, and firing rate data were collected on a computer equipped with Spike 2 software (version 2.18, Cambridge Electronic Design, UK). Visual inspection of digital neuronal activity and raster displays were useful complements to the computer-based analysis of the discharge patterns of these units. The isolated units were monitored for at least 10 min to ensure the stability of their firing rate, firing pattern and spike morphology, and then 5-10 min of spontaneous activity was recorded. The selective D<sub>1</sub>-class dopamine agonist SKF38393 (Sigma, St Louis, MO, 10 nmol/0.5 µl), or the selective D<sub>2</sub>-class agonist Quinpirole (Sigma, St Louis, MO, 10 µmol/0.5 µl) was injected in the striatum [coordinates AP -0.8 mm, ML 3.0 mm relative to bregma, and DV 1.3 mm from the dura]. This procedure required less than 2 min, and the needle was left in place until the end of the recording, when the location of the tip of the recording microelectrode was marked, at -15 uA for 20-30 min, by an iontophoretic deposit of Pontamine Sky Blue.

The mean firing rate, the mean interspike interval (ISI), autocorrelogram and discharge pattern were investigated for each neuron. The ISIs allowed an evaluation of the neurons' degree of burst frequency, following an algorithm described by Hutchison et al.<sup>10,11</sup>. Bursting cells had a degree of burstiness score of more than 10, which was calculated from the reciprocal of the modal interval divided by the mean firing rate.

## Histology and immunohistochemistry

After the extracellular single unit recording, rats were anesthetized and transcatheterially perfused with 125 ml of normal saline followed by 250 ml of ice-cold 4% paraformaldehyde. Brains were removed, postfixed for 10 hours, and submerged in 30% sucrose until equilibrated. Twenty micrometer sections were cut and then immunoreacted with a primary, polyclonal antibody against rat tyrosine hydroxylase (TH, Pel-freeze, Rogers, AK) at a dilution of 1 : 750, and then with a biotinylated goat anti-rabbit IgG (Vector Labs, Burlingame, CA) secondary antibody. The signal was amplified using avidin and biotinylated horseradish peroxidase using an Elite ABC Vectastain Kit (Vector, Burlingame, CA). 3, 3'-Diaminobenzidine tetrachloride dehydrate was used as a chromogen and cobalt chloride/nickel ammonium was used to intensify color changes. This immunostaining allowed the determination of the extent of dopaminergic cell degeneration. Only rats with a total loss of TH immunoreactivity were used for the electrophysiological analysis. The STN lesions and the localization of the recorded basal ganglia nuclei were studied in 20- $\mu$ m sections stained with cresyl violet.

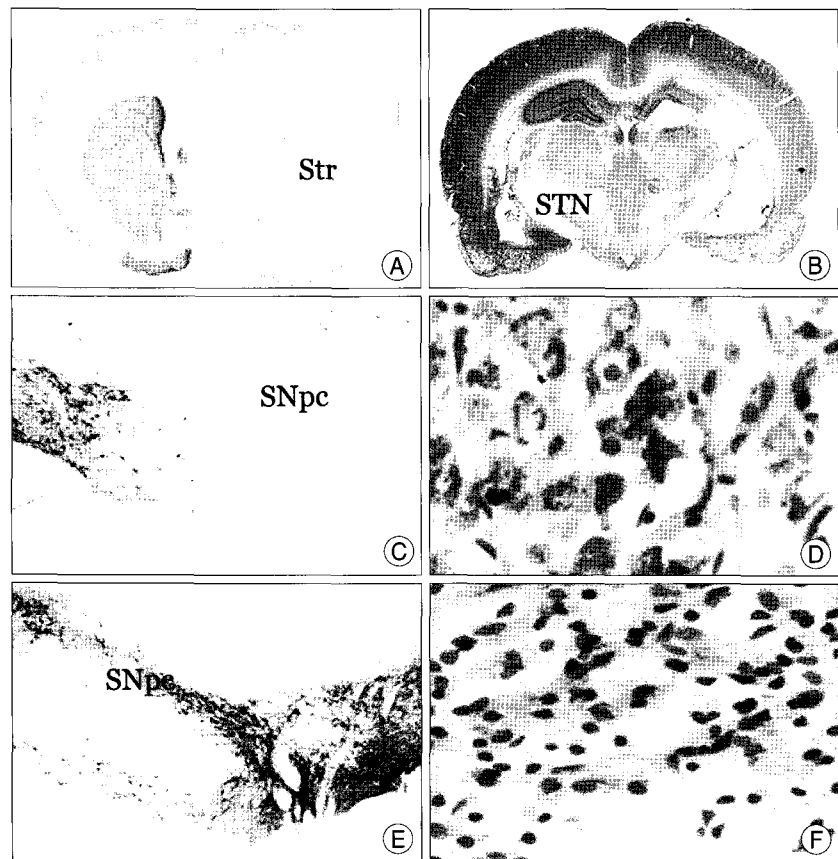
## Data analysis

Statistical analysis was performed with the SPSS version 11.0 statistical software packages (SPSS Inc., Chicago, IL). Comparisons of the firing rates from different rats in each group were performed using analysis of variance (ANOVA). Results showing significant differences between groups were compared using Kruskal-Wallis one-way ANOVA and then the Mann-Whitney U-test. Statistical significance was set at  $p < 0.05$ .

## RESULTS

### Histological findings of rat parkinsonian models

The extent and location of the lesions induced by 6-OHDA were confirmed by assessing the loss of TH-immunoreactive cells in SNpc in a rat parkinsonian model with 6-OHDA. All 6-OHDA lesioned rats used throughout these experiments



**Fig. 2.** Photomicrographs of a representative 6-OHDA lesion of the nigrostriatal bundle using immunohistochemistry of tyrosine hydroxylase in the striatum (A) and kainic acid lesion of the STN (B). The tyrosine hydroxylase immunopositive cell shows total degeneration of dopamine cell body in the lesion sides of the pars compacta of substantia nigra (C) compared to normal side (E). STN lesion with kainic acid showing a nearly complete loss of neurons and an intense gliosis reaction compared to the intact contra lateral side (D, F). Str : Striatum; SNpc : Substantia nigra pars compacta; STN : Subthalamic nucleus; 6-OHDA : 6-hydroxydopamine.

showed more than 100 full contralateral net turns during 1 hour after administration of apomorphine (0.1 mg/kg i.p.). TH immunohistochemistry was used to confirm the completeness of the 6-OHDA lesion of the nigrostriatal pathway. All rats receiving unilateral 6-OHDA injections showed almost total loss of TH-immunoreactive cells from the substantia nigra and the striatum on the lesion side (Fig. 2). The STN lesions were also evaluated after conducting the experiments and they revealed local gliosis at the STN level. The cresyl violet Nissl staining was used to confirm the completeness of the kainic acid lesion of the STN. All rats receiving STN lesions showed virtually complete (>90%) cell loss in the STN, with little or no damage to surrounding structures (Fig. 2). The localizations of the recorded SNpr were also confirmed by cresyl violet staining (Fig. 2).

### Effects of STN lesions on firing rate and firing patterns

In each group, the mean firing rates and the total number of cells recorded are shown in Table 1. The number of cells

**Table 1.** Spontaneous activity of SNpr single units recorded from 6-OHDA lesioned rats with a kainic acid lesion of the STN and intrastriatal selective D<sub>1</sub>, D<sub>2</sub> agonist microinjection

		Control	MFB	MFB+STN	MFB+STN sham
Control	Neurons (n)	35	47	27	21
	Mean firing rate (Hz)	20 ± 1.9	28 ± 1.5*	21 ± 1.8	28 ± 2.0
	Interspike interval (sec)	0.047 ± 0.0071	0.029 ± 0.0036	0.037 ± 0.0049	0.032 ± 0.0056
SKF38393	Neurons (n)	16	25	18	14
	Mean firing rate (Hz)	21 ± 1.6	21 ± 2.7	20 ± 2.3	20 ± 4.2
	Interspike interval (sec)	0.033 ± 0.0050	0.045 ± 0.0074	0.041 ± 0.0052	0.059 ± 0.0150
Quinpirole	Neurons (n)	12	24	15	11
	Mean firing rate (Hz)	28 ± 2.4*	16 ± 1.3*	20 ± 3.6	18 ± 1.1
	Interspike interval (sec)	0.026 ± 0.0045	0.041 ± 0.0079	0.036 ± 0.0062	0.024 ± 0.0083

The values mean ± SEM. \**p* < 0.05 in comparison with values from control subjects. SNpr : substantia nigra pars reticulata; 6-OHDA : 6-hydroxydopamine; MFB : medial forebrain bundle; STN : subthalamic nucleus

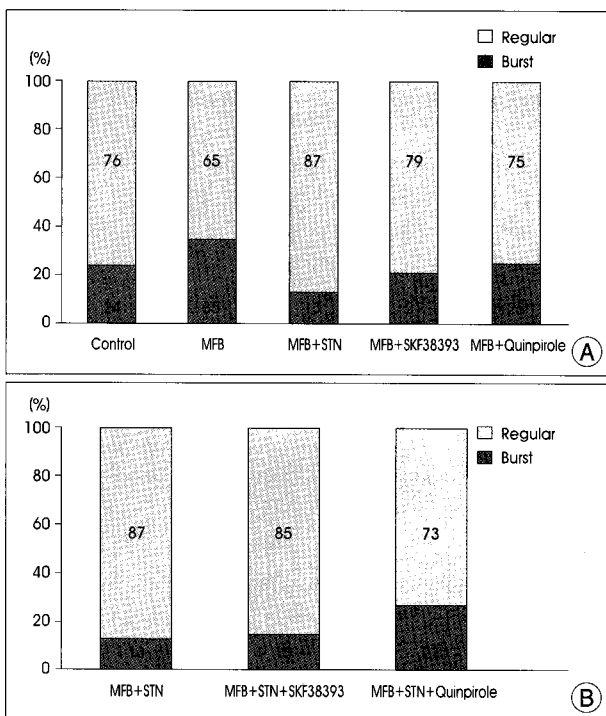
recorded per track was similar for each group. The firing patterns in SNpr were classified into a regular non-burst pattern and a burst pattern. In normal unlesioned rats, the mean firing rates of neurons in SNpr (n=35) were 20 ± 1.9 spikes/s (Table 1). Compared with the normal control rats, parkinsonian rat models with 6-OHDA exhibited significantly increased mean firing rates in SNpr (28 ± 1.5 spikes/s, *p* < 0.05). Following STN lesion in parkinsonian rats, the mean firing rate in SNpr was reduced compared to that of parkinsonian rats (21 ± 1.8 vs. 28 ± 1.5 spikes/s, respectively,

*p* < 0.05). No statistically significant difference was observed between the mean firing rates of MFB lesioned and sham STN lesioned parkinsonian rats. Regular neurons represented 76% of the neurons in normal rats, and burst neurons, 24% (Fig. 3). In 6-OHDA lesioned rats, the number of burst neurons increased from 24% to 35%. The STN lesions in the 6-OHDA lesioned rats increased the percentage of regular neurons to 87% in the

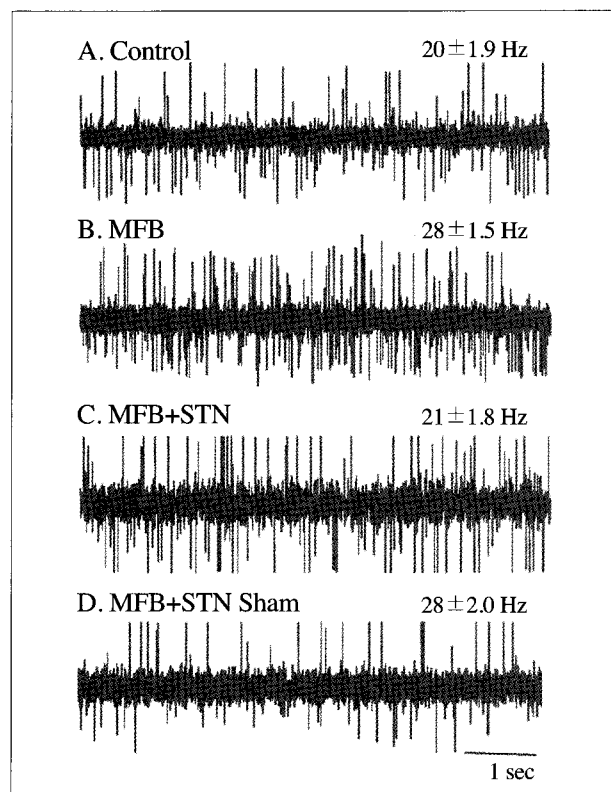
group of STN lesioned rats versus 76% in the normal rats. Representative discharge pattern of units recorded from SNpr of control group, MFB group, MFB+STN group, and MFB+STN sham group were presented (Fig. 4).

**Effects of SKF38393 on the firing rates and firing patterns**

The effect of the D<sub>1</sub> agonist, SKF38393, applied by intrastriatal injection, on the firing rate of SNpr units is shown in Table 1. The administration of SKF38393 decreased SNpr



**Fig. 3.** The effects of D<sub>1</sub> agonist (SKF38393) and D<sub>2</sub> agonist (Quinpirole) on the firing pattern of substantia nigra pars reticulata neurons in rat parkinsonian models. A : The proportion of burst neurons in the substantia nigra pars reticulata of each group. B : The effects of SKF38393 and Quinpirole on the firing pattern of substantia nigra pars reticulata neurons in rat parkinsonian models after the subthalamic nucleus lesion. MFB : medial forebrain bundle; STN : subthalamic nucleus.



**Fig. 4.** Representative discharge pattern of units recorded from substantia nigra pars reticulata of control group, MFB group, MFB+STN group, and MFB+STN sham group. MFB : medial forebrain bundle; STN : subthalamic nucleus.

neuronal firing rates in 6-OHDA lesioned rats (from  $28 \pm 1.5$  to  $21 \pm 2.7$  spikes/s,  $n=25$ ), but did not significantly alter the mean firing rate of SNpr neurons in the intact rat ( $21 \pm 1.6$  vs. the control at  $20 \pm 1.9$  spikes/s,  $n=16$ ). SKF38393 did not alter the mean neuronal firing rate in the SNpr neurons of MFB+STN lesioned rats ( $20 \pm 2.3$  vs.  $21 \pm 1.8$  spikes/s, respectively,  $n=18$ ). In rats with 6-OHDA lesions of MFB, SKF38393 induced a decrease in the percentage of burst neurons (from 35% to 21%). Additional SKF38393 injection in STN lesioned and MFB lesioned rats increased the percentage of burst neurons (from 13% to 15%) but the change was not significant.

### Effects of Quinpirole on the firing rate and firing patterns

The excitatory effect of dopamine on the neuronal activity of STN in parkinson's disease appeared to be largely via the dopamine D<sub>2</sub>-like receptor agonist. Quinpirole increased the mean firing rate of SNpr neurons in normal rats from  $20 \pm 1.9$  to  $28 \pm 2.4$  spikes/s ( $p < 0.01$ ). However, in neurons prepared from 6-OHDA lesioned rats, Quinpirole decreased the spontaneous firing rate from  $28 \pm 1.5$  to  $16 \pm 1.3$  spikes/s ( $p < 0.01$ ). In rats with 6-OHDA lesions of MFB, Quinpirole induced a significant change in the percentage of burst neurons (from 35% to 25%). However, Quinpirole after the additional STN lesion in rats with 6-OHDA lesions of MFB induced a significant increase in the percentage of burst neurons (from 13% to 27%).

## DISCUSSION

### Effects of STN lesions on the firing rates and firing patterns of SNpr in rat parkinsonian model

In accordance with predictions, our data demonstrated that SNpr neurons recorded in rat parkinsonian models also exhibited basal firing rates of SNpr neurons that were faster in MFB lesioned rats ( $28 \pm 1.5$  Hz) than those observed in SNpr of normal rats ( $20 \pm 1.9$  Hz). We observed that rat PD models had more burst neurons (35%) in SNpr than the control rats (24%). Following STN lesioning for the rat PD models, the percentage of burst neurons decreased by 13% ( $p < 0.05$ ). This finding suggested that STN lesion decreased the percentage of SNpr burst neurons<sup>12</sup>.

However, several authors have reported controversial results. Kreiss et al.<sup>13</sup> reported that rat PD models had more regular neurons in STN than the control rats did. Rohlfs et al.<sup>22</sup> reported that SNpr neuronal activity in rat parkinsonian models was significantly lower than the respective activity in the control groups, and that, in contrast, contralateral SNpr neuronal activity in rat parkinsonian models was significantly

higher than the respective activity in the contralateral SNpr neuronal activity of control rats. In addition to the significant reduction in the mean firing rate, they also reported that many neurons in SNpr on the lesioned side exhibited a burst pattern. MacLeod et al.<sup>15</sup> suggested that the continuous burst type of firing could be an indication of a compensatory physiological mechanism for the loss of spontaneous firing, and that the decreased mean firing rate of ipsilateral SNpr neurons, observed in rats within 2 weeks post-lesion, can be explained by assuming a postsynaptic inhibitory action of dopamine in the striatum. However, our data did not seem to support these suggestions. All of our rat parkinsonian models with 6-OHDA clearly demonstrated an increase in the mean firing rates in SNpr. In addition, the results of our rat PD models with STN lesions further supports the theory that the mean firing rates in SNpr are reduced by the presence of STN lesions.

### Effects of SKF38393 and Quinpirole on the firing rates and firing patterns of SNpr in rat parkinsonian model with STN lesion

The STN hyperactivity is based on the hypothesis that the loss of dopamine in the striatum reduces the activity of the inhibitory GABAergic pallido-subthalamic pathway<sup>1,16</sup>. Our results also demonstrate that SKF38393 and Quinpirole decreased the mean firing rate in SNpr of rats with MFB lesion with 6-OHDA. However, we did not find a further decrease in the SNpr firing rate after the administration of SKF38393 or Quinpirole in additional STN lesions of MFB lesioned rats with 6-OHDA. This may suggest that D<sub>2</sub> agonist has a stronger influence on the firing rates of SNpr because it could affect the function of STN and pedunculopontine nucleus<sup>12</sup>. The interaction between indirect pathway and direct pathway, or some roles for STN in the genesis or maintenance of SNpr neural activity might be considered as well.

Under the balanced condition between direct and indirect pathways, which is a normal control group and an STN and MFB lesioned group, augmentation of D<sub>1</sub> receptor hardly affected the firing rate and firing pattern of SNpr. However, augmentation of D<sub>2</sub> receptor resulted in increasing firing rate (control group) and increasing the proportion of burst neurons (MFB+STN group). This means D<sub>1</sub> or D<sub>2</sub> dopamine agonist alone is not sufficient to affect the SNpr neural activity. Other reports support the consistent results<sup>13,17</sup>. Kreiss et al. indicated that the integration of dopamine D<sub>1</sub> and D<sub>2</sub> receptors rather than predominant action of dopamine D<sub>2</sub> receptors was considered to regulate STN neuronal activity<sup>13</sup>. Calabresi et al. reported that stimulation of both D<sub>1</sub> and D<sub>2</sub> dopamine receptors is required for the expression of

long term depression at the single cell level in striatal slices<sup>5</sup>. Other in vitro studies have shown that D<sub>1</sub> and D<sub>2</sub> dopamine receptors expressed in the same cell were able to interact synergistically<sup>3,21</sup>. Gerfen et al. have demonstrated that D<sub>1</sub> agonists are able to modify the expression of an immediate early gene mRNA exclusively in striatal enkephalin-negative neurons and that D<sub>2</sub> agonists have an opposite effect exclusively on enkephalin-positive neurons<sup>7</sup>. The coadministration of D<sub>1</sub> and D<sub>2</sub> agonists produced a potentiated effect in enkephalin-negative neurons. These results also suggest that this synergistic action seen at the single cell level results from interneuronal interactions between separate populations of striatal neurons sensitive either to D<sub>1</sub> or D<sub>2</sub> receptor agonists. While Other reports have shown that microiontophoretically administered D<sub>1</sub> and D<sub>2</sub> dopamine receptor agonists do not interact synergistically at the single cell level within the striatum<sup>9,23</sup>, suggesting that the D<sub>1</sub>-D<sub>2</sub> receptor interaction could also involve other mechanisms. An alternative mechanism could be an interplay between the direct striatonigral and the indirect striato-pallido-subthalamo-nigral pathways at the SNr level, resulting in a greater number of responding units in the SNr when both pathways are activated by the appropriate dopamine receptor agonists. Alternatively, burst activity could originate in other structures projecting to STN, such as the sensorimotor cortex or the intralaminar thalamic nuclei<sup>22</sup>.

Recent studies have provided evidence that an irregular or burst firing pattern might correlate better than firing rate with signs of PD<sup>2,8</sup>. In our experiment, the proportion of burst neurons in SNpr of 6-OHDA lesioned rats was significantly reduced by STN lesions. These results suggest that the interruption of the indirect pathway by a STN lesion regularizes the SNpr neuron discharge pattern in 6-OHDA lesioned rats. From recent evidence, it appears that STN participates in the genesis of the burst pattern activity of globus pallidus (GP) and SNpr neurons in rats with 6-OHDA lesions, and that STN lesions can reverse this abnormal spontaneous pattern<sup>4,17,18</sup>.

## CONCLUSION

This study demonstrated that dopamine agonists and STN lesion decreased the hyperactive firing rate of SNpr neurons in 6-OHDA lesioned rats, respectively. Concerning the firing pattern, the STN lesion reduced the percentage of burst neurons in 6-OHDA lesioned rats. However, Quinpirole with STN lesion demonstrated a higher percentage of burst neurons than did STN lesion in 6-OHDA lesioned rats. D<sub>1</sub>-D<sub>2</sub> receptor interactions may be considered. To clear the exact interactive mechanism of D<sub>1</sub> and D<sub>2</sub> agonist and the

corresponding location, it should be followed by a study using a nonselective dopamine agonist and D<sub>1</sub>, D<sub>2</sub> selective antagonist.

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