

## Increased Burst Firing in Substantia Nigra Pars Reticulata Neurons and Enhanced Response to Selective D2 Agonist in Hemiparkinsonian Rats After Repeated Administration of Apomorphine

Intermittent administrations of dopaminergic agents in hemiparkinsonian rat enhances the behavioral response to subsequent administration of the drugs. This phenomenon is known as "priming" and thought as comparable to drug-induced dyskinesia in patients with Parkinson's disease. We investigated the behavioral and electrophysiological changes in 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian rats after repeated administrations of apomorphine. Administration of apomorphine (0.32 mg/kg, intraperitoneal, i.p.) twice daily for 6 days enhanced the rotation induced by apomorphine from 341 turns/hour at the beginning to 755 turns/hr at the end. At the same time, the response to selective D2 agonist quinpirole (0.26 mg/kg, i.p.) was also enhanced from 203 to 555 turns/hr. Extracellular single unit recording revealed no significant difference in the basal firing rates of substantia nigra pars reticulata (SNr) neurons between the ipsilateral and contralateral side of the 6-OHDA lesion regardless of the repeated administrations of apomorphine. In SNr of the lesion side, the units with burst firing pattern were found more frequently after repeated administrations of apomorphine and the suppressive effect of quinpirole on the firing rate was enhanced. These findings suggest that the increased percentage of the burst units is the important electrophysiological change in the development of enhanced response to selective D2 agonist.

**Key Words :** *Parkinsonian Disorders; Quinpirole; Dyskinesias; Substantia Nigra*

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## INTRODUCTION

Long-term treatment of Parkinson's disease with dopamine-replacing agents such as L-3,4-dihydroxy-phenylalanine (L-DOPA) is compromised by many side-effects including involuntary movements termed L-DOPA-induced dyskinesia, which is one of the most common complications (1, 2). In contrast to L-DOPA, de novo administration of the D2-like dopamine agonist such as bromocriptine or lisuride is associated with the lower incidence of significant dyskinesia either in patients or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys (3-5). However, selective D2 agonist produces severe dyskinesias comparable with that induced by L-DOPA once L-DOPA was administered and elicited dyskinesias (6-8). In 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian rat model acute challenge with dopamine-replacing agents elicits a rotational response contraversive to the lesion. This rotational response shows plasticity and repeated administration of L-DOPA or apomorphine is accompanied by a marked enhancement in

this response (9-11). This phenomenon is known as priming and has pharmacological characteristics similar to L-DOPA-induced dyskinesia seen in MPTP-lesioned primates and men (12). We investigated the change of the rotation response to a selective D2 agonist quinpirole in hemiparkinsonian rat model with an intermittent administration of apomorphine. Electrophysiological changes associated with priming and the effect of quinpirole on neuronal activity were examined in substantia nigra pars reticulata (SNr) using extracellular single unit recording.

## MATERIALS AND METHODS

### Nigrostriatal lesions

Adult male Sprague-Dawley rats (200-220 g) were anesthetized with ketamine (150 mg/kg, intraperitoneal, i.p.) and fixed to a stereotaxic frame (David Kopf Instruments, Tujunga, CA, U.S.A.). The skull was exposed, and a burr

hole was drilled. Animals were lesioned by injecting 2.5  $\mu$ L and 2  $\mu$ L of 6-OHDA hydrobromide (Sigma, St. Louis, MO, U.S.A., 3  $\mu$ g free base/ $\mu$ L in 0.2% ascorbate-saline) into 2 sites at the right side nigrostriatal pathway with the following stereotaxic coordinates respectively: tooth bar 2.4 mm below the interaural line, 4.4 mm posterior and 1.2 mm lateral with respect to the bregma, and 7.8 mm ventral with respect to the dura; tooth bar 3.4 mm above the interaural line, 4.0 mm posterior, and 0.8 mm lateral, and 8 mm ventral. Injection was done at a rate of 1  $\mu$ L/min using a Hamilton 10  $\mu$ L syringe with 26-gauge needle.

#### Drug treatment and behavioral analysis

Three weeks after the operation, rats were injected with apomorphine (0.32 mg/kg, i.p.) (Sigma, St. Louis, MO, U.S.A.) and the number of complete 360 degree rotations ipsiversive and contraversive to the lesion were counted over 1 hr using rotometer (Rotorat, Med Associates Inc., Lafayette, IN, U.S.A.) connected to a personal computer. The number of net rotations was obtained by subtracting the number of ipsiversive rotations from that of contraversive rotations. Only the rats with more than 100 turns of net rotations were used for further experiment. On the following day, quinpirole (0.26 mg/kg, i.p.) (Sigma) was injected and rotations were counted. From the third day of the drug treatment, one group of rats (apomorphine treatment group) were repeatedly injected with apomorphine (0.32 mg/kg, i.p.) twice daily (9 a.m. and 5 p.m.) for 6 days. The other group of rats (vehicle treatment group) were injected with sterile water with the same schedule. All the rats were injected with quinpirole once again on the day following 6 days of drug or vehicle treatment. Rotations were counted at every injections of apomorphine, quinpirole, and sterile water.

#### In vivo extracellular single unit recording

Extracellular single unit recording in SNr was performed in rats anesthetized with urethane (1.2 g/kg, i.p.) (Sigma) and secured to a stereotaxic frame. Single unit activity in SNr was recorded bilaterally using the following stereotaxic coordinates: 5.4 mm posterior and 2.2 mm lateral with respect to the bregma, and 6.6 mm ventral with respect to the dura. A glass-coated platinum-iridium microelectrode was introduced using hydraulic microdrive (David Kopf Instruments, Tujunga, CA, U.S.A.) and single unit activity was recorded in the range of 6.6 to 7.8 mm ventral to the dura. When isolation of single unit and continuous recording with enough duration was not possible, the second trajectory was located 0.3 mm medial from the first one. The exposed tip of the microelectrodes ranged from 5 to 10  $\mu$ m and the electrode impedance ranged from 0.5 to 1.0 M $\Omega$ . Raw neural activity was amplified and displayed on an oscilloscope and stored on computer using a neurophysiological

data acquisition and analysis package (Spike2, Cambridge Electronic Design, Cambridge, England). Spontaneously active neurons with 10 Hz or higher frequency of firing were recorded for at least 5 min. In each animal, one unit from the ipsilateral side of the lesion was finally selected to record response to quinpirole. Increasing doses of quinpirole (0.0325, 0.065, 0.13, 0.26, and 0.52 mg/kg) were given through the tail vein at intervals of 10 min.

#### Histology

The bottom of the last track was marked by direct current (+100  $\mu$ A, 30 sec). The rat was killed by pentobarbital overdose, exsanguinated and perfused with warm saline and followed by 10% formalin. The brain was removed and postfixed in formalin overnight. It was sectioned on a freezing microtome at a 100  $\mu$ m thickness and stained with hematoxylin/eosin and cresyl violet. The locations of the recorded neurons were reconstructed with reference to the histology and only those located within SNr were used for further analysis.

#### Data Analysis

Difference in the number of rotations between apomorphine and vehicle treatment groups was tested by Student t-test for statistical significance. Difference according to repeated drug treatment was tested by repeated measure ANOVA with post hoc adjusted comparisons (Newman-Keuls procedure).

The stored digital record of neural activity was retrieved and analyzed off-line. The numbers of spontaneous action potentials (spikes) were counted for at least 5 min for all recorded units and the mean firing rate was calculated. The mean firing rate over a period from 5 min to 10 min after injection of quinpirole was obtained to evaluate the effect of the drug. The firing patterns of each individual cells were analyzed and classified into the burst and non-burst units by visual inspection, the frequency distribution of the interspike intervals (ISI), autocorrelograms and coefficient of variation of at least 500 intervals obtained from the representative segments of signal. The one-way ANOVA with post hoc adjusted comparisons (Newman-Keuls procedure) and Fisher's exact test were used to determine the statistical significance of differences in firing rate, coefficient of variation, and incidence of the burst units. Statistical significance was defined as *p* value less than 0.05.

## RESULTS

#### Behavioral evaluation

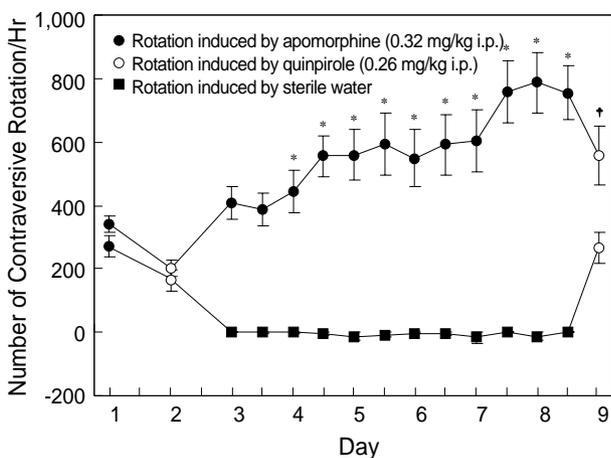
Lesioning, behavioral test, drug treatment, and electro-

physiological recording were completed in 20 rats. There were 12 rats in apomorphine treatment group and 8 rats in vehicle treatment group. In apomorphine treatment group, apomorphine-induced rotations increased significantly in proportion to the number of apomorphine injection from  $341 \pm 28$  turns/hr (mean  $\pm$  standard error of mean, SEM) at the beginning to  $755 \pm 87$  turns/hr at the end of 6 days' treatment (Fig. 1). Also quinpirole-induced rotations increased significantly after 6 days of repeated apomorphine

**Table 1.** Spontaneous activity of substantia nigra pars reticulata units in unilateral 6-OHDA-lesioned rats: firing rates and coefficients of variation\*

	Basal firing rate <sup>†</sup>		Coefficient of variation <sup>‡</sup>	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
<b>Apomorphine treatment group</b>				
Ipsilateral (n=28)	27.3 $\pm$ 3.2	0.70 $\pm$ 0.07		
Contralateral (n=27)	29.0 $\pm$ 4.5	0.35 $\pm$ 0.03		
<b>Vehicle treatment group</b>				
Ipsilateral (n=21)	25.6 $\pm$ 3.8	0.50 $\pm$ 0.06		
Contralateral (n=20)	29.6 $\pm$ 4.5	0.35 $\pm$ 0.02		
All groups (n=96)	27.9 $\pm$ 1.9	0.49 $\pm$ 0.03		

\*The data are the mean  $\pm$  standard error of mean of n cells per group. <sup>†</sup>The spontaneous firing rates did not differ among groups: one-way ANOVA. <sup>‡</sup>Ipsilateral SNr had significantly higher coefficient of variation than contralateral side regardless of treatment. Also ipsilateral SNr of apomorphine treatment group had a higher coefficient of variation than that of vehicle treatment group ( $p < 0.05$ , Newman-Keuls procedure after a significant one-way ANOVA,  $p < 0.05$ ).



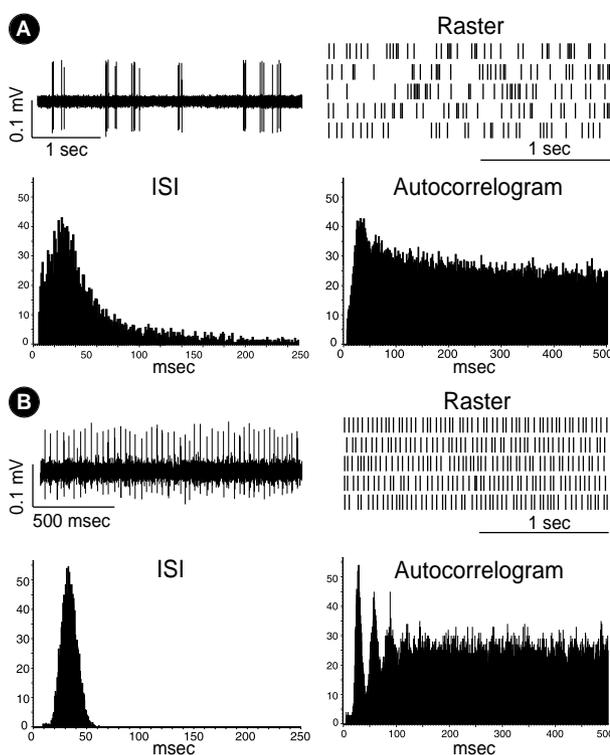
**Fig. 1.** Behavioral hyperkinesia following repeated apomorphine administration in 6-OHDA-lesioned rats. Net 360 degree rotations contraversive to the lesion were measured following twice-daily (9 AM and 5 PM) injections of apomorphine or sterile water. At the beginning and the end of the test, rotations induced by quinpirole were measured. Data are expressed as mean  $\pm$  standard error of mean. (n=12 for apomorphine treatment group, n=8 for vehicle treatment group; \* $p < 0.05$  compared to day 1 apomorphine administration, repeated measures ANOVA followed by Newman-Keuls test; <sup>†</sup> $p < 0.05$  compared to day 2 quinpirole administration and day 9 of vehicle treatment group, Student *t*-test).

administration ( $203 \pm 26$  turns/hr before apomorphine treatment vs.  $555 \pm 93$  turns/hr after apomorphine treatment,  $p < 0.01$ ) (Fig. 1). In vehicle treatment group quinpirole-induced rotations also increased at the end of the test, however, it was not statistically significant ( $164 \pm 34$  turns/hr vs.  $266 \pm 51$  turns/hr,  $p > 0.05$ ).

**Table 2.** Incidence of substantia nigra pars reticulata units in unilateral 6-OHDA-lesioned rats with different firing patterns

Type of unit *	Apomorphine treatment group		Vehicle treatment group		Coefficient of variation <sup>†</sup>
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	
Burst	15 (54%)	0	5 (24%)	0	0.93 $\pm$ 0.08
Non-burst	13 (46%)	27 (100%)	16 (76%)	20 (100%)	0.38 $\pm$ 0.02

\*Ipsilateral SNr had significantly higher incidence of the burst units than contralateral SNr in each treatment group. Ipsilateral SNr of apomorphine treatment group showed higher incidence of the burst units than that of vehicle treatment group ( $p < 0.05$ , Fisher's exact test). <sup>†</sup>The data are the mean  $\pm$  standard error of mean. Burst units had significantly higher coefficient of variation than non-burst units ( $p < 0.05$ , student *t*-test).



**Fig. 2.** Single unit recordings in the substantia nigra pars reticulata of 6-OHDA-lesioned rats. They could be classified into two types on the basis of their firing pattern. (A) A typical burst unit showed a high frequency firing interrupted by pause, an asymmetric interspike interval frequency distribution, and flat autocorrelogram with a single initial peak. (B) A typical non-burst unit with regular firing pattern showed a symmetric interspike interval frequency distribution and several peaks in autocorrelogram occurring with intervals approximating mean interspike interval.

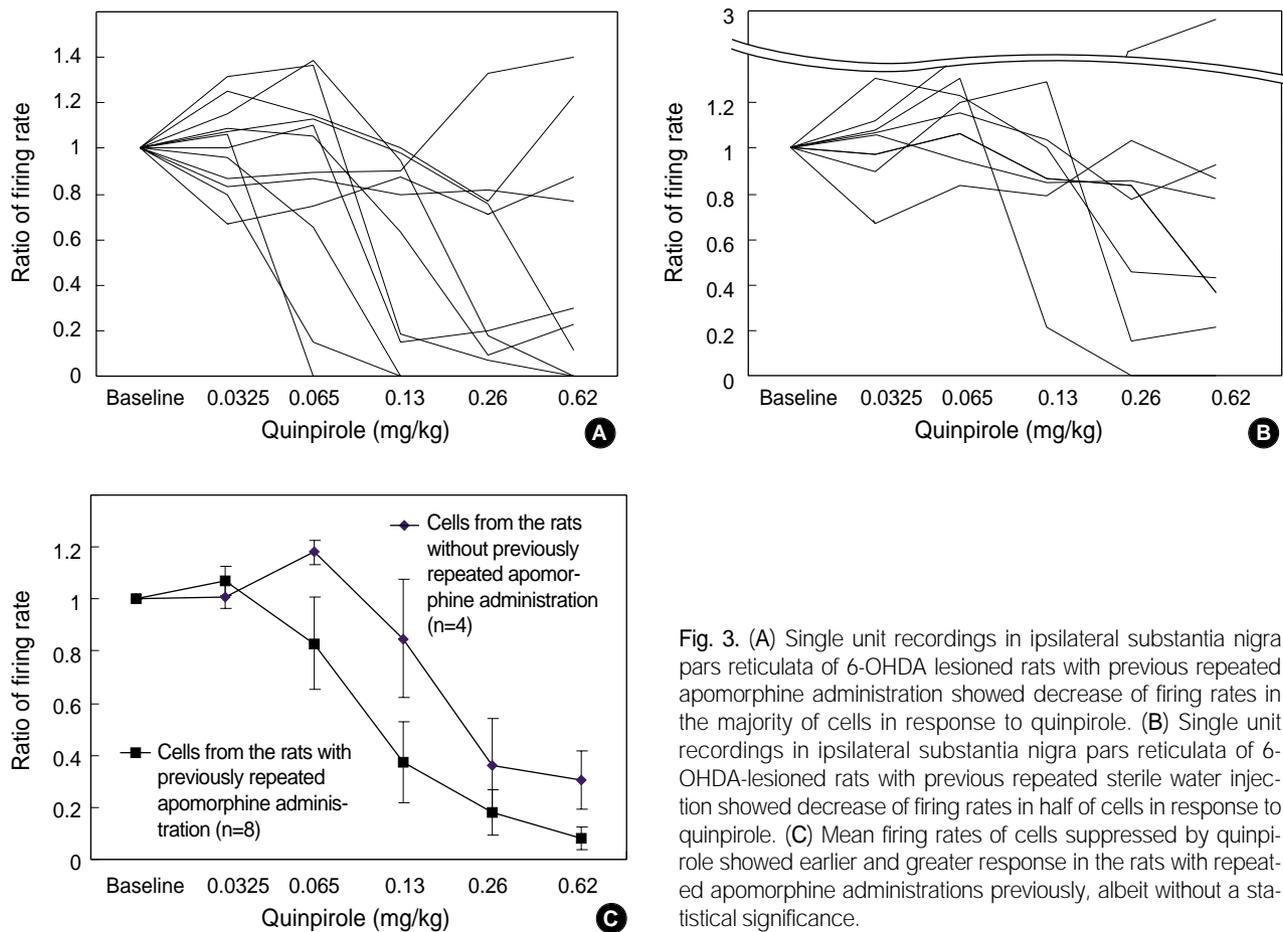


Fig. 3. (A) Single unit recordings in ipsilateral substantia nigra pars reticulata of 6-OHDA lesioned rats with previous repeated apomorphine administration showed decrease of firing rates in the majority of cells in response to quinpirole. (B) Single unit recordings in ipsilateral substantia nigra pars reticulata of 6-OHDA-lesioned rats with previous repeated sterile water injection showed decrease of firing rates in half of cells in response to quinpirole. (C) Mean firing rates of cells suppressed by quinpirole showed earlier and greater response in the rats with repeated apomorphine administrations previously, albeit without a statistical significance.

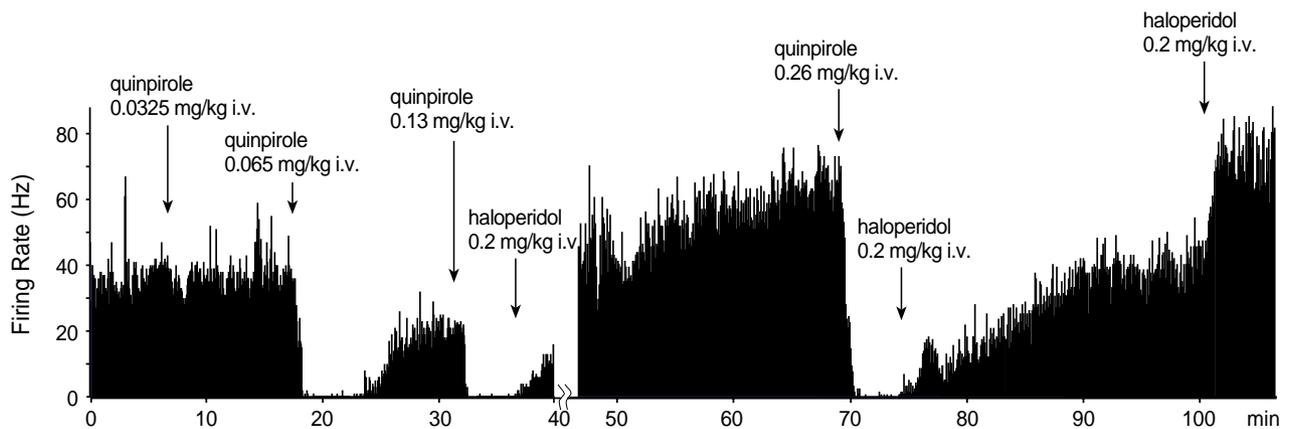


Fig. 4. Effect of quinpirole and haloperidol on the single unit firing in substantia nigra pars reticulata of the 6-OHDA-lesioned rat is shown as a histogram. Apomorphine was administered repeatedly for 6 days in this rat. Continuous recordings over 110 min period showed a suppression of firing by relatively low dose of quinpirole that was reversed by haloperidol.

### Electrophysiological recording

Single units isolated in SNr of 20 rats (n=96) were recorded and analyzed. The basal firing rates in the ipsilateral and contralateral side of 6-OHDA lesion were  $25.6 \pm 3.8$  Hz (mean  $\pm$  SEM, n=21) and  $29.6 \pm 4.5$  Hz (n=20),

respectively, in vehicle treatment group and  $27.3 \pm 3.2$  Hz (n=28) and  $29.0 \pm 4.5$  Hz (n=27), respectively, in apomorphine treatment group (Table 1). The differences in basal firing rates between either treatment groups or hemispheres were not statistically significant, however, coefficient of variation was significantly higher in ipsilateral SNr of apo-

morphine treatment group than in contralateral side or vehicle treatment group. Typical burst firing pattern with long-duration high-frequency action potentials separated by a period of low-frequency tonic activity or complete absence of discharge (13) was identified in 20 units exclusively in the ipsilateral side of the 6-OHDA lesion regardless of apomorphine treatment (Table 2). The other 76 units showed variable degree of irregularity in firing pattern which could not be classified into the burst units. The burst units had autocorrelograms without peaks or with a single initial peak, a very asymmetric ISI frequency distribution, and very high coefficients of variation ( $0.92 \pm 0.09$ ). The non-burst units with typically regular firing had autocorrelograms with multiple peaks, a symmetric and narrow range of ISI frequency distribution, and low coefficients of variation ( $0.42 \pm 0.02$ ) (Fig. 2). In ipsilateral SNr, 15 (54%) among 28 units of apomorphine treatment group and 5 (24%) among 21 units of vehicle treatment group showed burst firing pattern. The differences in incidence of burst units between ipsilateral and contralateral side of the lesion or treatment groups were statistically significant. Quinpirole suppressed 8 (67%) of 12 units (7 burst and 5 non-burst units) in ipsilateral SNr of apomorphine treatment group and 4 (50%) of 8 (3 burst and 5 non-burst units) in ipsilateral SNr of vehicle treatment group (Fig. 3A, B). Five burst and 2 non-burst units responded to quinpirole in apomorphine treatment group and 2 burst and 2 non-burst units in vehicle treatment group. The suppressive effect of quinpirole was confirmed by spontaneous recovery of firing over time or reversal of suppression by dopamine antagonist haloperidol (0.2 mg/kg, intravenous) (Fig. 4). The units responding to quinpirole showed more sensitive dose-response relation in apomorphine treatment group than in vehicle treatment group with a trial of increasing dose (Fig. 3C), albeit without a statistical significance.

## DISCUSSION

The main findings of this study could be summarized as follows: after repeated administrations of apomorphine, (1) the behavioral response to selective D2 agonist was enhanced; (2) SNr of 6-OHDA-lesioned rats showed increased percentage of units with bursting activity; (3) selective D2 agonist quinpirole suppressed higher percentage of units more effectively though it could not be confirmed statistically.

It is widely known that dopamine replacement therapy elicits rotational behavior in the 6-OHDA-lesioned rats (14, 15). The direction of this rotation is contraversive to the side of the lesion and is generally considered to represent an antiparkinsonian effect (15). However, following repeated treatment, this response shows a markedly enhanced plasticity (9-11). Though the behavior in rats

shows none of the complex movements that are characteristic of dyskinesia in MPTP-treated monkeys or patients with Parkinson's disease, the enhanced behavioral response to repeated dopamine replacement therapy in 6-OHDA-lesioned rats has pharmacological characteristics similar to L-DOPA-induced dyskinesia seen in MPTP-treated monkeys and men (12). So it has been suggested that the enhanced response might be the result in changes in neural activity that are similar to those that underlie L-DOPA-induced dyskinesia in man and in the MPTP-treated monkey. Our result of behavioral test is consistent with those in previous literatures showing progressively increased rotation with repeated administrations of apomorphine. In the rats primed with apomorphine selective D2 agonist alone also caused a markedly enhanced response as in drug-induced dyskinesia in men or MPTP-treated monkeys. According to our results, quinpirole-induced rotation seems to be also enhanced in vehicle treatment group. This can be understood as an combined effect of priming which can elicit an enhanced response even with a single dose (12) and progressive degeneration of dopaminergic neurons after 6-OHDA lesioning (16).

Extracellular single unit recording is a useful method for the measurement of neuronal activity *in vivo*, and basic information acquired by it is about firing rate and pattern. In this study, firing pattern was classified mainly by visual analysis and there were units with firing pattern of variable irregularity though they were classified as non-burst units. When the pattern of unit activity could not be overtly defined by the inspection of the spike train, the digital raster display, ISI histogram, and autocorrelogram, bursts were identified according to the definition of Legéndy and Salcman (17). Burst was defined as at least three consecutive ISIs with a duration shorter than half of the mean ISI and units showing more than 5% of the spikes within bursts were classified as burst units.

The presence of burst units is probably the most constant finding in the spontaneous activity of basal ganglia output nuclei neurons in Parkinson's disease. They were found in 6-OHDA-lesioned rats (13, 18, 19), in acute monoamine-depleted rats (20), in monkeys after electrolytic lesions of the ventromedial midbrain (21), in monkeys after chronic treatment with haloperidol or reserpine (21), and in MPTP-lesioned monkeys (22-25). Similar finding was reported also in patients with Parkinson's disease (26). On the other hand, changes in the basal firing rate of output nuclei cells were found inconsistently: there was no differences in monkeys with ventromedial midbrain lesions or after chronic treatment with haloperidol or reserpine (21), while other study observed an increased basal firing rate of internal pallidal neurons in MPTP-lesioned monkeys (22, 23). Moreover, it has been reported that the changes in basal firing rate of internal pallidal cells of MPTP-lesioned monkeys were inconsistent among animals and behavioral states (24).

The reports from experiments done in rat models were also inconsistent. Burbaud et al. (18) showed an increase in the mean firing rate of SNr units in 6-OHDA-lesioned rats, while Weick and Walters (27) reported no difference. Robledo and Féger (20) did not observe an increase in firing rate of SNr neurons in reserpinized rats. Besides, Rohlf's et al. (19) reported that basal firing rate of SNr in ipsilateral side of 6-OHDA lesion was lower than that in contralateral side. Therefore, it was suggested that the neuronal firing pattern, rather than the mean firing rate of output nuclei neurons, is modified in parkinsonism (13, 19). Our results also support this hypothesis with a new finding that the percentage of the burst units in SNr ipsilateral to 6-OHDA lesion increased in apomorphine treatment group. It suggests that drug treatment itself changes the physiology as well as anatomical lesion in parkinsonian rat though we cannot absolutely exclude the possibility that different degree of completeness of the lesion in each animal group may have partly contributed to this finding. Though we did not try to compare the firing rates from parkinsonian rat with that of normal rat, the findings from the contralateral side of the lesion reveals that unilateral lesion or repeated drug treatment does not cause significant changes in firing pattern in contralateral hemisphere without dopamine depletion. It is known that selective D2 agonist suppresses neuronal activity in SNr differentially depending on the firing pattern, that is, the burst units are more frequently suppressed by quinpirole (28). So it is predictable that more units are suppressed by quinpirole in apomorphine treatment group. One hypothesis about bursting activity is that it is originated from the subthalamic nucleus and the change in firing pattern of SNr units is the consequence of striatal denervation and is mediated by the indirect pathway (13, 28). Alternatively, bursting activity could be originated in other structures projecting to the subthalamic nucleus such as the sensorimotor cortex (29) or the intralaminar thalamic nuclei (30). Our experiment shows that burst units appear after 6-OHDA lesioning and apomorphine treatment exaggerates this tendency with an increasing behavioral response. However, the mechanisms of these changes are still unknown. In addition to the higher percentage of units suppressed by quinpirole after repeated apomorphine injections, our results showed a left-shift of the dose-response curve. It is thought that the increased D2 receptor expression following 6-OHDA lesioning (31) may be exaggerated by apomorphine treatment. Alternatively, qualitative change in striatal outflow after priming (32) may be accompanied by an increased sensitivity to D2 agonist.

In conclusion, this study suggests that an increased percentage of burst firing units in SNr reflects a plasticity responding to repeated dopamine replacement in 6-OHDA-lesioned rats and is related with the enhanced behavioral response comparable to drug-induced dyskinesia in man. In addition, the concomitant enhancement of

behavioral and electrophysiological responses to quinpirole with priming suggests that the mechanism acting on D2 dopamine receptor is important in the development of dyskinesia.

## ACKNOWLEDGMENT

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