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Action sites of rotation and unit firing induced by *l*-stepholidine and DA agonists in basal ganglia of 6-OHDA-lesioned rats[1]

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KEY WORDS stepholidine; rotation; basal ganglia; kainic acid; oxidopamine; dopamine agonists; 6-hydroxydopamine; apomorphine; substantia nigra; globus pallidus

ABSTRACT

AIM: To elucidate the action sites of *l*-stepholidine (SPD) in the basal ganglia. **METHODS**: Counting the rotations after intra-nucleus microinjection and recording the neuron firing by microiontophoresis of SPD and DA agonists in the basal ganglia of 6-hydroxydopamine (6-OHDA)-lesioned rats. **RESULTS**: The DA immunoreactive substance was markedly reduced in the 6-OHDA-lesioned rats. The intra-neostriatum microinjection of apomorphine (Apo, D_1/D_2), SK&F 38393 (D_1), and SPD elicited remarkable rotation, and the characteristics of SK&F 38393-produced rotation were of long latency and long duration. The intra-substantia nigra pars reticulata (SNR) injection of Apo, SK&F 38393, and SPD induced the rotation response, while the selective D_2 agonist quinpirole hydrochloride (Ly171555) did not because of scarce D_2 receptors in the SNR. The intra-globus pallidus (GP) injection of DA agonists and SPD failed to evoke rotation, but the GP nucleus still had the contribution to rotation elicited by ip injection of DA agonists and SPD in the 6-OHDA-lesioned rats with successive kainic acid (KA) lesion. Besides, the successive lesion of entopeduncular nucleus (EP) on rotation was less important than that of GP nucleus. The microiontophoresis of Apo and SPD into the SNR could evoke the neuron firing, but failed to activate the GP neurons, which were activated by sodium glutamate (Glu) and inhibited by γ-aminobutyric acid (GABA). **CONCLUSION**: The action sites of SPD-induced rotation and neuron firing via the D_1 receptors are in the neostriatum and SNR instead of GP. The direct neurocircuit through SNR is the most important for rotation of 6-OHDA-lesioned rats.

INTRODUCTION

The substantia nigra pars compacta (SNC) DA neurons are intimately related to the motor coordination. Destroy of unilateral SNC DA neurons results in the imbalance between ipsilateral versus contralateral sides. Under normal conditions, the rats can keep the body balance. However, if prompted by the DA receptor agonists, the rats rotate towards the unlesioned side[1]. The mechanisms related to the extrapyrimidal motor regulation remain unclear. Recently, both direct and indirect loops have been proposed to function in motor coordination[2,3]. The direct loop comprises cortex → neostriatum → entopeduncular nucleus (EP)/substantia nigra pars reticulata (SNR) → thalamus → cortex. The indirect loop includes cortex → neostriatum → globus pallidus (GP) → subthalamic nucleus → EP/SNR → thalamus → cortex (Fig 1).

l-Stepholidine (SPD), an alkaloid isolated from *Stephania intermedium* LO has been characterized as an antagonist to D_2 receptors and agonist to D_1 receptors based on a large body of evidence in receptor binding assay and biochemical, electrophysiological and behavioral experiments[4-7], thus exerted dual action on DA receptors. In rats with unilateral 6-hydroxydopamine (6-OHDA) lesion of DA neurons in

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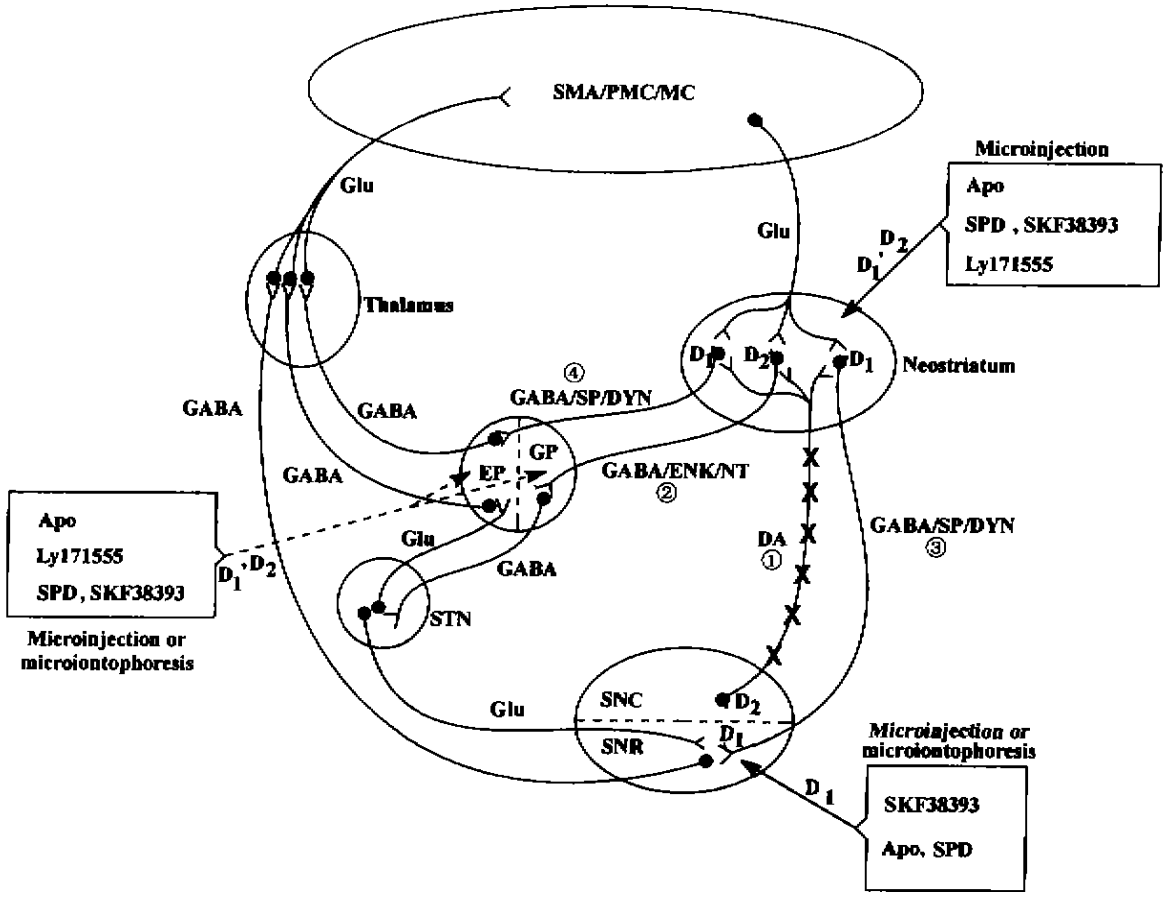

Fig 1. Action sites in basal ganglia of SPD and DA agonists on rotation and neuronal firing. APO (D_1/D_2), SK&F 38393 (D_1) and SPD (D_1) effectively cause the rotation in 6-OHDA-lesioned rats by microinjection into both SNR and neostriatum, while Ly171555 (D_2) only effectively in the neostriatum. But all these agonists are ineffective in both GP and EP under the same conditions. However, the successive lesions of GP and EP lower the rotation activity induced by D_1 and D_2 agonist in the 6-OHDA-lesioned rats. The results of microiontophoresis of APO or SPD into the SNR or GP support the above observations. → showing activated by micro-injection or iontophoresis; - - → showing no activation by micro-injection or iontophoresis; × × × showing 6-OHDA lesion; ① SNC-Striatal DA pathway; ② Indirect circuit; ③, ④ Direct circuit

SNC, SPD induced contralateral rotation which mimics the effects of selective D_1 agonist SK&F 38393[7,8]. Such a bizarre phenomenon has not been found among the other dopaminergic drugs. Based on the above-mentioned neurocircuits of the extrapyrimidal motor regulation, preliminary results from the rotational behavior of rats with successive lesion of the SNR neurons (likely GABAergic) indicates that SNR is one of the action site for SPD to exert its D_1 agonism[7]. A question thus emerges: if the other nuclei of the basal ganglia participate in the SPD-induced rotation in the 6-OHDA-lesioned rats. The present work is designed to elucidate the action sites of SPD induced rotation in the basal ganglia by intra-nucleus microinjection and microiontophoresis of D_1 and D_2 receptor agonists in the 6-OHDA-lesioned rats.

MATERIALS AND METHODS

6-OHDA-lesioned rats preparation Sprague-Dawley rats (♂, 170 g ± 10 g, Grade Ⅱ, Shanghai Experimental Animal Center, Certificate № 005 conferred by Animal Management Committee, Chinese Academy of Sciences) were used. Rats for lesion of

SNC were anesthetized with pentobarbital (40 mg·kg^{-1}, ip) and 4 μL of 6-OHDA·HBr (8 μg 6-OHDA free base, in 0.1 % ascorbic acid and 0.9 % NaCl solution) was injected into the right SNC as described elsewhere[8]. One month later, the lesioned rats were screened according to their responses to SPD and D_1/D_2 mixed agonist apomorphine (Apo). Only those rats showing steady contralateral rotation (more than 6 turns per min) to both Apo (0.2 mg·kg^{-1}, ip) and SPD (4 mg·kg^{-1}, ip) were used in the subsequent experiments.

DA immunohistochemistry DA immunohistochemistry was carried out according to Geffard *et al* (1984) with some modifications. Rats were deeply anesthetized with chloral hydrate (600 mg·kg^{-1}, ip) and perfused intracardially with chilled perfusate washing buffer (containing 1 % sodium metabisulfite, 0.05 mol·L^{-1} sodium cacodylate, 1 % sodium metabisulfite, pH 7.6). Fifteen min later, the rats were perfused with stop washing buffer (containing 0.05 mol·L^{-1} Tris-HCl, 1 % sodium metabisulfite, pH 7.6). Brains were removed and prepared to section by a Vibratome (40 μm; Technologic Products International, St Louis, MO) immediately. Sections containing the substantia nigra collected were processed for DA immunohistochemical studies. The sections were rinsed three times with washing buffer (containing Tris-HCl buffer 0.05 mol·L^{-1}, 0.9 % sodium chloride, 1 % sodium metabisulfite, pH 7.6). After incubated in the pre-incubation buffer (containing 10 % normal sheep serum, 0.05 mol·L^{-1} Tris-HCl buffer, 0.9 % sodium chloride, 1 % sodium metabisulfite, pH 7.6), the sections were transferred to a 1∶500 solution of primary DA antiserum raised in rabbit (INCATAR) in Tris-HCl buffer 0.05 mol·L^{-1}, 0.9 % sodium chloride, 1 % sodium metabisulfite, 0.3 % Triton X-100, 1 % normal sheep serum (pH 7.6). Following a 24-h incubation at 4 ℃, the sections were rinsed in Tris-HCl buffer 0.05 mol·L^{-1}, 0.9 % sodium chloride (pH 7.6) twice and incubated in a 1∶200 solution of biotinylated anti-rabbit immunoglobulin G (IgG) raised in sheep (Vector) (diluted with 0.05 mol·L^{-1} Tris-HCl buffer, 0.9 % sodium chloride, 0.3 % Triton X-100, 1 % normal sheep serum, pH 7.6) for 1 h at 37 ℃. After rinsed repeatedly, the sections were transferred to ABC solution-PBS 0.01 mol·L^{-1} for 1 h. 3, 3′-Diaminobenzidine (DAB) (Sigma) in Tris-HCl buffer 0.05 mol·L^{-1}, 0.9 % sodium chloride (pH 7.6), supplemented with 0.01 % H_2O_2, served as chromogen in the subsequent visualization reaction. The sections were mounted on gelatin-coated slides, left to dry overnight, dehydrated in ascending alcohol concentrations and cleared in xylene. Coverslips were mounted with neutral balsam. Positive DA immunoreactive structures including neuronal soma and processes, which were stained brown-like dots, were observed with light microscope.

Cannula implantation The lesioned rats were randomly divided into three groups which were implanted with cannula into right GP (Bregma: P1.4, L2.8, V6.0 mm), neostriatum (Bregma: A0.6, L3.0, V4.5 mm) and SNR (Lambda: A3.2, L2.2, V7.5), respectively (Paxino & Watson, 1986).

The cannula set comprised of guide and injection cannula[9]. The guide cannula (22-gauge stainless steel) were lowered into the brain and targeted for a site 0.5 mm dorsal to the nucleus. The guide cannula was permanently affixed to the skull using anchor screws and dental acrylic, and a replaceable dummy stylet (28-gauge stainless steel) was immediately inserted into the guide cannula after surgery. The injector was designed to extend 0.5 mm from the guide cannula tip and penetrate ventrally into the brain parenchyma of the nucleus. The injection cannula (28 gauge stainless steel, Plastic One) were connected through PE 10 tubing to a 0.25-mL syringe on a constant-velocity microinjection pump. The total volume injected was less than 1 μL. Normal saline was also injected as vehicle control. Normal rats (270 g ± 15 g) were used as unlesion control.

If needed, antibiotics were used to prevent the animal from infection. The count of rotation was conducted one week after the implantation. After all the experiments concluded, pontamine sky blue 1 μL was injected and the site of the deposition was verified by histological examination. The incorrect drug delivery samples were excluded from the data analysis.

Secondary lesion of nuclei with kainic acid (KA) The rats bearing prior 6-OHDA lesion were firstly ip injected with nitrodiazepam 5 mg·kg^{-1}. Then KA 1 μL (2.5 μg) were injected into the right EP (Bregma: P2.8, L2.9, V6.9 mm) or GP. The rate of the drug injection was 1 μL per 5 min. Two weeks later, the turning induced by ip DA agonists or SPD

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were counted and compared with those before the secondary KA lesion.

Single-unit recording and microiontophoresis[6] The animal pre-treatment and the electrophysiological recording techniques have been detailed elsewhere[10,11]. Briefly, the 6-OHDA lesioned rats were anesthetized with choral hydrate (0.4 $g \cdot kg^{-1}$, ip) and fixed in a stereotaxic instrument. A burr hole was drilled over the SNR (Bregma: P3.2, L2.2, V6.8 – 8.0 mm) or GP (Bregma: A0.8 – 1.4, L2.8, V5.6 – 6.5 mm), respectively according to the atlas of Paxinos and Watson (1986). Single cell activities were recorded extracellularly in these nuclei using a glass microelectrode (filled with NaCl 2 $mol \cdot L^{-1}$, 7 MΩ attached along a five-barreled micropipette (outer diameter 15 – 20 μm). The iontophoretic pipettes were filled with drug solutions: Apo (10 $mmol \cdot L^{-1}$, pH 5), SPD (20 $mmol \cdot L^{-1}$, pH 5), Glu (10 $mmol \cdot L^{-1}$, pH 8), GABA (10 $mmol \cdot L^{-1}$, pH 5), and NaCl 2 $mol \cdot L^{-1}$ solution for automatic current balancing. The chemicals were inotophoretically applied using a five-channel Micro Constant Current Supply (Medical Systems Co USA, Model BH-2B). Electrical signals were amplified and displayed on an oscilloscope. A computer (IBM/386) automatically recorded the firing rate, constructed the rate histogram and analyzed the change of firing during drug microiontophoresis. At the end of experiments, the locations of each recording site and extrude tracks were verified histologically.

Statistics Data were expressed as $x \pm s$ and compared by t-test.

RESULTS

DA immunoreactive substance in 6-OHDA lesioned rat brain section The DA immunoreactive substance in 6-OHDA lesioned rat brain section was presented in Fig 2.

Positive immunoreactive substance was represented as dark brown particles on the photograph. There were plenty of dark brown substances in the intact SNC and VTA area, which representing positive DA immunoreactive neurons. Comparatively, the number of dark brown substances in the lesioned SNC was much lower *vs* that in intact SNC, suggesting that the positive DA immunoreactive neurons were markedly reduced after 6-OHDA lesion. Meanwhile, the degree of decrease of dark brown substances in the VTA of lesioned side was less than that of the ipsilateral SNC.

Rotation induced by intra-nucleus microinjection of DA receptor agonists and SPD The 6-OHDA lesioned rats showed the marked rotations in response to DA agonists Apo (D_1/D_2), SK&F 38393 (D_1), quinpirole hydrochloride (Ly171555, D_2) and SPD at 0.2, 4, 0.2, and 4 $mg \cdot kg^{-1}$ (ip), respectively (Fig 3). Three days later, these rats were used for the intra-neostriatum microinjection of DA receptor agonists, 10 – 20 $mmol \cdot L^{-1} \times 1$ μL, respectively, which also elicited marked rotations (48 – 374 turns)

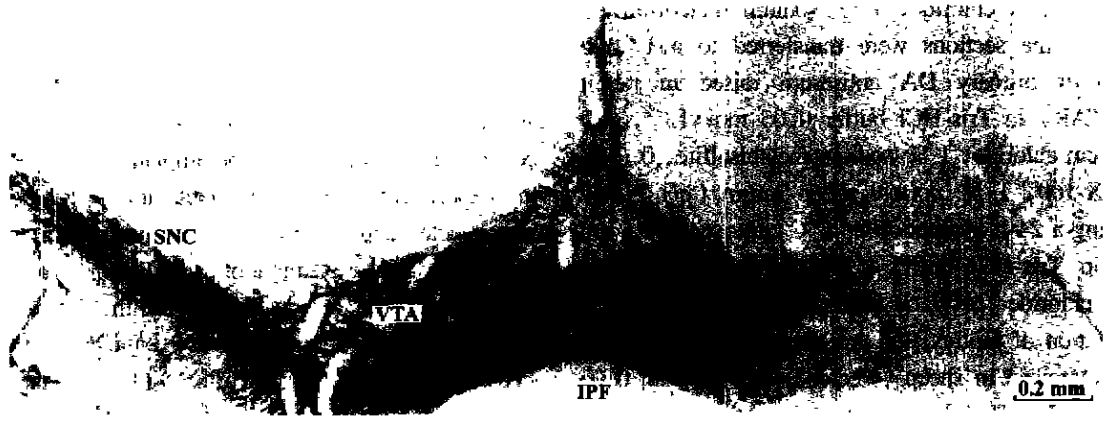

Fig 2. DA immunohistochemisry of SNC in 6-OHDA-lesioned rat (× 100). The right side was lesioned and the left unlesioned. IPF: interpeduncular fossa; SNC: substantia nigra compact zona (A9); VTA: ventral tegmental area (A10).

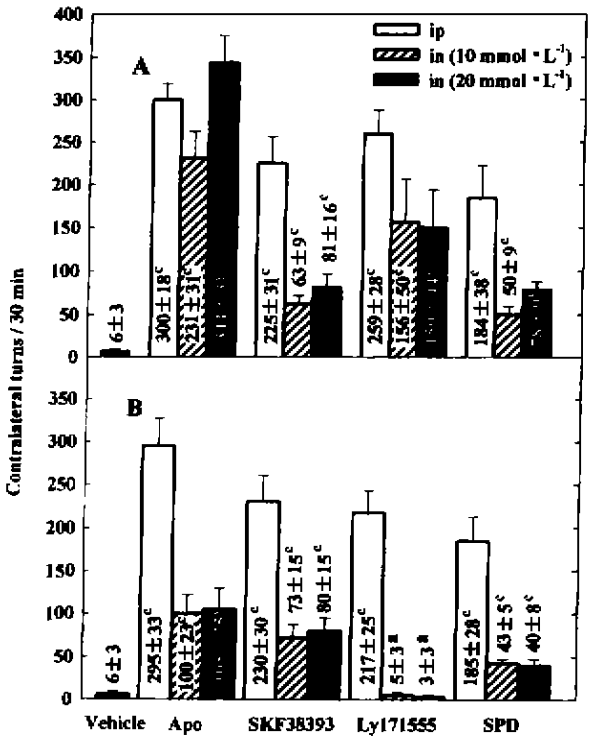

Fig 3. Rates of rotation induced by intra-neucleus injection of Apo, SK&F 38393, Ly171555, and SPD. Each drug was given at the dose of 10 – 20 mmol·L^{-1} × 1 μL. Intraperitoneal injections of Apo, SK&F 38393, Ly171555, and SPD were 0.2, 4, 0.2, and 4 mg · kg^{-1}. (A) All the drugs-induced (intra-neostriatum injection) rotation was significantly different from that of vehicle ($^cP < 0.01$ *vs* vehicle, $n = 9$). (B) Ly17555 (intra-SNR injection) failed to cause rotation ($^aP > 0.05$ *vs* vehicle, $n = 5$). The 3 other drugs-induced rotation was different from that of vehicle ($^cP < 0.01$ *vs* vehicle, $n = 9$).

within the 30 min with a significantly difference against the vehicle ($P < 0.01$, $n = 6 - 9$) (Fig 3A). The results indicated the neostriatum was an important site for DA agonists and SPD. Particularly, Apo had the most potent effect owing to simultaneously stimulating both D_1 and D_2 receptors.

However, the rotation produced by SK&F 38393, a selective D_1 agonist, was characterised by a long latency and a long duration. In the dose of 10 mmol·L^{-1} × 1 μL, the turning counts within the first, second and third 30 min after microinjection were 61 ± 10, 183 ± 8, and 287 ± 38. The rotations within the second 30 min were significant increased *vs* the first one, and the third one significant *vs* the second one ($P < 0.01$ and $P < 0.05$, respectively). In addition, the remarked rotation lasted for 4 h after microinjection of the drug. But, these features could not be observed from Apo, Ly17555 and SPD. The effects of SPD lasted only 15 – 20 min.

At the same dose of (10 – 20) mmol·L^{-1} × 1 μL, the DA agonists and SPD microinjected into the GP nucleus failed to evoke contralateral rotation (Tab 1). Nor other behavioral responses were observed.

Tab 1. Comparison of rotation induced by DA agonists between ip and intra-nucleus injection (Turns/30 min).

Drug	ip (mg·kg^{-1})	Intra-GP (10 mmol·L^{-1})	Intra-GP (20 mmol·L^{-1})
Vehicle	1.2 ± 0.4		
Apo	248 ± 21 (0.2)	3.5 ± 0.7	0.8 ± 0.3
SK&F 38393	232 ± 33 (4)	0.6 ± 0.2	0.4 ± 0.3
Ly171555	220 ± 23 (0.2)	1.0 ± 0.5	0.5 ± 0.7
SPD	184 ± 14 (4)	1.5 ± 0.6	1.1 ± 0.5

The intra-SNR injection of DA agonists and SPD induced different responses. The rotation induced by SK&F 38393 did not show a long duration as in intra-neostriatum injection. Apo and SPD also induced the marked rotation (Fig 3B). In contrast to its ip administration, Ly171555, a selective D_2 agonist induced no rotation ($P < 0.01$, $n = 5$). The results showed that the SNR was the site of action for D_1 agonist rotation, but not for D_2 agonist.

In normal, unlesioned rats ($n = 7$), DA agonists or SPD (10 – 20 μmol·L^{-1} × 1 μL) were injected into the GP, SNR and neostriatum respectively. No obvious rotational behavior was observed except that the slight sniffs were seen with Apo injected into the neostriatum in a few cases.

Effects of successive lesion of nucleus on the rotation induced by ip SPD and DA agonists After the lesion of EP nucleus by KA, the ip injection DA agonists or SPD induced rotation in 6-OHDA-lesioned rats was attenuated against before lesion ($P < 0.05$, $n = 5$) (Fig 4A). And the percentage of rotations induced by Apo, SK&F 38393, Ly171555, and SPD was reduced to 60 % ± 10 %, 47% ± 8 %, 55 % ± 9 %, and 49 % ± 9 %, respectively. It was indicated that the EP nucleus had some contribution to

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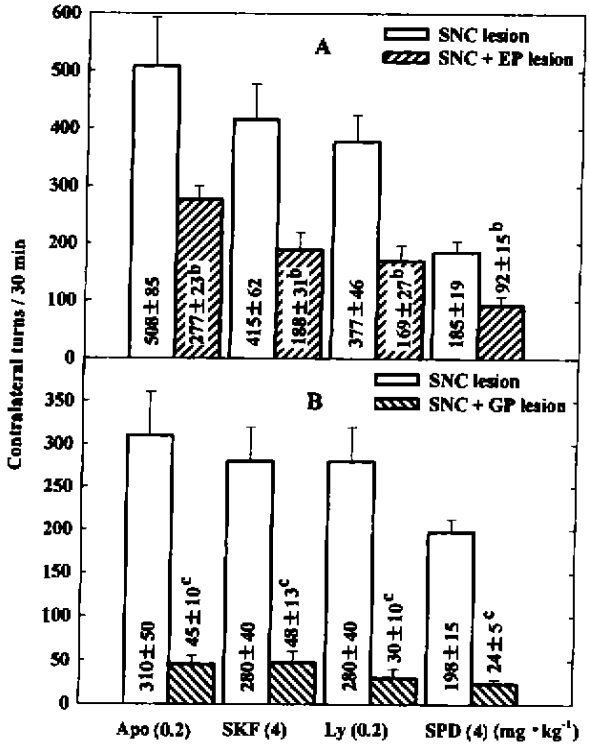

Fig 4. Effects of EP and GP lesion with KA on DA agonists and SPD-induced rotation in rats bearing a prior impairing of ipsilateral nigrostriatal pathway. A) After the EP lesion, all the rotation was significantly reduced as compared with the pre-EP lesion rotation evoked by the same dose ip ($^bP < 0.05$, $n = 5$). B) Secondary GP lesion with KA dramatically attenuated the DA agonists and SPD-induced rotation in 6-OHDA-lesioned rats ($^cP < 0.01$, $n = 6$).

the rotation induced by DA agonists.

As for successive lesion of the GP nucleus by KA, the rotation induced by ip injection of Apo, SK&F 38393, Ly171555, and SPD were markedly attenuated *vs* the results from the 6-OHDA-lesioned rats ($P < 0.01$ *vs* pre-KA lesion, $n = 6$). After KA lesion, their rotations were reduced to 9 % ± 4 %, 21 % ± 7 %, 16 % ± 6 %, and 9 % ± 3 %, respectively *vs* pre-KA lesion (Fig 4B). Thus, GP nucleus was very important to DA agonists to elicit rotation.

Neuron firing after microiontophoresis of SPD onto the SNR and GP in the 6-OHDA-lesioned rats Microiontophoresis of Apo intensified the firing activity of 4/9 SNR neurons recorded. Among the 4 neurons, there were inotophoresis with SPD. The activation of SPD to the neurons was observed, and its effect potentiated the activation of Apo in the same neurons (Fig 5A). This indicates SPD and Apo directly activate the D_1 receptors in the SNR. However, microiontophoresis of Apo and SPD (4 neurons) failed to affect the GP neurons firing (Fig 5B). In contrast, Glu and GABA profoundly increased and inhibited the firing respectively with a dose-dependent manner. It means that the GP neurons have few DA receptors, but sensitive to Glu and GABA.

DISCUSSION

The present study has demonstrated that the microinjection of DA agonists (including Apo, SK&F 38393, Ly171555) or SPD into the nuclei of GP, SNR or neostriatum exhibit the continuous rotation only in the 6-OHDA unilateral rats, but not in the normal, unlesioned rats. This indicates the rotation induced by SPD or DA agonists has a pre-requisite that is a serious imbalance of DA function between both sides of the basal ganglia.

As Fig 1 shows, the neostriatum, receiving the innervation from the cortex and sending its projection to the other nuclei in the basal ganglia, is a crucial regulatory center for motor coordination contributed by D_1 and D_2 receptors[2,3]. All the microinjection of D_1 or D_1/D_2 agonists and SPD into the neostriatum caused the rotation behavior in the 6-OHDA-lesioned rats owing to the activation of D_1 and/or D_2 receptors in the direct and indirect circuits (Fig 1). It thus is easily to understand the reason why the Apo-induced rotation is the most potent than the D_1 or D_2 agonist alone. However, in the previous report[12], the neostriatum nucleus was considered as only for D_2 agonists, but not for D_1 agonist.

The SNR is a very important nucleus for the output flow from the direct and indirect circuit in the basal ganglia. There are only D_1 receptors locateing on GABAergic endings, which project from the neostriatum[3]. Therefore, the intra-SNR microinjection of D_1 or D_1/D_2 agonists and SPD are available to induce rotation in the present study. This is consistent with the previous reports[14]. The substantial results supported the idea that the SNR was an action site of D_1 agonist-induced rotation[13], but not D_2[14]. Our previous results of rotation also supported this conclusion[7].

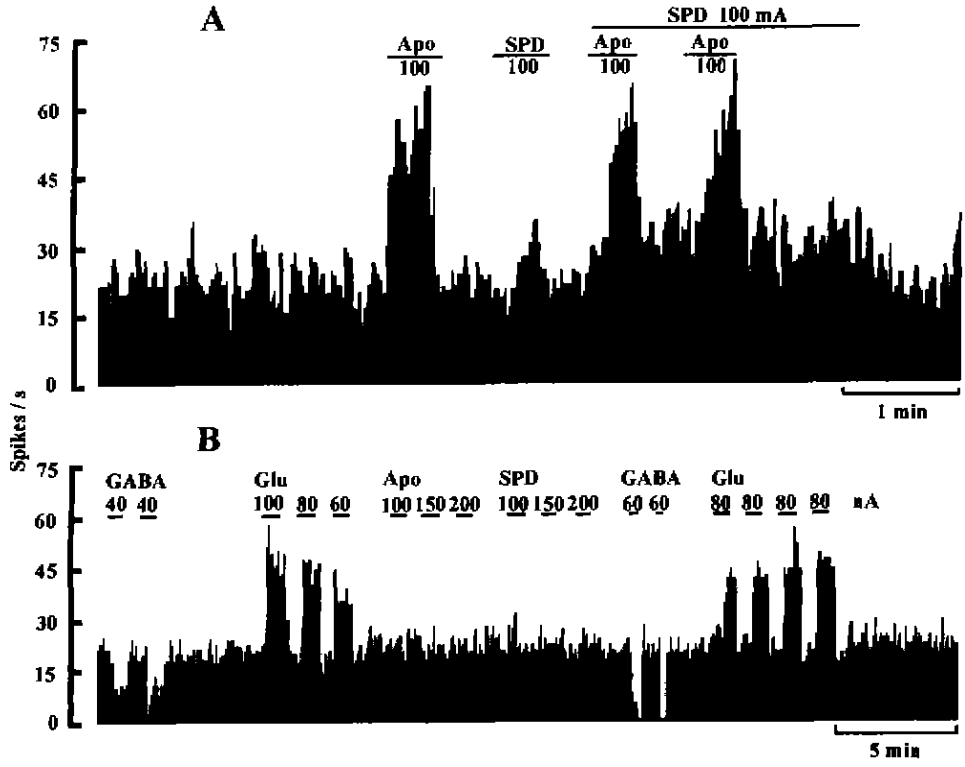

Fig 5. A) Microiontophoresis of Apo increase the firing rate of SNR neuron in 6-OHDA lesioned rat. SPD had the similar effects as well. B) Microiontophoresis of Apo and SPD onto the GP neuron did not alter the firing activity. In contrast, Glu enhanced the firing in a dose-dependent manner, while GABA dramatically inhibited the discharge.

The GP also is another important nucleus in the neuronal circuits of basal ganglia. The microinjection of D_1, D_2, D_1/D_2 agonists or SPD into the GP had no rotation in the lesioned-rats. It has shown that this nucleus has no direct contribution to the rotation due to little or tiny amounts of DA receptors (D_1 or D_2) in it[15]. Nevertheless, the GP nucleus remains its effect in the successive KA lesioned rats by ip injection of the drugs. Based on the action principles of relay station of the neuronal circuits, the GP nucleus had no direct activation by intranucleus injection of DA agonists or SPD, but exhibited its contribution in rotation by ip injection of DA agonists via both direct and indirect circuits from the neostriatum. Therefore, the GP is still involved in the circuit regulation. Similarly, the EP also has the contribution to rotation, but it is less important than that of the GP.

In the present work, the neuron firing by microiontophoresis strongly supported the above viewpoint that SPD and Apo directly acted on D_1 receptors in the SNR nucleus, but did not on the GP nucleus (Fig 5) due to existence of few DA receptors there[15]. The decrease of DA immunoreactive substance was observed in the SNC lesioned by 6-OHDA microinjection (Fig 2). This morphological evidence was coincident with the behavioral and electrophysiological evidence, supporting the reliability of rotation and electrophysiological firing under the 6-OHDA lesion.

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左旋千金藤立定和 DA 受体激动剂对 6-OHDA 损毁大鼠旋转行为和基底核神经元放电的作用部位[1]

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关键词 千金藤立定; 旋转; 基底神经核; 卡英酸; 羟多巴胺; 多巴胺激动剂; 6-羟基多巴胺; 阿朴吗啡; 黑质; 苍白球

目的: 确定 *l*-SPD 在基底神经核的作用部位. **方法**: 6-OHDA 损毁大鼠单侧黑质致密区(SNC), 核团内微注或微电泳给予 *l*-SPD 或 DA 激动剂, 作旋转实验和神经元放电记录. **结果**: 1) 大鼠纹状体损毁侧 DA 免疫反应物减少. 2) 新纹状体或黑质网质区(SNR)内微注 DA 激动剂 Apo (D_1/D_2), SK&F 38393(D_1)或 SPD 引起大鼠强烈旋转, 而微注 Ly171555 (D_2)于 SNR 或 DA 激动剂和 *l*-SPD 于苍白球(GP)均不引起旋转. 卡英酸进一步损毁 GP 或脚间核(EP), DA 激动剂或 *l*-SPD 诱发大鼠旋转显著下降. 3) 微电泳 Apo 或 SPD 引起 SNR 神经元放电, 但对 GP 神经元无效. **结论**: *l*-SPD 诱发大鼠旋转和神经元放电由 D_1 受体介导, 基底核新纹状体和 SNR 是其作用部位, 而不是 GP. 通过 SNR 的直接环路在旋转行为中起重要作用.

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