The selective 5-HT_{1A} receptor antagonist WAY-100635 inhibits neuronal activity of the ventromedial prefrontal cortex in a rodent model of Parkinson's disease

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Abstract: Objective The ventral part of the medial prefrontal cortex (mPFC) plays an important role in initiation and control of voluntary movement, mood and cognition. However, after the degeneration of the nigrostriatal pathway, the neuronal activity of the ventral mPFC and the role of serotonin_{1A} (5-hydroxytryptamine, 5-HT_{1A}) receptors in the firing of the neurons are still unknown. The present study is to investigate the change of neuronal activity in the ventral mPFC and the effect of systemic administration of the selective 5-HT_{1A} receptor antagonist WAY-100635 on the activity of the neurons in normal and 6-hydroxydopamine (6-OHDA)-lesioned rats. **Methods** Single unit responses were recorded extracellularly with glass microelectrodes from ventral mPFC neurons in normal rats and 6-OHDA unilaterally lesioned rats *in vivo*. **Results** 6-OHDA lesion of the substantia nigra pars compacta (SNc) significantly increased the firing rate with no change in the firing pattern of neurons of the ventral mPFC in rats. Systemic administration of WAY-100635 (0.1 mg/kg, i.v.) did not change the mean firing rate and firing pattern of ventral mPFC neurons in normal rats. In contrast, WAY-100635 significantly decreased the mean firing rate of the neurons in rats with 6-OHDA lesion of the SNc. **Conclusion** These data suggest that the degeneration of the nigrostriatal pathway results in an increase of neuronal activity of ventral mPFC and dysfunction of 5-HT_{1A} receptor.

Keywords: medial prefrontal cortex; 5-HT_{1A} receptor; WAY-100635; Parkinson's disease; electrophysiology

1 Introduction

In Parkinson's disease (PD), the degeneration of the nigrostriatal pathway triggers a cascade of functional changes affecting the whole basal ganglia network. However, the function of other brain areas as well as several neurotransmitter systems are also affected in PD^[1,2]. The medial prefrontal cortex (mPFC), which consists of the ventral and dorsal part, is involved in many central nervous system functions, including initiation and control of

voluntary movement, cognitive and memory processing and emotional behaviour^[3]. Function and metabolism of mPFC are altered in PD^[2,4,5]. And, cognitive impairments in severe PD patients are mediated by derangements in brain circuits involving the mPFC^[4,6]. There is also growing evidence that the serotonergic pathways originating in the dorsal and median raphe nuclei (DRN and MRN, respectively) may play an important role in mPFC function. Anatomical studies have shown that several subtypes of serotonin (5-hydroxytryptamine, 5-HT) receptors are expressed in mPFC, with a particular abundance of the 5-HT_{1A} and 5-HT_{2A} subtypes^[7], and activation of these receptors modulates the neuronal activity of mPFC^[8,9]. In PD, both neurochemical and neuropathological studies have shown that levels of 5-HT and its main metabolite 5-hydroxyindolacetic acid are significantly decreased in the basal gan-

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glia and cerebral cortex except loss of 5-HT neurons in the raphe nuclei of parkinsonian patients^[2,10]. These studies suggest that serotonergic system is affected by the disease process. However, the neuronal activity of mPFC and the role of 5-HT_{1A} receptor on neurons of mPFC after unilateral lesion of the nigrostriatal pathway in rats are unknown. In the present study, we used electrophysiological recording method to investigate the effects of systemic administration of the selective 5-HT_{1A} receptor antagonist WAY-100635 on neuronal activity of the ventral mPFC in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of Parkinson's disease. Additionally, the firing rate and pattern of spontaneously active neurons of the ventral mPFC were examined.

2 Materials and methods

2.1 Animals and drugs Forty-six adult male Sprague-Dawley rats, weighing 250-350 g, were used in this study. Animals were housed under a 12 h light/dark cycle with food and water available. The experiments were performed according to the guideline of the Institutional Animal Care Committee of the University. All efforts were made to minimize the number of animals used and their suffering. The drugs used in this study were desipramine, 6-OHDA hydrochloride, apomorphine hydrochloride and WAY-100635 (Sigma). Desipramine, apomorphine and WAY-100635 were prepared in 0.9% saline; 6-OHDA in distilled water containing 0.01% ascorbic acid. These drugs were prepared on the day of the experiment.

2.2 Lesion of the substantia nigra pars compacta Thirty minutes prior to the injection of 6-OHDA, rats were pre-treated with desipramine (25 mg/kg, i.p.) in order to protect noradrenergic neurons. Then they were anaesthetized with 4% chloral hydrate (300 mg/kg, i.p.). Four microlitre 6-OHDA hydrochloride solution (2 µg/µL) were injected into the right substantia nigra pars compacta (SNc) following the coordinates: AP 5.0-5.3 mm posterior to bregma, ML 1.9-2.1 mm from the midline, DV 7.1-7.4 mm from the dura^[11]. After injection, the micropipette was left in the place for an additional 5-10 min before being slowly withdrawn. Two weeks post-surgery, rats were given apomorphine (0.05 mg/kg, s.c.) and those exhibiting more than 20 contralateral turns per 5 min were chosen for the electrophysiological investigation^[12].

2.3 Electrophysiological recordings and firing pattern analysis Extracellular single unit recordings were made in

rats anaesthetized with urethane (1.2 g/kg, i.p.). Electrophysiological recordings were done in normal rats and in rats with 6-OHDA lesion of the SNc at 3 weeks after 6-OHDA injection. A tracheal cannula was inserted to facilitate spontaneous respiration, and the right jugular vein was catheterized for the administration of additional anesthetic or WAY-100635. Glass microelectrodes (10-20 MΩ) filled with 2% Pontamine Sky Blue in 0.5 mol/L sodium acetate were placed into the right ventral mPFC according to the coordinates: AP 2.2-3.2 mm anterior to bregma, ML 0.3-0.8 mm from the midline, DV 4.5-6.5 mm from the dura^[11]. Extracellular spikes were amplified, bandpass-filtered, displayed on an oscilloscope and stored in a computer equipped with the Spike 2 analysis system (Cambridge Electronic Design, UK) for off-line analysis. The baseline activity of each neuron was recorded for 5-10 min before injection and changes in neuronal firing were measured for 10 min after injection of normal saline or WAY-100635. WAY-100635 was administered i.v. at 0.1 mg/kg, and working solutions (0.1 mL) were injected intravenously at appropriate concentrations within 1 min. The change of basal firing rate above 20% was considered a significant alteration for an individual neuron. Only the neuron that has single-spike neuronal activity, good signal-to-noise ratio and stable firing was observed for administration of WAY-100635 per animal.

The firing patterns were determined by comparing the interspike interval histogram (ISI_H; bin width = 4 ms) together with visual inspections of the spike trains similar to the methods described previously^[13]. According to the ISI_Hs and the spike trains, firing patterns were classified into the following types: (i) regular or slightly irregular neuron, characterized by a nearly symmetrical distribution of the ISI_H; (ii) irregular neuron, characterized by an asymmetrical distribution of the ISI_H; (iii) the burst firing pattern with an ISI_H exhibiting an obviously positive skewness with a long progressive decline. These patterns were determined using a minimum of 500 spikes. Visual inspection of digital neuronal activity and raster displays were useful complements to the analysis of firing patterns of the neurons.

2.4 Histology and immunocytochemistry At the end of each experiment, the recording site was marked by the ejection of Pontamine Sky Blue (−20 µA, 15 min). The rat was given an overdose of urethane, and perfused with saline followed by 4% paraformaldehyde. The brain was removed, frozen, sectioned at 40 µm and stained with Cresyl violet

Fig. 1 A: Histological photomicrograph showing the recording site (shown by arrow) in the ventral mPFC marked with iontophoretically injected Pontamine Sky Blue. Scal bar 0.5 mm; B: Immunocytochemistry of TH showing the total degeneration of dopaminergic neurons in the SNc on the 6-OHDA injected side (right) compared to normal side (left). Scal bar: 2 mm. fmi, forceps minor corpus callosum; LV, lateral ventricle; SNc, substantia nigra pars compacta.

Fig. 2 Comparisons of mean firing rates (A) and distribution of firing patterns (B) of the ventral mPFC neurons in normal and SNc-lesioned rats. * $P < 0.001$ versus normal rats.

for histological verification and reconstruction of recording sites (Fig. 1A). The sections of the SNc received 6-OHDA injection were examined by immunocytochemical staining of tyrosine hydroxylase (TH) to determine the extent of nigral dopaminergic degeneration, as previously described^[14]. The rats with a total or subtotal loss of TH immunoreactivity in the SNc were used to analyse electrophysiological recordings (Fig. 1B).

2.5 Statistical analysis Differences of the firing rates between two groups and within group were analysed by Student's *t*-test, and the proportions of different responses of ventral mPFC neurons to WAY-100635 and firing patterns in all the experimental conditions were compared using the χ^2 test. All data were expressed as mean $\pm$ SEM or as percent of basal firing rate. $P < 0.05$ was considered to be statistical significance.

3 Results

3.1 Neuronal activity of the ventral mPFC in normal and

6-OHDA-lesioned rats The action potential duration of the ventral mPFC neurons recorded in normal ($n = 23$) and 6-OHDA-lesioned rats ($n = 30$) was (1.17 ± 0.04) ms and (1.15 ± 0.05) ms, respectively. The action potential duration of all these neurons was above 0.9 ms. Therefore, these neurons were considered to be pyramidal neurons^[15]. In twenty three normal rats, the ventral mPFC neurons displayed a firing rate that varied from 0.97 to 4.48 spikes/s. The mean firing rate of these neurons was (2.3 ± 0.19) spikes/s ($n = 23$; Fig. 2A). According to the methods used for the analysis of the firing pattern, the distribution of firing patterns was 31% irregular and 69% bursting neurons, while the neurons with regular firing pattern were not found (Fig. 2B). In thirty 6-OHDA-lesioned rats, the firing rate of the ventral mPFC neurons varied from 1.1 to 9.2 spikes/s. The mean firing rate increased significantly to (3.81 ± 0.34) spikes/s compared to that of the normal rats ($n = 30$, $P < 0.001$; Fig. 2A). These neurons also showed two firing patterns, 43% of neurons fired irregularly and 57% fired bursts (Fig. 2B). The firing

pattern slightly shifted towards a more irregular firing without reaching significant level.

3.2 Effects of WAY-100635 on the ventral mPFC in normal and SNc-lesioned rats The systemic administration of normal saline did not affect the neuronal firing of the ventral mPFC in a control experiment using normal rats ($n = 3$). The administration of the specific 5-HT_{1A} receptor antagonist WAY-100635 (0.1 mg/kg, i.v.) produced different neuronal firing in the ventral mPFC of normal rats and SNc-lesioned rats. In normal rats, systemic administration of WAY-100635 at 0.1 mg/kg increased the firing in seven neurons and decreased the firing in four neurons, but did not change the firing in eleven neurons (Tab. 1). The mean firing rates of these neurons were (2.4 ± 0.22) spikes/s before and (2.5 ± 0.23) spikes/s after the administration [mean change, (-3.5 ± 6.3)% of basal firing rate, $n = 22$; Fig. 3A, 3B]. There was no significant difference between the two mean values. In SNc-lesioned rats, the firing rates of neurons of the ventral mPFC increased in four observed neurons and decreased in fifteen neurons, but did not change in eight neurons after administration of same dose WAY-

Tab. 1 Responses of mPFC neurons to selective 5-HT_{1A} receptor antagonist WAY-100635 in normal and SNc-lesioned rats

	Excitation		Inhibition		No effect		
Group	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	Total neurons
Normal	7	32	4	18	11	50	22
SNc-lesion	4	15	15	55*	8	30	27

Only one mPFC neuron was observed per animal for injection of WAY-100635 (0.1 mg/kg, i.v.) and the change of basal firing rate above 20% was considered a significant alteration for an individual neuron. * $P < 0.001$ versus normal rats.

100635 (Tab. 1). The percentage of the neurons inhibited was significantly higher than that of normal rats ($P < 0.001$; Tab. 1). The mean firing rate of the ventral mPFC neurons in SNc-lesioned rats before administration of WAY-100635 was (4.4 ± 0.45) spikes/s, which decreased to (3.3 ± 0.53) spikes/s after administration of WAY-100635. This change of responses was significant [mean change, (-26.1 ± 7.9)% of basal firing rates, $n = 27$, $P < 0.005$; Fig. 3C, 3D]. The firing patterns of neurons in the ventral mPFC of normal and SNc-lesioned rats did not change after systemic administration of WAY-100635.

Fig. 3 Representative samples of the firing activity and the corresponding rate histograms of two ventral mPFC neurons observed showing the mean firing rate did not change in normal rat (A) and significantly decreased in 6-OHDA-lesioned rat (C) after systemic administration of WAY-100635 at 0.1 mg/kg. Changes of the mean firing rates of the ventral mPFC neurons in normal (B) and 6-OHDA-lesioned (D) rats after administration of WAY-100635. Only one ventral mPFC neuron was observed per animal for the administration of WAY-100635. * $P < 0.005$ versus pre-injection. Arrows indicate the time points of i.v. administration of WAY-100635.

4 Discussion

This study examined the change of neuronal activity in the ventral mPFC after 6-OHDA lesion in the SNc of rats and the effect of 5-HT_{1A} receptor antagonist WAY-100635 on the ventral mPFC neuronal activity in normal and SNc-lesioned rats. Our results indicate that: (i) 6-OHDA lesion in SNc induced significant increase in firing rate with no change in the firing pattern of neurons in the ventral mPFC compared to those in the normal rats; (ii) systemic administration of the selective 5-HT_{1A} receptor antagonist WAY-100635 (0.1 mg/kg, i.v.) induced a significant decrease in the firing rate in neurons of the ventral mPFC in SNc-lesioned rats, whereas the firing rate and firing pattern of the neurons in normal rats were not changed.

The increased neuronal activity in the ventral mPFC of 6-OHDA-lesioned rats could be explained by following hypothesis. First, the ventral tegmental area (VTA) and midbrain raphe nuclei (DRN and MRN) send efferents towards the ventral mPFC^[16,17]. Electrical stimulation of these nuclei inhibits spontaneous firing of the vast majority of the mPFC neurons^[8,18], and similar inhibition of spontaneous mPFC activity in rat has been observed in response to microiontophoresis of dopamine (DA)^[18]. In addition, the ventral mPFC also receives a projection from the locus ceruleus (LC)^[19]. The LC stimulation increases release of noradrenaline (NA) in the mPFC and microiontophoresis of NA induces inhibitory effect on prefrontal cortex neurons of the rat *in vivo*^[20,21]. In PD, both neuropathological and neurochemical studies have shown that the amount of dopaminergic neurons in the VTA, serotonergic neurons in the raphe nuclei and noradrenergic neurons in the LC was significantly reduced^[10,22,24] and levels of DA, 5-HT, NA and their metabolites were also significantly reduced in basal ganglia, raphe nuclei, hippocampus, cerebral cortex and cerebrospinal fluid of PD patients and MPTP-treated monkeys^[2,5,24]. The downregulation of the D₁ and D₂ receptor expression and reduction of the 5-HT_{1A} binding sites in prefrontal cortex, hippocampus and raphe nuclei of PD patients and MPTP-treated monkeys has been described^[5,25]. The receptor binding study has found increase of α_1 - and β_1 -adrenergic receptors in prefrontal cortex of PD patients, while α_2 -adrenergic receptor decreased^[26]. Second, the prefrontal cortex receives a projection from the thalamic mediodorsal nucleus (MD) and stimulation of the MD at 5–10 Hz results in an increase of the firing rate in an majority of

neurons in deep layers of the prefrontal cortex of rats^[27]. Moreover, the firing rate of neurons of the MD in PD patients increases^[28]. As mentioned above, we can infer that the decrease of inhibitory inputs and increase of excitatory inputs to the ventral mPFC result in the hyperactivity of neurons of the ventral mPFC in rats with 6-OHDA lesion of the SNc.

The 5-HT_{1A} receptors widely distribute in the brain, which couple to K⁺ channels through G-proteins, therefore, activation of the receptors results in an enhanced K⁺ conductance that leads to inhibition of neuronal activity^[29,30]. Recent data indicate that 50–60% of the pyramidal neurons and 20–30% of the GABAergic interneurons in mPFC express 5-HT_{1A} receptors^[31]. WAY-100635 has been proven to be a potent and selective antagonist on pre- and most postsynaptic 5-HT_{1A} receptors, and lacks the affinity for other 5-HT receptors^[32]. In the present study, systemic administration of WAY-100635 did not change the mean firing rate and pattern of neurons of the ventral mPFC in normal rats, whereas significantly decreased the firing rate with no change in firing pattern of the neurons observed in SNc-lesioned rats. The results from the normal rats are in good agreement with previous data reported in the literature^[33]. On an individual neuron basis, however, three types of responses were observed in the ventral mPFC after the administration of WAY-100635 in normal and 6-OHDA-lesioned rats, respectively. Furthermore, 50% of the neurons in normal rats did not change their firing rates after WAY-100635 administration, whereas WAY-100635 induced a decrease of the firing rate in 55% of the neurons in 6-OHDA-lesioned rats. The intravenous or microiontophoretic administration of WAY-100635 alone does not significantly influence the activity of either serotonergic neurons in the DRN or dopaminergic neurons in the VTA^[34,35], whereas inhibits the spontaneous firing activities of noradrenergic neurons of the LC^[35]. Therefore, WAY-100635-induced excitations in normal and 6-OHDA-lesioned rats may reflect the direct blockade of 5-HT_{1A} receptors in the recorded neurons, and attenuate suppression mediated by a decrease of noradrenergic input from the LC. The inhibitory effect of WAY-100635 might result from the increase of local inhibitory inputs through GABAergic interneurons expressing 5-HT_{1A} receptors in normal rats. Systemic administration of WAY-100635 did not modify a mean firing activity of 5-HT neurons of the DRN in normal rats, but in LC-lesioned rats using either 6-OHDA or N-2-chloroethyl-N-ethyl-2-

bromobenzylamine hydrochloride (DSP-4), WAY-100635 significantly increased the mean firing rate of 5-HT neurons^[34], which suggested that the noradrenergic system tonically activated the firing activity of 5-HT neurons. Besides the dopaminergic system deficiency in PD, other neurotransmitter systems are also affected as mentioned above. For example, noradrenergic neurons in the LC has a vast loss^[22,37]. In fact, the neuronal loss was found to be greater in the LC than in the substantia nigra in Parkinsonian patients^[37]. Therefore, the degeneration of noradrenergic neurons in the LC after lesion in the SNc with 6-OHDA decreases the modulation of the noradrenergic system on 5-HT neurons of the DRN. Thus, the administration of WAY-100635 induced an increase of firing activity of 5-HT neurons in the DRN, consequently resulting in the inhibition of the neuronal activity of the ventral mPFC in SNc-lesioned rats. If excitatory and inhibitory actions on the ventral mPFC neurons reach a balance, the net results are the unchanged firing rate of the neurons. In addition, 5-HT_{1A} receptors exist in low density in thalamic nuclei^[38]. Likewise, WAY-100635 may modulate the activity of ventral mPFC pyramidal neurons through the blockade of 5-HT_{1A} receptors in other brain areas anatomically or functionally related to the ventral mPFC. However, the degeneration of the nigrostriatal pathway causes a marked reduction in 5-HT_{1A} receptor density in these areas^[5]. Thus, it is unlikely that the WAY-100635 could contribute to the suppressant effect on ventral mPFC neurons firing activity through the blockade of 5-HT_{1A} receptors in these areas.

In conclusion, the present study shows that the unilateral lesion of the nigrostriatal pathway in rats induces an increase of mean firing rate with no change in the firing pattern of neurons of the ventral mPFC. Systematic administration of the selective 5-HT_{1A} receptor antagonist WAY-100635 does not change the mean firing rate of neurons of the ventral mPFC in normal rats, whereas significantly decrease the mean firing rate of the neurons in 6-OHDA-lesioned rats. The present results suggest that the degeneration of the nigrostriatal pathway causes a dysfunction of the 5-HT_{1A} receptor. Therefore, these data may help to understand the neural mechanisms involved in depression and anxiety of PD.

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选择性 5-HT_{1A} 受体拮抗剂 WAY-100635 抑制帕金森病模型大鼠腹内侧前额叶皮质的神经活动

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摘要: **目的** 腹内侧前额叶皮质在随意运动的起始和控制、情感以及认知中具有重要作用。然而, 黑质-纹状体通路变性后腹内侧前额叶皮质的神经活动和 5-HT_{1A} 受体的作用仍不清楚。本研究观察了 6-羟基多巴胺(6-hydroxydopamine, 6-OHDA)损毁黑质致密部(substantia nigra pars compacta, SNc)后大鼠腹内侧前额叶皮质神经活动的变化和体循环给予选择性 5-HT_{1A} 受体拮抗剂 WAY-100635 后神经元活动的改变。**方法** 采用在体玻璃微电极细胞外记录方法, 记录正常大鼠和 SNc 单侧损毁大鼠的腹内侧前额叶皮质神经元的活动。**结果** 6-OHDA 损毁 SNc 大鼠的腹内侧前额叶皮质神经元放电频率显著增加, 放电形式没有明显改变。体循环给予 WAY-100635 (0.1 mg/kg, i.v.) 不改变正常大鼠腹内侧前额叶皮质神经元的平均放电频率和放电形式, 而显著降低了 SNc 损毁大鼠前额叶皮质神经元的平均放电频率。**结论** 黑质-纹状体通路的变性可导致腹内侧前额叶皮质神经活动增强, 5-HT_{1A} 受体拮抗剂 WAY-100635 可以抑制这种活动增强, 提示可能存在腹内侧前额叶皮质 5-HT_{1A} 受体功能失调。**关键词:** 内侧前额叶皮质; 5-HT_{1A} 受体; WAY-100635; 帕金森病; 电生理学