Effects of pallidal neurotensin on haloperidol-induced parkinsonian catalepsy: behavioral and electrophysiological studies

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Abstract: Objective The globus pallidus plays a critical role in movement regulation. Previous studies have indicated that the globus pallidus receives neurotensinergic innervation from the striatum, and systemic administration of a neurotensin analog could produce antiparkinsonian effects. The present study aimed to investigate the effects of pallidal neurotensin on haloperidol-induced parkinsonian symptoms. **Methods** Behavioral experiments and electrophysiological recordings were performed in the present study. **Results** Bilateral infusions of neurotensin into the globus pallidus reversed haloperidol-induced parkinsonian catalepsy in rats. Electrophysiological recordings showed that microinjection of neurotensin induced excitation of pallidal neurons in the presence of systemic haloperidol administration. The neurotensin type-1 receptor antagonist SR48692 blocked both the behavioral and the electrophysiological effects induced by neurotensin. **Conclusion** Activation of pallidal neurotensin receptors may be involved in neurotensin-induced antiparkinsonian effects.

Keywords: globus pallidus; neurotensin; Parkinson's disease; single unit recordings

1 Introduction

Parkinson's disease is characterized by a progressive, irreversible and ultimately disabling motor deficit. The cardinal symptoms of Parkinson's disease are akinesia, rigidity and tremor^[1]. The globus pallidus in rodents, equivalent to the external globus pallidus in primates, is located in the central position of the basal ganglia circuit^[2,3]. It mainly receives GABAergic inputs from the striatum and local axon collaterals, and glutamatergic afferents from the subthalamic nucleus^[4-6]. Meanwhile, the globus pallidus sends its GABAergic output to all the basal ganglia nuclei including the subthalamic nucleus, the striatum, the entopeduncular nucleus and the substantia nigra^[2,7,8]. Different lines of evi-

dence reveal that the globus pallidus plays a significant role in mediating movement in both physiological and pathological states. Previous electrophysiological studies have shown that the firing rate of the globus pallidus neurons decreases in parkinsonian patients and non-human primates^[9-11]. In addition, the oscillatory bursts firing induced by deprivation of normal dopaminergic innervation is related to the symptoms of parkinsonian tremor^[12-15].

Neurotensin is a tridecapeptide first isolated and characterized by Carraway and Leeman^[16]. Biochemical studies have suggested the role of neurotensin as a primary neurotransmitter and/or neuromodulator^[17-19]. Currently, 3 neurotensin receptors have been identified, including neurotensin receptor type 1 (NTS1), type 2 (NTS2) and type 3 (NTS3/sortilin)^[20-22]. Morphological studies have revealed that both NTS1 and NTS2 are expressed in the globus pallidus^[23,24]. Recently, Martorana A *et al.*^[25] have reported that NTS1 is localized in both parvalbumin-positive and

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parvalbumin-negative globus pallidus neurons. Besides, expression of neurotensin and neurotensin receptors in globus pallidus is implicated in the regulation of motor behavior. For example, expression levels of neurotensin receptors in globus pallidus are markedly decreased in parkinsonian patients^[26,27]. However, the neurotensin immunoreactivity in globus pallidus is increased in 6-hydroxydopamine (6-OHDA)-treated rats and parkinsonian patients. Besides, systemic administration of a neurotensin analog that can cross the blood-brain barrier produces antiparkinson-like effects in 6-OHDA-lesioned rats^[28]. Haloperidol-induced catalepsy has been proved to serve as a reliable model of parkinsonism and can be selectively reversed by all clinically effective antiparkinsonian drugs^[29]. Our previous *in vitro* and *in vivo* electrophysiological studies have revealed the excitatory effects of neurotensin on pallidal neurons^[30,31]. The aim of this study was to investigate the effects of neurotensin in globus pallidus on haloperidol-induced catalepsy.

2 Materials and methods

2.1 Animals Adult male Wistar rats (weighting 200-300 g) were supplied by Qingdao Animal Center and raised at (25±1) °C with a humidity of 50%-55%, under a 12:12 h light/dark cycle (lights on at 07:00), with free access to food and water. All behavioral experiments were performed between 10:00 and 17:00. Rats were allowed to be habituated for at least 1 week in the animal room before the experiment. All the experiment procedures were approved by the University guidelines on animal ethics.

2.2 Behavioral studies The rats were anesthetized with 8% chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic frame (Narishige SN-3, Tokyo, Japan). According to the stereotaxic atlas of Paxinos *G et al.*^[32], 2 stainless steel guide-cannulae (outside diameter 0.4 mm, inside diameter 0.3 mm) were bilaterally implanted into the globus pallidus (1.0 mm posterior, 3.0 mm lateral from the bregma, 6.9 mm ventral from the skull surface). The cannulae were fixed to the skull with stainless steel screw and dental acrylic. Stainless steel stylets were used to keep the cannulae sealed.

Following at least 5 d of recovery, catalepsy tests were performed by i.p. injection of haloperidol (0.25 mg/kg). One

hour later, the globus pallidus was microinjected with 0.5 µL normal saline ($n=7$), 0.5 µL neurotensin (0.1 mmol/L, $n=7$), 0.5 µL SR48692 (1 mmol/L, $n=7$) or SR48692 plus neurotensin at a total volume of 0.5 µL ($n=7$). At the end of microinjection, the cannula was left in the globus pallidus for an additional 1 min before removal, and then it was replaced by a stylet.

Haloperidol-induced catalepsy was assessed with the standard bar test and grid test. In the bar test, both forepaws of the rats were placed on a horizontal metal rod positioned 9 cm above the floor. The time elapsing before at least one of the forepaws climbing down from the bar was recorded in seconds (with a maximal “cut-off” of 300 s) and indicated as the descent latency. This test was performed in each 10 min during the total period of 1 h. In the grid test, all paws of rats were placed on a 60°-inclined grid. After 30-s habituation, the duration that they stayed in the same position was measured within 300 s. This test was also performed in each 10 min during the total period of 1 h.

2.3 Electrophysiological recordings Rats were deeply anaesthetized with 20% urethane (1 g/kg, i.p.) and placed in a stereotaxic apparatus. An incision was made in the scalp to expose the skull, and a burr hole was drilled in the skull. Rectal temperature was maintained at 36 °C -38 °C by a heated pad.

Three-barrel microelectrodes were fastened at each end with metal tubing and prepared using a Stoelting pipette puller (Illinois, USA). The tips of microelectrodes were broken to 3-10 µm under a microscope. The resistance of microelectrodes ranged from 10-20 MΩ. The recording electrode was filled with 0.5 mol/L sodium acetate containing 2% pontamine sky blue dye. The other 2 micro-pressure ejection barrels were connected to 4-channel pressure ejector (PM2000B, Micro Data Instrument, Inc., USA). The 2 micro-pressure ejection barrels contained neurotensin and vehicle (normal saline), SR48692 and vehicle (DMSO), SR48692 and SR48692 plus neurotensin, or neurotensin and neurotensin plus SR48692. The electrode was then placed into the globus pallidus with coordinates of 0.8-1.2 mm posterior and 2.5-3.5 mm lateral to the bregma, 5.5-7.2 mm vertical from the dura^[32]. Neurons were identified as pallidal on the basis of their location and electrophysiological features. Drugs were ejected onto the

surface of firing cells with short pulse gas pressure (1500 ms, 5.0-15.0 psi).

The pallidal neurons were recorded after haloperidol (0.25 mg/kg, i.p.) administration. The recorded electrical signals were amplified by a micro-electrode amplifier (MEZ-8201, Nihon Kohden, Tokyo, Japan) and displayed on a memory oscilloscope (VC-11, Nihon Kohden, Tokyo, Japan), while being fed to an audiomonitor. The amplified electrical signals were passed through low and high pass filters into a bioelectricity signal analyzer and computer. Spike times were pre-processed online and further analyzed offline using the program of Histogram version 1.00 (Shanghai Medical University, Shanghai, China) for spike data analysis. The firing rates were recorded in 1-s bins. Drug infusion was performed only once for each recording and a period of at least 30 min was allowed before another recording in the same track. Consistent with the 1-h duration of the catalepsy test, the electrophysiological study also lasted for 1 h.

At least 5-min stable basal firing was collected from each neuron before drug ejection onto the globus pallidus. The frequency of basal firing was determined by the average frequency of 120 s baseline data before drug administration. The maximal change of frequency within 50 s following drug application was considered as drug effect. At least 20% change of basal firing rate during drug application was considered to be significant^[33]. Drug application was performed only once for each recording and a period of 30 min was allowed to pass before another recording in the same track.

2.4 Histological controls To identify the position of single unit recording, pontamine sky blue was ejected from the recording electrode tip by iontophoresis (10 μ A, 20 min). To verify the position and the extent of drug microinjection, 0.5 μ L pontamine sky blue was microinjected into the globus pallidus. All the rats employed in electrophysiological and behavioral experiments were sacrificed and perfused with 4% paraformaldehyde solution transcardially. The brain was removed and frozen, and sections were cut at a thickness of 50 μ m. All the recording and microinjection sites were identified under light microscope.

2.5 Reagent Neurotensin and haloperidol were obtained

from Sigma. SR48692 {2-[(1-(7-chloro-4-quinolinyl)-5-2(2,6-dimethoxyphenyl)pyrazol-3-yl)carbonylamino]-tricyclo(3.3.1.1.3.7)-decan-2-carboxylic acid} was a generous gift from Dr. Daniellie Gully (Sanofi Recherche, France).

2.6 Statistics Data were presented as mean $\pm$ SEM. The time of catalepsy was analyzed by the Kruskal-Wallis test followed by the Mann-Whitney test. Paired *t* test was used to compare the firing rates before and after treatment. Statistical comparisons between groups were determined with Student's *t* test. *P* < 0.05 was considered as statistically significant.

3 Results

3.1 Effects of pallidal neurotensin on haloperidol-induced catalepsy

3.1.1 Bar test As shown in Fig. 1A, i.p. injection of haloperidol induced a steady catalepsy state in rats. During the 60 min following intrapallidal vehicle microinjection, the maximum mean descent latency of the bar test was (256.0 $\pm$ 29.9) s at 10 min, and the minimum mean descent latency time was (182.4 $\pm$ 21.8) s at 30 min. On the other hand, neurotensin (0.1 mmol/L) significantly reversed haloperidol-induced catalepsy during the 60-min testing period (*P* < 0.01, *n*=7). The anticataleptic effects reached the peak at 60 min, with a descent latency of (57.9 $\pm$ 11.4) s.

Morphological studies have revealed that both NTS1 and NTS2 are expressed in the globus pallidus^[23,24]. To determine the receptor subtype mediating neurotensin-induced anticatalepsy, SR48692, a specific antagonist of NTS1, was employed. As shown in Fig. 1A, SR48692 treatment (1 mmol/L) alone did not affect haloperidol-induced catalepsy (*P* > 0.05, *n*=7). However, bilateral microinjection of a mixture of SR48692 and neurotensin into the globus pallidus significantly attenuated the neurotensin-induced anticatalepsy (*P* < 0.01 vs neurotensin alone, *n*=7). During the 60 min following mixture administration, the minimal mean descent latency was (194.6 $\pm$ 26.4) s at 30 min. The mean descent latency was not significantly different from that of vehicle injection at each time point (*P* > 0.05, Fig. 1A). This result suggested that NTS1 is implicated in neurotensin-induced anticataleptic effects.

3.1.2 Grid test In the grid test, microinjection of neurotensin

Fig. 1 Time courses of bar (A) and grid (B) tests showing the effects of neurotensin on haloperidol-induced catalepsy. Descent latency was regarded as an index of intensity of the catalepsy. Both tests indicated that neurotensin significantly reversed haloperidol-induced catalepsy, and that SR48692, a specific antagonist of NTS1, significantly reversed neurotensin-induced anticataleptic effects. * $P < 0.05$, ** $P < 0.01$ vs saline; # $P < 0.05$, ## $P < 0.01$, SR48692+neurotensin vs neurotensin alone. NT: neurotensin. NS: normal saline.

Fig. 2 Effects of systemic administration of haloperidol on the spontaneous firing rate of globus pallidus neurons. A: Typical frequency histograms showed that haloperidol decreased the firing rate by 39.2% in this cell. The firings of the neuron, displayed at a faster time base at different stages of the experiment were shown in lower traces. B: Pooled data summarized the effects of haloperidol on the spontaneous firing of globus pallidus neurons ($n = 6$). ** $P < 0.01$.

significantly reversed haloperidol-induced catalepsy ($P < 0.01$ vs saline, $n=7$, Fig. 1B). Besides, consistent with the bar test, SR48692 treatment alone did not significantly affect the haloperidol-induced catalepsy, as compared with the normal saline group ($P > 0.05$). However, co-treatment with SR48692 and neurotensin significantly reversed neurotensin-induced anticataleptic effects ($P < 0.05$ vs neurotensin alone, $n=7$).

3.2 Effects of neurotensin on the spontaneous firing of globus pallidus neurons in haloperidol-treated rats Previous electrophysiological studies revealed that all the recorded neurons showed a biphasic positive/negative waveform, and these neurons were characterized as type II globus pallidus

neurons^[34,35]. As shown in Fig. 2, in 6 out of 8 pallidal neurons, systemic administration of 0.25 mg/kg haloperidol significantly decreased the firing rate [basal (17.3 ± 5.3) Hz vs haloperidol (10.3 ± 3.9) Hz, $n=6$, $P < 0.01$]. On average, the firing rate was decreased by (53.3 ± 11.6)%. However, micro-pressure ejection of 0.1 mmol/L neurotensin significantly increased the spontaneous firing rate of pallidal neurons in haloperidol-treated rats. In 15 out of 35 pallidal neurons, 0.1 mmol/L neurotensin increased the firing rate from (11.3 ± 1.6) Hz to (14.8 ± 1.9) Hz ($n=15$, $P < 0.001$, Fig. 3A), by (34.9 ± 3.2)% on average. This was significantly different from that of vehicle (normal saline) treatment ($P < 0.01$), by which the firing

Fig. 3 Intrapallidal micro-pressure ejection of neurotensin increased the spontaneous firing rate of pallidal neurons in haloperidol-treated rats. A: Typical frequency histograms showed that 0.1 mmol/L neurotensin increased the firing rate by 32.8%. The firings of the neuron, displayed at a faster time base at different stages of the experiment were shown in lower traces. B: Pooled data summarized the increase in firing rate by normal saline or neurotensin in haloperidol-treated rats ($n=15$). ** $P < 0.01$.

Fig. 4 Effects of SR48692 on neurotensin-induced excitation of pallidal neurons. **A:** Typical frequency histograms showing that SR48692 alone did not induce any change in the spontaneous firing rate, and that its presence blocked neurotensin-induced increase in firing rate. The firings displayed at a faster time base were shown in lower traces. **B:** In one cell which was activated by neurotensin, co-treatment with SR48692 and neurotensin blocked neurotensin-induced increase in firing rate. The firings displayed at a faster time base were shown in lower traces.

rate was increased by $(1.3 \pm 1.5)\%$ on average [basal (13.9 ± 1.2) Hz, vehicle (14.0 ± 1.2) Hz, $n=22$, Fig. 3B].

3.3 Effects of SR48692 on neurotensin-induced increase in firing rate of globus pallidus neurons in haloperidol-treated rats In 32 pallidal neurons of haloperidol-treated rats, 1 mmol/L SR48692 alone did not significantly affect the firing rate [basal (12.7 ± 1.9) Hz, SR48692 (12.9 ± 1.6) Hz; increased by $(4.7 \pm 3.5)\%$, $n=32$, $P > 0.05$]. In 20 neurons that then received SR48692 and neurotensin treatment, the firing rate was not significantly changed [basal (13.9 ± 1.5) Hz; neurotensin+SR48692 (14.5 ± 1.5) Hz, $P > 0.05$, Fig. 4A]. The average percentage of change was $(6.5 \pm 4.4)\%$, which was significantly decreased compared to that of neurotensin treatment alone ($P < 0.001$). In a separate set of rats, administration of vehicle (DMSO) did not alter the spontaneous firing rate of pallidal neurons [basal (12.5 ± 1.8) Hz; vehicle (12.7 ± 1.8) Hz; increased by $(2.5 \pm 2.4)\%$, $n=12$, $P > 0.05$].

Considering that only a proportion of pallidal neurons responded to neurotensin, we further performed another group of experiments to apply neurotensin first and then SR48692 with neurotensin. In 7 pallidal neurons with response to micro-pressure ejection of 0.1 mmol/L neurotensin [basal (12.5 ± 3.6) Hz; neurotensin (18.3 ± 4.7) Hz; increased by $(53.7 \pm 9.1)\%$], co-ejection of SR48692 with neurotensin did not significantly change the firing rate, compared with the basal level [basal (12.2 ± 3.9) Hz; neurotensin+SR48692 (11.2 ± 3.6) Hz, $P > 0.05$]. The average percentage of change was $(2.7 \pm 8.8)\%$, which was significantly lower than that of neurotensin alone [$(53.7 \pm 9.1)\%$, $P < 0.001$, Fig. 4B].

4 Discussion

The present behavioral study showed that bilateral microinjection of neurotensin into the globus pallidus could significantly reverse haloperidol-induced catalepsy. The selective NTS1 is involved in neurotensin-induced anticataleptic effects. The globus pallidus receives neurotensinergic innervation arising from the striatum^[36]. Previous morphological studies have indicated that in 6-OHDA-induced parkinsonian rats, the immunoreactivity of neurotensin in globus pallidus is increased, which may reflect a compensatory mechanism^[37,38]. Furthermore, systemic administration of a

neurotensin analog produced antiparkinson-like effects in 6-OHDA-lesioned rats^[28]. The present findings suggest that the globus pallidus may be one of the possible targets for neurotensin-induced antiparkinsonian effects. It is possible that intrapallidal application of neurotensin compensates the hypoactivity of the globus pallidus induced by haloperidol.

Haloperidol-induced catalepsy and akinesia represent a useful model of Parkinson's disease. According to the classical scheme of basal ganglia circuit^[39], it has been proposed that haloperidol blocks dopamine D₂ receptor in the striatum and therefore increases GABA release in the external segment of the globus pallidus. The resulting hypoactivity of the globus pallidus enhances thalamic inhibition, which in turn leads to the akinesia and catalepsy of parkinsonian symptoms^[40,41]. Therefore, improvement in the activity of globus pallidus may be important in producing anti-parkinsonian effects. To provide electrophysiological evidence for intrapallidal neurotensin-induced anticatalepsy, we further observed the effects of neurotensin on the firing rate of globus pallidus neurons in haloperidol-treated rats. Consistent with our previous *in vivo* and *in vitro* studies^[30,42], neurotensin excited the pallidal neurons in haloperidol parkinsonian rats. Previous morphological studies have revealed that both NTS1 and NTS2 are present in the globus pallidus^[23,41]. Here the specific NTS1 antagonist could completely block neurotensin-induced anticatalepsy, indicating the involvement of NTS1 in the pallidal neurons.

Besides directly exciting the globus pallidus neurons, neurotensin is closely related with dopamine system^[43]. Morphological studies have revealed that neurotensin receptors, particularly NTS1, are highly prevalent in midbrain neurons. Neurotensin receptors are expressed in approximately 80% of the dopamine cells in the ventral tegmental area and substantia nigra pars compacta^[23,44,45]. Furthermore, neurotensin-like immunoreactivity and neurotensin-binding sites are widely distributed on the surface of midbrain dopamine neurons^[44,46]. Intracerebroventricular administration of neurotensin can increase the concentrations of dopamine in the striatum and the amygdala^[47]. Furthermore, microinjection of neurotensin into the substantia nigra pars compacta caused increases in the levels of dopamine and dopamine

metabolites in the globus pallidus and the striatum^[48]. The concentration of extracellular dopamine in the nucleus accumbens of 6-OHDA-lesioned rats is significantly increased following neurotensin microinjection into the ventral tegmental area^[49]. Therefore, the therapeutic effect of systemic administration of neurotensin would depend on the interaction with the whole basal ganglia nuclei.

In conclusion, the present behavioral and electrophysiological findings demonstrate that neurotensin exerts anticonvulsant effects by exciting globus pallidus neurons. Since the globus pallidus and the neurotensin system are involved in the pathophysiology of Parkinson's disease, our data may provide a rationale for further investigating the potential value of the neurotensin system in the treatment of motor disorders originating from the basal ganglia.

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苍白球神经降压素对氟哌啶醇所致帕金森病僵直症状的影响：行为学和电生理学研究

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摘要：目的 苍白球在机体运动功能调节中发挥重要作用。形态学研究证实苍白球接受来自纹状体的神经降压素能纤维支配。有研究报道全身给予神经降压素类似物可诱导产生抗帕金森病效应。本研究旨在探讨苍白球神经降压素对氟哌啶醇所致的帕金森病僵直症状的影响。**方法** 用行为学实验检测大鼠的帕金森病僵直症状，用电生理学实验方法记录苍白球神经元的自发放频率。**结果** 双侧苍白球微量注射神经降压素可以缓解氟哌啶醇所致的帕金森病僵直症状。在氟哌啶醇条件下，微量注射神经降压素可以兴奋苍白球神经元。选择性神经降压素 1 型受体拮抗剂 SR48692 可以拮抗神经降压素所致的行为学和电生理学效应。**结论** 上述结果提示，神经降压素的抗帕金森病作用可能与苍白球神经降压素受体的激活有关。

关键词：苍白球；神经降压素；帕金森病；单细胞记录