Full-length article

Modulation of synaptic GABA_A receptor function by zolpidem in substantia nigra pars reticulata¹Li-li ZHANG^{2,3}, Lei CHEN², Yan XUE², Wing-ho YUNG^{3,4}²Department of Physiology, Qingdao University, Qingdao 266071, China; ³Department of Physiology, The Chinese University of Hong Kong, Shatin, Hong Kong**Key words**substantia nigra pars reticulata; benzodiazepine; zolpidem; GABA_A receptors¹ Project supported by the Research Grants Council of Hong Kong (N_o CUHK 4175/02M to Dr Wing-ho YUNG) and the Foundation of Health Department of Shandong Province (N_o 2005HW021 to Dr Lei CHEN).⁴ Correspondence to Dr Wing-ho YUNG.

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Abstract

Aim: The substantia nigra pars reticulata (SNr) constitutes one of the output centers of the basal ganglia, and its abnormal activity is believed to contribute to some basal ganglia motor disorders. Different lines of evidence revealed a major contribution of GABA_A receptor-mediated synaptic inhibition in controlling the activity of SNr. The benzodiazepine binding site within the GABA_A receptor is a modulation site of significant clinical interest. A high density of benzodiazepine binding sites has been reported in the rat SNr. In the present study, we investigate the effects of activating benzodiazepine binding sites in the SNr. **Methods:** Whole-cell patch-clamp recordings and motor behavior were applied. **Results:** Superfusion of zolpidem, a benzodiazepine binding agonist, at 100 nmol/L significantly prolonged the decay time of GABA_A receptor-mediated postsynaptic currents. The prolongation on decay time induced by zolpidem was sensitive to the benzodiazepine antagonist flumazenil, confirming the specificity on the benzodiazepine site. Zolpidem at 1 μmol/L exerted a stronger prolongation on the decay time. A further experiment was performed on behaving rats. A unilateral microinjection of zolpidem into the rat SNr caused a robust contralateral rotation, which was significantly different from that of control animals receiving the vehicle injection. **Conclusion:** The present *in vitro* and *in vivo* findings that zolpidem significantly potentiated GABA currents and thus inhibited the activity of the SNr provide a rationale for further investigations into its potential in the treatment of basal ganglia disorders.

Introduction

The substantia nigra pars reticulata (SNr) occupies one of the output centers of the basal ganglia circuit. It is well known that the inhibitory neurotransmitter γ-aminobutyric acid (GABA) is the major neurotransmitter used in the SNr, which suggests that GABA-mediated neurotransmission in this nucleus plays an important function^[1]. Anatomical and electrophysiological evidence has shown that the major sources of GABAergic inputs in the SNr are the striatum, globus pallidus, and local axon collaterals of GABAergic output neurons^[2–5].

Moderate to high densities of GABA_A receptors were expressed in the SNr^[6,7], which mediate fast inhibitory synaptic

transmission. GABA_A receptors are heteropentameric structures assembled from various subunits, including α1–6, β1–4, γ1–3, δ, ε, π, θ, and ρ1–3. The subunit combination of a particular GABA_A receptor plays a crucial role in determining its pharmacological properties and physiological functions. Most GABA_A receptors contain at least both α and β subunits, with 1 or more of the other subunits. There are several binding sites within GABA_A receptors that interact with a diverse range of compounds^[8]. The benzodiazepine binding site is one of the potent modulating sites, which leads to anxiolytic, anticonvulsant, and sedative effects by potentiating GABA currents. Zolpidem is an imidazopyridine agonist with a high affinity on the benzodiazepine site containing the α1 subunit. Early studies indicated that the highest level of

zolpidem binding sites occurred in the SNr^[9]. Quantitative autoradiography has shown that 6-hydroxydopamine lesion significantly increased the binding of zolpidem in SNr, which may reflect a compensatory alteration^[10,11]. The systemic administration of zolpidem produced an inhibition on the firing of the SNr neurons^[12]. The microinfusion of zolpidem and other benzodiazepine agonists into the SNr produced anti-convulsant effects on clonic and tonic-clonic seizures^[13,14]. Recently, a few clinic reports suggested that zolpidem exerted a therapeutic effect on some groups of Parkinson's patients^[15–17]. However, the direct pharmacological effects of zolpidem in the SNr are not known. In the present study, whole-cell patch-clamp recordings and intranigral microinjection were used to study the function of zolpidem in the rat SNr.

Materials and methods

***In vitro* slice preparation** Sprague-Dawley rats aged 12–14 d were used for the preparation of acute brain slices. The animals were killed by decapitation. The brains were then immediately removed and placed in ice-cold artificial cerebrospinal fluid (ACSF) of the following composition (in mmol/L): NaCl 125, KCl 2.0, MgSO₄ 1.2, CaCl₂ 2.5, KH₂PO₄ 1.2, glucose 11, and NaHCO₃ 26, which was continuously bubbled with 95% O₂ and 5% CO₂. Midbrain coronal slices (250 μ m) containing the SNr were sectioned using a vibrating microtome (Camden Instruments, Loughborough, UK) as previously described^[18]. Briefly, after equilibration for at least 1 h, the slices were transferred to a small volume chamber mounted on an upright microscope (Zeiss Axioskop, Oberkochen, Germany) and superfused with ACSF at a rate of 1.5–2.0 mL/min maintained at a temperature of 34 °C. Neuronal soma of the SNr neurons was directly visualized by a combination of differential interference contrast optics and contrast-enhanced infrared video microscopy.

Patch-clamp recording Whole-cell patch-clamp recordings from the SNr neurons were obtained using a patch-clamp amplifier (LM/PCA, List Medical, Darmstadt, Germany). Whole-cell pipettes typically had a resistance of 3–4 M Ω when filled with an internal solution of the following composition (in mmol/L): KCl 140, EGTA 1.0, MgCl₂ 2.0, Na₂ATP 2.0, Tris GTP 0.4, and HEPES 10; the pH was adjusted to 7.25–7.30 with 1 mol/L KOH. The inclusion of 140 mmol/L KCl in the recording pipettes reversed the polarity of GABA_A receptor-mediated currents from outward to inward. Monitoring through a camera, a pipette was placed on the soma of a SNr neuron and whole-cell recording was made. Normally, no series resistance compensation was

applied, but the cell was rejected if the series resistance increased significantly (>20%) during recording. (F)-2-Amino-5-phosphonopen-tanoic acid (AP5; 50 μ mol/L) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 20 μ mol/L) were included to eliminate glutamate receptor-mediated synaptic currents. Miniature postsynaptic currents (mPSC) were isolated by the addition of 0.5 μ mol/L tetrodotoxin (TTX) to the ACSF. Inhibitory postsynaptic currents were recorded at a holding potential of -70 mV. The current signal was filtered at 3 kHz. Online or offline digitization (10 kHz) was made via the Digidata-pClamp system (Axon Instruments, California, USA). Computer files containing information of synaptic currents were analyzed by the mini analysis program (version 6, Synaptosoft, Decatur, GA, USA), which automatically generates various parameters, including the time of occurrence, peak amplitude, and kinetics.

***In vivo* surgery** Sprague-Dawley rats (250–280 g) were used. The animals were individually housed in a temperature regulated room and maintained on a 12 h:12 h light/dark cycle. All rats had free access to food and water. On the day of surgery, the rats were anesthetized with chloral hydrate (400 mg/kg, intraperitoneally) and placed in a stereotaxic frame. A guide cannula constructed from stainless steel (outer diameter: 0.4 mm; inner diameter: 0.3 mm) was implanted into the SNr (5.5 mm posterior, 2.3 mm lateral from the bregma, 8.0 mm ventral from the skull surface) on either side. The cannulae were fixed to the skull with stainless steel screws and dental acrylic. Stainless steel stylets were used to keep the cannulae sealed.

Rotational test Following at least 3 d of recovery, the rats were tested for motor/turning behavior. Drugs (0.2 μ L) were microinjected into the SNr in awake animals over a 2 min period. Injection cannulae were connected to a 1.0 μ L microsyringe and a drug was injected. At the end of injection, the cannula was left in the SNr for an additional 1 min before removal and then replaced by a stylet. The net rotational behavior was calculated for 30 min.

Histological controls After the test, the rats were perfused with 10% formalin solution transcardially. Fifty micrometer brain slices were cut to examine the sites of injection. Only the data obtained from animals with correct placement of the cannulae were used for the analysis.

Drugs and statistics Zolpidem and flumazenil were purchased from Tocris (Avonmouth, UK). AP5, CNQX, bicuculline, and TTX were obtained from Sigma (St Louis, MO, USA). The data are expressed as mean $\pm$ SEM. The Kolmogorov-Smirnov test was used to compare 2 distributions of synaptic current inter-event intervals, amplitudes, decay time, and rise time setting the threshold of signifi-

cance at a probability (P) of 0.05. Otherwise, paired or unpaired Student's t -test was applied using a value of 0.05. The net rotational behavior was analyzed by the non-parametric one-way Kruskal-Wallis test followed by the Mann-Whitney U-test.

Results

Identification of GABA and dopamine neurons It is known that 2 types of neurons, GABA and dopamine neurons, exist in the SNr. In the present study, the distinction between dopamine and GABA neurons was based on their electrophysiological characteristics^[19,20]. Briefly, dopaminergic neurons displayed a low resting firing rate, slow hyperpolarization after each action potential, and inward rectification in response to hyperpolarizing current injection. In contrast, GABAergic neurons were characterized by a relatively high-frequency firing and absence of the inward rectification. The neurons obtained in the present study were medium-sized neurons, which exhibited the electrophysiological characteristics of GABAergic neurons.

Effects of 100 nmol/L zolpidem on mPSC The mPSC were found in all the SNr neurons, which were sensitive to the GABA_A receptor antagonist bicuculline (10 μ mol/L). As shown in Figure 1, superfusion of 100 nmol/L zolpidem significantly prolonged the decay time, the time required for the amplitude of the mPSC to decay to half its peak value, without any change in the amplitude, rise time, and inter-event intervals. In 6 cells recorded, 100 nmol/L zolpidem significantly prolonged the decay time (control: 7.4 ± 0.5 ms; zolpidem: 10.3 ± 0.3 ms, $P < 0.01$). The prolongation on decay time was only partially reversed after 20 min of washing. No significant change was observed in amplitude (control: 64.7 ± 5.8 pA; zolpidem: 70.5 ± 7.6 pA, $P > 0.05$), rise time (control: 3.0 ± 0.3 ms; zolpidem: 3.1 ± 0.2 ms, $P > 0.05$) and frequency (control: 2.9 ± 0.6 Hz; zolpidem: 3.0 ± 0.6 Hz, $P > 0.05$).

Benzodiazepine antagonist blocked the zolpidem-mediated prolongation of mPSC A further experiment was performed to investigate the effects of the benzodiazepine binding site antagonist flumazenil on the zolpidem-mediated prolongation of the decay time. As shown in Figure 2, 10 μ mol/L flumazenil alone did not induce any change on decay time (control: 6.8 ± 0.3 ms; flumazenil: 6.9 ± 0.4 ms, $n=8$, $P > 0.05$), amplitude (control: 66.7 ± 11.2 pA; flumazenil: 65.2 ± 11.6 pA, $P > 0.05$), frequency (control: 4.1 ± 0.7 Hz; flumazenil: 3.5 ± 0.8 Hz, $P > 0.05$), and rise time (control: 2.9 ± 0.2 ms; flumazenil: 3.1 ± 0.3 ms, $P > 0.05$) of mPSC. However, in the presence of flumazenil, the zolpidem-induced prolongation of the decay time could be

completely prevented (flumazenil+zolpidem: 7.1 ± 0.4 ms, $P > 0.05$ compared with flumazenil alone). No significant difference was observed for amplitude (flumazenil+zolpidem: 68.8 ± 13.9 pA, $P > 0.05$), frequency (flumazenil+zolpidem: 3.2 ± 0.7 Hz, $P > 0.05$), and rise time (flumazenil+zolpidem: 3.1 ± 0.2 ms, $P > 0.05$) after flumazenil and zolpidem cosuperfusion.

Effects of 100 nmol/L zolpidem on spontaneous PSC The effects of zolpidem on spontaneous PSC (sPSC) were tested. As shown by the example in Figure 3A, 100 nmol/L zolpidem prolonged the decay time and rise time of sPSC significantly. In the 7 neurons studied, zolpidem prolonged the decay time from 7.0 ± 0.2 ms to 10.5 ± 0.4 ms ($P < 0.01$) and the rise time from 2.7 ± 0.1 ms to 3.4 ± 0.1 ms ($P < 0.01$). There was no significant effect on amplitude (control: 80.1 ± 8.8 pA; zolpidem: 77.0 ± 8.0 pA, $P > 0.05$) and frequency (control: 7.1 ± 1.4 Hz; zolpidem: 6.7 ± 1.3 Hz, $P > 0.05$). Figure 3B summarizes the effects of 100 nmol/L zolpidem on sPSC. The increase on the decay time of sPSC ($49.9\% \pm 5.4\%$) was similar to that of mPSC ($40.7\% \pm 4.4\%$, $P > 0.05$).

Effects of 1 μ mol/L zolpidem on mPSC and sPSC Further studies were performed to observe the effects of a higher concentration of zolpidem on both mPSC and sPSC. In 6 neurons studied, 1 μ mol/L zolpidem prolonged the decay time of mPSC from 6.2 ± 0.4 ms to 11.6 ± 0.6 ms ($P < 0.01$) and amplitude from 65.5 ± 5.9 pA to 77.1 ± 7.2 pA ($P < 0.05$). There was no significant change in the rise time (control: 2.5 ± 0.3 ms; zolpidem: 3.0 ± 0.2 ms, $P > 0.05$) and frequency (control: 3.8 ± 0.7 Hz; zolpidem: 3.7 ± 0.4 Hz, $P > 0.05$). The increase in the decay time induced by 1 μ mol/L zolpidem was $87.8\% \pm 8.1\%$, which was significantly stronger than that induced by the concentration of 100 nmol/L ($40.7\% \pm 4.4\%$, $P < 0.05$, Figure 4A).

In another 9 neurons studied, 1 μ mol/L zolpidem prolonged the decay time of sPSC from 6.9 ± 0.3 ms to 11.3 ± 0.5 ms ($P < 0.01$) and the rise time from 2.5 ± 0.1 ms to 3.0 ± 0.1 ms ($P < 0.01$). There was no significant change in amplitude (control: 67.1 ± 9.3 pA; zolpidem: 79.1 ± 7.9 pA, $P > 0.05$) and frequency (control: 6.5 ± 1.1 Hz; zolpidem: 6.2 ± 1.0 Hz, $P > 0.05$). The increase in the decay time induced by 1 μ mol/L zolpidem was $65.6\% \pm 10.4\%$, which was significantly stronger than that induced by 100 nmol/L zolpidem ($49.9\% \pm 5.4\%$, $P < 0.05$, Figure 4B). However, no difference was observed between the prolongation of the decay time of mPSC ($87.8\% \pm 8.1\%$) and sPSC ($65.6\% \pm 10.4\%$, $P > 0.05$).

Effects of zolpidem on rotational behavior To determine the modulation of zolpidem on motor behavior *in vivo*, zolpidem was microinjected into the SNr. In 7 rats tested, a unilateral microinjection of zolpidem (1 mmol/L, 0.2 μ L) in-

Figure 1. Effects of 100 nmol/L zolpidem on mPSC of the SNr neurons. (A) raw traces showing that 100 nmol/L of zolpidem prolonged the decay time of mPSC. (B) summary of the effects of zolpidem on mPSC ($n=6$). 100 nmol/L zolpidem significantly prolonged the decay time without significant change on amplitude, rise time, and frequency. ^c $P<0.01$ vs TTX.

duced a robust contralateral rotation (32.7 ± 2.9 turns/30 min). However, the vehicle microinjection only induced 0.7 ± 0.3 turns/30 min contralateral rotation ($n=6$, $P<0.01$ compared with zolpidem). In another 5 rats, a unilateral microinjection of flumazenil (3 mmol/L, 0.2 μ L) alone did not produce any significant rotation (2.2 ± 2.1 turns/30 min contralateral rotation, $P>0.05$ compared with the control). However, the presence of flumazenil could completely block the contralateral rotation induced by the zolpidem microinjection (2.9 ± 2.7 turns/30 min contralateral rotation, $n=7$, $P<0.05$ compared

with zolpidem alone). These data are summarized in Figure 5.

Discussion

It is well known that the subunit combination is critical in determining the physiological functions and pharmacological properties of the GABA_A receptor in the brain^[8,21–23]. Early morphological studies, including *in situ* hybridization, have shown that the SNr expressed high levels of $\alpha 1$ subunits on the GABA_A receptor^[7,24]. Zolpidem has high affinity for the GABA_A receptor containing $\alpha 1$ subunits^[25,26]. Therefore,

Figure 2. Effects of benzodiazepine antagonist flumazenil on the zolpidem-induced prolongation of the decay time of mPSC. (A) typical traces showing the effects of flumazenil (10 μ mol/L) on zolpidem-induced potentiation of mPSC. (B) summary of the effects of flumazenil ($n=8$). Flumazenil prevented the effects of zolpidem on the decay time of mPSC, while it alone did not have any significant effect on the decay time.

neurons with relatively high densities of $\alpha 1$ subunits on the GABA_A receptor usually exhibit high binding sites and sensitivity for zolpidem^[27,28]. In the present study, all neurons recorded in the SNr exhibited sensitivity to 100 nmol/L zolpidem, suggesting the functional presence of $\alpha 1$ subunits in the rat SNr.

Morphological evidence has revealed that the SNr received GABAergic innervation from the striatum, globus pallidus, and local axon collaterals. The action potential-dependent inhibitory PSC of the SNr neurons mainly origi-

nate from the axon collaterals because the striatal neurons are quiescent. However, the action potential-dependent pallidal GABAergic inputs are blocked under coronal sectioning. To investigate the possible difference of the GABA_A receptor subunit composition arising from striatonigral, pallidonigral, and nigronigral GABAergic innervation, we further compared the effects of zolpidem on mPSC and sPSC. The present results showed that zolpidem exerted similar potency on the prolongation of the decay time of mPSC and sPSC, suggesting that $\alpha 1$ subunit expres-

Figure 3. Effects of 100 nmol/L zolpidem on sPSC. (A) typical traces showing the effects of 100 nmol/L zolpidem on sPSC. (B) summary of the effects of 100 nmol/L zolpidem on sPSC ($n=7$). ^c $P<0.01$ vs ACSF.

sion may be similar in the SNr. However, it was impossible to isolate the PSC arising from different sources and examine the effects of zolpidem on them directly.

Much evidence has shown that the SNr is involved in the control of several kinds of epileptic seizures. The firing rate of SNr increased significantly at the beginning of seizure^[29]. The anticonvulsant drug gabapentin decreased the firing rate of the SNr^[30]. Furthermore, deep brain stimulation of the SNr prevents seizures^[31].

GABAergic transmission in the SNr is critical for seizure control. Previous studies have shown that GABA_A receptor expression is reduced in the SNr of some epileptic models^[32]. However, a recent study revealed that the GABA_A receptor mediated inhibitory PSC, and α subunit expression were not

reduced in the SNr of gerbils with inherited epilepsy^[33]. Functional studies have shown that a microinjection of muscimol into the SNr suppressed the electroshock model of epilepsy^[34], while bicuculline infusions are proconvulsant^[35]. The intranigral transplantation of GABA-producing cells have been shown to exhibit significant anticonvulsant effects in experimental epilepsy^[36]. Recently, Gonzalez Ramirez *et al* reported that benzodiazepine binding was enhanced in the SNr in hyperthermia-induced seizure rats^[37]. Microinfusions of zolpidem had anticonvulsant effects on clonic and tonic-clonic seizures^[13]. The present findings prompted us to hypothesize that the direct potentiation on GABA transmission is the major mechanism of zolpidem-induced antiepileptic effects in the SNr.

Figure 4. Comparison of 1 μmol/L and 100 nmol/L zolpidem on the decay time of both mPSC and sPSC. 1 μmol/L zolpidem produced stronger prolongations on the decay time of both mPSC (A) and sPSC (B). ^b*P*<0.05.

In conclusion, the present *in vitro* studies demonstrated that zolpidem enhanced GABA transmission in the SNr by activating the benzodiazepine site. Moreover, the finding on the effects of zolpidem in the SNr may provide a rationale for further investigations into its potential in the treatment of some neurological diseases.

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Figure 5. Rotational behavior in 30 min after a unilateral microinjection of vehicle (control), zolpidem, flumazenil, and zolpidem with flumazenil into the SNr. (A) zolpidem induced significant net contralateral rotation. Flumazenil completely prevent the action of zolpidem, which itself did not induce rotation. ^b*P*<0.05. (B) confirmation of the microinjection sites in the SNr. Symbols represent different drug injections: control (triangle, n=6), zolpidem (circle, n=7), flumazenil (asterisk, n=5), and flumazenil+zolpidem (square, n=7).

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