

Origins of GABA_A and GABA_B Receptor-Mediated Responses of Globus Pallidus Induced after Stimulation of the Putamen in the Monkey

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The external and internal segments of the pallidum (GPe and GPi) receive heavy GABAergic innervations from the neostriatum, an input nucleus of the basal ganglia. The GPe neurons provide another major GABAergic innervation to the GPe itself and GPi. Although these GABAergic inputs are considered to play key roles in controlling the level and pattern of firing activity of pallidal neurons in both normal and pathophysiological conditions, these inputs have not been well characterized *in vivo*. Here, we characterized the responses of pallidal neurons to single and burst stimulation of the putamen (Put) in awake monkeys. Unit recordings in combination with local infusion of drugs and a chemical blockade of the subthalamic nucleus (STN), the major origin of excitatory afferents, revealed the following. Under STN blockade, the duration of single Put stimulation induced gabazine (a GABA_A antagonist)-sensitive responses differed greatly in the GPe (~400 ms long) and in the GPi (60 ms long). Burst stimulation of the Put induced CGP55845 [(2S)-3-[[[(1S)-1-(3,4-dichlorophenyl)ethyl]amino-2-hydroxypropyl]](phenylmethyl)phosphinic acid] (a GABA_B antagonist)-sensitive responses in the GPe and GPi. However, the data suggested that the origin of the GABA_B responses was the GPe, not the Put. Local CGP55845 application increased the spontaneous firing of GPe and GPi neurons, suggesting that GABA released from the axons of GPe neurons effectively activates GABA_B receptors in the GPe and GPi and contributes significantly to the control of the level of neuronal activity.

Key words: globus pallidus; putamen; unit recording; GABA_A responses; GABA_B responses; awake monkey

Introduction

The external (GPe) and internal (GPi) segments of the pallidum (GPe/GPi) play key roles in the physiology and pathophysiology of the basal ganglia. GPe/GPi receive their main GABAergic inputs from the neostriatum, an input nucleus of the basal ganglia, and GPe. The GPe projects to most of the basal ganglia nuclei, including the GPe itself (Robledo and Feger, 1990; Kita and Kitai, 1991; Kita, 1992, 1994; Parent and Hazrati, 1995; Kita et al., 1999). Thus, the GPe may play a significant role in controlling the level and pattern of firing activity of neurons in various nuclei of the basal ganglia (Kita, 1992, 1994). The GPi is a major output nucleus of the basal ganglia, receiving major inputs from the neostriatum, GPe, and the subthalamic nucleus (STN), and projecting to the thalamus.

The level and pattern of firing activity of GPe/GPi neurons changes with the development of basal ganglia diseases, including

Parkinson's disease and hemiballism (Pan and Walters, 1988; Tremblay et al., 1989; Filion and Tremblay, 1991; Sterio et al., 1994; Nini et al., 1995; Beric et al., 1996; Lenz et al., 1998; Vitek et al., 1999; Boraud et al., 2001; Wichmann and Soares, 2006). Thus, exploring the mechanisms controlling their firing activity is important for understanding basal ganglia function in normal and pathological conditions. Although anatomical and *in vitro* physiological evidence suggests that GABAergic inputs from the neostriatum and GPe to GPe/GPi may exert different effects on the postsynaptic neurons through different receptors located at different loci (Parent and Hazrati, 1995; Shink and Smith, 1995; Ogura and Kita, 2000; Kaneda and Kita, 2005), *in vivo* studies that evaluate the actions of these receptors are scarce. Studies with cortical stimulation suggested that the duration of GABA_A receptor-mediated inhibition in the GPe and GPi differ greatly (Nambu et al., 2000; Kita et al., 2004). Recent studies using monkeys revealed basic roles of ionotropic GABAergic inputs in the control of the level and pattern of firing activity of GPe/GPi neurons (Kita et al., 2004, 2005). Existence of ambient and synaptically evoked GABA_B responses in the primate GPe/GPi (Galvan et al., 2005) and rat GPe (Kaneda and Kita, 2005) was also revealed recently. GPe neurons have more burst firing in parkinsonian conditions (Filion and Tremblay, 1991; Sterio et al., 1994; Nini et al., 1995; Beric et al., 1996; Boraud et al., 2001; Wichmann and Soares, 2006). This burst firing may be more effective for a large

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release of GABA and for GABA_B receptor activation. Thus, the aim of the present study was to test the hypothesis that the activity of GPe/GPi neurons is controlled by continuous GABA_A and GABA_B receptor-mediated inputs originating from spontaneously active GPe neurons. Specifically, we examined whether putamen (Put) stimulation did indeed evoke different inhibitions in the two nuclei by pharmacological identifications and characterize GABA_A and GABA_B receptor-mediated responses of GPe/GPi neurons to single and burst Put stimulation in awake monkeys.

Materials and Methods

Monkey preparation. This study was performed in compliance with the guidelines of National Institutes of Health *Guide for Care and Use of Laboratory Animals* and the National Institute of Physiological Sciences for the Use and Care of Laboratory Animals in Research. The monkey preparation methods used in the present study were very similar to those reported previously (Nambu et al., 2000; Kita et al., 2004, 2005). In short, a *Macaca fuscata* and a *Macaca mulatta* were trained to sit in a monkey chair quietly. Before surgery, monkeys were anesthetized and placed in a homemade acrylic stereotaxic apparatus, and then magnetic resonance images of the monkey head were taken. The monkeys then received surgery to fix their heads painlessly to a stereotaxic frame attached to the chair. Under sodium pentobarbital (25 mg/kg, i.v.) and ketamine hydrochloride (10 mg/kg, i.m.) anesthesia, the skull of the monkey was widely exposed, small stainless screws were attached to the skull as anchors, the exposed skull and screws were completely covered with transparent acrylic resin, and two stainless steel pipes were mounted in parallel over the frontal and occipital areas for head fixation. A few days after the initial surgery, a second surgery was performed to implant a stimulus electrode into the hand region of the primary motor cortex (M1). The M1 stimulation was used to locate the hand areas of the Put, GPe/GPi, and STN (for details, see Nambu et al., 2000). Monkeys were anesthetized with ketamine hydrochloride (10 mg/kg, i.m.) and xylazine hydrochloride (1–2 mg/kg, i.m.) and were seated in a monkey chair with its head fixed in a stereotaxic frame. To access the M1, a hole was drilled in the skull. After recovery from the anesthesia, a glass-coated Elgiloy (Hampstead, NH) alloy microelectrode (0.5–1.5 M Ω at 1 kHz) was inserted perpendicular to the cortical surface. Extracellular unit activity was recorded in 1–1.5 mm intervals, and the neuronal responses to somatosensory stimuli (skin touch and passive joint movement) were examined. After extracellular unit recording, intracortical microstimulation, a train of 12 cathodal pulses (200 μ s duration at 333 Hz) with currents of <50 μ A, was delivered, and movements evoked in the various body parts were observed. According to the electrophysiological mapping, a bipolar stimulating electrode (made of 200- μ m-diameter enamel-coated stainless steel wire; intertip distance, 2 mm) was implanted into the hand region of the M1. Monkeys were reanesthetized, and two holes (10–15 mm diameter) were drilled in the skull to access the Put, pallidum, and the STN. A rectangular-shaped plastic chamber covering both holes, 30- and 55-mm-long in the rostrocaudal and mediolateral directions, was fixed with an \sim 20° tilt from the horizontal plane onto the skull with acrylic resin.

Electrode assembly for unit recording and local injection of drugs. The method for GPe/GPi units recording was very similar to previous studies (Nambu et al., 2000; Kita et al., 2004). During the experimental sessions, the monkeys were seated in a monkey chair with their heads restrained. Single-unit recordings in combination with local applications of GABA_A or GABA_B antagonists were performed with an electrode assembly consisting of a platinum–iridium wire (catalog #7675; A-M Systems, Carlsborg, WA) placed in a silica tube [outer diameter (OD), 147 μ m; inner diameter (ID), 74 μ m; part #2000018; Polymicro Technologies, Phoenix, AZ] for unit recordings and two other silica tubes (OD, 146 μ m; ID, 31 μ m; part #2000012; Polymicro Technologies) for drug delivery (for more detail on the electrode assembly, see Kita et al., 2004). The impedance of the unit-recording electrode ranged from 0.7 to 1.2 M Ω (measured with 1 kHz alternating current).

The electrode assembly was penetrated obliquely (45° from vertical) into GPe/GPi with reference to the recording regions used in previous studies (see hand region of GPe/GPi) (Yoshida et al., 1993; Nambu et al.,

2000) and from the responses to M1 stimulation. Throughout the course of the experiment, x-ray images of the frontal and sagittal planes were taken frequently to locate the electrodes. Recordings were made from GPe/GPi neurons that responded to M1 stimulation but not from other neurons. The GABA_A antagonist gabazine (0.2 mM) and the GABA_B antagonist CGP55845 [(2S)-3-[[[(1S)-1-(3,4-dichlorophenyl)ethyl]amino-2-hydroxypropyl] (phenylmethyl)phosphinic acid] (a final concentration of 0.5 mM from a 50 mM stock in DMSO) were dissolved in saline, and a total volume of 0.1–0.2 μ l was injected to the recording site at a rate of 0.03 μ l/min (i.e., the total injection time was 3–7 min) by advancing the plungers with computer-controlled stepping motor-driven actuators. Our previous study using the same injection method indicated that the drug effect became maximum 5–10 min after the injection, and the radius of the effective area was <1 mm with a 0.2 μ l injection (Kita et al., 2004, 2005). Thus, once an injection was made, the next injection site was separated by at least 1 mm from the previous injection site. In an initial stage of the experiment, we confirmed that injections of saline alone (four neurons each in the GPe and GPi) or saline with 1% DMSO (four neurons each in the GPe and GPi) did not alter the firing rate, firing pattern, or Put stimulation-induced responses.

The method for blockade of the STN with the GABA_A receptor agonist muscimol was also the same as that described previously (Nambu et al., 2000; Kita et al., 2004). In short, the area of the STN responding to M1 stimulation was mapped by unit recording with an Elgiloy electrode. A tungsten wire attached to the 30 gauge needle of a 10 μ l Hamilton micro-syringe was then used to penetrate vertically into the mapped location of the STN using a hydraulic microdrive with unit recordings and x-ray images as guides. Muscimol (0.5 μ g/ μ l in saline, 0.5–1.0 μ l) was injected only once a day.

Put stimulation, unit recordings, and data analysis. The Put was mapped by unitary responses to M1 stimulation to locate the wrist/digits region. Concentric-bipolar electrodes fabricated with a stainless steel center lead (diameter, 120 μ m) and a stainless steel outer tube (OD, 0.35 mm), with a tip separation of 0.5 mm and an impedance of \sim 5 k Ω (measured with 1 kHz alternating current), was chronically implanted in the area of the Put that responded to M1 stimulation (for the location, see Nambu et al., 2002). The duration of the stimulus current pulses was 300 μ s. Other stimulus parameters were as follows: for single stimulation, strength up to 0.7 mA, delivered every 1.4 s; for burst stimulation with 10 burst pulses (up to 100 Hz), strength up to 0.4 mA, delivered every 5.4 s.

The unit recordings were amplified, passed through a 0.7–2 kHz band-pass filter and then to a homemade time-amplitude-window discriminator that has a threshold selection and a window setting mechanism (a modified version of Mano and Yamamoto, 1978). The window can be placed at a specified delay time from the initial threshold setting. For instance, a level above noise is selected for the threshold, and a window is set at the peak of the desired spikes to exclude other spikes of different sizes or widths and stimulus artifacts. The stimulus artifacts to strong intensity stimulation of the Put created short, one or two bins, gaps, or shortening of bins in the peristimulus time histograms (PSTHs) immediately after the stimulation. However, the artifacts did not affect the analysis in the present study. The responses of GPe/GPi neurons to the Put stimulation were assessed by constructing PSTHs for 50 single stimulation trials and 25 burst stimulation trials. The ordinate of all of the PSTHs was converted to the firing rate. PSTHs with a 1 ms bin width were constructed on-line for initial evaluations. For analysis of the slow inhibitory responses lasting >100 ms to burst stimulation, PSTHs with a 4 ms bin width were generated off-line. The firing during the 100 ms preceding the stimulation was considered to be the base discharge. The changes in the firing activity in response to Put stimulation were judged to be significant if the firing rate during at least two consecutive bins of the PSTHs exceeded the 95% confidence interval of the base discharge (one-tailed *t* test for each bin). The amplitude of fast excitations and inhibitions was obtained from the average of the two consecutive highest or lowest bins, respectively. The magnitude of the slow inhibitory responses occurring after the termination of burst Put stimulation was obtained in the following manner. The duration of the inhibition with its initiation and end points was determined by having two consecutive bins exceeding the significance level. The mean firing rate of the base discharge minus that of the inhibition (i.e., the area of the inhibition) was obtained as the mag-

nitude of the inhibition. Changes in the slow inhibitory responses from local injections of CGP55845 were similarly assessed by comparing the areas of the inhibition (see Fig. 3). Because the drug effects became strongest 5–10 min after injection and decayed very slowly with partial recovery at 45–60 min after injection (Kita et al., 2004), the spontaneous firing rate, the amplitudes, and the durations of the responses to Put stimulation obtained immediately before and 5–10 min after completion of drug injection were evaluated by ANOVA with Bonferroni's/Dunn's *post hoc* test or paired *t* test. In some experiments, a second drug injection was made 12–15 min after the first injection, and effects of the second drug were similarly assessed 5–10 min after completion of drug injection. The rates and patterns of firing were analyzed by calculating the mean rates and autocorrelograms (bin width, 0.5 ms) from 50 s of digitized recordings. The regularity of the firing was assessed from the presence of multiple peaks and their height in the autocorrelograms. The 50 s of data were also used to obtain burst indexes. We chose the proportion of spikes in bursts (percentage) as the index because this was frequently used in other studies and was not correlated with the background firing rate of neurons (Wichmann and Soares, 2006). Bursts were detected by the "surprise" method of Legendy and Salcman (1985) with the surprise value of at least three and the number of spikes of at least three in a burst. These values were adopted from a recent detailed study on burst in monkey pallidum and STN (Wichmann and Soares, 2006).

Histology. Several of the recording and drug injection sites were marked by passing a cathodal direct current (20 μ A for 30 s) through the recording electrode. At the end of the final experiment, the monkeys were deeply anesthetized with sodium pentobarbital (50 mg/kg, i.v.) and perfused transcardially with 2 liters of PBS, pH 7.3, followed by 5 liters of 4% paraformaldehyde in 0.1 M phosphate buffer. The monkeys were then perfused with 3 liters of 0.1 M phosphate buffer containing 10% sucrose and, finally, with 2 liters of the phosphate buffer containing 30% sucrose. The brains were cut serially into 60- μ m-thick frontal sections on a freezing microtome. These sections were mounted onto gelatin-coated glass slides and stained with 1% neutral red. The recording and drug injection sites were reconstructed according to the lesions made by current injections and the traces of the electrode tracks (data not shown).

Results

Responses of GPe/GPi neurons to single and burst Put stimulation

The neurons that responded to stimulation of the Put included 38 GPe and 14 GPi neurons recorded before the STN block and 16 GPe and 11 GPi neurons recorded after the STN block. The neurons from the two monkeys were pooled because the spontaneous firing rates and amplitudes of inhibitory and excitatory responses to single Put stimulation obtained from these monkeys were the same (ANOVA). Before the STN blockade, the patterns

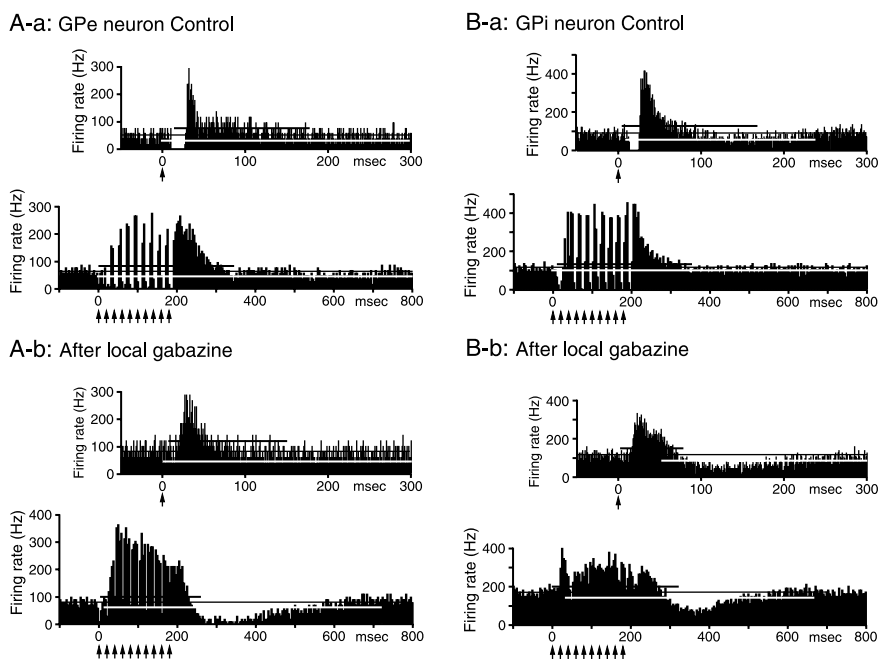


Figure 1. Single and burst Put stimulation evoked similar responses in GPe (**A**) and GPi (**B**) neurons. **A-a, B-a**, Single Put stimulation with 0.7 mA evoked an inhibition followed by an excitation in both the GPe and GPi neurons. Burst Put stimulation with 0.4 mA (10 pulses with 50 Hz) evoked short inhibitions and excitations to each burst stimulation. **A-b, B-b**, Local application of gabazine (0.2 mM, 0.2 μ l) to the same neurons increased the rate of spontaneous firing and also greatly reduced or blocked the short-duration inhibitions to single and burst stimulations. After gabazine application, the excitations of both the GPe and GPi neurons to burst stimulations were followed by a slow inhibition. In this and the following figures, the PSTHs for single and burst stimulations (marked by black arrows) were constructed with 1 and 4 ms bins, respectively. Also, in this and some of the following figures, the mean firing rate and the significance levels of excitations and inhibitions, determined by one-tailed *t* tests using the base firing from the 100 ms before stimulation, are indicated by a long, thin black line, a thick black line, and a white line.

Table 1. Latency and half-duration of single putamen stimulation induced responses

Recording Site	Total No. of Neurons	Inhibition		Excitation	
		Latency	Duration	Latency	Duration
Before muscimol blockade of the STN					
GPe	38	10.5 \pm 3.2	16.8 \pm 7.4	26.5 \pm 6.7 (n=35)*	48.2 \pm 28.3
GPi	14	13.1 \pm 3.5	13.8 \pm 4.7	27.5 \pm 6.7 (n=13)*	28.4 \pm 18.0
After local application of gabazine					
GPe	13			22.6 \pm 5.0	53.4 \pm 31.3
GPi	8			21.0 \pm 3.5	37.1 \pm 16.3
After muscimol blockade of the STN					
GPe	16	9.4 \pm 3.7	412.3 \pm 174.2		
GPi	11	12.2 \pm 3.9	57.2 \pm 22.8		

GPe and GPi: external and internal segment of the pallidum, respectively. STN: subthalamic nucleus. Latencies and durations are mean \pm S.D. in ms. *: The number of excited neurons to single Put stimulation differ from the total number of neurons because three GPe and one GPi neurons responded with an inhibition only.

* $p < 0.02$, * $p < 0.01$, * $p < 0.0001$ ANOVA with Bonferroni/Dunn *post hoc* tests

of responses evoked by single or burst Put stimulation were similar in both the GPe and the GPi. Single Put stimulation induced an inhibition in all responded neurons, and the inhibition was followed by an excitation in the majority of the GPe (35 of 38) and GPi (13 of 14) neurons (Fig. 1A-a,B-a). Three GPe neurons and one GPi neuron induced an inhibition only. Table 1 shows the latencies and the half-durations of the inhibitions and excitations evoked by single, up to 0.7 mA, stimulation. The latency of the inhibition was \sim 2.5 ms shorter in the GPe than in the GPi ($p < 0.01$, ANOVA). The mean duration of the inhibition in the GPe was \sim 3 ms longer than in the GPi, but the difference was insignificant. The

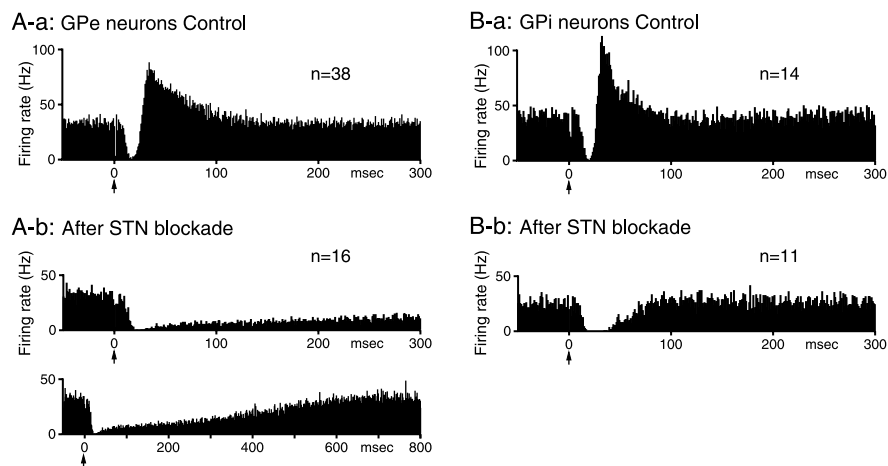


Figure 2. Population responses of GPe (**A**) and GPi (**B**) neurons to single Put stimulation. **A-a, B-a**, PSTHs of all GPe and GPi neurons responding to single Put stimulation with 0.7 mA obtained in control conditions were averaged. **A-b, B-b**, PSTHs of all GPe and GPi neurons responding to single Put stimulation with 0.7 mA obtained after the blockade of the STN were averaged. In **A-b**, an averaged PSTH is shown with different timescales.

latencies of the excitations were similar in the two nuclei. The duration of the excitations was significantly longer in the GPe than in the GPi ($p < 0.02$, ANOVA). These statistical differences can also be seen in the population responses, the averaged PSTHs, of all of the GPe and GPi neurons that responded to single Put stimulation (Fig. 2*A-a, B-a*). Occasional experimentation with very strong, up to 1.2 mA, stimulation revealed 2–3 ms latency inhibitions in both GPe and GPi neurons, as expected from the direct stimulation of the axons of GPe neurons projecting to the Put (Kita and Kitai, 1994; Bevan et al., 1998; Kita et al., 1999; Ogura and Kita, 2000). These short-latency responses were excluded from the present report.

In most of the GPe and GPi neurons, burst Put stimulation (10 pulses with 50 or 100 Hz) induced repeated occurrences of short inhibitions and excitations, forming a comb-like appearance in the PSTHs. Termination of the stimulation was followed by either an excitation lasting 150–200 ms ($n = 22$ in GPe; $n = 12$ in GPi) (Fig. 1) or an excitation followed by a slow inhibition lasting >100 ms in a small number (4 of 26 GPe and 3 of 15 GPi) of neurons.

Effects of local gabazine and CGP55845

Local application of the GABA_A antagonist gabazine increased the rate and regularity of spontaneous firing as reported previously (Kita et al., 2004) and greatly decreased or abolished single-stimulation-induced inhibition in all GPe and GPi neurons tested (Fig. 1). After gabazine application, the latency of the excitations was ~ 4 ms shorter in the GPe ($p < 0.01$, ANOVA) and 6.5 ms shorter in the GPi ($p < 0.01$; Table 1). The peak amplitude of the single-stimulation-induced excitations in the GPe and GPi was reduced by 34.2% ($p < 0.02$, paired t test; $n = 13$) and by 27.2% ($p < 0.05$, paired t test; $n = 8$), respectively. The duration of the excitation in GPi increased by ~ 9 ms as the blockade of the inhibition uncovered the early part of the excitations (Fig. 1, Table 1), although the change in the GPe was insignificant.

Gabazine also greatly decreased or abolished the early inhibitions that were induced during burst Put stimulation (Fig. 1). After the excitations to burst stimulation, 11 of 13 in GPe and 10 of 12 in GPi neurons evoked a slow gabazine-insensitive inhibition lasting 100–200 ms (Fig. 1). The remaining neurons had no slow inhibition. Three of the GPe neurons that showed the slow

inhibition were tested with various frequencies of burst Put stimulation. Using a fixed number of stimulus pulses, 50 or 100 Hz stimulation most effectively evoked the excitation during stimulation and the gabazine-insensitive inhibition in these GPe neurons (Fig. 3).

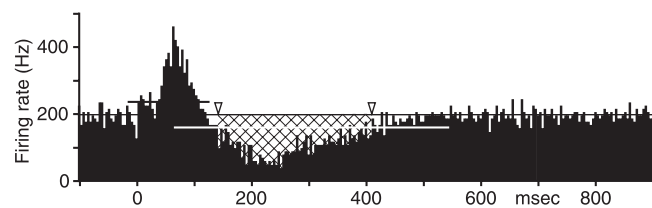
Local application of the GABA_B antagonist CGP55845 was performed on nine GPe and nine GPi neurons that were pretreated by gabazine 12–15 min before the CGP55845 injection. CGP55845 increased the spontaneous activity of all of these GPe and GPi neurons and also greatly decreased the gabazine-insensitive slow inhibition to burst Put stimulation (Fig. 4). The burst indexes of most of the gabazine-treated neurons, both before and after CGP55845 application, were 0 or nearly 0. CGP55845 was also tested on four GPe and three GPi neurons recorded before local gabazine application. CGP55845 increased the spontaneous firing rate without altering the firing patterns (Figs. 4*C, D*, 5*A*).

CGP55845 decreased the burst indexes of all four GPe neurons (from 9.3, 6.8, 8.7, and 14.2% to 2.5, 2.3, 0.6, and 6.3%, respectively; $p < 0.005$, paired t test) and also for all three GPi neurons (from 6.5, 1.1, and 18.0% to 1.2, 0.8, and 3.9% respectively; $p > 0.05$). CGP55845 did not change the short-latency inhibitions of the GPe and GPi neurons to single (Fig. 5*A*) and repetitive stimulation of the Put (data not shown).

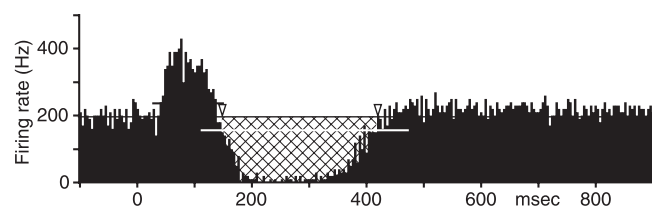
Effects of muscimol blockade of the STN

To block the excitations originating from the STN, muscimol was injected in the STN. In previous studies, we showed that local injection of the GABA_A agonist muscimol results in a complete cessation of the unitary activity of the STN, in alterations in the firing activity in the GPe and GPi, and in some instances, but not always, in the induction of dyskinesias 15–60 min after the injection (for details, see Nambu et al., 2000; Kita et al., 2004). The data presented here were collected before the development of dyskinesias. During generation of strong dyskinetic movements, the recording was terminated, and ketamine hydrochloride (10 mg/kg, i.m.) and pentobarbital (10–15 mg/kg, i.m.) were given to suppress the movement. The STN blockade eliminated the excitatory responses to single Put stimulation in the GPe and greatly prolonged the duration of the inhibition (Table 1, Fig. 6*A-a, B-a*). In the GPi, the inhibitions to single Put stimulation were also prolonged but to a smaller degree than with the GPe neurons (Table 1). These statistical differences can also be seen in the population responses, the averaged PSTHs, of all of the GPe and GPi neurons that responded to single Put stimulation (Fig. 2*A-b, B-b*). In 5 of 11 GPi neurons, the inhibition was followed by a gabazine-sensitive rebound-like excitation (Fig. 6*C*). These responses in the GPe and GPi were very similar to the responses to motor cortex stimulation (Nambu et al., 2000; Kita et al., 2004). Responses to burst Put stimulation after the STN blockade also differed in the GPe and GPi. In the GPe, burst stimulation induced an inhibition lasting 405.5 ± 37.4 ms ($n = 9$), followed by a slow excitation lasting >1 s (Fig. 6*A-a, B-a*). In the GPi, burst stimulation induced an inhibition with the duration of 207.4 ± 22.5 ms ($n = 7$). Unlike the GPe, the inhibition ended shortly after termination of the repetitive stimulation (Fig. 6*C-a*). In

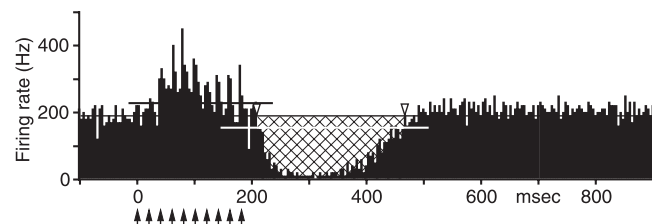
A: A GPe neuron after local gabazine, 200 Hz stim.



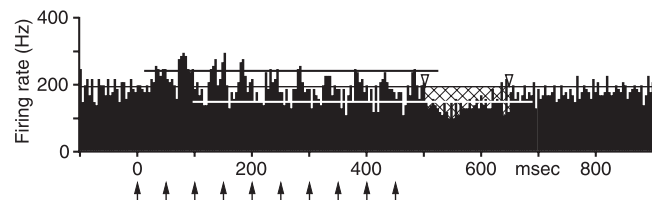
B: 100 Hz stim.



C: 50 Hz stim.



D: 20 Hz stim.



E:

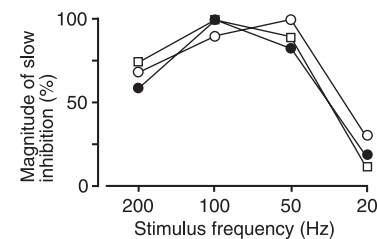


Figure 3. A–D, Responses of a local gabazine (0.2 mM, 0.2 μ l)-treated GPe neuron to burst Put stimulation (10 pulses, 0.4 mA) with different stimulus frequencies. PSTHs obtained from the GPe neuron show that burst stimulation with 100 Hz evoked the strongest excitations during the burst stimulation and was followed by the strongest slow inhibition. In this and in Figure 4, the hatched areas indicate the magnitude of slow inhibitions. The open arrowheads mark the statistically defined beginning and end of the slow inhibitions. E, The magnitudes of the inhibitions from three gabazine-treated GPe neurons were normalized by the maximum inhibition and plotted. Burst stimulation with 100 or 50 Hz evoked the strongest inhibition.

three of the seven GPi neurons, the inhibition was followed by a very weak rebound-like excitation.

Local gabazine application increased the level of spontaneous activity of GPe/GPi and greatly reduced the occurrence of the spontaneous long pauses in the GPe, as reported previously (Kita et al., 2004). In the GPe, gabazine completely blocked the inhibi-

tions to single Put stimulation (Fig. 6A,B). Gabazine also blocked the long inhibitions evoked after the termination of the burst stimulation in five of nine neurons (Fig. 6A). When gabazine blocked the long inhibition, the following slow excitation was also eliminated. However, in the remaining four neurons, gabazine slowed the onset of the inhibition but prolonged the duration of the inhibition to burst stimulation instead of blocking it (Fig. 6B). These four neurons were tested with multiple applications of gabazine, repeated three times in 5 min intervals with a total application of 0.6 μ l. It was confirmed that the second and third applications of gabazine did not block the inhibition (Fig. 6B). In the GPi, gabazine completely eliminated the inhibitions to single and burst Put stimulation (Fig. 6C–b).

Application of CGP55845 increased the spontaneous firing rate of all five GPe neurons (39.0 ± 14.6 to 52.9 ± 16.6 Hz; $p < 0.001$, paired t test) (Fig. 5B) and four GPi neurons (35.7 ± 6.1 to 43.0 ± 6.7 Hz; $p < 0.005$) tested after the blockade of the STN. Although CGP55845 did not alter the firing pattern (Fig. 5B), the burst indexes decreased in both GPe (73.8 ± 17.8 to $51.6 \pm 27.4\%$; $p < 0.05$, paired t test) and GPi neurons (27.3 ± 8.3 to $14.1 \pm 12.2\%$; $p < 0.02$). The burst index of GPe neurons after the STN blockade was very high because of the development of strong active and silent phases (Nambu et al., 2000; Kita et al., 2004). However, the effects of CGP55845 on single Put-stimulation-induced gabazine-sensitive inhibition were insignificant ($p > 0.05$ in paired t tests in both GPe and GPi) and inconsistent. CGP55845 decreased the duration of the inhibition in four GPe and three GPi neurons and increased the duration in two GPe and one GPi neuron. CGP55845 also had no significant effect on burst-stimulation-induced gabazine-insensitive inhibition in the GPe (data not shown; $p > 0.05$ in paired t tests in both GPe and GPi). Thus, no GABA_B receptor-mediated responses to Put stimulation could be identified in either the GPe or the GPi after the blockade of the STN.

Discussion

Responses to single Put stimulation

Response patterns of GPe/GPi neurons to single Put stimulation in control conditions were similar to those published previously (Ohye et al., 1976; Tremblay and Filion, 1989; Yoshida et al., 1993). Based on anatomical and physiological evidence, the initial inhibitions in GPe/GPi were attributable to GABAergic Put–GPe/GPi inputs (Kita and Kitai, 1991; Kita, 1994; Parent and Hazrati, 1995; Shink and Smith, 1995). The inhibition should consist of both monosynaptic and polysynaptic components because Put stimulation could activate cortical and thalamic axons terminating on nearby Put neurons (Kita, 1993). When the STN was blocked, the duration of Put stimulation-induced-inhibition in the GPe was much longer than in the GPi. We made a similar observation with motor cortex stimulation (Nambu et al., 2000; Kita et al., 2004). Thus, the differences in the inhibitions in the two nuclei were not specific to cortical stimulation. The long-duration inhibition in the GPe is puzzling because *in vitro* recordings never evoked such inhibitions (Nambu and Llinás, 1994; Stanford and Cooper, 1999; Ogura and Kita, 2000; Kaneda and Kita, 2005). Some possible explanations for the long inhibition are (1) that membrane properties or GABA uptake mechanisms differ in monkey and rodent GPe and (2) that stimulation of the Put might activate dopamine and serotonin systems that modulate GABAergic inhibition. For instance, activation of dopamine D₁ receptors in the substantia nigra pars reticulata enhances GABAergic inhibition (Radnikow and Misgeld, 1998). However, in our preliminary *in vitro* study, dopamine reduced the

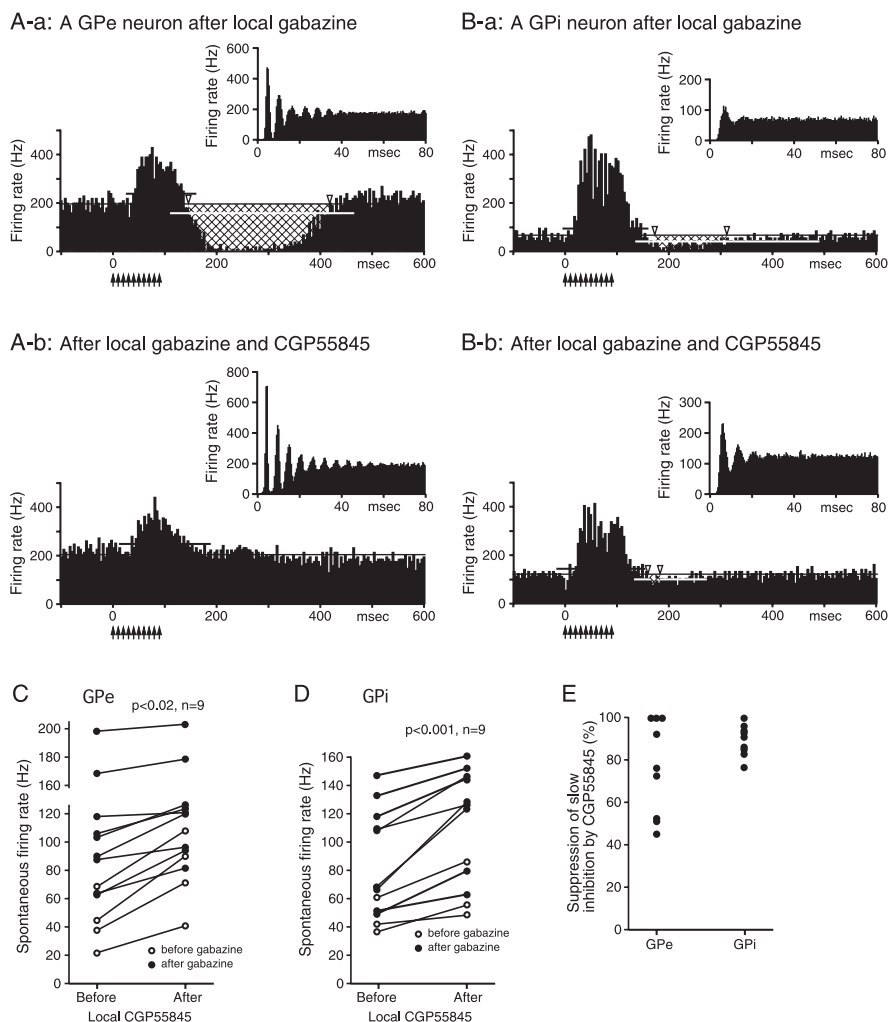


Figure 4. Effects of CGP55845 on GPe and GPI neurons pretreated with local gabazine (0.2 mM, 0.2 μ l) application. **A, B,** Autocorrelograms and PSTHs to burst Put stimulation (10 pulses, 0.4 mA, 100 Hz) of a GPe (**A-a, A-b**) and a GPI (**B-a, B-b**) neuron recorded before and after local application of the CGP55845 (0.5 mM, 0.2 μ l). **C, D,** Summaries show that CGP55845 significantly increased the spontaneous firing rate of the GPe and GPI neurons. The neurons recorded after the gabazine applications were used for the paired *t* tests. **E,** A summary shows that CGP55845 significantly suppressed or blocked the gabazine-insensitive slow inhibition to burst stimulation of the Put. The magnitude of the inhibition was assessed from PSTHs as described in Materials and Methods (also see the legend for Fig. 3), and the effect of each neuron was normalized by the inhibition in the PSTH recorded before the application of CGP55845.

GABAergic IPSCs in GPe (Hashimoto et al., 2001), probably attributable to presynaptic D_2 receptor activation (Cooper and Stanford, 2001). We do not think that serotonin prolonged the inhibition because our preliminary results suggested that serotonin decreased the inhibition (Hashimoto and Kita, 2002). The relatively short-duration inhibition in the GPI was attributable, at least in part, to activation of rebound mechanisms, because the inhibition often ended abruptly with gabazine-sensitive excitation.

In control conditions, the inhibition of GPe/GPI to single Put stimulation was followed by an excitation that could be decreased by the STN blockade. Put stimulation excites the STN through multiple pathways. One is the Put–GPe–STN pathway that disinhibits the STN during Put stimulation. The reduction of the excitation in GPe neurons after local gabazine application can be attributed to this pathway, similar to the responses to cortical stimulation (Kita et al., 2004). Another route is the activation of cortical and thalamic axons in the Put that monosynaptically or polysynaptically (for instance, through the cortex) activates the

STN. Because our main interest of the present study was to characterize the Put–GPe/GPI inhibitory inputs, additional attempts to isolate these connections were not made.

GABA_B responses

In control conditions, burst Put stimulation induced slow inhibitions in only a small number of GPe/GPI neurons. However, most of the neurons induced a slow inhibition when gabazine was applied to block GABA_A responses. Possible reasons for the induction of the slow inhibition are that gabazine increased the firing rate (i.e., depolarized the neurons), making the slow inhibition easier to detect in unit recordings, and that GABA_A responses may have effectively shunted the GABA_B responses. Presynaptic GABA_A inhibition of GABA release is unlikely because GABA_A receptors have not been found on GABAergic terminals in GPe/GPI (Charara et al., 2005). Our previous *in vitro* study showed no significant direct gabazine effects on the amplitude of the local repetitive stimulation-induced GABA_B response in rat GPe (Kaneda and Kita, 2005). Another possibility applicable to the GPe is that gabazine increased the firing during stimulation, thus evoking stronger slow inhibition. This last possibility is based on the assumption discussed below that GPe activation is the source of the slow inhibition.

We found that the blockade of the STN eliminated not only the excitations to burst Put stimulation but also the CGP55845-sensitive inhibitions, although the gabazine-insensitive responses remained. These observations suggest that GPe neurons, but not Put neurons that form GABAergic synapses in GPe/GPI, effectively evoke GABA_B responses. It should be noted that, unlike GPe neurons, GPI neurons in both monkey and rat do not have extensive local collaterals (Nakanishi et al., 1991; Parent et al., 1999). The most effective burst Put stimulus frequency to evoke the CGP55845-sensitive inhibition was 50 or 100 Hz, which was also the most effective stimulus to evoke strong excitations in the GPe. Receptor localization studies suggest that both striatal and local collateral synapses may evoke GABA_B responses (Chen et al., 2004). Thus, some possibilities for the failure of Put axons to evoke an appreciable GABA_B response are that the Put-axon terminals may have a small GABA release probability or, conversely, that the GABA released from Put terminals was taken up before reaching the receptors. Another factor may be that the distal dendritic location of the Put-axon synaptic site, opposed to the proximal dendritic location of GPe-axon synaptic site (Shink and Smith, 1995), may greatly dampen the response when recording at the soma (Hanson et al., 2004).

The observation that CGP55845 application consistently increased the firing frequency of GPe/GPI neurons suggested tonic activation of GABA_B receptors. It also supports the hypothesis

that ambient GABA levels in GPe projection sites play a significant role in the control of the rate and pattern generations in neuronal activities (Galvan et al., 2005; Hallworth and Bevan, 2005; Kaneda and Kita, 2005). This observation is consistent with our previous study suggesting that the spontaneous firing of most of GPe neurons *in vivo* is sufficient to release the GABA required to activate perisynaptic GABA_B receptors (Kaneda and Kita, 2005). The short and long pauses in the GPe before and after muscimol blockade of the STN were not abolished by CGP55845, although their intervals shorten as the firing rate increased, suggesting that the pauses were not initiated but were modulated by GABA_B receptor activation. CGP55845 reduced the burst indexes of GPe/GPi neurons, probably attributable to an increase in the mean firing rate, which itself regularized the firing intervals (Bar-Gad et al., 2001).

We tested the possibility that CGP55845 might block presynaptic GABA_B suppression and enhance the GABA_A inhibition to single Put stimulation (Kaneda and Kita, 2005). The experiments produced inconsistent results probably because the increase in the spontaneous firing obscured the enhancement of the GABA_A response. Alternatively, the tonic level of GABA might be insufficient to activate GABA_B receptors on Put-axons terminals. The examination of GABA_B receptors on the GPe-axon terminals was not performed in the present study because of technical difficulties.

Other responses

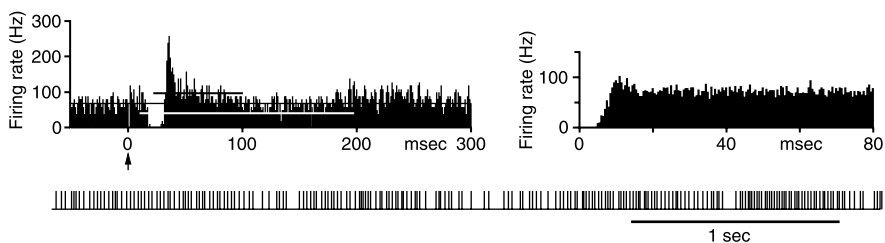
After STN blockade, the slow inhibition to burst Put stimulation was followed by strong slow excitations in the GPe or by short excitations in the GPi. These excitations were considered to be rebounds because the blockade of the preceding inhibitions also blocked the excitations. The difference in the duration of the excitations in the GPe and GPi suggests that there are different mechanisms to induce rebounds such as the prominent involvement of the persistent sodium current in the GPe versus the low-threshold calcium current in the GPi (Nakanishi et al., 1990; Kita and Kitai, 1991; Chen et al., 2004).

After the STN blockade, burst Put stimulation revealed gabazine- and CGP55845-insensitive slow inhibition in ~40% of the GPe neurons. The nature of the inhibition is unknown at present.

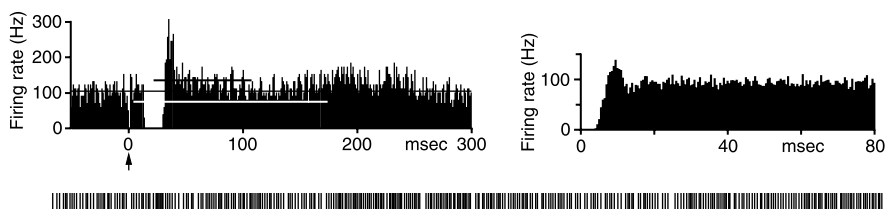
Conclusions

One of the main findings in the present study was that Put stimulation given after the muscimol blockade of the STN evoked very-long-duration inhibitions in the GPe and short-duration inhibitions in the GPi. We speculate that the long-duration inhibition in the GPe observed after STN blockade may underlie, at least in part, the frequent occurrence of relatively long gabazine-

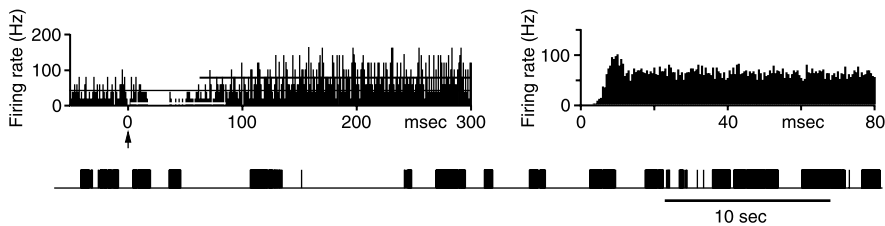
A-a: A GPe neuron



A-b: After local CGP55845



B-a: A GPe neuron after STN blockade



B-b: After CGP55845

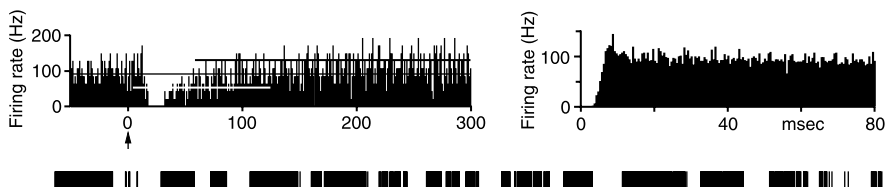


Figure 5. Effects of CGP55845 on GPe neurons. **A-a, A-b**, Responses of a GPe neuron to single 0.4 mA Put stimulation. An autocorrelogram and a digitized spike trace of the neuron before and after local CGP55845 application (0.5 mg/μl, 0.2 μl). **B-a, B-b**, Another GPe neuron similarly recorded after muscimol (0.5 μg/μl, 1.0 μl) blockade of the STN. In both cases, CGP55845 increased the firing rate without significantly altering the responses to Put stimulation or the firing patterns.

sensitive pauses in the GPe, because local gabazine abolished the pauses in some GPe neurons (Kita et al., 2004). Another main finding was that GABA released from GPe axons may effectively activate GABA_B receptors in GPe/GPi and contribute significantly to the control of the level of the neuronal activity. From this and previous *in vivo* and *in vitro* findings, it can be suggested that GABA_B receptors at the GPe innervation sites, including the GPe, GPi, and STN, are activated by ambient extracellular GABA released from GPe axons and that these receptors contribute significantly to the feedback and feedforward controls of the neurons in the target structures (Galvan et al., 2005; Hallworth and Bevan, 2005; Kaneda and Kita, 2005). In patients and in the animal models of Parkinson's disease, GPe neurons have more burst firing than in normal conditions (Filion and Tremblay, 1991; Sterio et al., 1994; Nini et al., 1995; Beric et al., 1996; Boraud et al., 2001; Wichmann and Soares, 2006) that might effectively activate GABA_B receptors at their innervation sites. The expression of GABA_B receptors in the pallidum and STN was altered in parkinsonian subjects (Calon et al., 2001, 2003; Johnston and Duty,

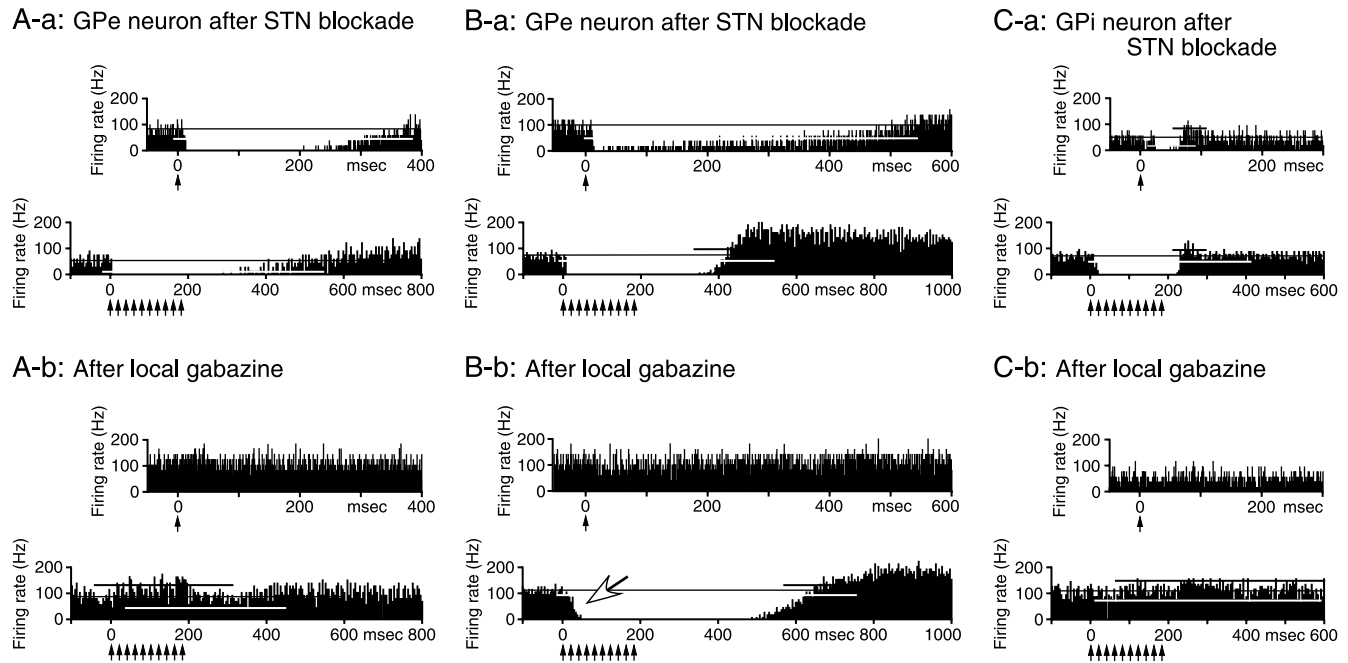


Figure 6. Responses of GPe and GPI neurons to single (0.7 mA) and burst (10 pulses, 0.4 mA, 50 Hz) Put stimulation recorded after muscimol (0.5 $\mu\text{g}/\mu\text{l}$, 1.0 μl) blockade of the STN. **A**, Both single and burst stimulation induced a long-duration inhibition in a GPe neuron (**A-a**), and local gabazine (0.2 mM, 0.2 μl) application completely blocked the inhibitions (**A-b**). **B**, Another GPe neuron induced a similar slow inhibition to both single and burst stimulation (**B-a**). Local gabazine (0.2 mM, 0.6 μl) application blocked the inhibition to single stimulation, whereas the inhibition to burst stimulation was prolonged although the initiation of the inhibition was slowed (marked by an open arrow in **B-b**). **C**, Single and burst stimulation induced a relatively short-duration inhibition followed by a short excitation in a GPI neuron (**C-a**), which was completely blocked by gabazine (0.2 mM, 0.2 μl) (**C-b**).

2003). Additional studies are required to clarify the roles of the GABA_B responses in movement control in normal and in basal ganglia disorder conditions and to develop strategies for using GABA_B reagents for the treatments of basal ganglia disorders.

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