Brief Communication

GABA, Not Glutamate, Controls the Activity of Substantia Nigra Reticulata Neurons in Awake, Unrestrained Rats

François Windels and Eugene A. Kiyatkin

Behavioral Neuroscience Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland 21224

Substantia nigra pars reticulata (SNr) receives both GABAergic and glutamatergic (GLU) inputs that are believed to act together to regulate neuronal activity in this structure. To examine the role of these inputs, single-unit recording was coupled with iontophoresis of GLU and GABA in rats under two conditions: awake, unrestrained and under chloral hydrate anesthesia. Although GABA potently inhibited SNr cells in both conditions, freely moving rats showed lower sensitivity than anesthetized animals. Likewise, GLU effectively induced excitations in most SNr neurons in anesthetized animals but was much less effective in awake, unrestrained animals in terms of both the number of sensitive cells and the magnitude of GLU-induced excitation. These findings, along with consistent excitations induced by bicuculline in awake, unrestrained rats, suggest that modulation of GABA inhibitory input, not the opposing actions of GLU and GABA, is the primary factor that regulates the activity state of SNr neurons.

Key words: **substantia nigra; GABA; glutamate; bicuculline; single-unit recording; freely moving animals; iontophoresis; anesthesia; basal ganglia**

Introduction

The basal ganglia is a group of subcortical structures implicated in a wide array of functions, such as motor activity, learning, and memory (Alexander et al., 1990; Packard and Knowlton, 2002). Their anatomy and physiology have been studied extensively, and models describing their functional role under normal and pathological conditions have been proposed (Albin et al., 1989; Alexander and Crutcher, 1990; Mink, 1996). According to these models, the striatum receives glutamatergic (GLU) inputs from most cortical areas and thalamus and then sends GABAergic projections to the substantia nigra pars reticulata (SNr) and entopeduncular nucleus (EP) complex through two distinct pathways. The first, or direct pathway, is composed of GABA efferents to the SNr and EP complex, whereas the second, or indirect pathway, relays successively to the globus pallidus (GP) and then to the subthalamic nucleus. This last structure sends GLU projections to SNr and EP, which then regulate the activity of specific thalamic nuclei.

On the basis of this structural organization, it is assumed that the activity of SNr cells is regulated primarily by a balance between GABA and GLU inputs. Although the inhibitory and excitatory effects of GABA and GLU on SNr cells have long been known and some of their specific receptor-mediated contributions to the overall neuronal activity have been described (Hammond et al., 1978; Collingridge and Davies, 1981; Waszczak and Walters, 1983; Nakanishi et al., 1987; Robledo and Feger, 1990; Celada et al., 1999; Schmitt et al., 1999), most of these studies have been conducted on anesthetized animals. Although this approach provides stable, controlled conditions under which neurons can be studied, the influence of anesthesia as a confounding factor on neural activity and afferent responsiveness remains unclear. This factor may account for some differences noted between studies.

To clarify this issue, we combined single-unit recording with iontophoresis to examine the effects of GLU and GABA on SNr neurons in rats under awake, unrestrained conditions and under chloral hydrate anesthesia. Therefore, our goals were twofold: to examine the effects of GLU and GABA under physiologically relevant conditions and to reveal the influence of general anesthesia as a factor modulating neuronal activity and afferent responsiveness.

Materials and Methods

Animals and surgery. Data were obtained from 28 male Long–Evans rats (400 ± 50 gm) obtained from Charles River Laboratories (Greensboro, NC). All animals were housed individually under standard laboratory conditions (12 hr light/dark cycle beginning at 7:00 A.M.) with food and water available *ad libitum*. Protocols were performed in compliance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (Publication 865-23) and were approved by the National Institute on Drug Abuse, Intramural Research Program Animal Care and Use Committee. The surgical procedures used have been described previously (Windels and Kiyatkin, 2003). Briefly, under general anesthesia (equithesin, 0.33 ml/100 gm, i.p.; dose of sodium pentobarbital, 32.5 mg/kg and chloral hydrate, 145 mg/kg), rats were implanted with a plastic, cylindrical hub designed to mate with a microelectrode holder (Rebec et al., 1993) during recording. This hub was centered over a hole drilled above the substantia nigra (5.2–6.0 mm posterior and 1.4–2.8 mm lat-

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Correspondence should be addressed to Dr. François Windels, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, 5500 Nathan Shock Drive, Baltimore, MD 21224. E-mail: fwindels@intra.nida.nih.gov.

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eral to bregma). After a 3–4 d recovery period, once-daily recording sessions were held over the next 2–5 d for unanesthetized, unrestrained rats ($n = 19$). A separate group of rats ($n = 9$), prepared as described above, underwent a single recording session under chloral hydrate anesthesia (400 mg/kg, i.p., followed by 120 mg $\cdot$ kg^{-1} $\cdot$ hr^{-1}). In these experiments, body temperature was monitored and maintained automatically at 37.2 ± 0.2°C with an electric heating pad.

Single-unit recording and iontophoresis. Four-barrel, microfilament-filled glass pipettes (Omega Dot 50744; Stoelting, Wood Dale, IL), pulled and broken to a diameter of 5 ± 1 μm, were used for single-unit recording and iontophoresis. The recording barrel contained 2% Pontamine Sky Blue in 3 M NaCl, and the balance barrel contained a 0.25 M solution of NaCl. The remaining barrels were filled with solutions of L-GLU monosodium salt (0.25 M, pH 7.5), GABA (0.25 M in 0.125 M NaCl, pH 4), or bicuculline methiodide (BIC) (0.02 M in 0.125 M NaCl, pH 4). All substances were obtained from Sigma (St. Louis, MO). The resistance of the drug-containing barrels ranged between 10 and 30 MΩ, whereas the recording channel had an impedance of 3–5 MΩ (measured at 100 Hz). Retaining (±8–10 nA) and ejecting (±5–60 nA) currents were applied with a constant-current generator (Ion 100T; Dagan, Minneapolis, MN). GABA and BIC were applied as cations, and GLU was applied as an anion. Each multibarrel pipette was filled with fresh solution less than 1 hr before use and fixed in a microdrive assembly that later was inserted into the skull-mounted hub. The electrode was then advanced 8.0 mm below the brain surface to the starting point of unit recording.

Neuronal discharge signals were sent to a head-mounted preamplifier (LF 441CN; National Semiconductor, Santa Clara, CA) and then additionally amplified, filtered (bandpass, 300–3000 Hz), and stored on the audio channel of a video cassette recorder. Spike activity was monitored with a digital oscilloscope and audio amplifier and analyzed using a Spike2 interface (Cambridge Electronic Design, Cambridge, UK). After the isolation of single-unit discharges (signal-to-noise ratio of at least 2:1), data collection for each neuron typically lasted 20–30 min. Our protocol typically included several 20 sec applications of GLU, GABA, and BIC performed at 90 sec intervals with different currents (0 to ± 60 nA). All iontophoretic applications used for statistical analysis were performed when the animals were at rest with no sign of overt movements.

Histology. After the last recording session, animals were anesthetized, if not already so, and Pontamine Sky Blue was deposited by current injection (−20 μA for 20 min) at the last recording site. The brain of each rat was then removed and immediately frozen on dry ice. Subsequent histological location of the marked site was made on 25-μm-thick frontal sections. The atlas of Paxinos and Watson (1998) served as the basis for histological analyses.

Data analysis. Each iontophoretic test was statistically evaluated, and the response was accepted (i.e., excitation or inhibition) if the mean firing rate during iontophoresis differed significantly ($p < 0.05$; two-tail Student's *t* test) from an equivalent period of baseline activity immediately preceding the iontophoretic application. These responses were also assessed in terms of absolute and relative magnitude, the effect of ejection current (i.e., dose–response relationship), and relationship to the rate of basal activity. Because the duration of each neuronal recording in freely moving rats varied from 5 to 30 min and the testing program for each unit was different, it was impossible to assess response thresholds and dose–response relationships in each individual unit. Therefore, our data are reported as number of both units and iontophoretic responses. To allow comparisons of GLU and GABA actions between anesthetized and awake, unrestrained conditions, comparable numbers of iontophoretic application of each neurotransmitter were performed in each group. Various relationships between impulse activity and iontophoretic responses were assessed with Student's *t* tests, Mann–Whitney *U* tests, correlation, regression analysis, and analysis of covariance (ANCOVA) that were followed by Fisher's *post hoc* tests.

Results

Data were obtained from 71 cells histologically verified to be located in SNr; 56 cells were recorded in awake, unrestrained and 25 in anesthetized conditions. In both groups, recorded units were spontaneously active, displaying biphasic spikes of comparable duration (awake, 1.88 ± 0.25, range, 1.23–2.23 msec; anesthetized, 1.78 ± 0.16, range, 1.90–2.19 msec). In awake, unanesthetized conditions, activity rate assessed before the first iontophoretic application (mean, 28.10 ± 2.27; range, 0.60–72.01 impulses/sec) was significantly higher ($p < 0.05$; Student's *t* test) than in anesthetized conditions (mean, 12.68 ± 1.62; range, 2.05–37.35 impulses/sec).

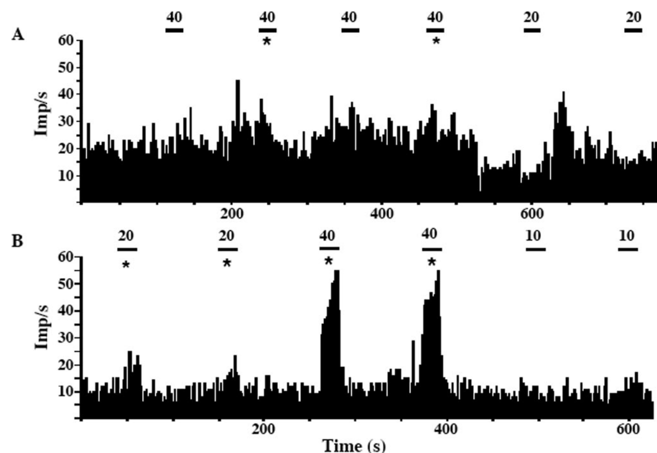

Figure 1. Rate-meter histograms showing individual neuronal responses to iontophoretic GLU applied at different currents in freely moving (*A*) and chloral hydrate-anesthetized (*B*) rats. Numbers above each iontophoretic application (solid lines, 20 sec) indicate ejection currents in nanoamperes. In all cases, neuronal activity is presented as impulses per second (imp/s). Each division of the ordinate represents 5 impulses/sec, and divisions of the abscissa represent 50 sec. For each application, asterisks refer to significant ($p < 0.05$; Student's *t* test) excitation or inhibition.

GLU responses

In anesthetized conditions, most SNr units were highly sensitive to GLU, showing consistent increases in discharge rate in 17 of 20 tested units or in 93 of 109 (87.50%) GLU applications (Fig. 1*B*). The GLU-induced excitation was dose dependent ($p < 0.05$; Mann–Whitney *U* test), with a 315.41 ± 70.76% increase at 20 nA (33 increases in 42 tests) and a 535.79 ± 123.40% increase at 40 nA (42 of 44). In contrast, in freely moving conditions, only 5 of 23 tested units showed consistent GLU-induced excitations after repeated applications. In eight units, no significant changes were observed, whereas 10 other units showed variable responses with weak excitations alternating with weak inhibitions and no changes during repeated GLU applications (Fig. 1*A*). The average magnitude of the GLU-induced activation (calculated for 41 of 117 tests with significant increases) was 188.25 ± 23.58% at 20 nA and 151.98 ± 10.09% at 40 nA. This increase was significantly ($p < 0.05$; Mann–Whitney *U* test) weaker at 40 nA than for the same currents in anesthetized conditions. In both groups, the magnitude of the GLU response was significantly dependent on basal activity rate (anesthetized, $n = 93$, $r = 0.51$, $p < 0.001$; freely moving, $n = 41$, $r = 0.80$, $p < 0.001$). Slower-firing cells showed the largest increase in activity to GLU application.

GABA responses

In anesthetized conditions, GABA potently affected most SNr units, showing consistent inhibitions in 17 of 19 tested units or in 97 of 110 (88.18%) applications. At 10–20 nA currents, the firing rate was reduced to 16.60 ± 2.66% of the baseline (range, 0.00–86.13%). Similarly, GABA significantly inhibited the activity of 25 of 27 tested units (115 of 123 tests; 93.49%) in awake, unrestrained conditions. The average magnitude of the inhibition var-

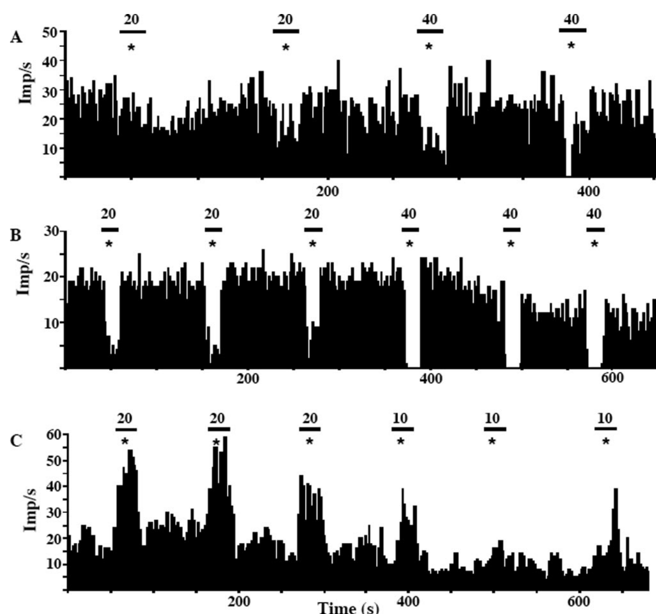

Figure 2. Rate-meter histograms showing individual neuronal responses to iontophoretic GABA and BIC applied at different currents in freely moving (*A*, *C*) and GABA in chloral hydrate-anesthetized (*B*) rats. Numbers above each iontophoretic application (solid lines, 20 sec) indicate ejection currents in nanoamperes. In all cases, neuronal activity is presented as impulses per second (imp/s). Each division of the ordinate represents 5 impulses/sec, and divisions of the abscissa represent 50 sec. For each application, asterisks refer to significant ($p < 0.05$; Student's *t* test) excitation or inhibition.

ied between 0.00 and 88.42% of baseline rate, with a mean of 29.98 ± 2.74% (10–20 nA), which was significantly weaker than in anesthetized conditions ($p < 0.001$; Mann–Whitney *U* test). In both groups, the magnitude of the GABA-induced inhibition in individual units depended on the ejection current (Fig. 2*A*, *B*), as well as on the basal firing rate (anesthetized, $n = 97$, $r = 0.51$, $p < 0.001$; freely moving, $n = 115$, $r = 0.56$, $p < 0.001$). The GABA-induced inhibition was greater in units with higher discharge rate. The difference observed in the magnitude of the GABA inhibition between the anesthetized and unanesthetized group was independent of the basal firing rate ($F_{(1,46)} = 4.04$; $p < 0.05$; ANCOVA).

BIC responses

In freely moving conditions, all 18 SNr units tested were highly sensitive to BIC, showing significant increases of discharge rate in 106 of 122 (94.64%) tests. In individual units, the BIC-induced excitation was current dependent (Fig. 2*C*), varying from 110.94 to 792.86% (mean, 231.54 ± 13.43%; 5–20 nA) of the baseline. Mean discharge rate during BIC application was 51.26 ± 3.66 impulses/sec. When tested, the effect of bicuculline was fully reversed by GABA.

Discussion

SNr neurons receive dense GABAergic inputs from the striatum, the GP, and neighboring cells via axon collaterals. This afferent organization gives GABA inhibition a major role in regulating SNr neuronal activity. Although our study confirms previous work (Waszczak and Walters, 1986; Celada et al., 1999) suggesting that GABA provides a strong inhibitory action on SNr neurons in awake, unrestrained animals, it also reveals that this action is greater in an anesthetized preparation. This difference is probably induced by trichloroethanol, the main metabolite of chloral hydrate and mediator of most of its anesthetic effect. Indeed, Lovinger et al. (1993) demonstrated that trichloroethanol enhances chloride current induced by GABA and thus reinforces the inhibitory action of GABA. This effect may be a factor lowering basal firing rate of the SNr cells recorded during chloral hydrate anesthesia. Such a mechanism is valid with respect to tonically active GABA afferents from the GP (Smith and Bolam, 1989; Kita and Kitai, 1991), the recurrent projections of SNr cells themselves, and phasically active striatal afferents.

The high GLU sensitivity of SNr units found in anesthetized rats is also strongly supported by abundant neuroanatomical and electrophysiological data (Hammond et al., 1978; Waszczak and Walters, 1983; Robledo and Feger, 1990; Schmitt et al., 1999). Under these conditions, most of the cells tested showed large and consistent increases in firing rate during GLU applications. The number of responsive cells and the magnitude of the effect increased with the dose. In contrast, in awake, unrestrained rats, the effect of GLU was limited in terms of magnitude and number of cells activated. The maximum effect in sensitive units was already reached with the lower current (dose) tested.

The reasons for such unusually low GLU sensitivity of SNr neurons found in animals under physiologically relevant conditions remain unclear. However, the freely moving condition cannot be the factor responsible for the poor effect of GLU on these cells because, in other structures, we observed dose-dependent and high-magnitude excitations induced by GLU (Kiyatkin and Rebec, 1998, 1999). Because discharge rate is a known factor affecting the magnitude of GLU-induced excitation in striatal (Kiyatkin and Rebec, 1999) and ventral tegmental area neurons (Kiyatkin and Rebec, 1998) and because SNr neurons tested showed the same correlation, higher activity rate in the awake preparation can be a possible factor limiting the GLU response. This factor alone, however, seems unlikely to contribute to a total lack of GLU-induced responses seen in many SNr cells, and it fails to explain the much lower magnitude of GLU-induced excitation in sensitive cells. Previous studies in anesthetized animals with an overall higher basal activity of SNr cells than in the present study, moreover, never reported a lack of GLU-induced excitations (Collingridge and Davies, 1981; Waszczak and Walters, 1983), although it is not clear whether all recorded units were tested with GLU or only the data obtained on GLU-sensitive units were reported. Although we assume that the two sets of experiments were conducted on a comparable population of SNr cells, anesthesia, through its effect on the GABA inhibitory action discussed above, may have shut down a subclass of cells that are unresponsive to GLU, thus allowing investigation of this population only in unanesthetized rats. Therefore, the population of active SNr neurons available in awake, freely moving conditions may be different from that in anesthetized conditions.

In contrast to anesthetized conditions in which GLU uniformly excited most SNr neurons, the majority of SNr neurons tested in awake, unrestrained conditions showed variable responses to GLU independent of the current used. This variability, at least in part, may be related to a variable activity state during which units were recorded. Although only the tests performed in quiet, resting conditions with no visually detected overt movements were analyzed, these conditions do not represent a true stationary state. Under these "quiet, resting conditions," environmental factors as well as physiological cycles can affect SNr cells and, consequently, change their responsiveness to GLU. Several studies revealed that the activity of SNr neurons is modulated by environmental context (Handel and Glimcher, 2000; Gulley et al., 2002) and by continuous oscillations of the wake–sleep cycle naturally occurring during quiet, resting conditions during day-

time recording (Miller et al., 1983). Because the activity of serotonin-containing neurons and serotonin release varies depending on the sleep–wakefulness cycle (for review, see Portas et al., 2000) and because this neurotransmitter has direct postsynaptic effects on SNr neurons via 5-HT_{2c} receptors and is involved in presynaptic regulation of GABA release via 5-HT_{1b} receptors (Rick et al., 1995; Stanford and Lacey, 1996), fluctuations in serotonin activity may be a factor determining the variability of basal activity and GLU responsiveness of SNr neurons. Therefore, anesthesia, by completely disrupting the sleep–wakefulness cycle and other cyclic influences and by blocking behavior, may modify the neurophysiology of SNr neurons.

Although *in vitro* recording of SNr neurons suggests that these cells are autoactive, generating stable high-rate discharges (with rates lower or comparable with those seen in our study) without extrinsic GLU and GABA afferents (Hajos and Greenfield, 1994; Richards et al., 1997), the weak effect of GLU observed in awake, unrestrained animals questions the mechanisms by which SNr cells can be activated. Because the effect of GABA was predominant on all of the cells tested, modulation of this input (i.e., disinhibition) appears to be the most efficient mechanism for activating SNr units. Consistent with this mechanism, BIC, a competitive $GABA_A$ antagonist, induced phasic excitations of all SNr units tested after low-current brief applications. Not only were all the cells tested sensitive to BIC but the BIC-induced excitations reached a higher mean firing rate than that observed with GLU applications. Interestingly, SNr neurons deprived of extrinsic GLU and GABA input are also activated by BIC (Yuan et al., 2004), suggesting a tonic, GABA-mediated inhibition from axonal collaterals as a factor restraining their impulse activity.

In conclusion, in contrast to the classic hypothesis postulating regulation by direct activation and inhibition, our results suggest that modulation of GABA input may serve as the primary force for both inhibiting and activating SNr units under physiologically relevant conditions. This GABA-mediated, inhibition–disinhibition mode of regulating the activity of SNr neurons might represent, at the neuronal level, the disinhibitory process proposed at the systemic level by Chevalier and Deniau (for review, see Chevalier and Deniau, 1990) for the expression of the basal ganglia function.

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