SYNAPSE 32:165–176 (1999)

$GABA_A$ and $GABA_B$ Antagonists Differentially Affect the Firing Pattern of Substantia Nigra Dopaminergic Neurons In Vivo

CARLOS A. PALADINI AND JAMES M. TEPPER*
Aidekman Research Center, Center for Molecular and Behavioral Neuroscience, Program in Cellular and Molecular Biodynamics, Rutgers, The State University of New Jersey, Newark, New Jersey 07102

KEY WORDS burst firing; catecholamine; bicuculline; picrotoxin; gabazine; saclofen; CGP-55845A; pars compacta

ABSTRACT The effects of local pressure application of the selective $GABA_A$ antagonists, bicuculline, gabazine, and picrotoxin, and the selective $GABA_B$ antagonists, 2-OH-saclofen and CGP-55845A, on the spontaneous activity of electrophysiologically identified substantia nigra dopaminergic neurons were recorded in vivo in urethane anesthetized rats. Blockade of $GABA_A$ inputs by bicuculline powerfully and reversibly induced burst firing in dopaminergic neurons along with a modest (25%) increase in firing rate, but the increase in burst firing was not correlated with the increase in firing rate. Picrotoxin and gabazine also produced an increase in burst firing without an increase in firing rate. In contrast, local application of $GABA_B$ antagonists did not produce bursting but rather caused a modest shift to a more regular firing pattern in 50% of the cases. These data demonstrate that dopaminergic neurons in vivo are under tonic GABAergic inhibition mediated by $GABA_A$ receptors and suggest that GABAergic afferents to substantia nigra comprise a major pathway by which the firing pattern of dopaminergic neurons is controlled in vivo. **Synapse 32:165–177, 1999.**

INTRODUCTION

The spontaneous activity of dopaminergic neurons of the substantia nigra pars compacta in vivo exists along a continuum of firing patterns with a pacemaker pattern at one end of the spectrum and a bursty pattern at the other end (Grace and Bunney, 1984a,b; Tepper et al., 1995; Wilson et al., 1977). The mechanisms controlling the firing pattern of dopaminergic neurons are of great interest since changes in firing pattern comprise an important physiological mechanism by which these neurons may alter their neurotransmitter output. For example, spikes clustered in bursts may be more effective at releasing dopamine in their target areas such as the neostriatum than spikes occurring during pacemaker activity (Gonon, 1988; Manley et al., 1992; but see also Limberger et al., 1991; Tepper et al., 1991). In addition, changes in firing pattern are observed during exploratory behavior (Freeman et al., 1985) and activation of these neurons, which is correlated with environmental stimuli relevant to reward contingencies and motor learning, may result in different firing patterns (Mirenowicz and Schultz, 1996; Schultz and Romo, 1987, 1990). Although much progress has been made at understanding the intrinsic properties of dopaminergic neurons (Grace, 1987; Grace and Bunney, 1984a,b; Johnson et al., 1992; Kang and Kitai, 1993; Shepard and Bunney, 1991), the fact that these neurons fire spontaneously in vitro only in the pacemaker mode (Grace, 1987; Lacey, 1993) while they exhibit pacemaker, random, and bursty patterns in vivo in anesthetized and unanesthetized preparations (Bunney et al., 1973; Freeman et al., 1985; Sanghera et al., 1984; Tepper et al., 1995; Wilson et al., 1977) suggests that the afferents to these neurons play a critical role in the modulation of their firing pattern.

Glutamatergic afferents originating from the prefrontal cortex and subthalamic nucleus acting on nigral NMDA receptors have been suggested to be the endogenous trigger for burst firing in dopaminergic neurons

Contract grant sponsor: National Institute of Neurological Diseases and Stroke; Contract grant number: NS-34865.

*Correspondence to: J.M. Tepper, Center for Molecular and Behavioral Neuroscience, Rutgers, The State University of New Jersey, University Heights, 197 University Avenue, Newark, NJ 07102. E-mail: tepper@axon.rutgers.edu

Abbreviations used: GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate.

Received 17 April 1998; accepted in revised form 1 September 1998

since iontophoretic application of glutamate or NMDA produces bursting activity (Overton and Clark, 1992, 1997; Zhang et al., 1994), and stimulation of prefrontal cortex (Gariano et al., 1988; Overton et al., 1996) or subthalamic nucleus (Chergui et al., 1993; Smith and Grace, 1992) can produce burst firing in vivo. Conversely, systemic as well as local application of NMDA antagonists has been reported to reduce burst firing and cause a regularization of dopaminergic neuron firing pattern (Chergui et al., 1993; Christoffersen and Meltzer, 1995; Connelly and Shepard, 1997; for review see Overton and Clark, 1997). In addition, lesions of subthalamic nucleus (Smith and Grace, 1992) or inactivation of prefrontal cortex by cooling (Svensson and Tung, 1989) or local injection of lidocaine (Murase et al., 1993) reduce bursting and promote pacemaker-like regular firing patterns. However, glutamatergic effects on burst firing may not be limited to NMDA receptor activation as evidenced by the ability of non-NMDA agonists to induce bursting in dopaminergic neurons (Meltzer et al., 1997) even in the presence of NMDA antagonists (Zhang et al., 1994), and for non-NMDA glutamate receptor antagonists to promote pacemaker-like firing (Charlety et al., 1991; Grenhoff et al., 1988).

GABAergic afferents comprise the major class of inputs to nigral dopaminergic neurons. Between 70 and 90% of all inputs onto pars compacta neurons are GABAergic and inhibitory as demonstrated by the symmetric morphology of the synapses and immunostaining for glutamic acid decarboxylase (Bolam and Smith, 1990; Hattori et al., 1975; Oertel et al., 1981; Ribak et al., 1976, 1980; Smith and Bolam, 1989). Although there is such a preponderance of GABAergic inputs, relatively few studies have investigated the effects of GABA agonists or antagonists on the firing pattern of dopaminergic neurons in vivo.

Early in vivo extracellular recording studies using GABAergic antagonists such as picrotoxin reported modest increases in firing rate of dopaminergic neurons after drug administration (Scarnati et al., 1979; Waszcak and Walters, 1980; Waszcak et al., 1980; Yim and Mogenson, 1980) without mention of any effects on firing pattern. More recently, Engberg et al. (1993) demonstrated that local application of the $GABA_B$ agonist, baclofen, regularizes the firing pattern of dopaminergic neurons, an effect that could be blocked by the selective $GABA_B$ antagonist CGP-35348. Application of CGP-35348 alone had no effect on the firing pattern, suggesting a lack of tonic $GABA_B$ input to these cells (Engberg et al., 1993). We have previously shown that recording with an electrode containing the $GABA_A$ antagonist, bicuculline, dramatically increases the proportion of cells found firing in a bursty pattern while recording with an electrode containing the $GABA_B$ antagonist, 2-OH-saclofen, caused a more modest increase in the proportion of cells found firing in a pacemaker-like pattern (Tepper et al., 1995). However, with that technique it was not possible to reliably obtain both pre- and post-drug data on most of the neurons and thus the effects of the GABAergic antagonists noted were on different populations of neurons.

In the present study, we employed local pressure application of different $GABA_A$ and $GABA_B$ antagonists to determine the effects of blockade of $GABA_A$ and $GABA_B$ receptors on the rate and pattern of the spontaneous activity of single dopaminergic neurons in the substantia nigra in vivo.

MATERIALS AND METHODS

Subjects

Experiments were carried out on 30 adult male Sprague-Dawley rats weighing between 225 and 350 g at the time of recording. All animals were housed two to a cage, maintained on a 12-hour light-dark cycle and allowed food and water ad libitum.

Rats were anesthetized with urethane (1.3 g/kg) administered intraperitoneally. The animals were then installed into a stereotaxic frame and the atlanto-occipital membrane was punctured to allow some drainage of the cerebrospinal fluid. All wound margins and points of contact between the animal and the stereotaxic apparatus were infiltrated with lidocaine solution (2%) and xylocaine ointment (5%), respectively. Body temperature was maintained at 37 $\pm$ 1°C and the electrocardiogram was monitored on an auxiliary oscilloscope. All animals were treated in strict accordance with guidelines set forth in the USPHS manual *Guide for the Care and Use of Laboratory Animals.*

After scalp removal, a small burr hole was drilled over the striatum (0.5 mm anterior to bregma, 3.7 mm lateral to the midline), for the insertion of a stimulating electrode. A recording hole approximately 3.0 mm in diameter was drilled above substantia nigra at coordinates 2.1 mm anterior to lambda and 2.0 mm lateral to the midline.

Stimulation

Bipolar stimulating electrodes consisted of two stainless steel enamel-coated wires (California Fine Wire, Grover Beach, CA) approximately 100 µm in diameter with a tip separation of approximately 150 µm. The in vitro impedance of the stimulating electrodes ranged from 10–30 kΩ. Electrodes were lowered to 4.1 mm below the cortical surface in striatum and affixed in place with cyanoacrylate glue and dental cement.

Constant current electrical stimuli were generated with a Winston A-65 timer and SC-100 constant current stimulus isolators (Winston Electronics Corp., Millbrae, CA). Stimuli consisted of single monophasic square wave pulses ranging in intensity from 0.1 to 2.0 mA with durations between 100 and 500 µseconds delivered at a rate of 0.67 Hz. At the end of each experiment, stimulating sites were marked with a small lesion

made by passing a 1.0 mA DC current for 1 second through the stimulating electrode.

Recording

Recording electrodes were constructed from 2.0-mm o.d. borosilicate capillary tubing (World Precision Instruments) on a Narishige PE-2 vertical pipette puller. The electrode tips were broken back under microscopic control to yield final tip diameters between 1.0 and 2.0 µm. These electrodes typically possessed resistances between 5 and 10 MΩ in vivo. Micropressure ejection barrels were constructed from 1 mm o.d. borosilicate glass tubing (Fisherbrand, Pittsburgh, PA) on a Narishige vertical puller. The tips were then broken back to final tip diameters between 7.5 and 10 µm. These barrels were then heated and bent to approximately 30° from center at approximately 10 mm from the tip. Two of these pressure ejection barrels were glued with epoxy to the shaft of the recording electrode under microscopic control and displaced approximately 50–100 µm behind the tip of the recording electrode in order to minimize any artifactual effect of drug diffusing to the cell before pressure ejection. Single unit extracellular recordings were amplified with a Neurodata IR183 preamplifier and displayed on a Tektronix 5113A storage oscilloscope. All data were recorded on magnetic tape for off-line analysis.

Drug Infusions

Drugs (bicuculline methiodide, 200–400 µM; picrotoxin, 200–1,000 µM; gabazine (SR-95531) 1,000 µM; 2-OH-saclofen, 200–1,000 µM; or CGP-55845A, 200–400 µM, in 0.9% saline solution, pH = 7) were applied locally through the side barrels by pressure ejection for a period of 100 to 500 mseconds at 20 p.s.i. using a Picospritzer® (General Valve Corporation, Fairfield, NJ). This resulted in an injected volume of 2–6 nl. The difference in volume injected between ejection barrel tips from 7.5 to 10.0 µm was only a 1 to 1.75 ratio. Drugs were applied in random order after pre-drug data were collected. All cells responded to the drugs after one or two applications.

Data Analysis

Data were analyzed off-line with a Macintosh computer equipped with a National Instruments MIO16L multifunction board running custom-designed data acquisition and analysis software (SpikeTrain). Methods for statistical analysis and classification of firing pattern have been previously described (Perkel et al., 1967; Tepper et al., 1995; Wilson et al., 1977). Briefly, autocorrelograms were constructed from samples of spontaneous spike trains of 1,000 to 2,000 spikes and classified as pacemaker, random or bursty. Cells that exhibited three or more equally spaced peaks in the autocorrelogram were defined as pacemakers, cells that exhibited an initial peak followed by a decay to a steady state were classified as bursty, and those that displayed an initial trough that rose smoothly to a steady-state value were classified as random. The number of peaks in the autocorrelogram that occurred at integral multiples of the mean interspike interval represented an additional quantitative index of the regularity of firing (Perkel et al., 1967), as did the coefficient of variation (CV), calculated as the ratio of the standard deviation of the interspike interval divided by the mean interspike interval. To further analyze the structure of burst firing, a computer was programmed to detect bursts, defined as starting with the first interspike interval of 80 msecond or less and terminating with the first interspike interval of 160 msecond or greater (Grace and Bunney, 1984b). The fraction of all action potentials that occurred in bursts containing 2, 3, 4, 5, 6, or more than 6 spikes for each neuron was calculated by dividing the number of spikes within bursts of specified durations by the total number of spikes recorded for each neuron. A similar breakdown was analyzed for only spikes that occurred within bursts to estimate the proportion of spikes within bursts that were fired in bursts of 2, 3, 4, 5, 6, or more than 6 spikes. Changes in firing rate were also measured. All data were analyzed with paired *t*-tests. Significant differences were declared at the $P < 0.05$ level. All values are expressed as the mean ± SEM.

Materials

The selective $GABA_A$ receptor antagonist, bicuculline methiodide, was obtained from Sigma (St. Louis, MO), the chloride channel blocker, picrotoxin, the selective $GABA_B$ receptor antagonist, 2-hydroxysaclofen, and the selective $GABA_A$ antagonist, gabazine (SR-95531), were obtained from Research Biochemicals Inc. (Natick, MA). The highly selective $GABA_B$ antagonist, CGP-55845A, was a generous gift from Ciba-Geigy (Basel, Switzerland).

Histology

At the end of each experiment, animals were given a lethal overdose of urethane and perfused transcardially with saline followed by 10% formalin. Brains were postfixed, sectioned, and stained with neutral red for verification of stimulating and recording sites.

RESULTS

All neurons in this report were identified as dopaminergic neurons by their slow spontaneous firing rates (4.81 ± 0.23 spikes/second, n = 48), regular, random,

or slow bursty patterns of firing, and long duration extracellularly recorded action potential waveform (>2 mseconds) that often exhibited a notch on the initial positive component corresponding to the initial segment portion of an initial segment-somatodendritic break. In addition, 35 of these neurons were further identified by their long latency antidromic response to striatal stimulation (12.60 ± 0.51 msecond, n = 35), which usually consisted of an initial segment spike only. The other neurons could not be antidromically driven but displayed all the other characteristics that are generally accepted as belonging to nigrostriatal dopaminergic neurons recorded extracellularly in vivo (Deniau et al., 1978; Guyenet and Aghajanian, 1978). Both sets of neurons were identical in firing rate, firing pattern distribution, extracellular waveform, and response to local application of bicuculline, gabazine, picrotoxin, saclofen, and CGP-55845A. Therefore, the data were combined into a single group assumed to represent nigrostriatal dopaminergic neurons.

Dopaminergic Neurons Fire Predominantly in a Random Firing Pattern

The most common pattern of spontaneous activity of nigrostriatal neurons in urethane-anesthetized rats under control conditions was the random pattern. Of the 48 cells recorded before any drug application 62.50% fired in a random pattern with a mean coefficient of variation of 0.45 ± 0.04 while pacemaker and bursty firing patterns were observed in 20.83% and 16.67% of the neurons recorded, respectively, with mean coefficients of variation of 0.17 ± 0.02 and 0.74 ± 0.15, respectively. The pacemaker neurons fired 0.45 ± 0.25% of their spikes in bursts while random firing neurons fired 15.79 ± 3.25% of their spikes in bursts and neurons classified as bursty neurons fired an average of 39.55 ± 7.38% of spikes in bursts.

Local $GABA_A$ Antagonist Application Causes Dopaminergic Neurons to Fire in a Bursty Pattern

Local application of the $GABA_A$ antagonists, bicuculline, gabazine, or picrotoxin, produced a dramatic shift to a bursty firing pattern regardless of the predrug firing pattern. Representative examples are shown in Figures 1 and 2. The overall proportion of spikes occurring in bursts was significantly increased by bicuculline (control: 8.40 ± 2.6%; bicuculline: 35.84 ± 6.13%, $t = -5.86$, $df = 20$, $P < 0.05$). This change in firing pattern was near immediate in onset and was easily discernible on the audio monitor as soon as bicuculline was applied to the cell. The increased burstiness induced by bicuculline application usually lasted between 5 and 10 minutes. Other measures of firing pattern also indicated a powerful change to a bursty firing pattern following bicuculline application. The coefficient of variation was significantly increased from 0.32 ± 0.04 to 0.72 ± 0.09 ($t = -4.94$, $df = 19$, $P < 0.05$) and the mean burst duration and mean number of spikes per burst increased from 156.35 ± 26.74 mseconds to 299.99 ± 66.18 mseconds ($t = -3.30$, $df = 14$, $P < 0.05$) and 2.20 ± 0.34 spikes/burst to 4.58 ± 0.60 spikes/burst ($t = -3.46$, $df = 19$, $P < 0.05$), respectively. Local application of bicuculline decreased the number of peaks in the autocorrelogram from an average of 3.14 ± 1.07 to 0.71 ± 0.24 peaks ($t = 2.41$, $df = 20$, $P < 0.05$), indicating a decrease in the regularity of firing. The average firing rate also increased from 4.60 ± 0.32 spikes/second to 5.77 ± 0.29 spikes/second ($t = -4.02$, $df = 20$, $P > 0.05$). There were no significant correlations between the change in firing rate and the increase in burstiness ($r = 0.14$, $df = 21$, $P > 0.05$) or between the increase in firing rate and the change in the coefficient of variation ($r = 0.35$, $df = 20$, $P > 0.05$) or the change in burst duration with the change in firing rate of the dopaminergic neurons ($r = 0.31$, $df = 16$, $P > 0.05$; as shown in Fig. 4). No significant correlation was observed between the baseline firing rate and the coefficient of variation ($r = 0.27$, $df = 52$, $P > 0.05$) or the percentage of spikes fired in bursts ($r = 0.14$, $df = 52$, $P > 0.05$). However, the pre-drug firing rate was significantly correlated with mean burst duration ($r = 0.72$, $df = 49$, $P < 0.05$; see Fig. 3).

Because it has recently been reported that bicuculline methiodide can potentiate burst firing in dopaminergic neurons in vitro by exerting an apamin-like effect to block calcium-activated potassium currents (Johnson and Seutin, 1997), the effects of local application of the chloride channel blocker, picrotoxin, and the selective $GABA_A$ receptor antagonist, gabazine (SR-95531), were also investigated. In all cases, picrotoxin and gabazine exerted essentially the same effects as bicuculline on the firing pattern of dopaminergic neurons. The overall percentage of spikes occurring in bursts was significantly increased by picrotoxin (control: 32.00 ± 6.15%; picrotoxin: 52.12 ± 7.88%, $t = -3.48$, $df = 11$, $P < 0.05$). The increased burstiness induced by picrotoxin was of longer duration than that caused by bicuculline and usually lasted throughout the length of the recording period. Other measures of firing pattern also indicated a powerful change to a bursty firing pattern due to picrotoxin application. The coefficient of variation was significantly increased from 0.58 ± 0.06 to 0.86 ± 0.09 ($t = -3.57$, $df = 11$, $P < 0.05$) by picrotoxin while the mean number of spikes per burst increased from 2.96 + 0.26 spikes to 3.84 + 0.35 ($t = -2.57$, $df = 11$, $P < 0.05$).

Gabazine produced changes in firing pattern similar to picrotoxin and bicuculline. The mean burst duration

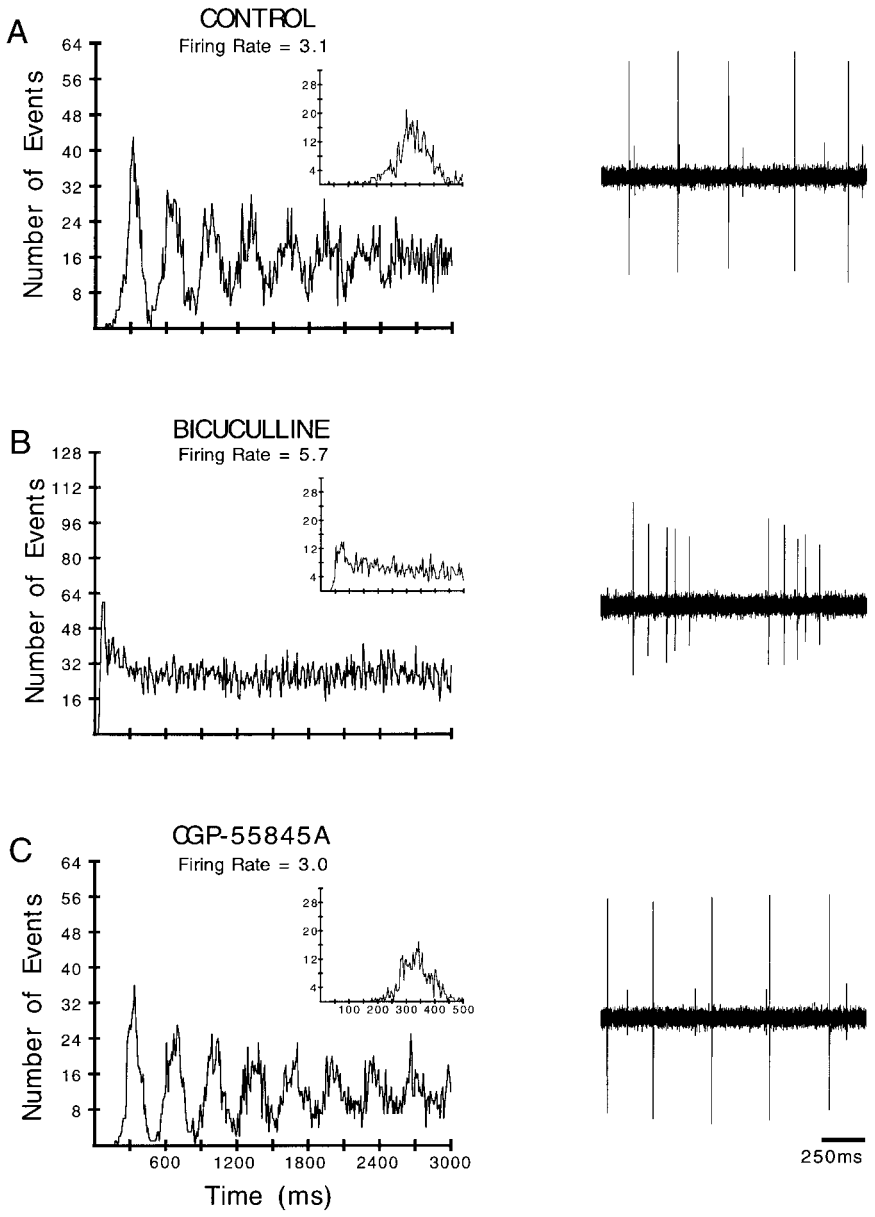

Fig. 1. Autocorrelograms from one typical electrophysiologically identified dopaminergic neuron in substantia nigra illustrating the effects of local application of the selective $GABA_A$ receptor antagonist, bicuculline, and the selective $GABA_B$ receptor antagonist, CGP-55348A. **Insets:** Initial portion of the same autocorrelation at higher temporal resolution. **A:** Before application of any drug, the neuron fired in a pacemaker pattern indicated by the regularity of interspike intervals in the oscilloscope trace to the right and several peaks in the autocorrelogram. **B:** After application of the $GABA_A$ receptor antagonist, bicuculline, the autocorrelogram shifted to an initial peak with a decay to a steady-state level indicating a bursty firing pattern. To the right of the autocorrelogram is an oscilloscope trace from the same neuron showing two of the bursts observed after bicuculline application. Note the progressively decreasing spike amplitude typical of spontaneously occurring bursts. This effect lasted for approximately 7 minutes. **C:** Application of the $GABA_B$ antagonist CGP-55845A increased the regularity of firing indicated by a more regular interspike interval seen in the oscilloscope trace and the increase in the number of peaks in the autocorrelogram. (1,000 spikes; Bin Width = 10 mseconds.)

was increased from 150.25 ± 49.89 to 261.67 ± 38.09 msecond ($t = -3.62$, $df = 3$, $P < 0.05$). The coefficient of variation was also significantly increased (control: 0.52 ± 0.12; gabazine: 0.68 ± 0.13; $t = -4.26$, $df = 3$, $P < 0.05$). Although not statistically significant, gabazine also increased the percentage of spikes fired in bursts from 17.19 ± 5.51 to 38.39 ± 12.42% and the mean number of spikes per burst from 2.83 ± 0.42 to 4.26 ± 0.71 (n = 4 for both measures).

Contrary to the effects of bicuculline, picrotoxin and gabazine did not significantly alter the firing rate of dopaminergic neurons (picrotoxin control = 5.21 ± 0.59; picrotoxin = 5.50 ± 0.43 spikes/second, n = 12; gabazine control = 4.89 ± 0.83; gabazine = 6.34 ± 0.91 spikes/second, n = 4). In several cases (n = 4), the firing rate decreased after application of picrotoxin as can be seen for one example in Figure 2. However, even in these cases, burst firing was induced.

The effects of local application of bicuculline, gabazine, and picrotoxin on the firing pattern of dopaminergic neurons could also be seen by analysis of the internal structure of the burst firing. Figure 4 illustrates a detailed breakdown of the effects of local $GABA_A$ (bicuculline, gabazine, and picrotoxin data pooled) and $GABA_B$ (saclofen and CGP-55845A data pooled) antagonist application on the proportion of spikes fired in bursts of different sizes. $GABA_A$ antagonists produced a significant increase in the proportion of spikes fired in bursts consisting of three or more spikes but not in bursts consisting of two spikes (Fig. 4A, $P < 0.05$ for all comparisons). If only the spikes fired in bursts were considered, $GABA_A$ antagonist

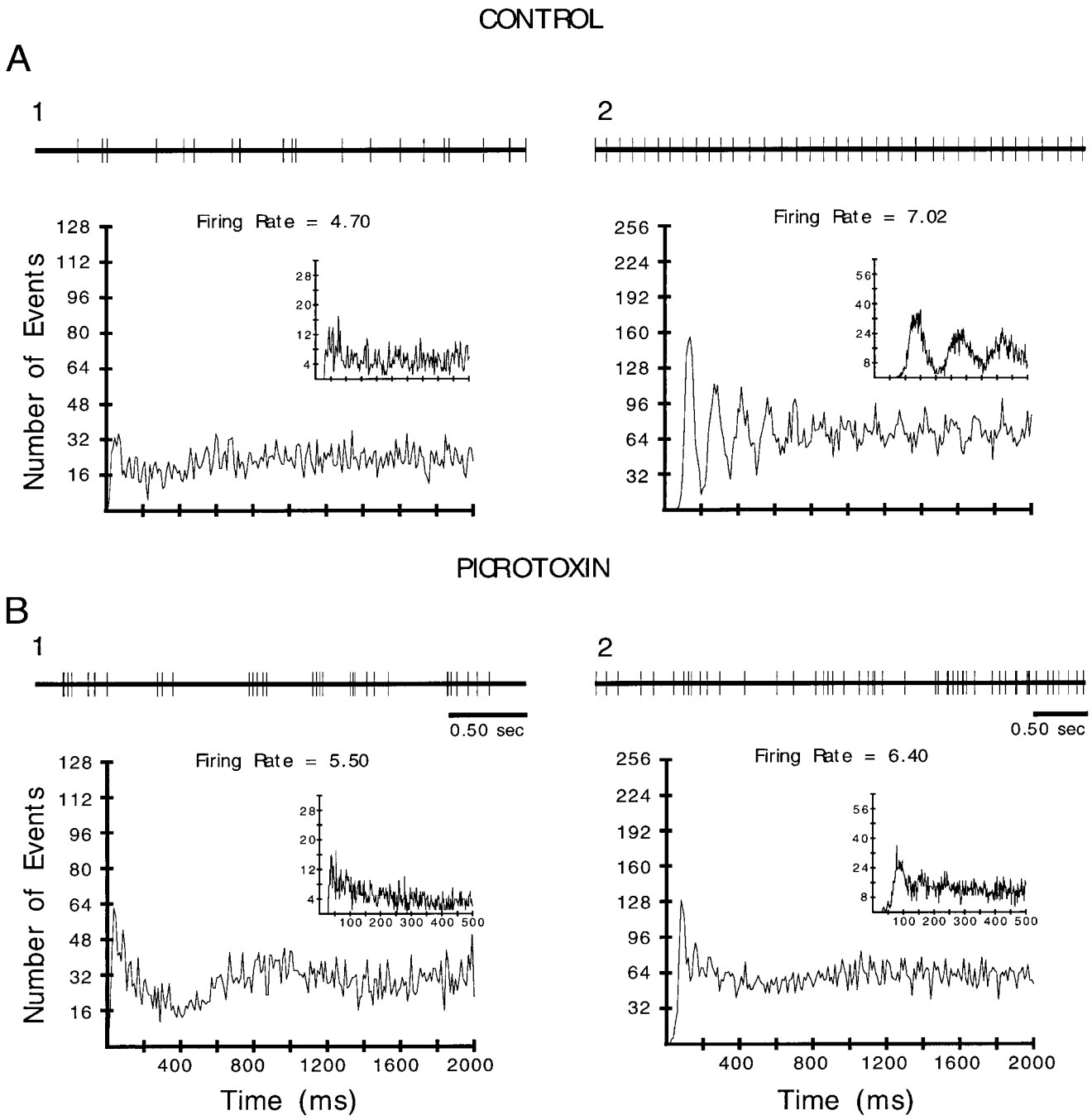

Fig. 2. Autocorrelograms showing the effects of local application of the chloride channel blocker picrotoxin on the firing pattern of two dopaminergic neurons. **Insets:** Initial portions of the same autocorrelation at higher temporal resolution. **A:** Sample spike trains and autocorrelograms of two cells before drug administration, one showing a random firing pattern (A1) and the other a pacemaker pattern (A2). **B:** After application of picrotoxin, both neurons show a marked switch to a bursty firing pattern indicated by the clustering of spikes in the spike train and an initial peak with a decay to a steady-state level in the autocorrelogram. Note that the change in firing pattern is not dependent on an increase in firing rate (A2 to B2). (1,000 spikes; Bin Width = 10 mseconds.)

application increased the proportion of spikes fired in bursts consisting of four or more spikes while decreasing the proportion of spikes fired in two spike bursts (Fig. 4B, $P < 0.05$ for all comparisons). There was no difference in the mean first interspike interval between bursts that occurred under control conditions (62.01 ± 2.83 mseconds before bicuculline application; 61.59 ± 2.12 mseconds before picrotoxin application; 66.80 ± 3.78 before gabazine) and those induced by the $GABA_A$ antagonists (61.13 ± 2.09 mseconds, 63.49 ± 3.69 and 60.71 + 2.10 for bicuculline, gabazine, and picrotoxin, respectively, $P > 0.05$).

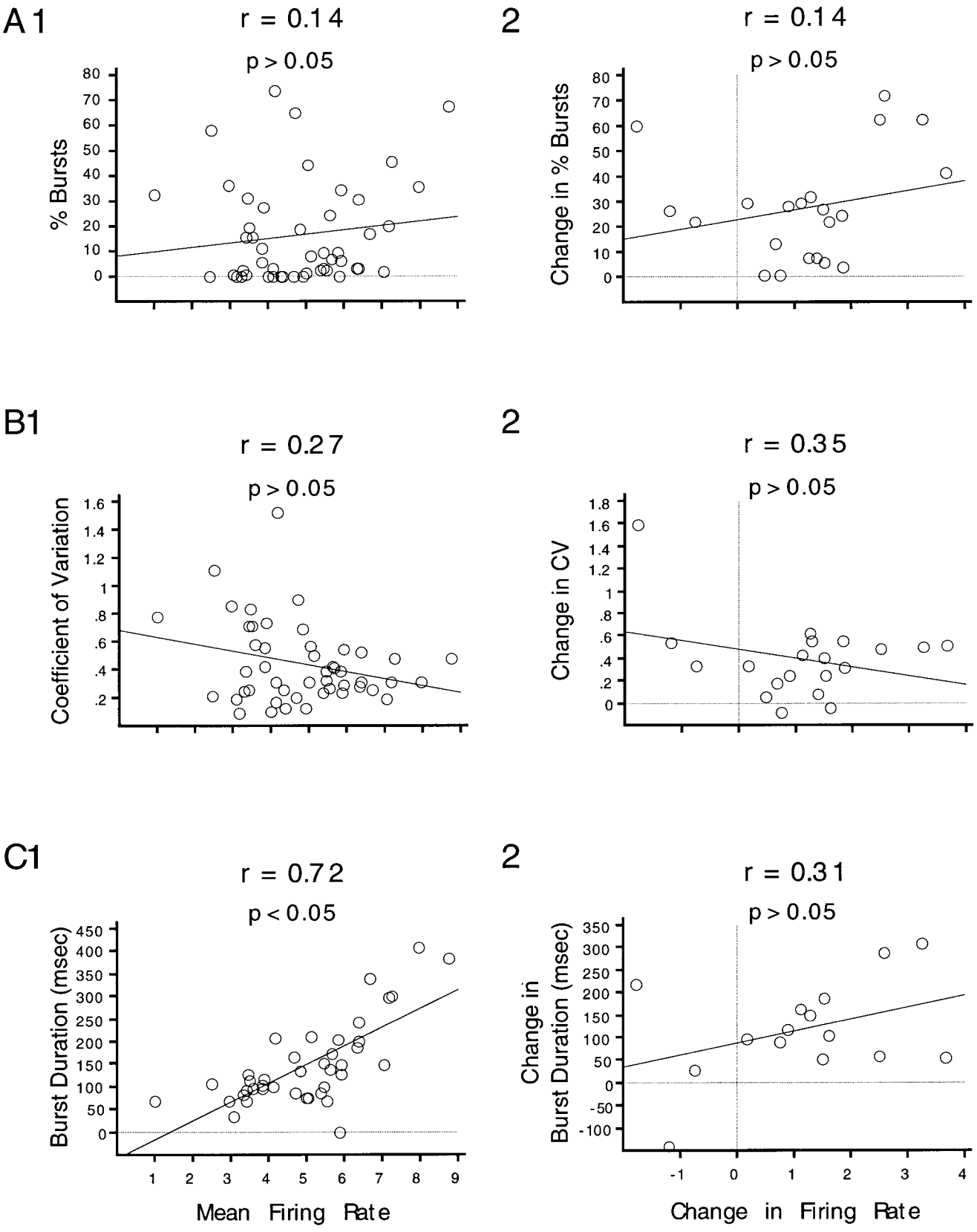

Fig. 3. Regression plots illustrating the lack of correlation between pre-drug firing rate and firing pattern (A1, B1, C1) and the change in firing pattern vs. the change in firing rate caused by local application of bicuculline (A2, B2, C2). **A1, B1:** No significant correlation was found between pre-drug firing rate and percentage of spikes fired in bursts or coefficient of variation (r = 0.14 and 0.27, respectively). **C1:** However, a significant correlation (r = 0.72) was found between pre-drug firing rate and mean burst duration. **A2:** The change in the percentage of the total number of spikes occurring in bursts after drug application was not significantly correlated with the change in firing rate (r = 0.14). **B2:** A lack of significant correlation was also observed when comparing the change in coefficient of variation with the change in firing rate after $GABA_A$ antagonist application (r = 0.35). **C2:** Similarly, there was no correlation between the change in firing rate and the change in burst duration (r = 0.31).

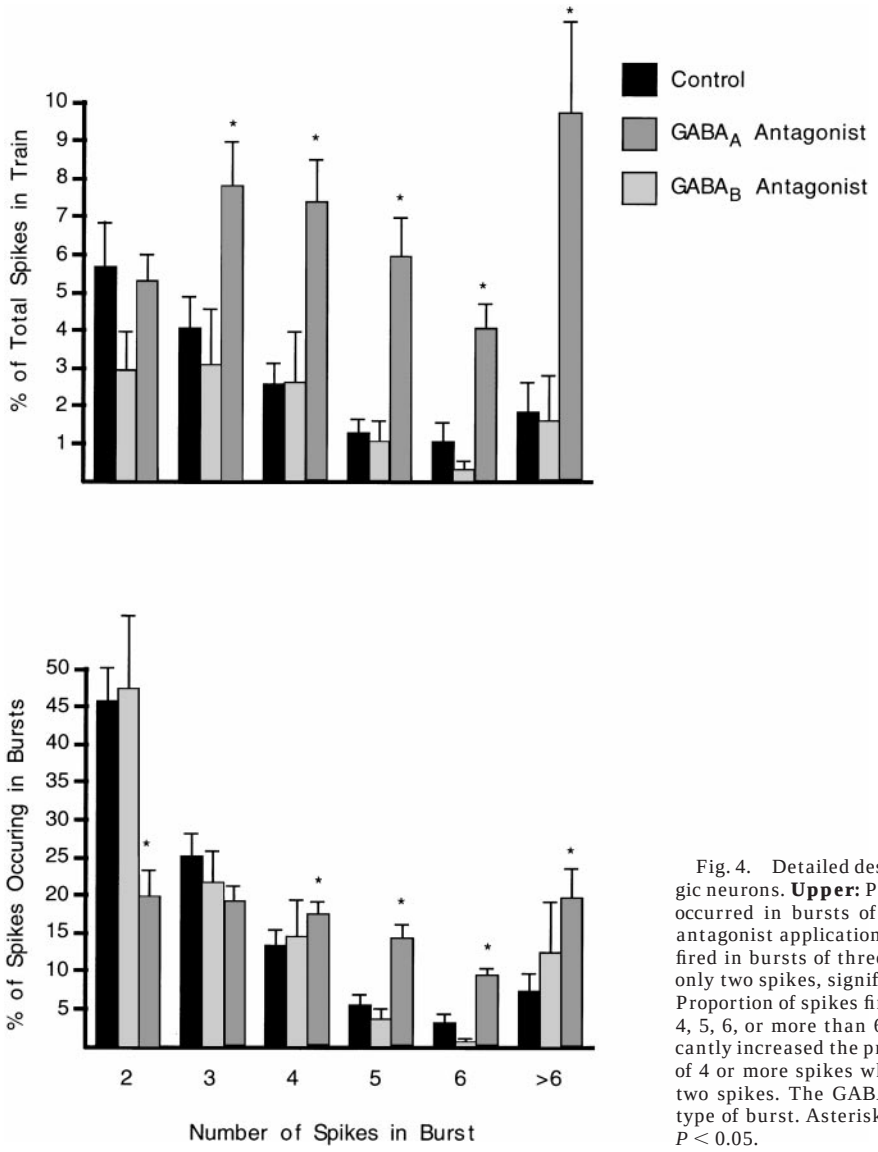

Fig. 4. Detailed description of the structure of bursts in dopaminergic neurons. **Upper:** Proportion of the total number of spikes fired that occurred in bursts of 2, 3, 4, 5, 6, or more than 6 spikes. $GABA_A$ antagonist application significantly increases the proportion of spikes fired in bursts of three or more spikes but not in bursts consisting of only two spikes, signifying an overall increase in burst firing. **Lower:** Proportion of spikes fired within bursts that occurred in bursts of 2, 3, 4, 5, 6, or more than 6 spikes. $GABA_A$ antagonist application significantly increased the proportion of spikes fired within bursts consisting of 4 or more spikes while decreasing the number of bursts with only two spikes. The $GABA_B$ antagonists did not significantly affect any type of burst. Asterisk denotes significantly different from control at $P < 0.05$.

Local $GABA_B$ Antagonist Application Can Cause a Regularization of Dopaminergic Neuron Firing Pattern

Application of either of the selective $GABA_B$ antagonists, CGP-55845A or 2-hydroxysaclofen, caused a modest change in the firing pattern of some dopaminergic neurons opposite to that of the $GABA_A$ antagonists. CGP-55845A shifted the firing pattern toward a more pacemaker-like pattern indicated by an increase in the number of peaks in the autocorrelogram from a mean of 1.38 ± 0.65 peaks before drug application to 2.38 ± 0.96 peaks after drug ($t = -2.37$, $df = 7$, $P < 0.05$). CGP-55845A also caused a slight decrease in the coefficient of variation (0.31 ± 0.03 to 0.25 ± 0.05, $n = 8$), percentage of spikes occurring in bursts ($2.80 \pm 0.88\%$ to $2.08 \pm 0.86\%$, $n = 8$), and mean firing rate (4.31 ± 0.55 to 3.91 ± 0.44 spikes/second, $n = 8$) although the differences in these latter measurements were not statistically significant ($P > 0.05$).

Saclofen exerted the same qualitative effects as CGP-55845A. The number of peaks in the autocorrelogram increased slightly from 1.917 ± 0.941 to 2.33 ± 0.84 peaks ($n = 12$). Saclofen also caused a slight decrease in the coefficient of variation (0.48 ± 0.12 to 0.36 ± 0.08, $n = 12$), percentage of spikes occurring in bursts (14.96 ± 7.10 to $13.24 \pm 7.09\%$, $n = 12$), and mean firing rate (4.52 ± 0.31 to 4.43 ± 0.33 spikes/second, $n = 12$). However, the differences in these measurements were not statistically significant ($P > 0.05$).

When the data for both $GABA_B$ antagonists were pooled, again no overall significant effect on spontaneous activity was measured. Closer inspection revealed that 11 out of the 21 neurons treated with the $GABA_B$ antagonists were significantly affected with a shift

toward a pacemaker-like firing pattern. The remaining 10 neurons showed no change in firing pattern or any other measured response. In the subset of responsive neurons the mean percentage of spikes fired in bursts was significantly decreased from 17.80 ± 9.50% to 13.90 ± 9.47% ($t = 2.54$, $df = 6$, $P < 0.05$). The mean burst duration and number of spikes per burst were also significantly decreased from 137.42 ± 20.57 mseconds to 109.02 ± 18.54 mseconds ($t = 3.90$, $df = 6$, $P < 0.05$) and 3.00 ± 0.35 spikes/burst to 2.55 ± 0.30 spikes/burst ($t = 4.14$, $df = 6$, $P < 0.05$), respectively. The coefficient of variation was not significantly reduced in these neurons (0.47 ± 0.11 to 0.31 ± 0.05, $P > 0.05$). However, there was a small but statistically significant decrease in the firing rate of these cells (4.52 ± 0.35 before drug to 4.28 ± 0.35 spikes/second after drug application; $t = 2.59$, $df = 10$, $P < 0.05$).

DISCUSSION

$GABA_A$ Antagonists Induce Burst Firing Independently of Any Change in Firing Rate

The present results demonstrate that dopaminergic neuron firing pattern can be reliably and significantly manipulated by local application of GABAergic antagonists in vivo. Blockade of $GABA_A$ receptors by bicuculline, gabazine (SR-95531), or picrotoxin caused a robust change to a bursty pattern regardless of the baseline firing pattern. Although local application of bicuculline increased both the burst firing and the mean firing rate of dopaminergic neurons, the increase in firing rate appears to be epiphenomenological since there was no correlation between the change in firing rate and the change in proportion of spikes fired in bursts. Similarly, there was no correlation between the change in firing rate and the change in the coefficient of variation of the interspike intervals or the change in burst duration.

The relationship between firing rate and bursts in dopaminergic neurons is complex. The same lack of correlation between changes in firing rate and changes in firing pattern was observed in dopaminergic neurons in freely moving rats (Freeman et al., 1985) and Grace and Bunney (1984b) reported that "the correlation is very low" ($r = 0.38$) between baseline firing rate and percentage of spikes fired in bursts. On the other hand, Grace and Bunney (1984b) also reported that the increase in the percentage of burst-related spikes induced by glutamate iontophoresis was found to be highly correlated with the increase in firing rate. Regression analysis in another study failed to show any significant correlation between firing rate and the coefficient of variation ($r = 0.1$, Zhang et al., 1993); yet still other studies reported an increase in burstiness and an accompanying increase in firing rate after local NMDA application although the correlation was not investigated formally (Chergui et al., 1993; Overton and Clark, 1992). Conversely, dopaminergic neurons show a decrease in burstiness after NMDA antagonist application without a decrease in firing rate (Overton and Clark, 1992), suggesting that NMDA receptor activation increases burst firing independently of any increases in firing rate. Connelly and Shepard (1997) have shown that the reduction in burst firing following systemic application of NMDA antagonists is due to a reduction in the number of spike doublets without any change in bursts of three or more spikes. Thus, the relationship between burst firing (the percentage of spikes fired in bursts) and firing rate appears to depend on whether the bursts are spontaneous or evoked (or inhibited) as well as the means by which the bursting was modulated.

In the present study, several neurons ($n = 7$) that exhibited dramatic switches to bursty firing after bicuculline or picrotoxin also responded to the drug with a *decrease* in firing rate (for example, see Fig. 2). Overall, both picrotoxin and gabazine did not produce any significant change in firing rate. It is possible that the increase in firing rate following local application of bicuculline methiodide is due in large part to blocking the calcium-dependent potassium conductance. This secondary effect of bicuculline methiodide also potentiated NMDA-induced bursting in vitro, similar to the effect of apamin (Johnson and Seutin, 1997). When picrotoxin was iontophoretically applied to ventral tegmental area dopaminergic neurons, 70% of the neurons tested increased their firing rate although an effect on firing pattern was not shown and the amount of firing rate increase was not mentioned (Yim and Mogenson, 1980). This is comparable to the present study where 66% of the neurons given picrotoxin showed an increase in firing rate while the remaining decreased, giving an overall increase in rate that was not statistically significant. In the present study, regardless of the change in firing rate, picrotoxin, gabazine, and bicuculline clearly and dramatically shifted the firing pattern of all dopaminergic neurons to which they were applied, to a bursty pattern. Thus, the potent induction of burst firing caused by blockade of the $GABA_A$ receptor is independent of firing rate.

A detailed analysis of the total number of spikes (Fig. 4) showed that the effects of bicuculline, gabazine, and picrotoxin only increased the number of spikes fired in bursts consisting of 3 or more spikes while the number of spikes in bursts consisting of only two spikes were not significantly increased. When only the spikes occurring in bursts were considered, $GABA_A$ antagonist application increased the proportion of spikes occurring in bursts consisting of four or more spikes while decreasing the proportion of spikes that occurred in two spike bursts. These data show that in addition to increasing the number of bursts, $GABA_A$ blockade produces bursts that are of longer duration and consist of larger number of spikes than "spontaneous" bursts. Taken together, these data also argue strongly that the burst firing

caused by blockade of $GABA_A$ inputs to dopaminergic neurons is not simply a result of increased firing rate.

Interaction of GABAergic and NMDA Inputs

One of the proposed mechanisms of bursting in dopaminergic neurons involves the entry of sodium ions through the NMDA channel, which produces a depolarization that, in turn, activates an ouabain-sensitive electrogenic sodium pump. The pump then hyperpolarizes the cell as it extrudes sodium, thereby closing the voltage-sensitive NMDA channel and ending the burst (Johnson et al., 1992). The NMDA-induced bursting appears to be generated at a distal dendritic location and can be blocked by application of dopamine or baclofen (Seutin et al., 1994).

Canavier (1998) has recently simulated the firing patterns of dopaminergic neurons in a compartmental model that may help explain why $GABA_A$ inputs reduce bursting in dopaminergic neurons. In this model, oscillatory behavior very similar to that observed by Johnson et al. (1992) in vitro was seen to result from the fixed point intersection of the sodium concentration and membrane potential nullclines at the middle branch of the potential nullcline cubic that was unstable due to its positive slope. The positive slope of the membrane potential nullcline was shown to be due to a negative slope region in the NMDA I-V curve. However, increasing a linear conductance in the model, simulating the effect of increasing a GABAergic input, linearized the membrane potential nullcline, occluding the unstable region and, therefore, eliminating the oscillation (burst firing). Conversely, decreasing the conductance in the model, simulating the effect of blocking a GABAergic tone with antagonists, was shown to enhance the positive slope region of the membrane potential nullcline (Canavier, 1999).

If endogenous bursts are dependent upon NMDA receptor stimulation, the burst initiation that occurs after disinhibition from $GABA_A$ inputs may be due to an enhancement of the unstable region in the potential nullcline due to the decreased conductance. Therefore, increased bursting could be promoted by increasing the input resistance of the dopaminergic neurons, thereby making the dendritic tree more electrotonically compact and the distal NMDA-induced effects more accessible to the proximal spike-generating region of the neuron (Seutin et al., 1994).

Disinhibition From a Tonic GABAergic Drive From Pars Reticulata May Be Critical for Initiating Bursty Activity in Dopaminergic Neurons

It was not possible in the present study to determine the source(s) of the GABAergic input that was blocked by the $GABA_A$ antagonists that led to the burst firing. The major inhibitory inputs to nigral dopaminergic neurons originate from striatum (Grofová, 1975; Somogyi et al., 1981), globus pallidus (Hattori et al., 1975; Smith and Bolam, 1989), and substantia nigra pars reticulata (Grofová et al., 1982; Hajós and Greenfield, 1994; Tepper et al., 1995). All of these nuclei appear to exert their inhibitory effects on dopaminergic neurons in vivo predominantly through activation of $GABA_A$ receptors (Paladini et al., 1998). However, several lines of evidence implicate the pars reticulata GABAergic neurons as critical in the control of the firing pattern of dopaminergic neurons (Tepper et al., 1995).

In addition, excitation of pallidal neurons causes an increase in burst firing of dopaminergic neurons along with a slight increase in firing rate concurrent with a near complete inhibition of firing of pars reticulata GABAergic neurons whereas inhibition of these neurons blocks spontaneously occurring burst firing and leads to pacemaker firing patterns in dopaminergic neurons along with a decrease in firing rate (Celada et al., 1998). Therefore globus pallidus seems to control dopamine neuron firing pattern indirectly, probably through its effects on pars reticulata GABAergic neurons (Celada et al., 1998).

Striatal GABAergic afferents to dopaminergic neurons (e.g., Somogyi et al., 1981) cannot be ruled out as a possible site of action of the $GABA_A$ antagonists in the present study. Electrical stimulation of striatum inhibits dopaminergic neurons in vivo (e.g., Grace and Bunney, 1985; Paladini et al., 1998; Tepper et al., 1990). However, the majority of striatal efferents terminate in pars reticulata, presumably upon non-dopaminergic neurons (Grofová, 1975) and kainic acid destruction of striatum produces only relatively small and transient effects on dopaminergic neuron activity (Braszko et al., 1981). In a recent study, pharmacological inactivation of striatal output neurons by DL-allyl glycine resulted in a significant reduction in the proportion of nigral dopaminergic neurons firing in the pacemaker mode along with an increase in the proportion of neurons firing in the random mode (Bioulac et al., 1997). Although this effect is consistent with our hypothesis/prediction that $GABA_A$ input should regularize the firing pattern of dopaminergic neurons, the fact that the change in firing pattern was accompanied by a significant inhibition of spontaneous activity rather than the increase that would be expected based on removal of a GABAergic input suggests that this effect may have been mediated, at least in part, polysynaptically.

$GABA_B$ Receptor Antagonists Can Regularize Dopaminergic Neuron Firing Pattern by Blocking Presynaptic $GABA_B$ Autoreceptors

Although the effect was much more modest, $GABA_B$ antagonists shifted the firing pattern in the opposite direction to that of the $GABA_A$ antagonists. Stimulation of postsynaptic $GABA_B$ receptors in vitro hyperpo-

larizes dopaminergic neurons by increasing a potassium conductance (Lacey et al., 1988; Lacey, 1993), and local application of the $GABA_B$ agonist, baclofen, has been shown to regularize the firing pattern of dopamine neurons in vivo (Engberg et al., 1993). Although the endogenous source(s) of the inputs that activate $GABA_B$ receptors in vivo remains unclear (Paladini et al., 1998, but see Cameron and Williams, 1993), spontaneously occurring IPSPs that appear to be mediated by a $GABA_B$ receptor have been observed in dopaminergic neurons in substantia nigra in vitro in juvenile rats with whole cell recording (Koós and Tepper, 1996).

However, $GABA_B$ receptors are also present as presynaptic autoreceptors on GABAergic afferents to substantia nigra (Häusser and Yung, 1994) and $GABA_B$ antagonists have been shown to increase stimulation-induced $GABA_A$-mediated inhibition of dopaminergic neurons (Paladini et al., 1998). With respect to the present results, $GABA_B$ receptor antagonists may exert their regularizing effects on firing pattern primarily by acting to block the presynaptic inhibitory $GABA_B$ terminal autoreceptors (Häusser and Yung, 1994), thereby increasing the amount of GABA released. The increase in $GABA_A$ inhibition that results would be expected to regularize the firing pattern of the dopaminergic cells and decrease their firing rate. This is what was observed in approximately 50% of the cells tested (11 out of 21). However, the modest effect of $GABA_B$ antagonists observed in this and a previous study (Engberg et al., 1993) argue against the presence of a significant postsynaptic $GABA_B$ tone on dopaminergic neurons in vivo.

Conclusions

Blockade of $GABA_A$ receptors causes dopaminergic neurons of the substantia nigra pars compacta to fire in a bursty pattern in vivo, regardless of their initial rate or pattern of activity. This change in firing pattern is independent of any change in firing rate. In contrast, local application of $GABA_B$ antagonists can cause a regularization of firing pattern although this effect is much more modest and appears to be due to an action at presynaptic $GABA_B$ autoreceptors on GABAergic afferents. These results indicate that the firing pattern of nigral dopaminergic neurons is modulated to an important extent in vivo by GABAergic afferents acting principally through $GABA_A$ receptors.

Although the exact mechanism of $GABA_A$ inhibition on burst firing could not be determined in this study, the effects of blocking $GABA_A$ inputs on dopaminergic neuron firing pattern were remarkably robust. We suggest that inhibitory afferents can act as a gating mechanism for dopaminergic neuron firing pattern in vivo. $GABA_A$ receptor activation hyperpolarizes dopaminergic neurons by opening a chloride conductance. A constant GABAergic tone on dopaminergic neurons would maintain a low-input resistance by keeping chloride channels open from the $GABA_A$ receptor inputs. It may be that a tonic excitatory input acting through excitatory amino acid receptors can only influence the firing pattern when the dopaminergic neurons are disinhibited from their tonic GABAergic input. We suggest that burst initiation and/or facilitation occurs when both the glutamatergic input is activated and the GABAergic input ceases. Conversely, burst termination and/or inhibition may occur when dopaminergic neurons are inhibited by increased activity in GABAergic afferents.

ACKNOWLEDGMENTS

Thanks go to Dr. M. Page for help with picrospritzing, Dr. E. Abercrombie, W. Cobb, A. Duque, T. Koós, D. Miller, and J. Zackheim for helpful comments on the manuscript and Ms. F. Shah for excellent technical assistance. This research was supported by NS-34865.

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