In: Graybiel, A.M. et al., (Eds.) *The Basal Ganglia VI*, Kluwer Academic Publishers, Norwell, 2002 pp 641-651

Afferent Control of Nigral Dopaminergic Neurons

The Role of GABAergic Inputs

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Key words: substantia nigra, firing pattern, burst firing, pars reticulata, globus pallidus, subthalamic nucleus, autocorrelogram, disinhibition

1. INTRODUCTION

In *in vivo* extracellular recordings from anesthetized adult rats, midbrain dopaminergic neurons fire spontaneously at low rates, averaging around 4 spikes/second (Bunney et al., 1973; Guyenet and Aghajanian, 1978; Deniau et al., 1978; Tepper et al., 1982). Under these conditions, the neurons exhibit 3 distinct patterns or modes of firing. The first is that of pacemaker-like firing, characterized by very regular interspike intervals (Wilson et al., 1977; Tepper et al., 1995). The second, and most common pattern of activity *in vivo* is a random, or occasional mode (Wilson et al., 1977), characterized by long post-firing inhibition which rises smoothly into a flat autocorrelation function indicating that the remaining interspike intervals are distributed randomly, best characterized by a Poisson distribution. The third, least common mode of firing, is burst firing, in which the neurons exhibit stereotyped bursts of 2-8 action potentials in which the first intraburst interspike interval is around 60 ms, followed by progressively increasing interspike intervals and progressively decreasing spike amplitudes (Grace and Bunney, 1984). The bursts are not usually rhythmic or continuous, and occur embedded in background random single-spike firing activity. Both in anesthetized and unanesthetized rats (Freeman et al., 1985), dopaminergic neurons often switch between different firing modes, and the three firing patterns are best thought of as a continuum, with the pacemaker-like firing on one end and burst firing on the other. However, *in vitro*, the burst pattern and the random pattern are not seen. Instead, virtually all dopaminergic neurons fire in the pacemaker mode (Grace, 1987; Kang and Kitai, 1993). The absence of the burst and random firing modes *in vitro* suggests very strongly that the different firing patterns of dopaminergic neurons are primarily controlled by afferent input. However, precisely which afferents are responsible for modulating the firing pattern of dopaminergic neurons has remained unclear.

Several studies have suggested that glutamatergic afferents, specifically those acting at NMDA receptors, may be responsible for the burst firing mode (see Over-

ton and Clark, 1997 for review). However, the predominant input to dopaminergic neurons is GABAergic (Ribak et al., 1976), yet the nature of the GABAergic modulation of dopaminergic neurons is only poorly understood. In this chapter we review some of the literature on the afferent control of dopaminergic neurons, focusing on the GABAergic afferents, and describe some of our recent attempts at understanding the role of GABAergic inputs in the control of the firing pattern of nigral dopaminergic neurons.

2. GABAergic Afferents to Substantia Nigra

The best characterized GABAergic inputs to nigral dopaminergic neurons arise from the striatum and the globus pallidus (GP, Grofov , 1975; Smith and Bolam, 1990; Somogyi et al., 1981). Pharmacological studies of the striatal input have led to some contradictory results. Dopaminergic neurons express both $GABA_A$ and $GABA_B$ receptors, and respond to agonists of each with hyperpolarization (Lacey, 1993). Whereas an early *in vivo* study showed that striatal-evoked inhibition of nigral dopaminergic neurons was blocked by systemic administration of the $GABA_A$ receptor antagonist, picrotoxin (Grace and Bunney, 1985), a subsequent *in vitro* study showed the presence of $GABA_B$ IPSPs presumably originating from striatum in VTA dopaminergic neurons (Cameron and Williams, 1993). The pharmacology of the pallidal input has not been studied previously.

When recorded extracellularly *in vivo* with multi-barrel pipettes allowing local pressure application of drugs, both striatal and pallidal stimulation-evoked inhibition could be completely blocked by bicuculline or picrotoxin. In contrast, the selective $GABA_B$ antagonists, 2-OH saclofen and CGP55845A, were ineffective at blocking the evoked inhibition. However, in many cases the $GABA_B$ antagonists produced an *increase* in the evoked inhibition, and in some cases even revealed an inhibition that could not be seen in the absence of $GABA_B$ receptor blockade (Paladini et al., 1999). In previous *in vitro* studies some of the GABAergic afferents to substantia nigra dopaminergic neurons have been shown to possess presynaptic $GABA_B$ autoreceptors that inhibit stimulus-evoked GABA release and reduce the size of $GABA_A$-mediated IPSPs or IPSCs (e.g., Ha sser and Yung, 1994; Shen and Johnson, 1997).

Taken together, these data indicate that *in vivo* the postsynaptic effects of striatal and pallidal afferents to nigral dopaminergic neurons are mediated predominantly or exclusively by $GABA_A$ receptors. The role of the postsynaptic $GABA_B$ receptors remains unclear. They may be activated by extra-striatal, extra-pallidal inputs, or they may respond to GABA overflow resulting from sustained and synchronous activation of striatal and/or pallidal inputs that are difficult to elicit under *in vivo* experimental conditions (see Paladini et al., 1999 for detailed discussion). In addition, both striatal and pallidal afferents to dopaminergic neurons possess presynaptic $GABA_B$ autoreceptors that are functional *in vivo* under normal physio - logical conditions where there is sufficient GABA tone to activate these receptors thereby suppressing GABA release. In the presence of $GABA_B$ antagonists, striatal and pallidal terminal autoreceptors are disinhibited, calcium- and activity-dependent

GABA release is increased thereby facilitating striatal and pallidal-evoked inhibition.

There Is An Important GABAergic Input To Nigral Dopaminergic Neurons Originating From The Axon Collaterals Of Pars Reticulata Projection Neurons

Although the substantia nigra is heavily innervated from striatum and GP, it was recognized relatively early on that there might be an extra-striatal, extra-pallidal source of GABAergic innervation to the dopaminergic neurons. Intracellular recording and staining of GABAergic pars reticulata projection neurons *in vivo* revealed that their axons emitted local collaterals that arborized both in the pars compacta and the pars reticulata (Grofov et al., 1982). Large kainic acid lesions of pars reticulata reduced GAD activity in pars compacta by 30-40%, while not significantly altering GAD activity in pars reticulata. In contrast, transections anterior to substantia nigra which eliminated striatal and pallidal GABAergic inputs reduced GAD activity in pars reticulata by up to 90% while reducing GAD activity in pars compacta by only 65% (Grofov and Fonnum, 1982; see also Nitsch and Risenberg, 1988). These data suggest that while most of the GABAergic innervation of pars reticulata originates from striatum and GP, a significant proportion of the GABAergic innervation of pars compacta originates in the pars reticulata.

Early electrophysiological evidence also suggested the existence of a pars reticulata GABAergic innervation of dopaminergic neurons. Simultaneous extracellular recordings of pars compacta dopaminergic neurons and unidentified GABAergic neurons in pars reticulata showed that the two cell types fired reciprocally with one another (Grace et al., 1980). This intriguing finding was consistent with an inhibitory effect of a GABAergic pars reticulata neuron on pars compacta dopaminergic neurons. However, the dendrites of dopaminergic neurons release dopamine (Cheramy et al., 1981) and extend deeply into pars reticulata (Juraska et al., 1977; Tepper et al., 1987), and one could not rule out the possibility that the reciprocal firing obtained was due to dopaminergic inhibition of pars reticulata neurons (Timmerman and Abercrombie, 1996) rather than from a GABAergic inhibition of the dopaminergic neuron. A subsequent *in vitro* study showed that stimulation of pars reticulata in slices taken from rats transected anterior to substantia nigra several days earlier to allow striatonigral and pallidonigral afferents to degenerate resulted in IPSPs in pars compacta dopaminergic neurons (Haj s and Greenfield, 1994). However, like the Grace et al. (1980) experiment, the identification of the pars reticulata neuron as an interneuron or a projection neuron could not be determined from these studies.

A monosynaptic GABAergic inhibition of pars compacta dopaminergic neurons by GABAergic pars reticulata projection neurons was subsequently demonstrated by stimulating the thalamus or tectum while recording from identified dopaminergic neurons *in vivo* (Tepper et al., 1995; Paladini et al., 1999). Because GABAergic pars reticulata output neurons but not dopaminergic neurons project to thalamus and/or superior colliculus and because there are no reciprocal projections from these regions back to substantia nigra, stimulation of thalamus or tectum could

be used to antidromically activate pars reticulata projection neurons selectively. Antidromic spikes in reticulata projection neurons resulted in a reliable, short latency inhibition of dopaminergic neurons. The onset of inhibition was not significantly longer than the average antidromic latency of the pars reticulata neurons suggesting that the orthodromic inhibition of the dopaminergic neurons was monosynaptic (Tepper et al., 1995). Like the inhibition evoked by stimulation of striatum or GP, the inhibition of dopaminergic neurons evoked by selective activation of pars reticulata projection neurons was blocked completely by the $GABA_A$ antagonists, picrotoxin or bicuculline (Tepper et al., 1995; Paladini et al., 1999). Also similar to the case with striatal and pallidal afferents, local application of the $GABA_B$ antagonists 2-OH saclofen or CGP55845A never abolished the inhibition; in about 50% of the cases application of 2-OH saclofen or CGP55845A *increased* the duration and/or the magnitude of the inhibition, indicating the presence of functional inhibitory presynaptic $GABA_B$ receptors on the pars reticulata axon collateral terminals, as is also the case with striatal and pallidal terminals (Paladini et al., 1999).

Anatomy of the Reticulata-Compacta Interaction

The morphological substrates of the thalamic and tectal-evoked inhibition were identified with *in vivo* intracellular recording and filling of antidromically identified pars reticulata neurons (Damlama et al., 1993). As noted previously (Deniau et al., 1982; Grofov et al., 1982), the axons of reticulata projection neurons issued local collaterals that arborized within both pars reticulata and pars compacta. The local collaterals were studded with large and small varicosities that were distributed at irregular intervals. In some cases, collaterals exhibited long stretches without varicosities followed by several varicosities in close

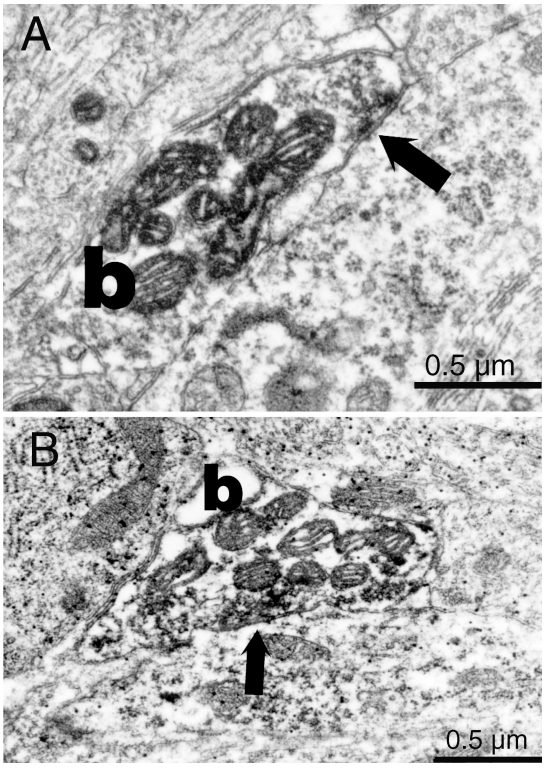

Figure 1. A. Labeled bouton from antidromically identified nigrothalamic neuron intracellularly labeled with biocytin *in vivo* makes symmetrical synapse (arrow) on presumed dopaminergic soma in pars compacta. B. Another labeled bouton makes a symmetrical synapse onto immunocytochemically identified proximal dopaminergic dendrite in pars compacta.

At the electron microscopic level, the varicosities proved to be synaptic boutons. They were large, approximately 1-2 m in diameter, contained 3-8 mitochon - dria and were loosely packed with pleomorphic vesicles, as shown in Figure 1. In pars compacta, labeled boutons were seen to form symmetric synapses with the cell bodies and proximal dendrites of dopaminergic neurons. In one case, a labeled axon was observed to form a pericellular basket around the soma and proximal dendrites of a dopaminergic neuron, similar to that reported for pallidal inputs to dopaminergic neurons (Smith and Bolam, 1990).

GABAergic Input Suppresses Burst Firing In Dopaminergic Neurons In Vivo

How does $GABA_A$-mediated inhibition modulate the firing pattern of nigral dopaminergic neurons? When $GABA_A$ antagonists, were applied locally, all dopaminergic neurons, regardless of baseline firing rate or pattern, immediately switched to a burst firing pattern, as characterized by the shape of the autocorrelation histogram, an increase in the coefficient of variation of the interspike interval (CV), an increase in the percentage of spikes fired in bursts and the mean number of spikes per burst (Tepper et al., 1995; Paladini and Tepper, 1999), as illustrated for one representative neuron in Figure 2.

The burst firing was not due to increased firing rate; although bicuculline significantly increased the mean firing rate (from about 4.6 to 5.8 spikes/sec), neither picrotoxin nor gabazine caused a significant increase in firing rate. None of the measures of burst activity (except for burst duration) was significantly correlated with either baseline firing rate or the change in firing rate after $GABA_A$ receptor blockade (Paladini and

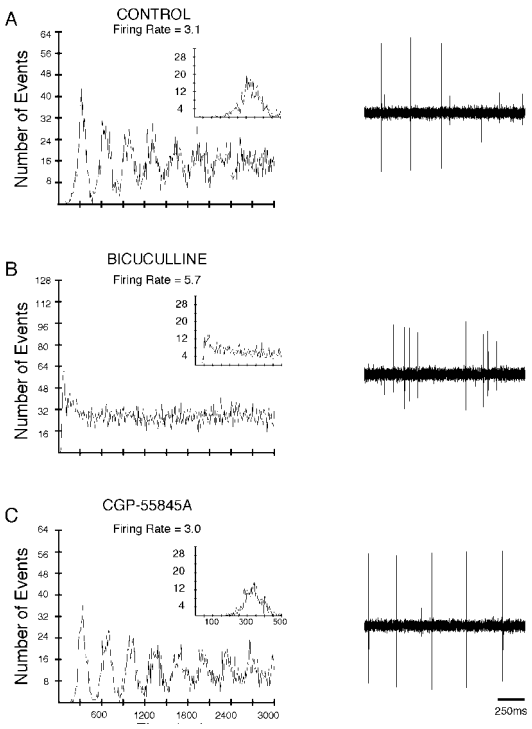

Figure 2. Effects of local administration of GABA antagonists on firing pattern of dopaminergic neuron recorded *in vivo.* A. Pre-drug, the neuron fires in a pacemaker pattern. B. Bicuculline causes dramatic shift to burst firing. C. After recovery from bicuculline, CGP55845A increases the regularity of firing over that of control (note the number of peaks in the autocorrelogram). From Paladini and Tepper, 1999 with permission.

Tepper, 1999). Local application of 2-OH saclofen or CGP55845A, never exerted these effects, but instead shifted the firing pattern away from burst firing towards more regular, pacemaker firing. This effect was presumably due to blockade of presynaptic $GABA_B$ autoreceptors on the terminals of the GABAergic inputs resulting in increased GABA release and increased activation of postsynaptic $GABA_A$ receptors (see above). These data indicate that GABAergic input to dopaminergic neurons, acting via $GABA_A$ receptors, serves to suppress burst firing *in vivo*.

Origin of the GABAergic Input that Suppresses Burst Firing in Dopaminergic Neurons

What is the source of the GABAergic input that suppresses burst firing in dopaminergic neurons *in vivo*? Among striatum, GP and the pars reticulata, the GP and the pars reticulata are the more likely because unlike striatal efferents, pallidal and nigral GABAergic neurons fire tonically at a high rate. To examine the involvement of the GP in the GABAergic control of dopaminergic neuron firing pattern, local infusions of muscimol or bicuculline were made into the GP in order to decrease or increase the firing rate of pallidal output neurons respectively, while recording the effects on the firing pattern of substantia nigra dopaminergic neurons in

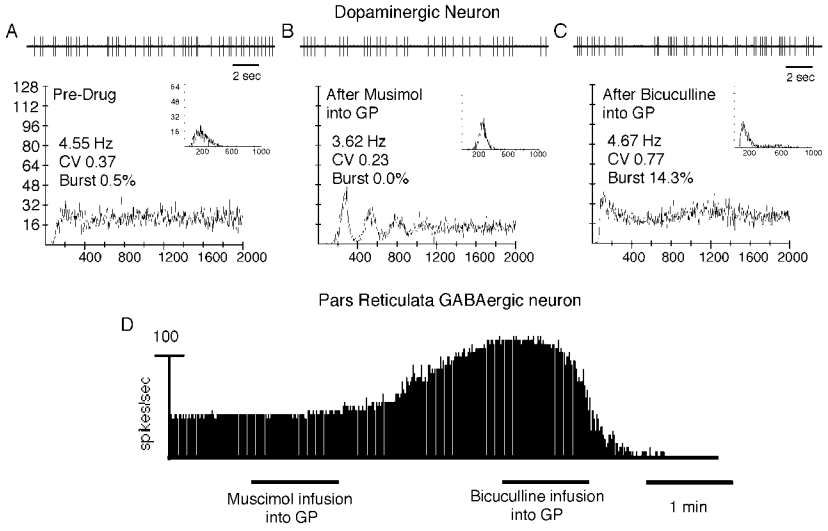

Figure 3. Effects of decreasing and increasing pallidal activity on the firing pattern of a pars compacta dopaminergic neuron and a pars reticulata neuron. A. Spike train, autocorrelogram and first order interval histogram of a typical dopaminergic neuron showing random firing under control conditions. B. After muscimol-induced inhibition of GP the firing rate decreased and the firing pattern shifted to the pacemaker mode. C. Subsequent infusion of bicuculline into GP increased the firing rate of the neuron and not only reversed the pacemaker effect of the prior muscimol infusion but shifted the dopaminergic neuron into the burst firing mode. D. Ratemeter showing effects of the same manipulations of GP firing rate on an unidentified pars reticulata GABAergic neuron. Modified from Celada et al., 1999 with permission.

anesthetized rats (Celada et al., 1999). Pallidal inhibition led to a powerful regularizing effect on the firing pattern of dopaminergic neurons; pallidal inhibition produced significant decreases in the CV, the percentage of spikes fired in bursts and the mean number of spikes/burst, and an increase in the number of peaks in the autocorrelogram. Increases in pallidal activity led to precisely the opposite effects measured by all of these parameters (Figure 3). The changes in firing pattern were associated with unexpectedly modest and anomalous changes in firing rate; pallidal inhibition produced a 17% *decrease* in spontaneous firing rate whereas pallidal excitation led to a 40% *increase* in firing rate.

These effects on burst firing and firing rate were opposite to what would be expected for manipulating a monosynaptic GABAergic pathway from GP to the dopaminergic neurons, and suggested that the effects seen were indirect, mediated by a second inhibitory neuron interposed between GP and the dopaminergic neuron. Examination of the response of pars reticulata GABAergic neurons (some of which were identified antidromically as nigrothalamic neurons) to manipulation of pallidal activity were consistent with this. Unlike the dopaminergic neurons, the firing rates of reticulata GABAergic neurons were dramatically altered by increases or decreases in pallidal activity in a manner consistent with the changes being due to alteration of a monosynaptic GABAergic pathway. Increasing pallidal activity led to a complete cessation of spontaneous activity in many neurons, while decreases in pallidal activity led to increases in firing rate of over 100% (Celada et al., 1999). These data were interpreted to mean that pars reticulata GABAergic neurons (certainly the projection neurons and possibly also interneurons) comprise a principal source of the GABAergic tone that suppresses burst firing in dopaminergic neurons, and that these neurons are themselves under the control of GABAergic efferents from GP. Although it remains to be demonstrated, presumably similar effects would obtain following manipulation of striatal output.

Interaction of Subthalamic Afferents with Intrinsic GABAergic Neurons

The data described above point toward an important role of intrinsic GABAergic circuitry in controlling the activity of nigral dopaminergic neurons. Might this circuitry also modulate the effects of excitatory afferents? The response of dopaminergic neurons to stimulation of the subthalamic nucleus (STN) is complex. Although the output of the nucleus is strictly glutamatergic, responses recorded in dopaminergic neurons after subthalamic stimulation are a mixture of excitation, inhibition followed by excitation, or inhibition (Chergui et al., 1994; Hammond et al., 1978; Robledo and F ger, 1990; Smith and Grace, 1992), although pars reticulata GABAergic neurons almost always respond with excitation (Nakanishi et al., 1987; Robledo and F ger, 1990).

Synaptic potentials were recorded intracellularly from pars compacta dopaminergic neurons in parasagittal slices in response to stimulation of the STN as illustrated in Figure 4 (Iribe et al., 1999). STN—evoked depolarizing synaptic responses in dopaminergic neurons reversed at approximately —31 mV, intermediate between the expected reversal potential for an EPSP and an IPSP. Blockade of $GABA_A$ receptors with bicuculline caused a positive shift in the reversal potential to

near 0 mV, suggesting that STN stimulation evoked a near simultaneous EPSP and IPSP. Both synaptic responses were blocked by application of the glutamate receptor antagonist, CNQX, indicating that the IPSP could not be monosynaptic and required glutamatergic excitation of a GABAergic neuron in substantia nigra.

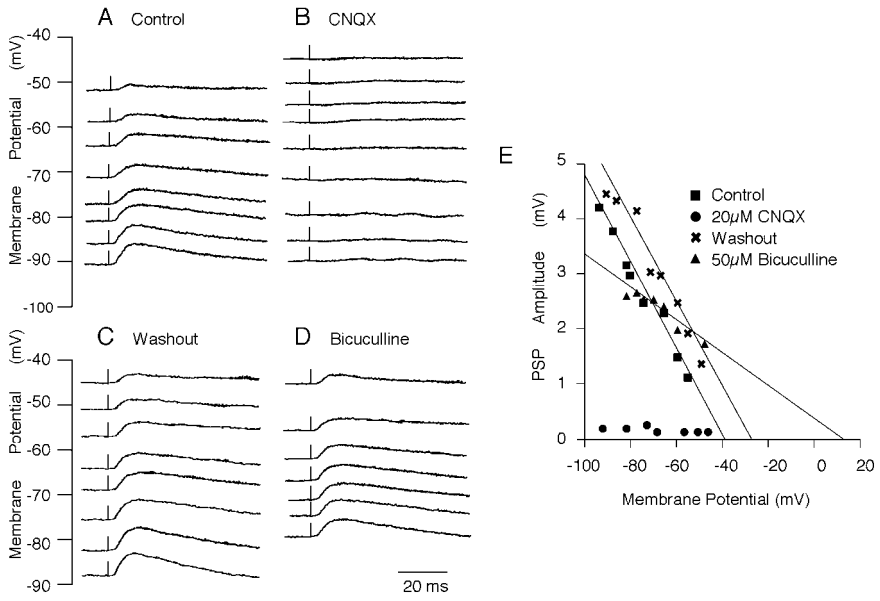

Figure 4. The IPSP component of the STN-evoked DPSP is polysynaptic. Under control conditions STN stimulation produced a DPSP with a reversal potential of —38.8 mV (A, E). Addition of CNQX completely abolished the DPSP (B,E). After a one hour wash, the DPSP returned and still exhibited a hyperpolarized reversal potential (C,E). Subsequent application of bicuculline shifted the reversal potential in the positive direction to 12.6 mV (D,E). Traces in A-D are the average of 4 single sweeps.. Modified from Iribe et al., (1999) with permission.

The confounding influence of inhibitory fibers of passage from GP and/or striatum by STN stimulation was eliminated by unilaterally transecting striatonigral and pallidonigral fibers three days prior to recording. The reversal potential of STN-evoked synaptic responses in dopaminergic neurons in slices from transected animals was approximately —30 mV. Bath application of bicuculline shifted the reversal potential to ~ 5 mV as it did in intact animals, suggesting that the source of the IPSP was within substantia nigra.

These data indicate that electrical stimulation of the STN elicits a mixed EPSP-IPSP in nigral dopaminergic neurons due to the co-activation of an excitatory monosynaptic and an inhibitory polysynaptic connection between the STN and the dopaminergic neurons of substantia nigra pars compacta. The EPSP arises from a direct monosynaptic excitatory glutamatergic input from the STN. The IPSP arises polysynaptically, most likely through STN-evoked excitation of GABAergic neurons in substantia nigra pars reticulata which produces feed-forward $GABA_A$-mediated inhibition of dopaminergic neurons through inhibitory intranigral axon collaterals. This is likely the reason that so many of the previous attempts to exam-

ine subthalamic effects on dopaminergic neurons reported mixed excitatory and inhibitory responses.

Summary and Conclusions

The activity of nigral dopaminergic neurons is significantly modulated by GABAergic afferents. In addition to striatum and GP, GABAergic synapses arising from the axon collaterals of pars reticulata GABAergic projection neurons (and perhaps also interneurons) exert a powerful modulation of the firing pattern of dopaminergic neurons. All three of these GABAergic inputs appear to exert their effects predominantly or exclusively through $GABA_A$ receptors, and GABA release from all three is subject to modulation from inhibitory presynaptic $GABA_B$ autoreceptors. Pharmacological blockade of $GABA_A$ receptors, or reduction in GABAergic tone caused by the inhibition of firing of pars reticulata GABAergic neurons produces a dramatic shift in dopaminergic neuron firing pattern to the burst mode, whereas increases in firing of reticulata neurons leads to pacemaker-like firing and a reduction in bursting. The ionic mechanisms underlying the burst firing unmasked by interruption of the tonic GABAergic input remain to be determined. Nevertheless, the firing pattern of dopaminergic neurons *in vivo* is controlled to an important extent by disinhibition exerted by changes in the activity of the pars reticulata GABAergic neurons, which in turn, is modulated by other GABAergic inputs from GP and striatum.

Thanks to Paul Bolam for taking the electron micrographs in Figure 1 and to Elizabeth Abercrombie for comments on the manuscript. Supported by NS-34865.

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