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CHAPTER 11

GABAergic control of substantia nigra dopaminergic neurons

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Abstract: At least 70% of the afferents to substantia nigra dopaminergic neurons are GABAergic. The vast majority of these arise from the neostriatum, the external globus pallidus and the substantia nigra pars reticulata. Nigral dopaminergic neurons express both $GABA_A$ and $GABA_B$ receptors, and are inhibited by local application of $GABA_A$ or $GABA_B$ agonists in vivo and in vitro. However, in vivo, synaptic responses elicited by stimulation of neostriatal or pallidal afferents, or antidromic activation of nigral pars reticulata GABAergic projection neurons are mediated predominantly or exclusively by $GABA_A$ receptors. The clearest and most consistent role for the nigral $GABA_B$ receptor in vivo is as an inhibitory autoreceptor that presynaptically modulates $GABA_A$ synaptic responses that originate from all three principal GABAergic inputs. The firing pattern of dopaminergic neurons is also effectively modulated by GABAergic inputs in vivo. Local blockade of nigral $GABA_A$ receptors causes dopaminergic neurons to shift to a burst firing pattern regardless of the original firing pattern. This is accompanied by a modest increase in spontaneous firing rate. The GABAergic inputs from the axon collaterals of the pars reticulata projection neurons seem to be a particularly important source of a $GABA_A$ tone to the dopaminergic neurons, inhibition of which leads to burst firing. The globus pallidus exerts powerful control over the pars reticulata input, and through the latter, disynaptically over the dopaminergic neurons. Inhibition of pallidal output leads to a slight decrease in firing of the dopaminergic neurons due to disinhibition of the pars reticulata neurons whereas increased firing of pallidal neurons leads to burst firing in dopaminergic neurons that is associated with a modest increase in spontaneous firing rate and a significant increase in extracellular levels of dopamine in the neostriatum. The pallidal disynaptic disinhibitory control of the dopaminergic neurons dominates the monosynaptic inhibitory influence because of a differential sensitivity to GABA of the two nigral neuron types. Nigral GABAergic neurons are more sensitive to $GABA_A$-mediated inhibition than dopaminergic neurons, in part due to a more hyperpolarized $GABA_A$ reversal potential. The more depolarized $GABA_A$ reversal potential in the dopaminergic neurons is due to the absence of KCC2, the chloride transporter responsible for setting up a hyperpolarizing Cl^- gradient in most mature CNS neurons. The data reviewed in this chapter have made it increasingly clear that in addition to the effects that nigral GABAergic output neurons have on their target nuclei outside of the basal ganglia, local interactions between GABAergic projection neurons and dopaminergic neurons are crucially important to the functioning of the nigral dopaminergic neurons.

Keywords: IPSP; disinhibition; pars reticulata; pars compacta; burst firing; reversal potential; pallidonigral

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Introduction

Identification of the afferents to nigral dopaminergic neurons and study of their physiological attributes is greatly complicated by the anatomical organization of the nucleus, in particular by the morphology of the dopaminergic neurons (for recent review, see Misgeld, 2004). The cell bodies of most nigrostriatal dopaminergic neurons are situated in the pars compacta. The pars compacta is a relatively thin, disk-shaped nucleus of densely packed cells dorsal and superior to the larger, more extensive, GABAergic neuron-containing pars reticulata, thus providing a flattened sheet that covers the pars reticulata for most of its dorsolateral and anterioposteror extent (Hanaway et al., 1970). Although the majority of the dopaminergic somata in substantia nigra are in the pars compacta, there exist scattered groups of dopaminergic neurons within pars reticulata. However, the morphology and physiology of these neurons appear identical to those of the pars compacta dopaminergic neurons (Richards et al., 1997).

The dendritic organization of dopaminergic neurons contributes to the anatomical complexity of the substantia nigra. Dopaminergic somata are medium-sized, and their dendrites aspiny. Several thick but rapidly tapering dendrites emanate from dopaminergic somata and extend into the neuropil of the pars compacta (Juraska et al., 1977; Tepper et al., 1987, 1994). All dopaminergic neurons also send one or occasionally two dendrites ventrally, perpendicular to the surface of the pars compacta, deep into pars reticulata. These dendrites, up to a millimeter in length, are often the largest emitted by the neuron and it is not unusual for them to traverse the entire extent of the pars reticulata and terminate in the crus cerebri (Tepper et al., 1987). Although the long, distal regions of these dendrites receive relatively few afferents, synapses abound on the more proximal dendritic segments that are closely intermingled with the somata and dendrites of the GABAergic pars reticulata neurons (Grofova et al., 1986). Thus there is no clear anatomical distinction between terminal zones of afferents to the dopaminergic neurons and those to the GABAergic neurons. This makes standard retrograde tracing techniques of only limited value when trying to determine if certain afferents innervate dopaminergic pars compacta and/or GABAergic pars reticulata neurons.

The electrophysiological properties of dopaminergic neurons have been studied in detail, both in vivo and in vitro (for recent review, see Diana and Tepper, 2002). Almost all nigrostriatal dopaminergic neurons fire spontaneously in vivo (Tepper et al., 1984; Dai and Tepper, 1998; but see Chiodo, 1988; Floresco et al., 2003) at relatively slow rates averaging between 4 and 5 spikes/s (Bunney et al., 1973; Deniau et al., 1978; Guyenet and Aghajanian, 1978; Bunney, 1979; Grace and Bunney, 1983). The spontaneous activity exists along a continuum of firing patterns that is only loosely related to the mean rate (Wilson et al., 1977; Freeman et al., 1985; Hyland et al., 2002). In urethane-anesthetized animals the most common pattern of activity (~55% of neurons) is a random mode in which the interspike intervals are described by a Poisson-like process. The next most common pattern is a regular, pacemaker-like activity (~30%) and the least common (15%) is a slow bursting pattern (Tepper et al., 1995; Paladini and Tepper, 1999). Bursts in dopaminergic neurons in anesthetized animals are most frequently comprised of 2–8 spikes with increasing interspike intervals ranging from about 40 to well over 100 ms (Bunney et al., 1973; Grace and Bunney, 1984). The spontaneous activity is very similar in unanesthetized freely moving rats (Freeman et al., 1985; Freeman and Bunney, 1987) and the same three distinct firing patterns are evident (Hyland et al., 2002). The bursting can be sparse, with only a few two or three spike bursts occurring over a several minute period, or it can be rhythmic, lasting for several seconds or minutes. The burst firing pattern is believed to be of particular significance to the reward and/or salience signaling functions of the dopamine system (for review see Schultz, 2006).

The production of the different firing patterns, especially burst firing, in dopaminergic neurons is currently the subject of considerable study, and there is likely to be more than a single mechanism responsible (e.g., Zhang et al., 1994; Overton and Clark, 1997; Kitai et al., 1999; Waroux et al., 2005;

Ji and Shepard, 2006). As the different patterns are essentially absent in vitro (Kita et al., 1986; Grace and Onn, 1989; but see Mereu et al., 1997) afferent input is considered to be a crucial modulator of firing pattern. Considerable evidence implicates an important role for glutamatergic input and especially NMDA receptor stimulation in the burst firing pattern (Johnson et al., 1992; Overton and Clark, 1992, 1997; Chergui et al., 1993; Christoffersen and Meltzer, 1995). These conclusions are supported by several recent computational modeling studies of burst firing in dopaminergic neurons (e.g., Canavier, 1999; Amini et al., 1999; Wilson and Callaway, 2000; Medvedev et al., 2003; Komendantov et al., 2004; Kuznetsov et al., 2006). Although the ability of NMDA receptor stimulation to evoke burst firing is well established, the endogenous trigger for "spontaneous" burst firing in vivo has not been demonstrated and in vivo, the firing pattern of nigrostriatal neurons is potently modulated by blockade of $GABA_A$ receptors (Tepper et al., 1995; Paladini et al., 1999a).

GABAergic afferents to nigral dopaminergic neurons

The vast majority of inputs to pars compacta dopaminergic neurons, somewhere over 70%, are GABAergic (Bolam and Smith, 1990). These arise principally from within the basal ganglia itself, with the densest projections emanating from the neostriatum (Grofova and Rinvik, 1970; Somogyi et al., 1981; Bolam and Smith, 1990), the globus pallidus (external segment) (Grofova, 1975; Smith and Bolam, 1990) and the GABAergic neurons of the substantia nigra pars reticulata (Grace and Bunney, 1979, 1985; Nitsch and Riesenberg, 1988; Hajos and Greenfield, 1993, 1994; Tepper et al., 1995; Mailly et al., 2003).

The striatonigral pathway (direct pathway) comprises about 50% of the spiny cell efferents with the remainder (indirect pathway) projecting to the globus pallidus. Striatonigral neurons colocalize substance P and dynorphin in addition to GABA (Gerfen and Wilson, 1996). Both pars reticulata GABAergic projection neurons as well as pars compacta dopaminergic neurons receive innervation from striatonigral neurons. The two cell populations are unlikely to receive the same set of afferent information from the striatum, however, as the major input to the GABAergic neurons comes from the striatal matrix compartment whereas that to the dopaminergic neurons, at least to their somata, arises from the patch compartment (Gerfen, 1985; Gerfen et al., 1987).

The striatonigral projection is relatively slowly conducting. It is by far the slowest of all the long-projecting GABAergic neurons in the basal ganglia (Kita and Kitai, 1991; Celada et al., 1999). The average antidromic conduction latency of striatonigral neurons in the anterior-central region of the striatum is about 10 ms corresponding to a conduction velocity around 1.4 m/s (Ryan et al., 1986). The membrane potential of the striatonigral neurons oscillates between a hyperpolarized down state during which the neurons never fire and a cortically driven, depolarized up state when firing becomes possible (Wilson, 1993). Overall, the mean firing rate is very low, in the range of 1 Hz or less (Wilson, 1993), suggesting that the effect of the striatum on the neurons of the substantia nigra is phasic and occurs only during up states.

Like the striatonigral afferents, the pallidonigral projection innervates both dopaminergic and non-dopaminergic nigral neurons (Bolam and Smith, 1990; Smith and Bolam, 1990). In contrast to the striatal input, however, the pallidonigral afferents are rapidly conducting with antidromic conduction latencies from substantia nigra of around 1 ms corresponding to a conduction velocity around 4 m/s (Kita and Kitai, 1991; Celada et al., 1999). The cells that give rise to the pallidonigral projection are among those neurons with the highest spontaneous firing rate of neurons in the basal ganglia, around 50 Hz in urethane-anesthetized rats (Celada et al., 1999).

Inputs to the dopaminergic neurons from pars reticulata GABAergic neurons arise from the local collaterals of the GABAergic output neurons (Tepper et al., 1995). These neurons are spontaneously active with a mean firing rate around 30 Hz in anesthetized rats (Celada et al., 1999) and have axonal conduction velocities similar to pallidal neurons, around 3–4 m/s (Deniau et al., 1978; Guyenet and Aghajanian, 1978).

At one time it was believed that the non-dopaminergic nigral neurons that were the source of the GABAergic input to the dopaminergic neurons were true local circuit neurons, leading them to be explicitly referred to as "interneurons" in the literature (e.g., Grace and Bunney, 1979, 1985; Mereu and Gessa, 1985; Araneda and Bustos, 1989; Yung et al., 1991; Johnson and North, 1992; Zhang et al., 1993; Bontempi and Sharp, 1997). However, the neuroanatomical and electrophysiological properties reported for the putative pars reticulata GABAergic interneurons are not very different from those of antidromically identified nigrothalamic and nigrotectal projection neurons (Matsuda et al., 1987; Yung et al., 1991; Lee and Tepper, 2007 but see also Grace and Bunney, 1979; Grace et al., 1980) that have been shown to send axon collaterals to the pars compacta which synapse onto dopaminergic neurons (Deniau et al., 1982; Grofova et al., 1982; Hajos and Greenfield, 1993; Tepper et al., 1995, 2002; Mailly et al., 2003). The best evidence for the existence of a nigral interneuron comes from a small population of pars compacta GABAergic neurons mapped with *c*-fos that are not retrogradely labeled from neostriatum (Hebb and Robertson, 2000). Virtually nothing is known about the afferent or efferent connections of these neurons however and their identity as interneurons remains to be conclusively determined. Like the dopaminergic neurons of the pars compacta, nigral GABAergic neurons also receive inhibitory input from the axon collaterals of GABAergic projection neurons (Deniau et al., 1982). At present, the balance of the evidence suggests that the bulk of the projection from the pars reticulata to the dopaminergic neurons arises from the axon collaterals of pars reticulata projection neurons, as opposed to locally projecting interneurons.

Each of the basal ganglia afferents to the substantia nigra innervates both dopaminergic and GABAergic nigral neurons with the majority of the afferents forming Gray's Type II symmetric synapses, mostly onto the dendrites of the GABAergic neurons (Rinvik and Grofova, 1970; Hattori et al., 1975; Somogyi et al., 1981; Smith and Bolam, 1990). The boutons originating from the globus pallidus and substantia nigra pars reticulata are larger than striatonigral boutons (von Krosigk et al., 1992; Tepper et al., 2002), contact proximal dendrites and somata more frequently than do the striatonigral afferents, and may innervate the dopaminergic neurons preferentially compared to the striatal inputs (Hattori et al., 1975; Smith and Bolam, 1990).

Dopaminergic substantia nigra neurons also receive GABAergic input from a number of sources outside the basal ganglia. These afferents are generally less well studied than the intrinsic basal ganglia connections. One such input originates from the superior colliculus (Comoli et al., 2003). Axons from the superior colliculus make symmetric and asymmetric synapses with both dopaminergic and GABAergic neurons in the substantia nigra (J. Boyes and J.P. Bolam, personal communication) and when stimulated, produce both inhibitory and excitatory effects in both nigral neuron types (Coizet et al., 2003; Comoli et al., 2003). A GABAergic afferent to nigral dopaminergic neurons arises from the lateral habenula, stimulation of which leads to inhibition (Bunney and Aghajanian, 1976; Christoph et al., 1986; Gao et al., 1996). Dopaminergic neurons are also inhibited in response to peripheral nociceptive stimulation (Tsai et al., 1980; Ungless et al., 2004). An additional input arises from the central nucleus of the amygdala that may preferentially innervate the pars compacta (Bunney and Aghajanian, 1976; Wallace et al., 1989, 1992; Gonzales and Chesselet, 1990; Vankova et al., 1992). The neurotransmitter used in the amygdalonigral projection is unknown but it is likely to be GABA.

Dopaminergic neurons express both $GABA_A$ and $GABA_B$ receptors somatodendritically (Bowery et al., 1987; Nicholson et al., 1992). Exogenous application of GABA, or selective $GABA_A$ or $GABA_B$ agonists, produces hyperpolarizing IPSPs in dopaminergic neurons in vitro. This is accompanied by a slowing or complete inhibition of spontaneous activity and a marked reduction in burst firing in vivo (Engberg et al., 1993). The $GABA_A$ inhibition is caused by an increase in conductance to chloride that leads to a hyperpolarization (Kaila, 1994; Gulacsi et al., 2003) whereas the $GABA_B$ inhibition is due to an increase in conductance to potassium (Lacey et al., 1988).

However, the response to endogenously released GABA evoked by afferent stimulation of striatal, pallidal, or reticulata GABAergic afferents in vivo is often complex, and depends on the type and/or intensity of stimulation.

GABAergic synaptic responses in dopaminergic neurons

In vivo recordings

In in vivo intracellular recordings, striatal stimulation produced short latency monosynaptic, chloride-mediated hyperpolarizing IPSPs in identified dopaminergic neurons (Grace and Bunney, 1985), suggesting strongly that these were $GABA_A$-mediated IPSPs even though no pharmacology was performed. Similar, but significantly larger and longer-lasting IPSPs were elicited in pars reticulata GABAergic neurons. Interestingly, the late phase of the IPSP in the GABAergic neurons was associated with a depolarization in the dopaminergic neurons (Grace and Bunney, 1985).

Extracellular in vivo recordings revealed that electrical stimulation of striatum, globus pallidus and/or pars reticulata projection neurons produced inhibition of pars compacta dopaminergic neurons that was completely blocked by local application of bicuculline or picrotoxin thus demonstrating mediation predominantly or exclusively by $GABA_A$ receptors (Paladini et al., 1999a) (Fig. 1). Local application of the highly specific and potent $GABA_B$ antagonists, saclofen or CGP 55845A, failed to block the inhibition evoked from any of these sites (Tepper et al., 1995; Paladini et al., 1999a) and in about 50% of the cases, slightly augmented the inhibition and decreased spontaneous burst firing (Paladini and Tepper, 1999; Paladini et al., 1999a). In a few cases, local application of $GABA_B$ antagonists revealed a previously unseen short latency inhibition that could subsequently be abolished by bicuculline or picrotoxin (Paladini et al., 1999a). An example of this is shown in Fig. 2. This unmasking effect is likely due to blockade of presynaptic $GABA_B$ receptors present on GABAergic afferents to substantia nigra (Giralt et al., 1990; Hausser and Yung, 1994; Shen and Johnson, 1997; Paladini et al., 1999a; Boyes and Bolam, 2003, see Misgeld, this volume), a property shared by the striatal, pallidal, and pars reticulata afferents (Paladini et al., 1999a but see Cameron and Williams, 1993). Thus, in vivo, most or all of the postsynaptic effects of striatal, pallidal, and pars reticulata GABAergic inputs in vivo appear to be mediated by $GABA_A$ receptors, with the $GABA_B$ receptors acting predominantly as presynaptic inhibitory autoreceptors.

In addition to blocking the GABAergic inhibition evoked from striatum, globus pallidus or pars reticulata, local application of $GABA_A$ antagonists exert potent effects on the spontaneous activity of dopaminergic neurons. Local application of bicuculline methiodide increases the spontaneous firing rate of dopaminergic neurons and shifts them to a robust burst pattern of firing (Tepper et al., 1995) (Fig. 3). Picrotoxin has a very similar effect on firing pattern with only a modest effect on firing rate (Paladini and Tepper, 1999) (Fig. 4), and with both drugs the effects on firing pattern were found to be independent of baseline firing rate or changes in firing rate suggesting that the mechanisms controlling the firing rate and those controlling the firing pattern are at least partially independent. It must be noted that bicuculline methiodide (and other quarternary salts, but not picrotoxin or bicuculline free base) are potent antagonists of the calcium-activated potassium channels (Johnson and Seutin, 1997; Seutin and Johnson, 1999) that underlie the long lasting spike after-hyperpolarization in dopaminergic and other neurons. Blocking this conductance also leads to increases in burst firing (Waroux et al., 2005; Ji and Shepard, 2006). Thus, the picrotoxin results are crucial for demonstrating the burst promoting effects of $GABA_A$ blockade on dopaminergic neuron firing pattern (Fig. 4).

Consistent with its lack of effects on synaptically evoked inhibition, local blockade of $GABA_B$ receptors on nigral dopaminergic neurons by application of the selective $GABA_B$ receptor antagonist, CGP 55845A or Z-hydroxysacloten, did not lead to burst firing. In fact, in about 50% of the cases, there was a modest but significant shift toward lower firing rates and more regular, less bursty firing patterns (Tepper et al., 1995; Paladini and

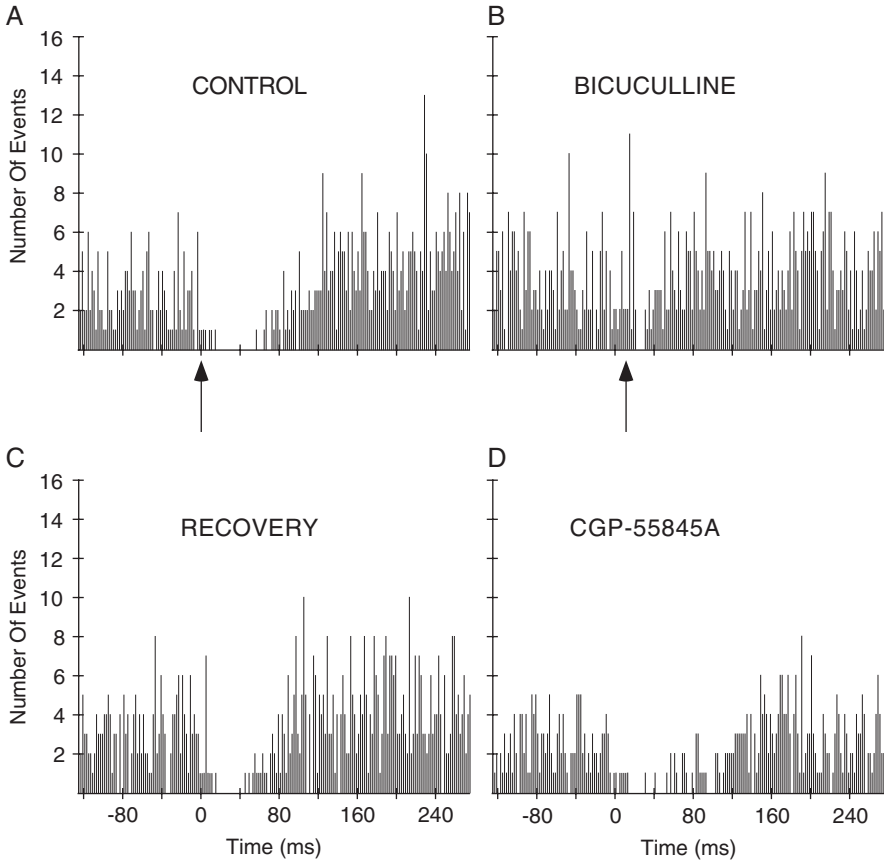


Fig. 1. Effects of globus pallidus stimulation (1.0 mA, 0.67 Hz) on a representative substantia nigra dopaminergic neuron. (A) Pallidal stimulation reliably inhibits the neuron (suppression to 10% of prestimulus firing rate, 59 ms duration). The inhibition is completely (B) and reversibly (C) blocked by bicuculline administration. (D) Application of the $GABA_B$ antagonist, CGP-55845A, not only fails to attenuate the evokd inhibition (suppression to 18% of prestimulus firing rate) but instead *increases* the duration (82 ms duration) of inhibition relative to recovery (13% inhibition, 46 ms duration in (C) and control (A). Each PSTH consists of 200 trials. Bin width = 2 ms. [*Source*: Reprinted from Paladini (1999a) with permission from Elsevier.]

Tepper, 1999) (Fig. 3). As was the case with the effects of $GABA_B$ antagonists on electrically evoked inhibition (Paladini et al., 1999a), these effects were interpreted to suggest that the primary locus of action of the $GABA_B$ antagonist was presynaptic, leading to increased GABA release and increased postsynaptic $GABA_A$ receptor stimulation (Paladini and Tepper, 1999).

However, there remains some controversy in the literature. While all studies agree that application of baclofen or other selective $GABA_B$ agonists inhibit the spontaneous activity of dopaminergic neurons, early studies showed that administration of the $GABA_B$ antagonist, CGP 35348, blocked this effect but did not otherwise affect spontaneous activity, suggesting the absence of a $GABA_B$ tone on dopaminergic neurons in vivo (Engberg et al., 1993). However, more recent results (Erhardt et al., 1999, 2002) indicate that administration of the $GABA_B$ antagonist, SCH50911, or higher doses of CGP35348 did in fact lead to increases in firing rate. The reasons for these discrepancies remain unclear although it is noted that different anesthetics were used in the two series of studies (urethane in the former and chloral hydrate in the latter). It is conceivable that the different recording conditions led to differences in spontaneous GABA release such that presynaptic effects of

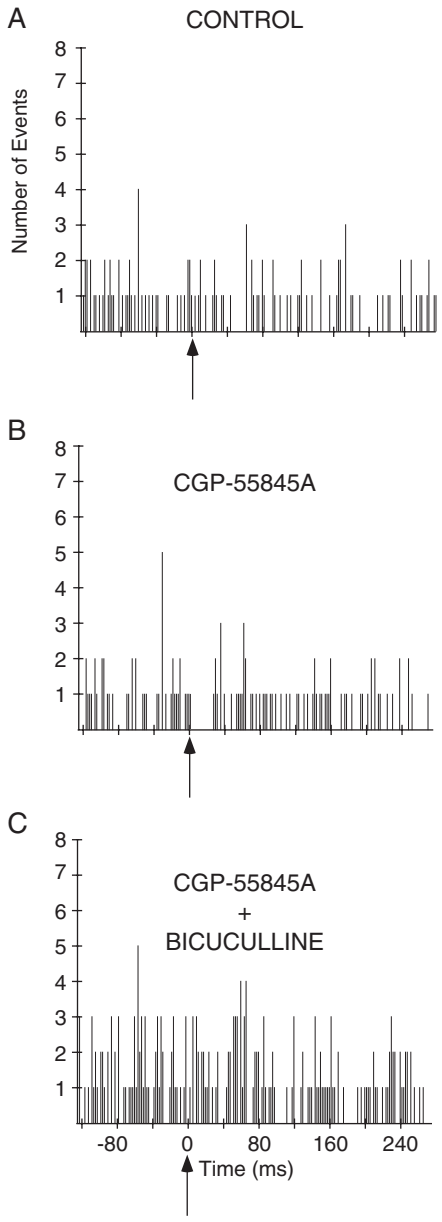


Fig. 2. Unmasking of $GABA_A$-mediated inhibition by CGP-55845A in an antidromically identified nigrostriatal dopaminergic neuron. (A) Stimulation of thalamus (1.0 mA, 0.67 Hz) has no detectable effect on the neuron. (B) Application of CGP-55845A reveals an inhibition (suppression to 0% of control for 24 ms). (C) Application of bicuculline together with CGP-55845A abolishes the unmasked inhibition. PSTH consists of 100 trials. Bin width = 2 ms. [*Source*: Reprinted from Paladini et al. (1999a) with permission from Elsevier.]

$GABA_B$ antagonists were accentuated in the former studies while postsynaptic effects were amplified in the latter. Regardless of the role of $GABA_B$ receptors, it is clear that interrupting $GABA_A$ inhibition of nigrostriatal neurons leads to phasic burst firing.

In vitro recordings

In contrast to the in vivo results, local stimulation of substantia nigra in vitro leads to both short latency and long latency (onset about 35 ms, time to peak around 150 ms; Hausser and Yung, 1994) IPSPs. The short latency IPSPs are blocked by bicuculline and picrotoxin whereas the long latency IPSPs are blocked by the selective $GABA_B$ receptor antagonists, CGP 35348 or 2-hydroxysaclofen, thereby identifying them as $GABA_A$ and $GABA_B$ IPSPs, respectively (Saitoh et al., 2004). Although $GABA_B$ IPSPs can sometimes be elicited by single pulse stimuli, they are usually not seen in response to minimal stimuli that evoke $GABA_A$ IPSPs (Hausser and Yung, 1994) and are most often reported to follow trains of stimuli at higher intensities (Johnson and North, 1992; Cameron and Williams, 1993; Hajos and Greenfield, 1993, 1994; Saitoh et al., 2004). Although spontaneous GABAergic IPSPs are frequently reported in dopaminergic neurons in vitro (e.g., Johnson and North, 1992; Hausser and Yung, 1994), these appear to be strictly $GABA_A$-mediated.

It was originally suggested that striatal-evoked GABAergic inhibition of dopaminergic neurons but not that arising from globus pallidus or substantia nigra pars reticulata, was mediated by $GABA_B$ receptors (Cameron and Williams, 1993). The evidence was that stimulation of D1 dopamine receptors in vitro selectively augmented $GABA_B$ IPSCs, and since of the striatal, pallidal, and nigral GABAergic neurons, only striatonigral neurons are known to express D1 receptors, striatonigral IPSP/Cs must be mediated predominantly or exclusively by $GABA_B$ receptors. However, more recent studies examining the effects of D1 antagonists on miniature IPSCs in the presence of TTX have revealed robust D1 modulation of $GABA_A$ IPSCs in both dopaminergic and GABAergic

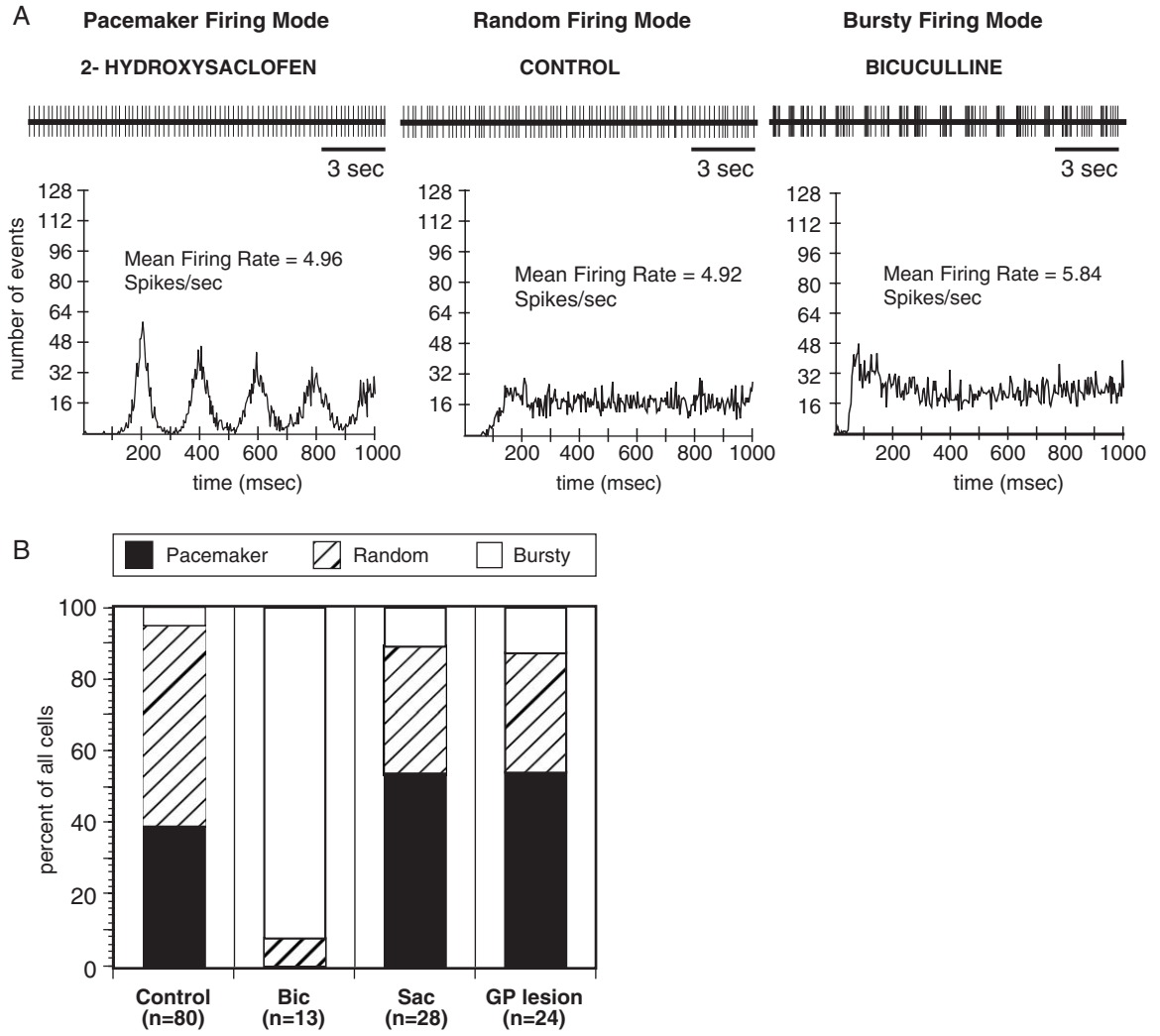


Fig. 3. Effects of bicuculline and 2-hydroxysaclofen on firing patterns of dopaminergic neurons. (A) Autocorrelograms of representative neurons exhibiting the three firing modes of dopaminergic neurons in vivo. Above each autocorrelogram is the first few seconds of the spike train used to create the autocorrelogram. The pacemaker firing neuron was obtained with a 2-hydroxysaclofen-containing micropipette, the random firing neuron with a saline micropipette, and the bursty firing neuron with a bicuculline-containing micropipette. Bin width = 3 ms. (B) Summary graph of the distribution of firing patterns recorded with control (1 M NaCl), Bic (1 M NaCl + 20 mM bicuculline methiodide) or Sac (1 mM NaCl + 20 mM 2-hydroxysaclofen) micropipettes, or with control micropipettes following kainic acid lesion of the ipsilateral globus pallidus in urethane-anesthetized rats. [*Source*: Redrawn from Tepper et al. (1995). Copyright 1995 by the *Society for Neuroscience*.]

neurons (Yanovsky et al., 2003). This suggests that the previous findings may have been due to network effects that obscured the $GABA_A$ modulation and the current view is that striatonigral and striatopallidal inhibition are mediated by both $GABA_A$ and $GABA_B$ receptors (Misgeld, 2004), consistent with in vivo results showing blockade of striatal and pallidal evoked inhibition by bicuculline or picrotoxin (Paladini et al., 1999a).

The higher thresholds for $GABA_B$ IPSPs and the lack of spontaneous $GABA_B$ IPSPs may be related. The $GABA_B$ receptors are located

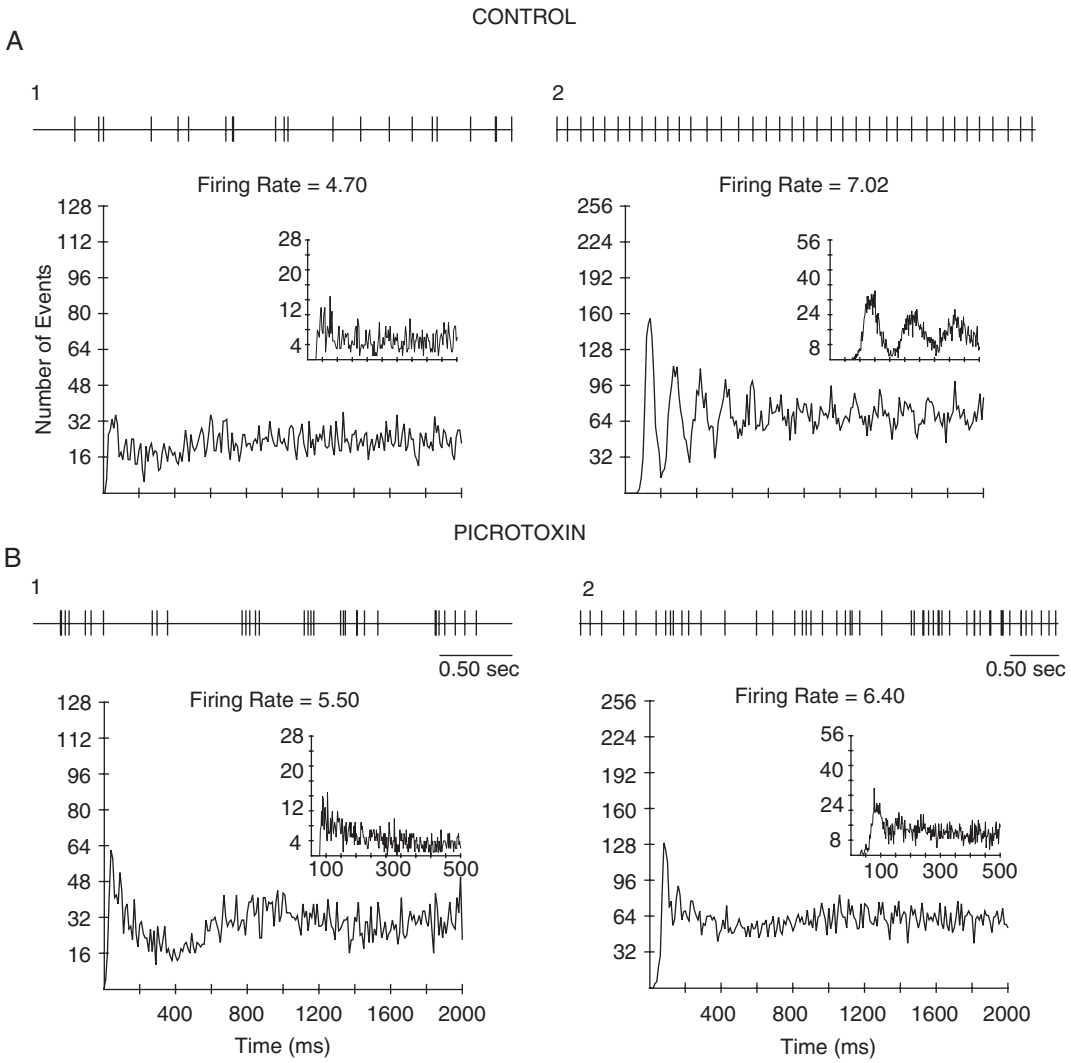


Fig. 4. Autocorrelograms showing the effects of local application of the chloride channel blocker, picrotoxin, on the firing pattern of two dopaminergic neurons. (Insets) Initial portions of the same autocorrelation at higher temporal resolution. (A) Sample spike trains and autocorrelograms of two cells 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 ms.) [*Source*: Adapted with permission from Paladini and Tepper (1999).]

extra-synaptically, at some distance from the active zone (Boyes and Bolam, 2003). Thus, relatively strong and/or prolonged presynaptic stimuli may be required to allow GABA to escape from the synaptic cleft and activate these receptors (e.g., Scanziani, 2000) compared to $GABA_A$ receptors which are believed to be located subsynaptically, in closer proximity to synaptically released GABA (Richards et al., 1987; Nicholson et al., 1992). The necessary stimulus for activation of postsynaptic $GABA_B$ receptors in the hippocampus is rhythmic, synchronous discharge in presynaptic inhibitory neurons or pharmacological block of GABA uptake (Scanziani, 2000) where $GABA_B$ receptors

have been shown to have a similar extrasynaptic distribution (Lopez-Bendito et al., 2004).

As noted earlier, postsynaptic $GABA_B$ receptor-mediated events are encountered in nigral dopaminergic neurons relatively frequently in vitro, but not in vivo under most conditions. This may be due to more efficacious electrical stimulation, a reduction in GABA uptake, and/or a decrease in presynaptic GABAergic inhibition in vitro. Train stimulation of the GABAergic afferents to nigral dopaminergic neurons has thus far been ineffective at eliciting postsynaptic $GABA_B$ receptor-mediated responses in vivo (Paladini et al., 1999a) so the substrates necessary for activating postsynaptic $GABA_B$ receptors in vivo remain to be determined.

In addition, dopamine itself has been reported to have a selective presynaptic inhibitory effect on $GABA_B$ IPSPs in dopaminergic neurons (Federici et al., 2002) that could also contribute to the relative inefficiency of $GABA_B$ transmission in pars compacta dopaminergic neurons (Saitoh et al., 2004).

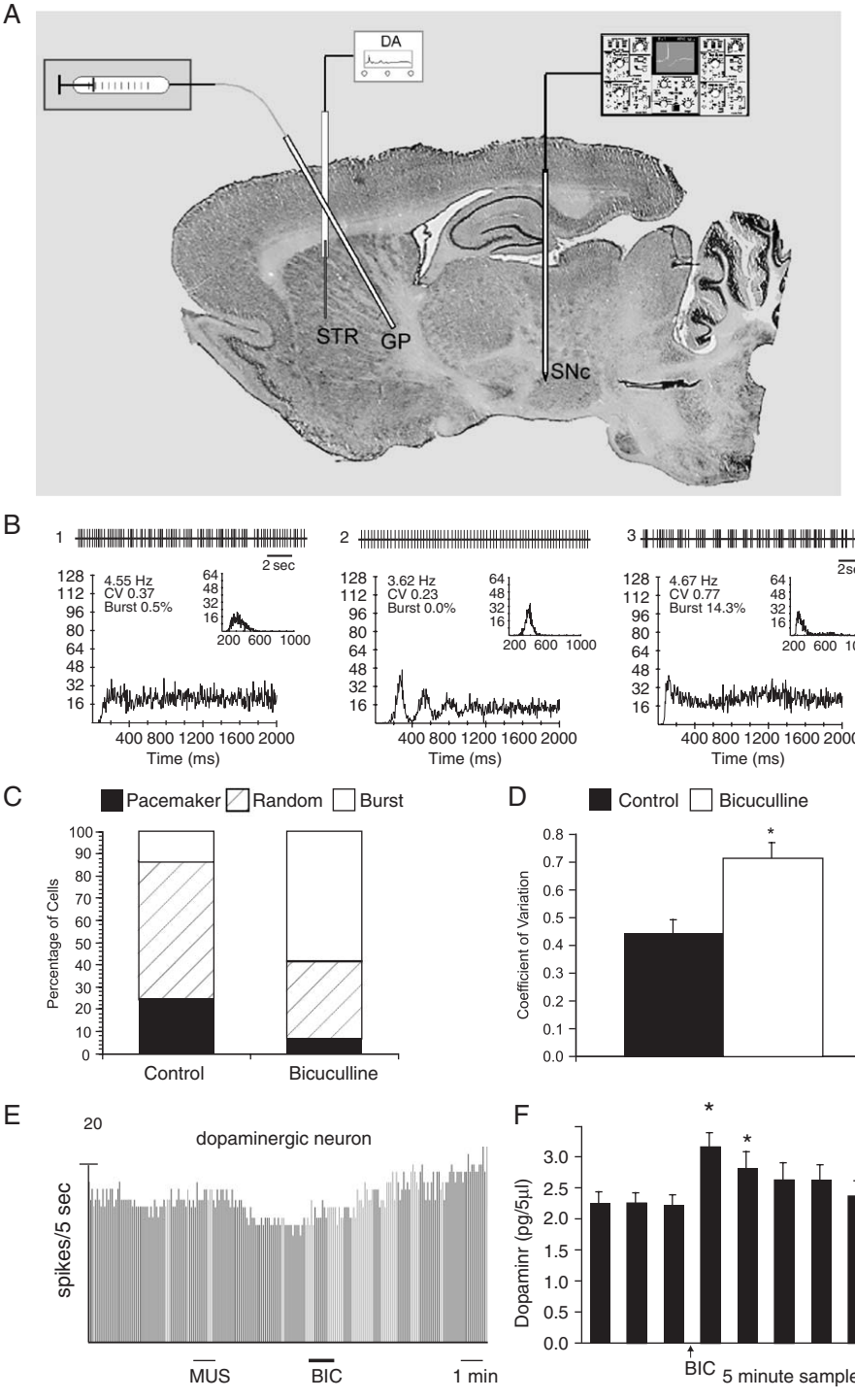
GABA can also affect the action of other neurotransmitters in substantia nigra, for example, glutamate. Although apparently different from spontaneous burst firing in vivo in certain important aspects, a type of burst firing can be elicited in vitro by the application of NMDA or NMDA plus apamin (Johnson et al., 1992). Burst firing induced in this way has been used to explore the effects of $GABA_A$ receptor stimulation and blockade on firing pattern in dopaminergic neurons (Paladini et al., 1999b). Under these conditions NMDA or NMDA plus apamin induced rhythmic bursting which was abolished by bath application of the $GABA_A$ agonist, isoguvacine. This was not simply due to a $GABA_A$-induced hyperpolarization, however, as hyperpolarizing NMDA-treated neurons with current injection did not eliminate the rhythmic membrane oscillations even when hyperpolarized sufficiently to block spiking. Rather, it appears that the $GABA_A$ receptor-mediated decrease in input resistance was the critical factor for the elimination of the oscillation (Paladini et al., 1999b), consistent with predictions made from compartmental models (Canavier, 1999; Amini et al., 1999; Medvedev et al., 2003; Komendantov et al., 2004; Kuznetsov et al., 2006).

GABAergic inputs from the pars reticulata

The inputs from the pars reticulata seem to have a prepotent effect on modulating the firing pattern of dopaminergic neurons compared to those from the striatum or the globus pallidus. This conclusion is based on several independent lines of evidence. In early studies of the effects of pars reticulata neurons on dopaminergic neuron activity, it was noted that lesion of the GP produced a modest decrease in the firing rate and burst firing of dopaminergic neurons (Tepper et al., 1995), which is the same effect seen if GABAergic tone (mediated by $GABA_A$ receptors) is increased (Paladini and Tepper, 1999; Paladini et al., 1999b).

Although electrical stimulation of globus pallidus produces short latency monosynaptic IPSPs and inhibition in nigrostriatal neurons (Tepper et al., 1986; Paladini et al., 1999a), chemical stimulation of globus pallidus with bicuculline produces a paradoxical modest increase in firing rate of nigrostriatal neurons along with a significant increase in burst firing (Celada et al., 1999; Lee et al., 2004) while inhibition of globus pallidus with muscimol infusion produces modest decreases in both firing rate and burst firing (Celada et al., 1999), as shown in Fig. 5. When the same

Fig. 5. (A) Experimental design showing simultaneous dopamine microdialysis in striatum (STR), drug infusion into globus pallidus (GP) and extracellular recording in substantia nigra pars compacta (SNc). (B1-3) Representative autocorrelograms from a single dopaminergic neuron under control conditions (1), after pallidal microinjection of muscimol (2), and after pallidal microinjection of bicuculline (3). Infusion of bicuculline into the GP shifted the distribution of dopaminergic neuron firing patterns from one consisting mostly of the random firing pattern to one where the bursty firing pattern was most prominent. (C, D) The shift toward the bursty firing pattern was accompanied by a significant increase in the CV. (E) Ratemeter of a representative dopaminergic neuron following infusion of muscimol and bicuculline into the ipsilateral globus pallidus. (F) Striatal dopamine levels after injection of bicuculline into the GP. The sample collection time was 5 min beginning 1 min after the start of the bicuculline infusion. The first three samples were obtained under baseline conditions during the 15 min immediately preceding a 1 min infusion of bicuculline (BIC) into the GP as indicated by the arrow. Striatal dopamine levels increased significantly following disinhibition of the GP in the two 5 min samples immediately following drug infusion and delay.


A
DA
STR
GP
SNc
B
1
2
3
2 sec
4.55 Hz
CV 0.37
Burst 0.5%
3.62 Hz
CV 0.23
Burst 0.0%
4.67 Hz
CV 0.77
Burst 14.3%
Time (ms)
C
Pacemaker
Random
Burst
Percentage of Cells
Control
Bicuculline
D
Control
Bicuculline
Coefficient of Variation
E
dopaminergic neuron
spikes/5 sec
MUS
BIC
1 min
F
Dopaminr (pg/5µl)
BIC
5 minute samples

manipulations were made while recording from pars reticulata projection neurons, bicuculline infusions into globus pallidus produced a dramatic inhibition of the reticulata neurons, sometimes completely suppressing spontaneous activity. Pallidal muscimol infusion on the other hand led to a near doubling of the spontaneous firing rate (Celada et al., 1999). When these experiments were replicated with a microdialysis probe in striatum to measure firing pattern and dopamine overflow before and after modulation of pallidal firing rate, bicuculline infusion again produced a robust switch to burst firing accompanied by a small (11.5%) increase in firing rate but a large (45.9%) increase in dopamine overflow (Lee et al., 2004) as illustrated in Fig. 5. These results demonstrate that the pallidonigral effects on dopaminergic neurons are mediated principally through disinhibition, via a preferential inhibition of the tonically active pars reticulata projection neurons. This is consistent with neuroanatomical findings showing a particularly dense projection from the globus pallidus to the pars reticulata GABAergic neurons (Smith and Bolam, 1989).

But, how could the effects of electrical stimulation of globus pallidus be manifest as monosynaptic inhibition while the effects of chemical manipulation are seen as disinhibition? We hypothesized that the opposite effects of electrical and chemical stimulation could be attributed to differences in the sensitivity of nigrostriatal dopaminergic neurons and GABAergic pars reticulata neurons to GABA. Several studies imply that GABAergic pars reticulata neurons are more sensitive to exogenously applied GABA and/or $GABA_A$ agonists (e.g., Grace and Bunney, 1979; Waszczak et al., 1980, 1981) or to synaptically released GABA than are the dopaminergic neurons (Grace and Bunney, 1985; Celada et al., 1999). This effect is so robust that the systemic administration of the $GABA_A$ agonist, muscimol leads to an increase in the spontaneous firing rate of dopaminergic neurons (Walters and Lakoski, 1978; Grace and Bunney, 1979; Grace et al., 1980) and elicits an increase in striatal dopamine levels (Martin and Haubrich, 1978; Santiago and Westerink, 1992), despite its expected inhibitory effects on dopaminergic neuron firing. The differences observed between low-intensity electrical stimulation and chemical stimulation of GABAergic afferents as opposed to when these afferents are stimulated electrically using more standard stimulation parameters likely comes about because GABAergic afferents produce a large *synchronous* release of GABA following strong electrical stimulation that is sufficient to inhibit both the more sensitive GABAergic neurons as well as the less sensitive dopaminergic neurons. Under these conditions the monosynaptic input to the dopaminergic neurons predominates and inhibition of the nigrostriatal neurons results along with decreased burst firing. However, with chemical stimulation or low-intensity electrical stimulation (e.g., Grace and Bunney, 1985), the resulting activation and GABA release is asynchronous and preferentially inhibits the more sensitive GABAergic neurons with only minimal direct effects on the dopaminergic neurons. This leads to a disinhibition of the dopaminergic neurons as the tonically active GABAergic neurons are silenced, resulting in an increase in burst firing and a consequent increase in striatal dopamine levels despite only a minimal increase in firing rate (Lee et al., 2004).

Since low-intensity stimulation of the striatal or pallidal afferents to the substantia nigra causes disinhibition of nigral dopaminergic neurons, the GABAergic afferents that most consistently act to inhibit dopaminergic neurons in vivo are those originating from the axon collaterals of nigral GABAergic projection neurons. Under many or most in vivo conditions, the indirect action of GABA on nigral dopaminergic neurons via disinhibition predominates thus making disinhibition a fundamental process underlying signal transmission in the substantia nigra. This process also likely underlies the actions of drugs of abuse that act as $GABA_A$ agonists such as ethanol (Mereu et al., 1984; Mereu and Gessa, 1985) and benzodiazepines (Ross et al., 1982; O'Brien and White, 1987). Although all of these manipulations likely add some direct inhibition of nigral dopaminergic neurons, they remove a far greater amount by inhibiting the tonically active GABAergic neurons of the pars reticulata.

Differences in $GABA_A$ responses between dopaminergic and GABAergic neurons

There are several possible explanations for the apparently greater sensitivity to GABA of the GABAergic pars reticulata neurons compared to nigrostriatal dopaminergic neurons. Since most of the GABAergic effects in vivo are mediated by $GABA_A$ receptors, we compared $GABA_A$ functioning in the two populations of neurons. As a ligand-gated chloride channel, $GABA_A$ receptor function is dependent on cellular chloride regulatory mechanisms (Kaila, 1994). In most mature CNS neurons, a neuron-specific K^+Cl^- cotransporter (KCC2) is responsible for extruding intracellular chloride, thereby generating an inwardly directed chloride gradient which makes increases in chloride conductance hyperpolarizing (Payne et al., 1996, 2003; DeFazio et al., 2000). Light and electron microscopic immunocytochemical labeling revealed the expression of KCC2 by GABAergic pars reticulata neurons (Gulacsi et al., 2003) (Fig. 6). However, nigral dopaminergic neurons do not express KCC2 but instead express the voltage-sensitive chloride channel (ClC-2) that is absent in pars reticulata GABAergic neurons (Fig. 6). This neuron type-specific expression of Cl^- regulatory mechanisms is reflected in differences in the reversal potential for $GABA_A$ IPSPs. $GABA_A$ IPSPs evoked by local stimulation and measured with perforated patch recordings in vitro exhibit a reversal potential that is significantly more hyperpolarized than those in the dopaminergic neurons, thus accounting in part for the increased sensitivity to GABA of the nigral GABAergic neurons compared to dopaminergic neurons (Gulacsi et al., 2003) (Fig. 7).

However, even in the absence of KCC2, the $GABA_A$ reversal potential is hyperpolarizing in nigral dopaminergic neurons, indicating the presence of an active chloride extrusion mechanism. Although ClC-2 can help clear chloride in the presence of increased intracellular chloride levels, it is passive and voltage dependent and cannot create the driving force needed to account for the hyperpolarizing chloride gradient in dopaminergic neurons. The most likely candidate mechanism that can generate the appropriate driving force is

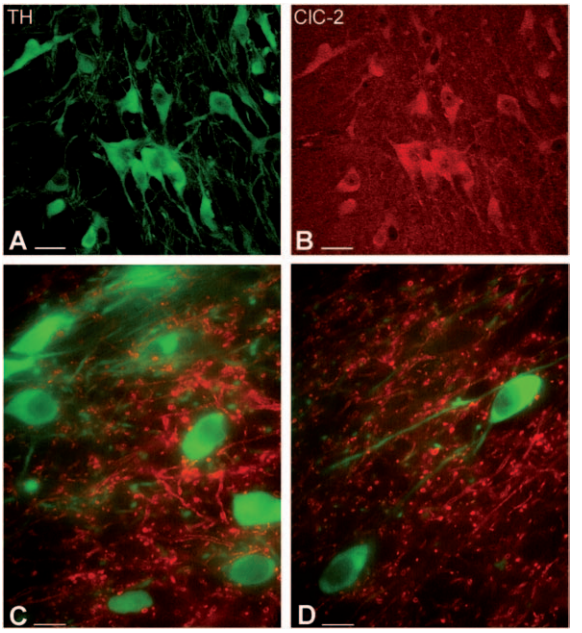
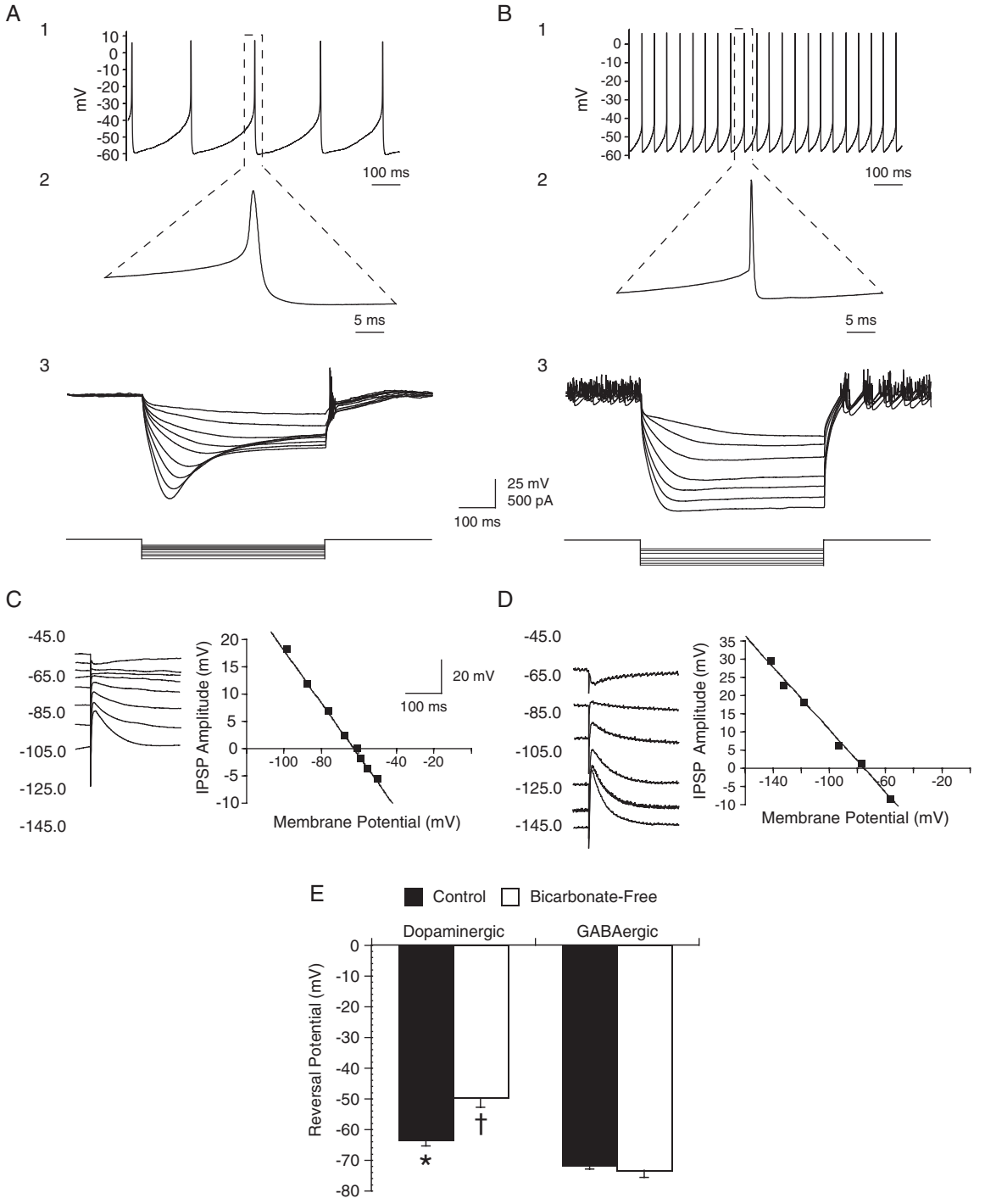


Fig. 6. Dopaminergic neurons express ClC-2 but not KCC2. (A) Green immunofluorescence labels dopaminergic neurons in the substantia nigra pars compacta neurons. (B) Same field under a different filters show red immunofluoresence for ClC-2. (C) and (D) Double immunofluoresence for KCC2 (red) and TH (green) shows that TH positive dopaminergic neurons in the pars compacta (C) and pars reticulata (D) do not express KCC2 whereas the dendrites of nigral GABAergic neurons in both regions express KCC2 but not ClC2 or TH. Scale bars 25 μm. [*Source*: Modified from Gulacsi et al. (2003). Copyright 2003, the *Society for Neuroscience*.]

the sodium-dependent anion exchanger that exchanges Cl^- for bicarbonate (NDAE; Payne et al., 2003; see Farrant and Kaila, this volume). When the IPSP reversal potential measurements were repeated in bicarbonate-free conditions that block the exchanger, the $GABA_A$ reversal potential in dopaminergic neurons was depolarized to around the resting membrane potential (−49 mV) whereas there was no significant change in the reversal potential in the GABAergic neurons (around −71 mV; Gulacsi et al., 2003) (Fig. 7). Thus, the driving force for a hyperpolarizing $GABA_A$ IPSP in dopaminergic neurons is maintained by the NDAE. However, the NDAE is much less efficient at clearing intracellular chloride than KCC2 (Kaila, 1994; Rivera et al., 1999; Payne et al., 2003), consequently nigral dopaminergic neurons


A
1
2
3
mV
10
0
-10
-20
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-40
-50
-60
100 ms
5 ms
25 mV
500 pA
100 ms
B
1
2
3
mV
0
-10
-20
-30
-40
-50
-60
100 ms
5 ms
C
-45.0
-65.0
-85.0
-105.0
-125.0
-145.0
IPSP Amplitude (mV)
20
15
10
5
0
-5
-10
-100
-80
-40
-20
20 mV
100 ms
Membrane Potential (mV)
D
-45.0
-65.0
-85.0
-105.0
-125.0
-145.0
IPSP Amplitude (mV)
35
30
25
20
15
10
5
0
-5
-10
-140
-100
-60
-20
Membrane Potential (mV)
E
Control
Bicarbonate-Free
Dopaminergic
GABAergic
Reversal Potential (mV)
0
-10
-20
-30
-40
-50
-60
-70
-80
*
†

exhibit a significantly less hyperpolarized $GABA_A$ IPSPs than nigral GABAergic neurons. This leads to greater sensitivity to $GABA_A$ receptor stimulation in the pars reticulata GABAergic neurons compared to the dopaminergic neurons.

Another factor that could account for the greater efficacy of GABAergic inhibition in GABAergic reticulata neurons is the subunit composition of their $GABA_A$ receptors. Both in situ hybridization and immunocytochemical studies have identified the existence of a number of $GABA_A$ receptor subunits in the substantia nigra (Nicholson et al., 1992, 1996; Wisden et al., 1992; Fritschy and Mohler, 1995; Pirker et al., 2000; Schwarzer et al., 2001). There are some differences in the expression pattern of $GABA_A$ receptor subunits between the neurons of the substantia nigra pars reticulata and those of the substantia nigra pars compacta. A common thread which emerges from different studies using different techniques is that neurons of the substantia nigra pars reticulata express $GABA_A$ receptors with the $\alpha 1$ and $\beta 2$ receptor subunits while neurons of the substantia nigra pars compacta express receptors with the $\alpha 3$ receptor subunit (Nicholson et al., 1992, 1996; Wisden et al., 1992; Fritschy and Mohler, 1995; Guyon et al., 1999; Pirker et al., 2000; Rodriguez-Pallares et al., 2000, 2001; Schwarzer et al., 2001; Okada et al., 2004; see Goetz et al., this volume). The functional significance of this segregation is unknown but these subunit differences could contribute to the differences in sensitivity to inhibition by GABA exhibited by GABAergic and dopaminergic neurons in the substantia nigra. There are also differences in the overall density of $GABA_A$ receptors with GABA/benzodiazepine immunoreactivity being much lower in the pars compacta than in the pars reticulata, consistent with a relatively reduced GABA sensitivity of the dopaminergic neurons (Nicholson et al., 1992).

Conclusions

The advances made in the past decade have shed light on several key elements underlying the afferent control of nigrostriatal dopaminergic neurons. Chief among them are GABAergic afferents from other parts of the basal ganglia that make up more than 70% of the inputs to nigral dopaminergic neurons.

Though it has been appreciated for some time that disinhibition is the major mechanism for signaling among GABAergic neurons in the basal ganglia (e.g., Chevalier et al., 1985; Deniau and Chevalier, 1985; Chevalier and Deniau, 1990), it is only more recently that this mode of control has been shown to apply to the nigrostriatal neurons as well. A crucial first step in understanding the neuronal interactions that control the activity of nigral dopaminergic neurons was the discovery that nigral GABAergic projection neurons strongly inhibit the dopaminergic neurons through their axon collaterals. It is now clear that disinhibition of the globus pallidus can lead to inhibition of nigral GABAergic projection neurons and a subsequent disinhibition of nigral dopaminergic neurons that is manifest primarily as an increase in burst firing. The burst firing results in a significant increase in striatal dopamine levels over those resulting from normal spontaneous firing in the pacemaker and random modes.

The seemingly contradictory excitation of dopaminergic neurons in vivo by GABA or systemic administration of GABA agonists can now be understood as a consequence of disinhibition

Fig. 7. The $GABA_A$ IPSP reversal potential is more hyperpolarized in GABAergic than in dopaminergic nigral neurons. (A1, B1) Perforated patch recordings of electrophysiologically identified substantia nigra pars compacta dopaminergic (A1) and pars reticulata GABAergic neuron (B1). (A2, B2) Higher sweep speed reveals the considerably longer duration action potential and large and longer duration spike after-hyperpolarization in the dopaminergic neuron (A2) compared to the GABAergic neuron (B2). (A3, B3) The dopaminergic neuron (A3) exhibits a marked sag in response to hyperpolarizing current pulses due to a slowly activating I_h and inward rectification whereas the GABAergic neuron displays little or no sag and a linear I–V relation. (C, D) Representative $GABA_A$-mediated IPSPs evoked locally in normal Ringer's solution in the presence of CGP 35348, CNQX and APV at different membrane potentials (left panels) reveal a more hyperpolarized reversal potential in the GABAergic neuron than in the dopaminergic neuron (right panels). (E) Summary bar graphs of effects of cell type and inhibition of NDAE on $GABA_A$ IPSPs in nigral neurons. * = significantly different from GABAergic neuron, $p < 0.01$.†

resulting from a more potent GABAergic inhibition of the pars reticulata GABAergic neurons than the dopaminergic neurons due, in part, to differences in the $GABA_A$ IPSP reversal potential. This difference is also ultimately responsible, at least in part, for a number of seemingly paradoxical excitations of nigrostriatal dopaminergic neurons by drugs acting at other receptors including the NMDA and mu opioid receptors (Hommer and Pert, 1983; Zhang et al., 1992) as well as the effects of ethanol and benzodiazepines discussed above (Ross et al., 1982; Mereu et al., 1984; Mereu and Gessa, 1985; O'Brien and White, 1987).

Understanding the activity and interactions of neurons in the substantia nigra is a necessary prerequisite to understanding the functioning of the basal ganglia in both normal and pathological behaviors. It has become increasingly clear that in addition to the effects that nigral GABAergic projection neurons have on their target nuclei outside of the basal ganglia, local interactions between GABAergic projection neurons and dopaminergic neurons are crucially important to the functioning of the substantia nigra and of the basal ganglia as a whole.

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