Chapter 16

Neurophysiology of Substantia Nigra Dopamine Neurons: Modulation by GABA

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I. INTRODUCTION

It has been more than three decades now since B.S. Bunney, G.K. Aghajanian and their colleagues at Yale published the first electrophysiological studies of midbrain dopamine (DA) neurons in vivo (Bunney et al., 1973a,b). These extracellular single unit recordings revealed that DA neurons in the substantia nigra (SN) pars compacta (SNc) and ventral tegmental area (VTA) of chloral hydrate-anesthetized rats fired spontaneously at low rates with occasional slow bursts. In addition, these investigators showed that DA neurons were powerfully inhibited by intravenous administration of amphetamine or apomorphine, effects that were completely reversed by administration of antipsychotic drugs. Moreover, the firing of DA neurons was also suppressed by iontophoretic application of DA directly to DA neurons themselves, suggesting the presence of "presynaptic" receptors for dopamine, now known as somatodendritic autoreceptors, on the DA neurons themselves. Subsequent studies revealed that the source of the DA that activated these autoreceptors was the dendrites of the DA neurons themselves (Groves et al., 1975; Geffen et al., 1976; Paden et al., 1976), and that these dendrites made synapses with other DA dendrites (Wilson et al., 1977a) thereby creating a self-inhibitory network of DA neurons. These pioneering studies were prompted, in large part, by a desire to understand the sites and mechanisms of action of antipsychotic drugs and provided the impetus for a myriad of subsequent electrophysiological and anatomical experiments by laboratories all over the world.

Over the succeeding 30 years, it has become clear that mesencephalic DA neurons and the DA innervation of the forebrain play crucial roles not only in the execution of voluntary movement and as sites of action for antipsychotic drugs and stimulant drugs of abuse, but also as core components of neural systems regulating reward, reinforcement

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and addiction, as well as several types of higher cognitive function including various forms of associative learning (Schultz, 1997, 2007). The number of papers published on DA neurons exceeds 25,000 (PubMed, February 2009), far too many for any one review to even attempt to cover. This chapter will limit itself to a review of the basic anatomy of the SN and the morphological and electrophysiological characteristics of SN DA neurons, and the control of these neurons by GABAergic inputs. Other aspects of the afferent control of DA neurons have been reviewed elsewhere (Kitai et al., 1999; Diana and Tepper, 2002; Misgeld, 2004; Tepper and Lee, 2007; Lee and Tepper, 2009) (see also Chapters 23 and 31).

II. NEUROCYTOLOGY OF NIGROSTRIATAL DOPAMINE NEURONS

Most of the cell bodies of origin of the *nigrostriatal* DA system are located in a densely packed, relatively thin shell, 300–500 μm thick, the SNc (A9 in the terminology of Dahlstrom and Fuxe, 1964), dorsal to the larger and more diffuse substantia nigra pars reticulata (SNr) that comprises predominantly GABA projection neurons (Lee and Tepper, 2007). There are approximately 25,000 DA neurons bilaterally in the rat SN (Oorschot, 1996; Nair-Roberts et al., 2008). Smaller numbers of striatally projecting neurons are also found in the adjacent retrorubral field (A8) as well as in isolated patches in the SNr (Deutch et al., 1986). It is worth pointing out that many "nigrostriatal" DA neurons have been shown by retrograde labeling to collateralize to multiple regions including the cingulate and the prefrontal cortices (Fallon, 1981; Takada and Hattori, 1986).

Nigral DA neurons have been divided into dorsal and ventral tier groups (Fallon and Moore, 1978) (see also Chapter 1). The dorsal tier neurons express calbindin whereas the ventral tier neurons do not (Gerfen et al., 1987a,b; but see also Neuhoff et al., 2002). It has been argued on the basis of retrograde tracing that the dorsal tier neurons preferentially innervate the striatal matrix compartment whereas the ventral tier neurons innervate the striosome/patch compartment (Gerfen et al., 1987a,b). However, a more recent study using a novel anterograde tracing technique shows quite clearly that single nigrostriatal neurons innervate both patch and matrix compartments (Matsuda et al., 2009). Similarly, it has been claimed that the dorsal tier neurons have dendrites oriented principally mediolaterally in pars compacta whereas the ventral tier neurons extend dendrites ventrally into the pars reticulata (Fallon et al., 1978). However, subsequent intracellular labeling studies suggest that many or most nigrostriatal neurons have dendrites that arborize within pars compacta as well as one or two ventrally directed dendrites (Kita et al., 1986; Tepper et al., 1987; Grace and Onn, 1989; cf Fig. 16.1).

In rats, nigral DA neurons are medium to large sized, 12–25 μm in diameter and exhibit multipolar, fusiform or polygonal somata that emit three to five thick, smooth dendrites that taper rapidly to about 1 μm or less in diameter. Dendrites are aspiny, but occasionally emit sparse thorn- or spine-like appendages. There are usually one or two ventrally directed dendrites that course through SNr perpendicular to the surface of the SNc. These are often the largest and longest dendrites issued by the neuron, can exceed 1 mm in length and extend throughout the entire dorsoventral extent of the SNr where they often form dendritic fascicles (Juraska et al., 1977; Kita et al., 1986; Tepper et al., 1994; 1987; cf Fig. 16.1). Most of the dorsal dendrites are shorter than the ventrally directed dendrites but are similar in other respects, and arborize in, and sometime extend beyond SNc, in all directions.

The earliest morphological descriptions of DA neurons from histofluorescence material stressed the varicose nature of their dendrites and the possible implications of the varicosities for dendritic DA release (e.g., Bjorklund and Lindvall, 1975). However, material from intracellular labeling with HRP, biocytin or Lucifer Yellow (Kita et al., 1986; Tepper et al., 1987, Grace and Onn 1989; Yung et al., 1991), or immunocytochemistry (Tepper et al., 1994) shows that most of the dendrites from DA neurons in mature animals are smooth, with some varicosities in the finer higher order dendrites. The previously observed varicosities were probably attributable to areas of aggregation of histofluorescent material rather than changes in dendritic caliber (Tepper et al., 1987).

It is sometimes claimed that the axon most commonly emerges from a dendrite at a relatively great distance from the soma (up to 240 μm; Hausser et al., 1995), but this observation may have arisen from a selection artifact for the largest neurons in vitro where dendritic recording is easiest, since observations from several other studies indicate that the axon typically emerges from the soma or a proximal dendrite, usually within 30 μm of the soma (Grace and Bunney, 1983a; Tepper et al., 1987; Grace and Onn, 1989; Matsuda et al., 2009; cf Fig. 16.1).

In marked contrast to the projection neurons of virtually all other basal ganglia nuclei, DA neurons of the SN do not emit local axon collaterals (Juraska et al., 1977;

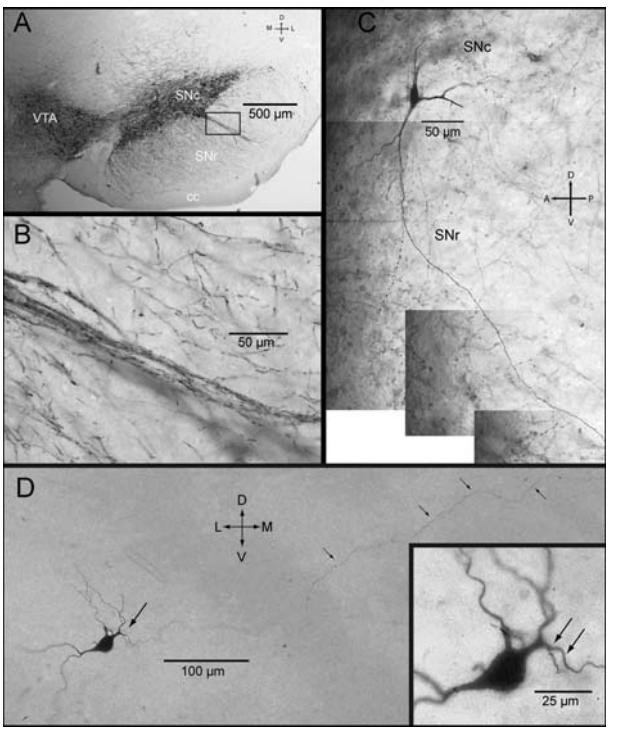

FIGURE 16.1 Neuroanatomical organization of substantia nigra and neurocytology of nigral DA neurons. A. Coronal section through rat midbrain immunostained for tyrosine hydroxylase, illustrating the densely packed DA neurons of the substantia nigra pars compacta (SNc) and the adjacent ventral tegmental area (VTA). Note the numerous DA fibers that penetrate deep into the pars reticulata (SNr). Substantia nigra is bordered ventrally by the cerebral peduncles or crus cerebri (cc). B. Higher magnification micrograph of the area within the box in A illustrating the fasciculation of some of the ventral dendrites, coursing perpendicular to the surface of the SNc. Note that the dendrites are for the most part non-varicose. C. Photomontage of an electrophysiologically identified DA neuron in the pars compacta (SNc) of the substantia nigra filled with biocytin after whole cell recording in vitro. The dorsal dendrites arborize mostly within pars compacta and the neuron extends one thick, smooth and unbranched dendrite several hundred microns ventral through pars reticulata (SNr). D. A photomicrograph of an electrophysiologically identified DA neuron in substantia nigra in a 350 μm coronal section stained with biocytin following in vitro whole cell recording. The axon (large arrow) could be followed (small arrows) as it coursed medially for several hundred microns in this single optical plane. Inset shows the axon emerging from a short, thick proximal dendrite approximately 25 μm from the center of the soma. Source: 16.1C modified from Iribe et al. (1999); used with permission.

Tepper et al., 1987; Matsuda et al., 2009). After emerging from the cell and exhibiting an often initially tortuous and recurving trajectory, the axons course medially and rostral to SN, coalesce into a tract often referred to as the *medial forebrain bundle* that traverses the fields of Forel and projects into the forebrain. As they ascend, the axons arborize sparsely in the subthalamic nucleus (STN; Cragg et al., 2004), and then continue rostral and anterior, fanning out laterally through the globus pallidus (GP) where they form a small arborization (Lindvall and Bjorklund, 1979; Matsuda et al., 2009) before reaching their principal target, the striatum. In the striatum the axons from single cells branch profusely and form large, dense arborizations of varicose processes that occupy an average volume of approximately 0.5 mm^3 (Matsuda et al., 2009). Nigrostriatal axons form Gray's Type II symmetrical synapses, mainly on the dendrites or the necks of the dendritic spines of the striatal spiny projection neurons. Interestingly, although some of the DA synapses are made by terminal boutons or en passant varicosities, many of the synapses very small and are formed by thinner intervaricose segments of the axons (Pickel et al., 1981; Freund et al., 1984; Groves et al., 1994). These are easy to miss in single electron microscopic thin sections, especially if one is concentrating on varicosities, and almost certainly have contributed to the confusion about whether DA terminals actually form typical morphologically defined synapses in the striatum or not (see, e.g., Groves et al., 1994; Descarries et al., 1996 for discussion).

III. ELECTROPHYSIOLOGICAL PROPERTIES OF NIGROSTRIATAL DOPAMINE NEURONS

A. Extracellular Recordings

In in vivo extracellular recordings from anesthetized adult rats or mice, nigral DA neurons fire spontaneously between approximately 2–8 spikes/sec, with a mean firing rate around 4 spikes/sec (Bunney et al., 1973a,b). Estimates of the proportion of mesencephalic DA neurons that are spontaneously active in vivo in anesthetized rats vary widely, with some authors claiming that up to 50% of the neurons are normally silent (e.g., Chiodo, 1988; Floresco et al., 2003) to others who claim that the large majority of the neurons are spontaneously active under normal conditions (e.g., Dai and Tepper, 1998). Spontaneous action potentials are unusually wide, between 2.5 and 4 ms long in duration depending on filter settings and electrode characteristics (Bunney et al., 1973a,b).

Nigrostriatal DA neurons are readily identified by antidromic activation following stimulation of the striatum, GP or medial forebrain bundle. Like other monoaminergic neurons nigrostriatal DA neurons exhibit slow conduction velocities in the range of 0.4–0.5 m/sec. Antidromic responses of nigrostriatal DA neurons usually consist of a small spike, termed the initial segment (IS) spike, even when antidromically activated at low rates. Very often when the antidromic

response is a "full" spike consisting of both the IS and the somatodendritic (SD) spike, there is a marked delay between the IS and SD components causing a notch in the initial positive part of the extracellularly recorded waveform. The same IS-SD break is often observed in spontaneous action potentials as well (Bunney et al., 1973a,b; Guyenet and Aghajanian, 1978; Deniau et al., 1978; Tepper et al., 1982, 1984a,b, 1997; Grace and Bunney, 1983a,b, 1984a,b; Trent and Tepper, 1991; cf Fig. 16.2).

DA neurons recorded in vivo in anesthetized rodents exhibit three distinct modes or patterns of firing that are clearly distinguishable from inspection of their autocorrelation histograms (Tepper et al., 1995). The most common pattern of activity is a random, or irregular mode of firing, characterized by an initial prolonged trough in the autocorrelation function representing a long post-firing inhibition. The next most common firing pattern is a regular, pacemaker-like firing, characterized by constant interspike

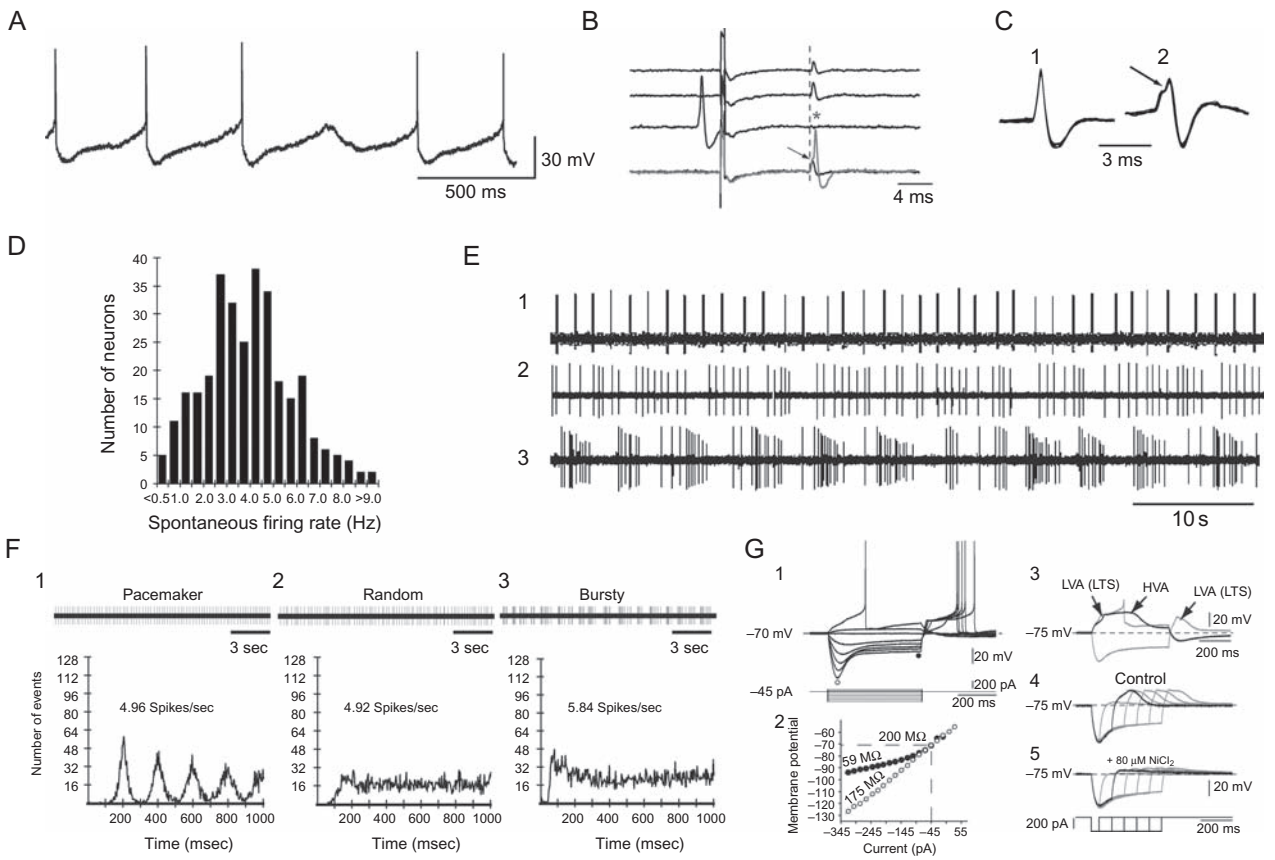

FIGURE 16.2 Basic electrophysiological characteristics of rodent nigral DA neurons. A. In vivo intracellular recording of an antidromically identified nigrostriatal neuron in a urethane-anesthetized rat. Note long, slow spike afterhyperpolarization and regular spontaneous firing pattern. The 4th spike in the train misses, revealing the underlying LVA Ca^{2+} membrane potential oscillation that drives spontaneous pacemaker spiking. B. Extracellularly recorded antidromic responses of a nigrostriatal neuron in a urethane-anesthetized rat. The asterisk marks a collision extinction in the 3rd sweep. Antidromic responses consist almost exclusively of the IS spike except for the red trace in the 4th sweep that is a full IS-SD spike. The arrow points to the IS-SD break. C. Extracellularly recorded action potentials from two different nigrostriatal neurons in a chloral hydrate-anesthetized mouse illustrate the typical long duration spike and IS-SD break (arrow). Each spike is the overlay of five spikes averaged from 10 consecutive spontaneous action potentials. D. Distribution of spontaneous firing rates of nigral DA neurons in a chloral hydrate-anesthetized rat. E. Extracellularly recoded spontaneous spike trains recorded from three different antidromically identified nigrostriatal neurons in chloral hydrate-anesthetized mice illustrating the three different patterns of spontaneous activity seen in vivo. F. Autocorrelograms generated from spike trains (insets) of three different nigrostriatal neurons illustrating the distinct histogram shapes that characterize the three firing patterns in urethane-anesthetized rats. G. In vitro whole cell recordings from SNc DA neurons in mice. G1. Hyperpolarizing current injections result in a slowly developing sag in the voltage response due to activation of I_h. that results in a time dependent inward rectification that reduces the input resistance of the neuron by about 67% (G2). G3. Depolarizing current injection in a DA neuron hyperpolarized to −75 mV results in an LTS and subsequent HVA Ca^{2+} spike as well as a rebound LTS. G4. Relaxation following hyperpolarizing current injections of varying durations show that the rebound spike is all-or-none. G5. Addition of a low concentration of Ni^{2+} blocks the rebound slow spike identifying it as an LTS. Source C: redrawn from Brazhnik et al. (2008). Copyright 2008 by the Society for Neuroscience; D: reprinted from Dai and Tepper (1998), used with permission; F: redrawn from Tepper et al. (1995). Copyright 1995 by the Society for Neuroscience. To view a color version of this image please visit http://www.elsevierdirect.com/companion/9780123747679

intervals, a low coefficient of variation, and a lack of bursting. The third and least common mode (but the one that has generated the most interest) is burst firing, characterized by stereotyped bursts of 2–8 action potentials in which the first intraburst interspike interval is typically around 60 ms, followed by progressively increasing interspike intervals and progressively decreasing spike amplitudes (Grace and Bunney, 1984a,b; Tepper et al., 1995; Paladini and Tepper, 1999; Brazhnik et al., 2008; cf Fig. 16.2). The maximal instantaneous intraburst firing rate in anesthetized rodents is typically in the range of 12–15 Hz (Grace and Bunney, 1984b; Tepper et al., 1990) although significantly higher maximal intraburst firing rates have been observed in unanesthetized behaving rats (e.g., Kiyatkin and Rebec, 1998; Hyland et al., 2002).

The same three patterns of activity are observed in unanesthetized and immobilized (Wilson et al., 1977b) and/or freely moving rats (Freeman et al., 1985; Diana et al., 1989; Hyland et al., 2002) although in general a higher proportion of nigrostriatal neurons in vivo exhibit burst firing whereas a lower proportion exhibit pacemaker-like firing in unanesthetized preparations. Single DA neurons can spontaneously change firing patterns, or be induced to change by various experimental manipulations and SN DA neuron firing patterns can best be thought of as a existing along a continuum, with the pacemaker-like firing on one end and bursty firing on the other (Tepper et al., 1995; Paladini and Tepper, 1999; Celada et al., 1999; Lee et al., 2004).

The mechanisms controlling the firing patterns are of great interest to basal ganglia researchers for many reasons. Different firing patterns could lead to qualitatively different effects with respect to dendritic release of DA in SN (Bjorklund and Lindvall, 1975; Groves et al., 1975; Cheramy et al., 1981) and/or release of DA in striatum. Experimentally induced burst firing (Suaud-Chagny et al., 1992; Lee et al., 2004) or electrical stimulation of the medial forebrain bundle that mimics burst firing (e.g., Gonon and Buda, 1985, Gonon, 1988, Bean and Roth, 1991, Manley et al., 1992; Chergui et al., 1994) leads to increased extracellular DA levels in striatum and/or cortex compared to pacemaker-like firing. This results from saturation of the DA transporter that is responsible for regulating extracellular DA levels (Chergui et al., 1994; Miller and Abercrombie, 1999; but see also Rice and Cragg, 2008) rather than from increased release per pulse. Higher extracellular levels of DA could lead to qualitatively different effects than lower levels if, for example, a significant fraction of striatal D_1 receptors were located predominantly extra- or perisynaptically (Caille et al., 1996; Gonon, 1997). Under most conditions, firing rate and pattern appear to regulate somatodendritic and axon terminal DA release in parallel. Under some conditions however, IS and/or axonal and SD activity become dissociated (e.g., Grace, 1990, Trent and Tepper, 1991) leading to independent regulation of DA release in SN and axon terminal regions (Cobb and Abercrombie, 2003). Perhaps most importantly, a number of studies have shown that DA neurons respond to reward, or stimuli that predict reward by firing a short burst (e.g., Schultz, 1997, 2007).

B. Intracellular Recordings

There have only been a handful of in vivo intracellular recording studies of nigral DA neurons due to substantial technical challenges including the depth of the substantia nigra, the need to traverse several heavily myelinated regions, the anatomical organization of the SNc, and the responses of the neurons to intracellular penetration. As such, these recordings, mostly obtained by Grace and Bunney in the early to mid 1980s, represented a technical tour de force and were extremely valuable. The results from their earlier recordings confirm those from the earliest extracellular recordings described above. In addition they revealed that nigral DA neurons exhibit a prolonged spike after hyperpolarization and a slowly developing depolarizing sag in the membrane potential in response to strong hyperpolarizing current injections, identified the presumed IS spike seen in extracellular recordings, and showed the first intracellularly recorded synaptic responses in DA neurons (Grace and Bunney, 1983a,b; 1984a,b; 1985; Tepper et al., 1987).

Virtually all subsequent intracellular recordings of DA neurons have been obtained in vitro, first with sharp electrodes (Kita et al., 1986; Grace, 1990; 1991) and more recently with whole cell recordings. These have confirmed and extended the in vivo recordings and showed that the sag in nigrostriatal neurons is due to activation of a hyperpolarization activated cation channel (HCN) that mediates the depolarizing current, I_h. The prolonged spike afterhyperpolarization is due to activation of the apamin-sensitive calcium-activated K^+ channel, SK (Shepard and Bunney, 1991). Finally these neurons express a variety of calcium channels enabling both low and high threshold Ca^{2+} spikes as well as a slow oscillatory potential that drives rhythmic single spiking in vitro and probably in vivo as well (Grace, 1991; Kang and Kitai, 1993a,b; Nedergaard et al., 1993;

Galarraga and Bargas, 1995; Wilson and Callaway, 2000). Nigrostriatal neurons were also shown to possess somatodendritic DA D_2 autoreceptors that hyperpolarize the neuron by opening an inwardly rectifying K^+ (GIRK) channel (Lacey et al., 1987, 1989).

IV. NEUROANATOMY OF GABA AFFERENTS TO NIGRAL DOPAMINE NEURONS

Most of the afferents to the SN are GABAergic and at least 70% of the synapses formed on nigral DA neurons are GABAergic (Rinvik and Grofova, 1970; Gulley and Smithberg, 1971; Ribak et al., 1976; Bolam and Smith, 1990). The SN is rich in both $GABA_A$ and $GABA_B$ receptors. These display regional segregation, with in situ hybridization and immunostaining showing that the $GABAB_{R1}$ and $GABAB_{R2}$ subunits (Charara et al., 2000) are expressed at significantly greater abundance in nigral DA neurons than in SNr GABA neurons, or in any other basal ganglia nucleus. Conversely, mRNA levels (Lu et al., 1999) and immunostaining for virtually all $GABA_A$ receptor subunits, particularly α_1 and α_2 subunits, are greater in the SNr than in the SNc. Most or all of the $GABA_A$ subunit immunostaining is constrained to postsynaptic specializations of symmetric synapses (Fujiyama et al., 2000), whereas $GABA_B$ subunits label both presynaptic terminals, where they serve as inhibitory GABA autoreceptors, as well as dendrites (for review, see Boyes and Bolam, 2007). Interestingly, a large proportion of the postsynaptic $GABA_B$ subunits appear to be located extrasynaptically (Boyes and Bolam, 2003). Although nigrostriatal DA and SNr GABA neurons express both $GABA_A$ and $GABA_B$ receptors, the responses of nigral neurons to GABA released from afferents is complex and varies depending on the nature of the afferent stimulation (Celada et al., 1999; Lee et al., 2004; cf Fig. 16.4).

The densest and best-characterized GABAergic inputs arise from the spiny projection neurons of the striatum (Grofová and Rinvik, 1970; Grofová, 1975; Hattori et al., 1973a,b; Somogyi et al., 1981; Bolam and Smith, 1990) and the GP (Hattori et al., 1975; Smith and Bolam, 1990). Striatonigral efferents colocalize substance P and dynorphin and arise from both the patch and matrix compartments (Gerfen and Young, 1988), which preferentially or selectively innervate the SNc and SNr respectively (Gerfen, 1984). However, DA and GABA dendrites overlap extensively in SNr, and the striatal inputs to DA neurons terminate mostly on distal dendrites (Bolam and Smith, 1990), so the degree of segregation of patch inputs to nigrostriatal neurons and matrix inputs to GABA neurons is probably not as clear-cut as is often assumed.

Striatal inputs to SN form symmetric Gray's Type II synapses (Grofova and Rinvik, 1970) and, as mentioned above, target the more distal dendritic regions of nigrostriatal and SNr neurons making only a relatively small proportion of synapses onto DA cell bodies (Bolam and Smith, 1990). This anatomical arrangement suggests that individual striatonigral neurons probably do not exert powerful inhibitory effects on nigrostriatal neurons and therefore simultaneous activation of a number of striatonigral neurons would be required to produce a substantial effect on a postsynaptic nigrostriatal neuron. Given the phasic and episodic nature of the spontaneous activity of striatal spiny projection neurons, and their very low overall mean firing rate (Wilson, 1993), it is unlikely that the striatum provides a significant GABA afferent tone to the nigrostriatal neurons.

Pallidal inputs to SN are also dense, with single GP GABA projection neurons often forming terminal arborizations in both SNc and SNr and innervating both DA and GABA neurons (Grofová 1975; Hattori et al., 1975; Totterdell et al., 1984; Smith and Bolam, 1989, 1990; Bevan et al., 1998). Pallidal boutons tend to be larger than striatal boutons, and form symmetric synapses on the cell bodies and proximal dendrites of nigrostriatal neurons, sometimes forming multiple repeated contacts and/or pericellular baskets around somata (Smith and Bolam, 1990). GP neurons typically fire spontaneously at 50–80 spikes/second in vivo in anesthetized rats (Celada et al., 1999) and can exceed 200 spikes/second (Kita, 2007). In contrast to the striatal inputs, given the electrotonically favored location of their synaptic inputs and high tonic firing rate, GP is likely a main contributor to the significant GABA tone that exists in SN in vivo (see below).

A third source of GABAergic inputs to nigrostriatal neurons arises locally (Grace and Bunney, 1979, 1985; Nitsch and Riesenberg, 1988) and is comprised of the local axon collaterals of the SNr GABA projection neurons (Tepper et al., 1995). These neurons emit a large diameter axon that issues several locally arborizing collaterals that exhibit varicosities en passant as well as terminal varicosities in SNr and SNc (Deniau et al., 1982; Grofova et al., 1982; Mailly et al., 2003; Lee and Tepper, 2009) before ascending to their principal sites of termination in the thalamus and tectum. Electron microscopic analyses reveal that

the varicosities are large boutons that form symmetric synapses with the somata and proximal dendrites of DA neurons in SNc and SNr. Individual collateral branches often form proximal multiple en passant synapses or pericellular baskets (Tepper et al., 2003; Lee and Tepper, 2007), similar to those formed by pallidal terminals (Smith and Bolam, 1990). SNr projection neurons typically fire spontaneously around 15–30 spikes/second in vivo and can exceed 100 spikes/second (Deniau et al., 2007). The SNr collateral input provides a crucial source of GABA to nigrostriatal neurons and plays a particularly important role in the modulation of their firing pattern and response to excitatory and inhibitory afferent inputs as described below.

V. NEUROPHYSIOLOGY OF GABA AFFERENTS

A. Responses to Striatal Stimulation

Both DA and GABA SN neurons in vivo respond to ipsilateral striatal stimulation with monosynaptic IPSPs (Yoshida and Precht, 1971; Grace and Bunney, 1983a, 1985) that lead to inhibition of spontaneous activity (Collingridge and Davies, 1981; Tepper et al., 1990). The latency to the onset of striatal-evoked inhibition is relatively long, (in rats and mice exceeding 10 ms; Tepper et al., 1990; Paladini et al., 1999a; Brazhnik et al., 2008), consistent with the relatively slow conduction velocity and long latency antidromic responses of striatonigral neurons (~10 ms) following nigral stimulation in rats (Ryan et al., 1986).

Interestingly, some nigrostriatal neurons respond to weak striatal stimulation with an *increase* in firing rather than a decrease (Collingridge and Davies 1981; Grace and Bunney, 1985). This is due to a preferential inhibition of the GABA SNr projection neurons by the weaker striatal stimuli. This occurs because DA neurons are considerably less sensitive to $GABA_A$ receptor activation than the SNr GABA neurons (Grace and Bunney, 1979, 1985; Waszczak et al., 1980, 1981; Collingridge and Davies 1981; Tepper et al., 1986; Gulacsi et al., 2003) and thus there is little or no monosynaptic inhibition in the nigrostriatal neurons to the weaker stimulation whereas the SNr neurons are potently inhibited. Because of this difference in sensitivity to $GABA_A$ receptor activation (see below) coupled with the fact that the SNr GABA projection neurons are tonically active at a high rate and innervate the nigrostriatal neurons at proximal locations, the end result of weak striatal stimulation is a disinhibition of the nigrostriatal neuron from the tonic SNr input. This disinhibition is a key factor in the functioning of nigrostriatal neurons and their response to many afferent inputs, discussed at greater length below.

B. Responses to Pallidal Stimulation

Nigrostriatal neurons respond to stimulation of ipsilateral GP with a short latency monosynaptic IPSPs (Tepper et al., 1986) and inhibition of spontaneous activity (Paladini et al., 1999), consistent with the anatomical findings. However, if the GP is stimulated chemically by local infusion of bicuculline (which increases the mean firing rate of GP neurons by 55%), nigrostriatal neurons respond with a modest but statistically significant *increase* in firing rate but a dramatic increase in burst firing (Celada et al, 1999; Lee et al., 2004; cf Fig. 16.4). The opposite occurs if muscimol is infused into GP. Under these conditions GP activity is almost completely suppressed and the nigrostriatal neurons respond with a modest decrease in firing rate and a shift away from bursty or random firing to a pacemaker-like firing pattern (Celada et al., 1999).

These effects are clearly opposite to what one expects from excitation or inhibition of a monosynaptic inhibitory input. The explanation for these seemingly incompatible results is the same as that for striatal-induced excitation of nigrostriatal neurons and depends again on the different sensitivities of DA and SNr GABA neurons to stimulation of $GABA_A$ receptors. When GP neurons are activated by an electrical stimulus, all the neurons within the field of the stimulating electrode are depolarized and induced to fire simultaneously. This causes a massive and nearly synchronous release of GABA in the SN a few ms later. The synchronous nature of electrically stimulated release probably leads to greater extracellular levels of GABA than those that result from the chemical stimulation of the GP which, although exciting large numbers of GP neurons, does so in an asynchronous manner. Thus, the extracellular levels of GABA that are controlled almost exclusively by diffusion and uptake into presynaptic terminals and glia (Schousboe and Waagepetersen, 2007; Kirmse et al., 2008) are likely to be lower following chemical stimulation of GP where the asynchronous release allows the uptake mechanisms to clear the released GABA more efficiently than after electrical stimulation when all of the GABA is released simultaneously putting a much greater load on the uptake system. This leads to the situation where following chemical stimulation, there is a much greater inhibitory

response from the SNr projection neurons than from the less sensitive DA neurons, resulting in a selective inhibition of the SNr GABA neurons and a consequent disinhibition of the DA neurons. Conversely, following electrical stimulation of GP, the synchronous release of GABA is sufficient to inhibit both the nigrostriatal neurons as well as the SNr GABA neurons and so the monosynaptic inhibition of the DA neurons becomes apparent, although it is no doubt opposed by simultaneous disinhibition from the SNr neurons.

Evidence in support of this hypothesis comes from in vivo recordings of SNr GABA projection neurons following infusions of muscimol or bicuculline into GP. Whereas such infusions cause modest disinhibition and inhibition of nigrostriatal neuron firing rates, respectively, in antidromically identified nigrothalamic neurons such infusions lead to greater than a doubling or a complete cessation of spontaneous activity, respectively (Celada et al., 1999; Lee et al., 2004).

This is almost certainly the same mechanism that is responsible for the paradoxical excitatory effects of locally or systemically administered muscimol on nigrostriatal neuron activity (MacNeil et al., 1978; Walters and Lakoski, 1978; Grace and Bunney, 1979) and striatal DA release (Martin and Haubrich, 1978; Santiago and Westerink, 1992), or the excitatory effects of μ opioids on DA neurons that lack μ receptors (Lacey et al., 1989) and illustrates the crucial role that the SNr neurons play in the responses of nigrostriatal DA neurons to many different drugs and afferent inputs.

A similar sort of "paradoxical" response occurs in nigral DA neurons to activation of an extra-basal ganglia afferent, the lateral habenula. Stimulation of the lateral habenula produces potent inhibition in nigral DA neurons in rodent and monkey whereas lesions of this area lead to increased forebrain DA release (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007; Hikosaka et al., 2008). The paradox arises from the fact that the output of the lateral habenula appears to be glutamatergic and would be expected to produce excitation of nigral DA neurons. There are a number of possible explanations for this, but a disynaptic loop involving lateral habenular projections to SNr projection neurons and feed forward inhibition of nigrostriatal neurons remains a distinct possibility.

As one final example of the complexity of the interactions of nigral afferents with intranigral microcircuitry, it has been reported that chemical or electrical stimulation of the STN produces excitation and burst firing in nigrostriatal DA neurons in vivo (Smith and Grace, 1992; Chergui et al., 1994). This should not be surprising since the STN is a glutamatergic nucleus and sends a monosynaptic projection to the SN (Hammond et al., 1978). Remarkably, however, in both of the experiments just referred to, the predominant *initial* response to chemical or electrical stimulation of STN was either no effect or inhibition of nigral neurons. Excitation and/or burst firing were only seen in a minority of the neurons. Once again, this was almost certainly due to preferential activation of pars reticulata GABA projection neurons by the subthalamic input, since 90% of the synapses made by subthalamic afferents synapse onto GABA dendrites in SNr and only about 10% synapse directly onto DA dendrites (Lee and Tepper, 2009). Subsequent in vitro intracellular recordings showed that nigral DA neurons respond to STN stimulation with a depolarizing synaptic potential (DPSP) that exhibits a reversal potential around −38 mV, a value very close to spike threshold (Iribe et al., 1999). Pharmacological dissection of the DPSP revealed it to be the result of near-simultaneous activation of a monosynaptic glutamatergic input with a reversal potential near 0 mV, presumably originating from STN, and a $GABA_A$ IPSP. The IPSP resulting from electrical stimulation of STN could have come from inadvertent activation of descending GABA fibers from striatum or GP, but this was ruled out when the IPSP survived knife cuts just anterior to STN several days before the recordings, and by the demonstration that blocking the glutamatergic input pharmacologically completely eliminated the IPSP (Iribe et al., 1999). These data showed that chemical or electrical stimulation of STN simultaneous activates a monosynaptic EPSP and a disynaptic $GABA_A$-mediated IPSP from the SNr projection neurons that together produce mixed, but initially inhibitory effects on DA neurons, as first reported by Robledo and colleagues (Robledo et al., 1988; Robledo and Feger, 1990). It also cannot be ruled out that the STN-elicited burst firing of nigrostriatal neurons is meditated in part through a monosynaptic excitation of GP neurons that then preferentially inhibit SNr neurons and produce bursting in nigrostriatal neurons via disinhibition just as chemical stimulation of the GP does (Celada et al., 1999; Lee et al., 2004).

Thus, under many conditions, the responses of nigrostriatal neurons to inhibitory and excitatory afferents are filtered by parallel innervation of the SNr GABA projection neurons, whose powerful inhibitory or disinhibitory effects on nigrostriatal neurons are a major factor in the response of the nigrostriatal neurons to afferent input.

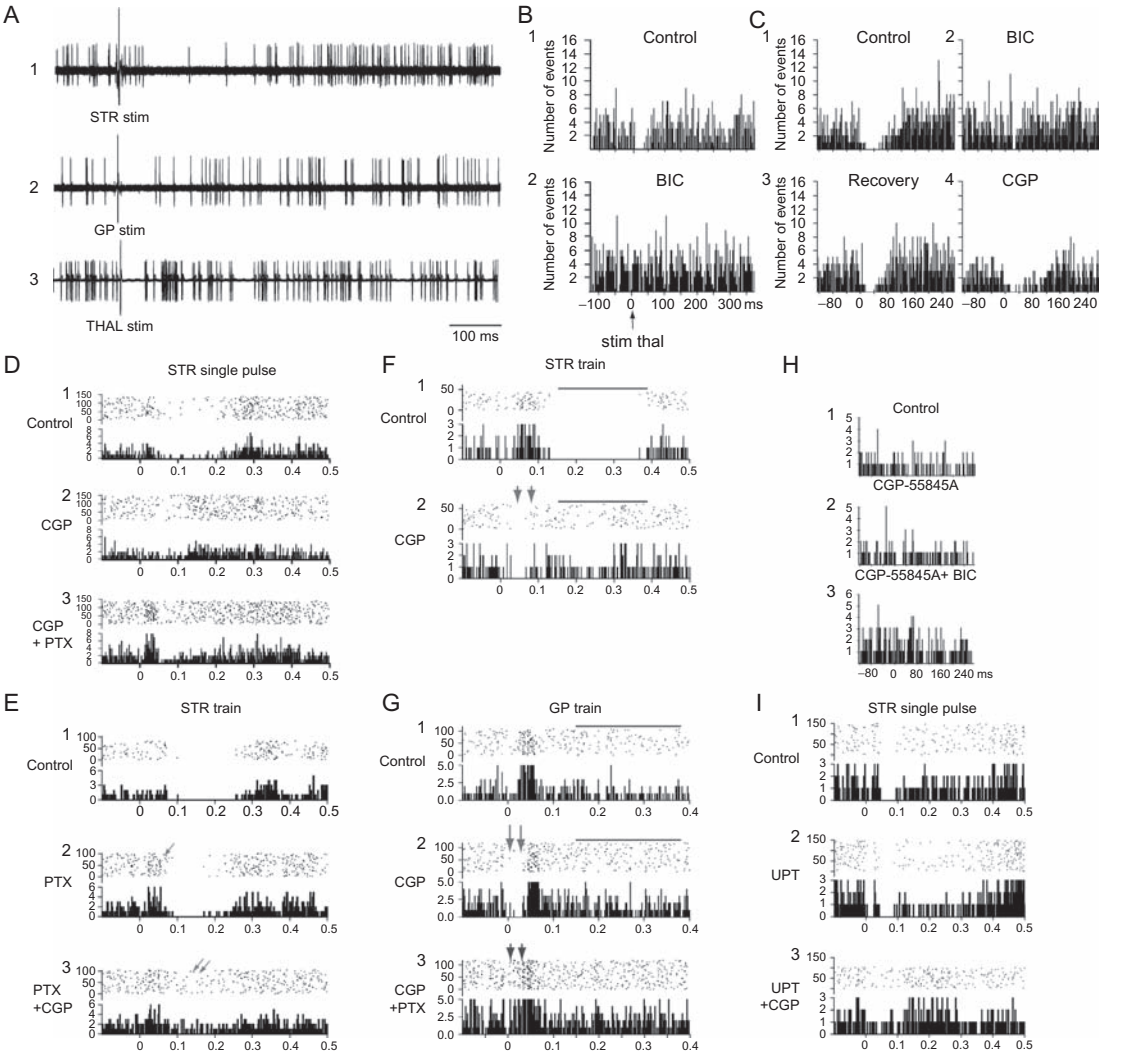

FIGURE 16.3 Inhibitory responses of nigral DA neurons following stimulation of GABAergic afferents. A. Raw spike trains recorded extracellularly illustrating responses to single pulse electrical stimulation of A1, dorsolateral striatum, A2, GP, and A3, ventromedial thalamus (which antidromically activates SNr GABA projection neurons) in mice. Each trace consists of the overlay of 25–37 consecutive sweeps at 0.67 Hz. Note the slow onset and long duration of the striatal-evoked inhibition compared to the rapid onset and shorter duration following activation of GP and SNr afferents. B. Typical PSTHs showing thalamic (SNr) elicited inhibition (B1) is eliminated when the recording pipette contains the $GABA_A$ selective antagonist, bicuculline (BIC) (B2). C. Inhibition elicited by single pulse GP stimulation (C1) is completely blocked by pressure application of BIC using multibarrel pipettes (C2). After recovery from BIC (C3), subsequent pressure application of the $GABA_B$-selective antagonist, CGP55845A (CGP) not only fails to block inhibition, but actually produces a slight augmentation and prolongation of the inhibition as well as a slight reduction in spontaneous firing rate (see text for explanation). D. PSTHs showing pharmacologically distinguishable early and late components of the inhibitory response of a nigral DA neuron to single pulse striatal stimulation in mice. D1. Control stimulation (660 μA pulse delivered at 0 msec) elicits a long duration (>200 ms) inhibition with a delayed onset. D2. Pressure application of CGP eliminates the late component of the inhibition but not the early component that is augmented by blockade of presynaptic $GABA_B$ autoreceptors. D3. Subsequent simultaneous application of CGP plus the $GABA_A$ antagonist, picrotoxin (PTX) eliminates both components of the evoked inhibition except for the small post-excitation inhibition following the PTX-induced increased firing. E. Same as D for a different cell but the order of drug application is reversed. E1. Striatal train stimulation elicits stronger inhibition than the single pulse stimulation in D1. E2. Application of PTX eliminates the early part of the inhibition but has no effect on the later portion. E3. Subsequent simultaneous application of PTX and CGP eliminates all inhibition. Note presence of similar excitatory response to stimulation in the presence of PTX as seen in D3. (See Paladini et al. (1999a) for explanation.) F. Simultaneous pre- and postsynaptic $GABA_B$ effects. F1. Striatal train stimulation elicits only a minimal early inhibition but a significant late inhibition (blue line). F2. Following CGP application, the same stimuli now evoke a clear early inhibition (red arrows) and the late inhibition is substantially attenuated. G. Facilitation of GABAergic inhibition is blocked by $GABA_A$ antagonists in mice. G1. GP train stimulation evokes inhibition with a weak early and strong late component. G2. Local CGP application greatly strengthens the early inhibition while completely eliminating the late inhibition. G3. Subsequent application of CGP and PTX eliminates all inhibitory responses. H. Presynaptic effects of $GABA_B$ antagonists. H1. Control PSTH with single pulse thalamic stimulation set to subthreshold current elicits no response. H2. Local application of CGP unmasks a clear inhibitory response to the identical stimulus. Note that there is a slight decrease background firing rate H3. Subsequent simultaneous application of the $GABA_B$ antagonist and the $GABA_A$ antagonist, bicuculline, eliminates the unmasked inhibition. I. Blocking GABA uptake greatly enhances the late component of the evoked inhibition. I1. Single pulse striatal stimulation elicits a strong early inhibition and a weaker late inhibition. I2. Local application of the selective GABA uptake inhibitor, nipecotic acid (UPT), selectively augments the late inhibition. I3. Subsequent application of CGP and UPT completely blocks the late component of the inhibition but not the early component. Data in A, D, G and I taken from extracellular recordings chloral-hydrate anesthetized mice. Data in B, C and H taken from extracellular recordings in urethane-anesthetized rats. Source B: redrawn from Tepper et al. (1995). Copyright 1995 by the Society for Neuroscience. C, H: redrawn from Paladini et al. (1999a), used with permission; D–G, I: redrawn from Brazhnik et al. (2008). Copyright 2008 by the Society for Neuroscience. To view a color version of this image please visit http://www.elsevierdirect.com/companion/9780123747679

C. Responses to SNr Stimulation

A reciprocal relation between the spontaneous activity of SNc DA neurons and an unidentified population of non-DA SNr neurons was first described by Grace and colleagues (Grace and Bunney, 1979, Grace et al., 1980) on the basis of simultaneous extracellular recordings. This was a landmark observation. Although Grace and Bunney (1979) were careful to consider several possibilities for the identity of the non-DA neuron, including the idea that it might be a SNr projection neuron, subsequent reports identified the SNr neuron as a unique "zona reticulata interneuron" located just ventral to the SNc on the basis of electrophysiological characteristics including lack of antidromic responding from thalamus, superior colliculus or striatum, an excitatory response to noxious stimuli and great sensitivity to GABA (Grace and Bunney, 1985; Bunney et al., 1991; Smith and Grace, 1992). From then on, the idea that there is a SNr GABA interneuron that engages in a feedforward inhibitory circuit with nigrostriatal DA neurons became firmly entrenched in the literature (e.g., Mereu and Gessa, 1985; Johnson and North, 1992; Santiago and Westerink, 1992; Zhang et al., 1992, 1993; Cameron and Williams, 1993, Yung and Hausser, 1993; Bontempi and Sharp, 1997).

There had been reports of presumed local circuit or interneurons in SNr based principally on Golgi studies (Gulley and Wood, 1971; Juraska et al., 1977; Schwyn and Fox, 1974; Francois et al., 1979), but for the most part these appeared to be smaller versions of the projection neurons whose size and dendritic orientation are known to vary with location in the SNr (Juraska et al., 1977). These neurons were not reported to be present in great abundance in SNr and there is little known about their afferent or efferent connectivities or even whether they truly represent a cell type distinct from the SNr projection neurons. There have also been reports of a small proportion of GABA neurons recorded in rostral SNc in vitro that were physiologically similar but not identical to SNr projection neurons (Yung et al., 1991), and a small population of GABA neurons in a restricted rostro-caudal region of the SNc has been shown to increase c-fos expression in response to DAergic stimulation (Hebb and Robertson, 2000). There are little or no data concerning the efferent connectivities, or function of these SNc neurons, but it is important to not overlook the potential importance of a neuronal population simply because it makes up a small proportion of the total cell number in a nucleus (Tepper et al., 2004, 2008; Tepper and Bolam, 2004).

However, it had been recognized for some time that SNr projection neurons emit axon collaterals, both in SNr as well as in SNc (Deniau et al., 1982; Grofova et al., 1982). Stimulation of the SNr in vitro produces IPSP/Cs in nigrostriatal neurons (Yung et al., 1991; Johnson and North, 1992; Hajós and Greenfield, 1993, 1994; Hausser and Yung, 1994) but it was impossible to determine if these arise from activation of a population of interneurons or by activation of SNr projection neurons that innervate DA neurons via their axon collaterals.

One approach to address this question in vivo was to record from nigrostriatal DA neurons while stimulating the ipsilateral ventral thalamus or superior colliculus (Tepper et al., 1995). Although there were no known monosynaptic projections from these nuclei to the nigrostriatal neurons, such stimuli would be expected to antidromically activate a population of SNr GABA projection neurons selectively without driving any putative GABA interneurons. Such stimuli would produce inhibition in nigrostriatal neurons if they were directly innervated by SNr collaterals, excitation if the nigrostriatal neurons were innervated by GABA interneurons that were themselves innervated by the SNr projection neurons, and no effect if there were no connection at all between the SNr projection neurons and the nigrostriatal neurons. The results were clear-cut, with thalamic or tectal stimulation producing strong inhibition of the nigrostriatal neurons at latencies only a little longer than the SNr neuron antidromic conduction times (Tepper et al., 1995; Paladini et al., 1999a; Brazhnik et al., 2008).

The SNr GABA axon collaterals were subsequently carefully mapped (Mailly et al, 2003), and electron microscopic evidence was provided for the existence of synapses formed by collaterals of SNr projection neurons onto nigrostriatal neurons (Tepper et al., 2002; Lee and Tepper, 2009). Results from a subsequent experiment where non-DA SNr neurons were recorded in vitro, stained with biocytin and reconstructed in order to compare their somatodendritic and axonal morphology with their electrophysiological characteristics revealed a morphologically and electrophysiologically homogenous population of neurons in SNr, differing only in co-expression of either parvalbumin or calretinin (Lee and Tepper, 2007). Thus the SNr GABAergic input to nigrostriatal DA neurons arises predominantly or exclusively from the axon collaterals of the SNr principal cells, which play a dual role as both projection neurons and the source of intranigral GABAergic inhibition (Deniau et al., 2007).

D. Why are SNr Neurons so Much More Sensitive to GABA than Nigrostriatal Neurons?

As mentioned earlier, SNr GABA neurons exhibit apparently greater sensitivity to inhibition by GABA or $GABA_A$ agonists than nigral DA neurons. There are several possible reasons. First, there is a differential distribution of $GABA_A$ subunits on DA and SNr GABA neurons (Boyes and Bolam, 2007), and different subunit combinations generate receptors with markedly different biophysical properties (for recent review see Goetz et al., 2007).

Second, there are markedly different chloride regulatory mechanisms in nigrostriatal and SNr neurons. SNr projection neurons express KCC2, the typical K^+-Cl^- co-transporter found in most mature CNS neurons (Rivera et al., 1999) that is responsible for maintaining the $[Cl^-]_i$ low enough so that $GABA_A$ IPSPs are hyperpolarizing (Farrant and Kaila, 2007). These IPSPs exhibit a reversal potential around – 71 mV measured with gramicidin perforated patch recordings in vitro. In contrast, DA neurons lack KCC2 and exhibit a significantly more depolarized $GABA_A$ IPSP reversal potential around – 63 mV (Gulácsi et al., 2003). Furthermore, the reversal potential in DA neurons, but not in SNr GABA neurons, is highly dependent on the presence of bicarbonate indicating that DA neurons depend on a less efficient Na^+- dependent Cl^-/bicarbonate exchanger (NDAE; see Farrant and Kaila, 2007 for review) in order to extrude $[Cl^-]_i$ and be capable of generating a hyperpolarizing IPSP. Thus, $GABA_A$ receptor activation produces a significantly smaller hyperpolarization in DA neurons than in SNr GABA neurons, and this is likely to account, at least in part, for their relative insensitivity to GABA compared to SNr output neurons (Gulácsi et al., 2003).

The difference in sensitivity to GABA of the two nigral neuron types is at the heart of much of the circuit-level phenomena that occur in SN including the increase in burst firing in nigrostriatal neurons triggered by disinhibition from the SNr neurons following chemical stimulation of the GP described above.

E. Pharmacology of GABAergic Synaptic Responses in Nigrostriatal Neurons In Vivo

In in vitro experiments, local stimulation in SN elicits biphasic IPSP/Cs in nigral DA neurons. The early component shows a rapid onset, relatively brief duration, exhibits a reversal potential near the Cl^- equilibrium potential, and is blocked by selective $GABA_A$ receptor antagonists, bicuculline or picrotoxin. The later component has a slower onset, a greatly increased duration, and is unaffected by $GABA_A$ antagonists but is blocked by selective $GABA_B$ receptor antagonists (Johnson and North, 1992; Cameron and Williams, 1993; Hajós and Greenfield, 1993, 1994; Hausser and Yung, 1994). The $GABA_B$ component is most consistently observed following stimulation with brief high frequency train stimuli (e.g., Hausser and Yung, 1991; Johnson and North, 1992; Saitoh et al., 2004).

However in vivo in rats, single pulse stimulation of striatum, GP or antidromic activation of SNr projection neurons with stimuli up to 1 mA produces inhibition of nigral DA neurons that is completely blocked by local application of $GABA_A$ antagonists (Tepper et al., 1995; Paladini et al., 1999a). The $GABA_B$ antagonists CGP35348 or CGP55845A not only fail to block the inhibition, but in many cases lead to an augmented inhibitory response (Fig. 16.3). Train stimuli similar to those used in the in vitro experiments elicited longer duration, more powerful inhibition from striatum or GP. In some of these cases bicuculline or picrotoxin completely blocked the augmented inhibition. In other cases only the early part of the inhibition was blocked and the later portion remained. However, as with single pulse stimulation the $GABA_B$ antagonists, saclofen or CG-55845A, did not block any of inhibition resulting from train stimulation nor did the SK channel blocker, apamin or the D2 receptor antagonist, eticlopride (Paladini et al., 1999a).

If the stimulus intensity is adjusted to be just below threshold for evoking inhibition, application of $GABA_B$ antagonists unmasks an inhibitory response that can then be blocked by application of picrotoxin or bicuculline (Paladini et al., 1999a; cf Fig. 16.3. Thus in vivo in rats, inhibition in nigral DA neurons evoked from all three principal GABA afferents appears to be mediated predominantly or exclusively through stimulation of postsynaptic $GABA_A$ receptors. The potentiation of the inhibition by application of $GABA_B$ antagonists arises from blockade of presynaptic inhibitory $GABA_B$ autoreceptors located on the terminals of striatal, pallidal and SNr neurons that synapse onto DA neurons (Giralt et al., 1990; Hausser and Yung, 1994; see Misgeld et al., 2007 for review). This blockade results in increased stimulus-evoked GABA release that produces larger $GABA_A$ receptor-mediated inhibition that can be completely blocked by $GABA_A$ antagonists (Paladini et al., 1999a).

It is rather puzzling that it is so difficult to elicit $GABA_B$ inhibition in DA neurons in vivo when the neurons

clearly have abundant expression of $GABA_B$ receptors and exogenous application of $GABA_B$ agonists both in vivo (Engberg et al., 1993; Ehrhardt et al., 1998, 2002) and in vitro (Lacey et al., 1988) result in strong hyperpolarization and inhibition. One explanation is that a significant fraction of postsynaptic $GABA_B$ receptors on SNc neurons is located at extrasynaptic sites some distance from the site of GABA release (e.g., Boyes and Bolam, 2003). Activation of these receptors would require particularly intense stimuli in order to evoke enough GABA release to overcome the uptake mechanisms and allow diffusion away from the synapse to reach the extrasynaptic $GABA_B$ receptors. This is precisely the case in hippocampus where interneuronal inhibition of pyramidal cells is mediated exclusively by $GABA_A$ receptors except when the interneuron is stimulated by high frequency trains or when a large population of interneurons is firing synchronously (Scanziani, 2000). Therefore it may simply be that most previous in vivo experiments with intact uptake mechanisms have been unable to stimulate striatum, GP or SNr neurons strongly enough for this synaptic overflow to occur.

Indeed this seems to be the case. Recent experiments in vivo in mice reveal that stimulation of striatum, GP or antidromic activation of SNr projection neurons with single pulses delivered at amplitudes similar to those used in previous experiments in rats evoked inhibitory responses of significantly greater duration than those observed in rats (Brazhnik et al., 2008). Furthermore, the inhibitory responses could be seen to be composed of two discrete components, an early inhibition that could be selectively blocked by $GABA_A$ receptor antagonists and a later component, not usually seen in rats, that was unaffected by bicuculline or picrotoxin but that was blocked by the selective $GABA_B$ antagonist, CGP55845A. Although the late component could be blocked by CGP55845A, as in rats, there was no evidence for a tonic $GABA_B$ mediated inhibitory tone (Brazhnik et al., 2008; cf Fig. 16.3).

Local application of CGP55845A not only potentiated the early $GABA_A$-mediated inhibition following activation of striatal, pallidal or SNr inputs as in rats, but also resulted in a significant *decrease* in spontaneous firing rate, a trend that was evident but not statistically significant in the previous studies in rats. Both of these effects were attributable to action at inhibitory presynaptic $GABA_B$ terminal autoreceptors, as in rats.

GABA uptake blockers had relatively little effect on the early part of the evoked inhibition but greatly augmented the late component, an effect that was selectively antagonized by $GABA_B$ antagonists (Brazhnik et al., 2008; cf Fig. 16.3). Masked postsynaptic $GABA_B$ inhibitory effects that can be revealed by the application of GABA uptake blockade have also been shown to occur in striatum (Kirmse et al., 2008). In all other respects, the responses to GABA afferent inputs were identical in rats and mice.

F. Why are Postsynaptic $GABA_B$ Responses Seen in Response to Stimulation of GABA Afferents in Mice In Vivo, but not in Rats?

There are several possible explanations for the appearance of $GABA_B$ postsynaptic effects in vivo in mice when previous experiments failed to see them in rats. Anesthetic differences is one possibility – most of the rat experiments were done under urethane anesthesia whereas the mice were anesthetized with chloral hydrate. Another possibility is that there is significant species difference in GABAergic signaling in SN between rats and mice, but that seems highly unlikely especially given the ready elicitation of $GABA_B$ IPSP/Cs in vitro in rat slices. Rather, the most likely explanation is simply the difference in size between rat and mouse brains. Neuronal packing density varies inversely with brain volume (Tower, 1954). This causes identical stimuli delivered in rat and mouse brain to stimulate a much larger *number* of neurons in the mouse. Further, since the mouse brain is smaller, a given volume of brain tissue corresponds to a greater *proportion* of all the cell in a given nucleus so stimulating equal volumes in rat and mouse would not only activate a larger number of neurons in the mouse but also a larger fraction of the total population of efferents, a variable that seems likely to be related to the maximum total receptor binding, uptake capacity and strength of synaptic response. Stimulation in a smaller brain is thus likely to result in greater extracellular levels of GABA some of which escapes the synapse and is available to diffuse to extrasynaptic $GABA_B$ receptors.

There are observations that support this hypothesis. A study of the postnatal changes in nigrostriatal neurons in rats showed that striatal evoked inhibition was especially potent in neonatal rat pups, lasting for several hundred ms, but by the time the rats had reached 21 days of age, the average duration of inhibition did not differ from that in adults. (Tepper et al., 1990). Three weeks of age is well before the rat striatum has fully matured anatomically or physiologically (Tepper and Trent, 1993; Tepper et al., 1998) but is a period when the size of the brain is close to that of adult rats. Additional support comes from in vitro

release studies where field stimulation of cortical or striatal slices released 80% more norepinephrine and 300% more DA in mouse slices than in rat slices using the same stimuli, indicating that identical stimuli released far more transmitter in mouse than in rat. Finally, in the in vivo mouse studies just described, electrical stimulation of striatum, GP or thalamus evoked much longer duration inhibition than identical stimulation in rats (Tepper et al., 1995, Paladini et al., 1999a; Brazhnik et al., 2008).

G. Effects of GABA Receptor Antagonists on Spontaneous Activity in Nigrostriatal Neurons

In addition to blocking striatal, pallidal or SNr-evoked inhibition of nigrostriatal neurons, GABA receptor antagonists also affected both the firing rate and firing pattern of the spontaneous activity of nigrostriatal neurons. Local application of bicuculline methiodide produced a modest but statistically significant 25% increase in firing rate (Tepper et al., 1995, Paladini and Tepper, 1999). Two other $GABA_A$ antagonists that do not block the SK channel as does bicuculline methiodide (Johnson and Seutin, 1997), picrotoxin and gabazine, exerted smaller, less consistent excitatory effects on firing rate (Paladini and Tepper, 1999). Local application of the selective $GABA_B$ receptor antagonists, 2-OH-saclofen or CGP55845A, exerted even more modest, but opposite effects on firing rate, producing small decreases in spontaneous activity (Tepper et al., 1995; Paladini and Tepper, 1999; cf Figure 16.3 C).

In marked contrast to the relatively modest effects on nigrostriatal neuron firing rate, $GABA_A$ antagonists, exerted consistent and dramatic effects on the firing patterns of SNc DA neurons. Local application of bicuculline methiodide produced a dramatic increase in the CV, the proportion of neurons firing in bursts and the percentage of spikes fired in bursts (Tepper et al., 1995; Paladini and Tepper, 1999). Other $GABA_A$ antagonists that lack the SK channel blocking ability of bicuculline methiodide (Johnson and Seutin, 1997), picrotoxin and gabazine, mimicked the potent effects of bicuculline at switching neurons from pacemaker or random firing to burst firing. (Paladini and Tepper, 1999; Brazhnik et al., 2008; cf Fig. 16.4). Regardless of the initial firing pattern, all the $GABA_A$ antagonists caused the majority of nigrostriatal neurons to shift to a bursty firing pattern. There was no correlation between the effects of $GABA_A$ antagonists on firing pattern and baseline firing rate or drug-induced changes in firing rate (Paladini and Tepper, 1999). This suggests that the mechanisms that modulate firing pattern and firing rate are different, and at least partially independent, and further, that altering GABAergic input to DA neurons has a greater effect on firing pattern than on firing rate.

In contrast, $GABA_B$ antagonists produced opposite effects on firing pattern. Although these effects were usually less dramatic then those of the GABA antagonists, local application of CGP35348 or CGP 55845A led to a shift along the firing pattern continuum away from burst firing towards the pacemaker-like pattern. The regularization in firing pattern was evident in a number of indices including a decreased CV, a decrease in the percentage of spikes fired in bursts, and increase in the mean number of peaks in the autocorrelation histogram, and decrease in the numbers of neurons firing in the bursty mode and an increase in the proportion of neurons firing in the pacemaker pattern (Tepper et al., 1995; Paladini and Tepper, 1999; Brazhnik et al., 2008).

These results indicated that in vivo there exists a GABA tone on nigrostriatal neurons that produces a tonic activation of $GABA_A$ receptors. The level of activation of nigrostriatal $GABA_A$ receptors seems able to modulate the firing pattern in a very effective and rapid way. One could imagine that momentary decreases in GABAergic input resulting from brief pauses in the high tonic firing rate of the SNr neurons would reduce the $GABA_A$ tone, and, like brief applications of $GABA_A$ antagonists, produce a burst. On the other hand increases in GABAergic input resulting from increased SNr activity would increase the level of $GABA_A$ receptor stimulation and suppress burst firing.

In contrast, there is no tonic stimulation of the postsynaptic $GABA_B$ receptors on nigrostriatal neurons, consistent with findings in other brain regions including striatum and hippocampus (Scanziani, 2000; Kirmse et al., 2008, but see Erhardt et al., 1999). The effects of the $GABA_B$ antagonists result from action at presynaptic $GABA_B$ autoreceptors on the terminals of the GABA afferents that lead to increased GABA release and increased $GABA_A$ receptor stimulation. The modest inhibitory effects of $GABA_B$ antagonists on spontaneous activity and the facilitation of $GABA_A$-mediated afferent induced inhibition suggest that unlike the postsynaptic $GABA_B$ receptors, the presynaptic $GABA_B$ autoreceptors, that are located on GABA afferents from striatum, GP and SNr, *are* tonically stimulated in vivo, albeit to a relatively small degree.

For reasons discussed above, the $GABA_A$ tone is unlikely to originate from the striatum, but could arise

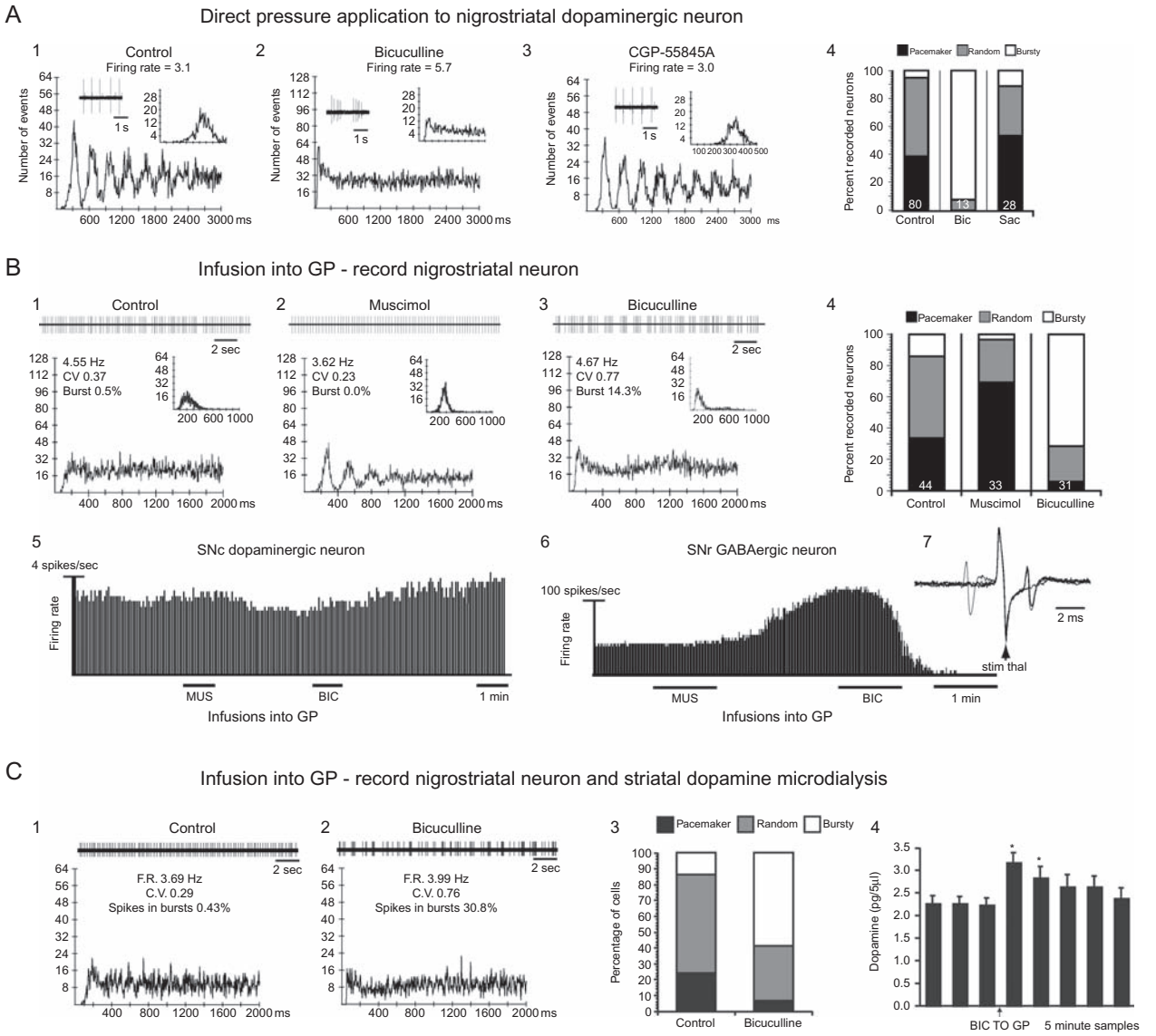

FIGURE 16.4 Blocking $GABA_A$ inputs to nigrostriatal neurons evokes bursty firing in vivo. A1. Pre-drug control neuron exhibits pacemaker firing. A2. Local application of the $GABA_A$ antagonist, bicuculline, produces a dramatic shift to a bursty firing pattern along with an increase in firing rate within a few seconds. A3. The effects of bicuculline wear off in about 7 minutes and the subsequent application of the $GABA_B$ antagonist, CGP55845A, fails to elicit burst firing, and in fact contributes to increased regularity of firing as indicated by an increase in the number of peaks in the autocorrelogram (9) compared to that in the pre-drug control (7). A4. Distribution of firing patterns of rat nigrostriatal neurons in vivo under control conditions, after local application of bicuculline or the $GABA_B$ antagonist, 2-OH saclofen, through the recording pipette. B. Manipulation of GP firing rate by infusion of drugs exerts paradoxical effects on SNc activity. B1. Control SNc neuron firing in the random mode. B2. Following infusion of muscimol into GP that produced almost complete inhibition of GP firing, the nigrostriatal neuron shifts to pacemaker firing accompanied by a small decrease in firing rate. B3. GP infusion of bicuculline produced a 58% increase in GP firing rate and caused the DA neuron to switch to busty firing, accompanied by a slight increase in firing rate. B4. Distribution of firing patterns for all SNc neurons following pallidal drug infusions. B5. Ratemeter record of the neuron shown in B1–3 shows that the dramatic changes in firing pattern are accompanied by very modest changes in firing rate. Note that the changes in firing rate and pattern are opposite to what would result from monosynaptic pallidal input to SNc neurons. B6. In contrast to the SNc neurons, the firing rate of one representative SNr projection neuron (B7) more than doubles following GP muscimol infusion and its spontaneous activity is completely suppressed following GP infusion of bicuculline, consistent with a powerful monosynaptic inhibitory pallidal input. C. Simultaneous recording of nigrostriatal neuron activity and striatal DA levels measured by microdialysis. C1. Control neuron firing randomly. C2. GP infusion of bicuculline causes neuron to shift to a bursty firing pattern with a modest increase in firing rate, the typical response as shown in C3. Simultaneous microdialysis in striatum reveals that the switch to the bursty firing pattern causes a 44% increase in extracellular DA levels. Source A1–3: redrawn from Paladini and Tepper (1999); A4: redrawn from Tepper et al. (1995), copyright 1995 by the Society for Neuroscience; B1–6: redrawn from Celada et al. (1999), used with permission; C: redrawn from Lee et al. (2004).

from either GP or SNr or both. However if we recall that pallidal-evoked inhibition of nigrostriatal neurons is only seen following the relatively strong, synchronous GABA release that occurs with electrical stimulation whereas the GABA release that accompanies pharmacological stimulation that causes asynchronous activation of GP produces disinhibition by preferentially inhibiting the SNr neurons, it seems most likely that the major source of the $GABA_A$ tone that modulates the firing pattern of the nigrostriatal neurons is the local axon collateral system of the SNr projection neurons.

The mechanism of the $GABA_A$-mediated burst suppression is not completely understood, but NMDA-induced burst firing of nigral DA neurons in vitro can be blocked by the selective $GABA_A$ agonist, isoguvacine. The blockade is independent of membrane polarization but is associated with a large conductance increase (Paladini et al., 1999b). This effect has been simulated in compartmental models of DA neurons by a few groups where it has been explained by alterations in the interactions of membrane potential, conductance and dendritic coupling (Canavier, 1999; Komendatov et al., 2004; Kusnetsov et al., 2006).

H. Afferent Regulation of Burst Firing in Nigrostriatal Neurons

The burst firing of DA neurons only occurs spontaneously in vivo, suggesting that in addition to intrinsic conductances, intact afferents are required for burst initiation and/or maintenance (Kita et al., 1986; Lacey et al., 1989, Grace and Onn, 1989). Bursts cannot be elicited by simple intracellular current injection but can be evoked by local electrical stimulation under appropriate conditions in vitro and/or pressure application of glutamate or NMDA (Morikawa et al., 2003; Blythe et al., 2007). Bursting can also be elicited by blocking the SK channel (Shepard and Bunney, 1988; Ji and Shepard, 2006), and stimulation of either nicotinic or muscarinic cholinergic receptors on DA neurons leads to depolarization and an increase in firing rate as well as to an increase in burst firing (Calabresi et al., 1989; Sorenson et al., 1998; Kitai et al., 1999). It is not inconceivable that there are multiple mechanisms interacting and/or acting independently to produce burst firing in nigral DA neurons in vivo (e.g., Canavier and Landry, 2006; Canavier et al., 2007).

Nevertheless, it is often assumed that the trigger for burst firing in vivo in SNc neurons is an excitatory glutamatergic input as it often is in other brain regions. Stimulation of nigral glutamate receptors in vivo, particularly NMDA receptors, induces burst firing whereas blocking NMDA receptors leads to a suppression of burst firing and a regularization of firing pattern (Grace and Bunney, 1984b, Charlety et al., 1991, Overton and Clark, 1992, 1997; Chergui et al., 1993, 1994). The principal glutamatergic afferents to SN come from the STN (Hammond et al., 1978), frontal cortex (Sesack and Carr, 2002) and pedunculopontine nucleus (that also provides cholinergic input to substantia nigra, Mena-Segovia et al., 2008) and electrical or chemical stimulation of these areas can increase burst firing in nigral DA neurons (but see above).

There is no little doubt that NMDA receptor stimulation, increases or causes burst firing in DA neurons in vivo although the mechanism remains controversial. An early hypothesis for this action identified a sodium-based mechanism dependent on an electrogenic sodium pump (Johnson et al., 1992) that was subsequently simulated in a compartmental model (Li et al., 1996; Canavier, 1999). However, the experimental data and the simulations replicate sustained plateau depolarizations far better than they do the burst itself, and both the experimental data and the model result in prolonged bouts of high frequency firing displaying reverse spike frequency adaptation riding on large plateau potentials that do not resemble in vivo bursts. Further the hypothesis cannot explain why NMDA receptor stimulation specifically promotes burst firing while depolarization of the membrane by non-NMDA glutamatergic agonists or current injection do not.

A more recent hypothesis, based on whole cell recording and calcium imaging studies of nigrostriatal neurons in vitro and supported by neuronal simulations suggests that DA neurons can be thought of as a series of coupled Ca^{2+}/Ca^{2+}-activated K^+ channel oscillators with the soma and proximal dendrites oscillating at a lower frequency than the thinner, more distal dendrites due to the difference in calcium clearance time as a function of surface area to volume ratio (Wilson and Callaway, 2000; Kusnetsov et al., 2006). Because the amplitude of the subthreshold dendritic oscillation is small compared to that of the soma and the compartments are tightly coupled, the neuron normally oscillates near the low frequency of the soma. NMDA receptor activation, because of its voltage dependence, leads to an increase in amplitude of the fast dendritic oscillation allowing it to become larger than the somatic oscillation and compete with or completely suppress the slower somatic oscillation, setting up the subthreshold conditions for a high frequency burst. It is the hyperpolarizing phase of the amplified subthreshold dendritic oscillation that allows the repolarization necessary for high frequency

spiking, something that does not occur with depolarizing current injection or AMPA receptor stimulation (Kusnetsov et al., 2006). Among the strengths of the model are that it incorporates the obviously important crucial role of Ca^{2+} in burst firing and explains why NMDA receptor stimulation, but not depolarization by injected current or AMPA receptor stimulation is capable of including a burst. Finally, simulations with the model generate bursts that more closely resemble natural bursts in vivo in terms of the maximum firing frequency and the appearance of spike frequency adaptation during the burst (Kusnetsov et al., 2006) than other current models (Komendatov et al., 2004; Canavier and Landry, 2006; Canavier et al., 2007).

But a model that successfully explains the mechanism by which NMDA receptor activation leads to burst firing in nigrostriatal neurons need not necessarily imply that phasic glutamatergic afferent activity input is the only, or even the principal trigger for burst firing in vivo. As mentioned above, the overwhelming majority of afferents that contact neurons in the substantia nigra, perhaps up to 90%, make symmetric inhibitory GABA synapses (Rinvik and Grofova, 1970, Gulley and Smithberg, 1971) [note that this applies specifically to substantia nigra; the situation appears to be different in the VTA where the most common type of synaptic input is glutamatergic and excitatory (Smith et al., 1996)]. As reviewed above, blockade of $GABA_A$ receptors on nigrostriatal neurons or interruption of GABAergic input from the SNr causes almost all nigrostriatal neurons to fire bursts. Conversely, exogenously applied GABAergic agonists or increases in firing rate of SNr projection neurons can completely suppress burst firing occurring spontaneously in vivo or induced by NMDA in vitro. Given the overwhelming predominance of GABA synapses on nigral DA neurons, the rapid kinetics of most $GABA_A$ receptors, and the remarkable effectiveness of stimulation or blockade of $GABA_A$ receptors on nigrostriatal neurons in modulating firing pattern, it seems not only possible but rather likely that one important trigger for eliciting a burst in a nigrostriatal neuron is a transient interruption in SNr firing.

As a tentative hypothesis, assume that the glutamatergic afferents to nigrostriatal neurons, arising principally from the pedunculopontine nucleus and also the subthalamic nucleus are tonically active and provide a more or less constant input to DA neurons, keeping them "primed" and burst-capable. They do not burst fire all the time because of substantial $GABA_A$ tone provided by the GABA afferents, the most crucial of which is the SNr projection neuron. The GABA tone suppresses the bursting, perhaps by altering the coupling between compartments as a result of increased membrane conductance. The SNr neuronal activity is tightly controlled by input from the GP. A transient increase in the activity of pallidonigral afferents (due to reduced striatal inhibition and/or increased STN input?) will lead to a similarly timed transient decrease in SNr GABAergic output, thereby disinhibiting the nigrostriatal neuron and allowing a burst. In contrast, brief decreases in output of pallidonigral neurons will disinhibit the SNr neurons, thereby increasing their activity and their GABAergic output to re-establish burst suppression in nigrostriatal neurons. In this model the glutamatergic/NMDA inputs are absolutely essential for burst firing, but do not trigger it.

VI. CONCLUDING REMARKS

The normal functioning of nigrostriatal DA neurons is crucial to a large array of behaviors ranging from voluntary motor function to higher cognitive processes. This remarkable variety of functions is even more impressive when one considers how few SN DA neurons there are (~25,000; Nair-Roberts et al., 2008) relative to, say, the striatum (2.9 Million; Oorschot, 1996). Nigrostriatal neurons in vivo fire in three distinct patterns, but unlike many other CNS neurons that exhibit multiple firing patterns in vitro, nigrostriatal neurons in vitro exhibit only a very regular, pacemaker-like pattern. This suggests that while the cellular mechanisms capable of generating the different firing patterns seen in vivo are intrinsic, afferent input is required to manifest the different firing patterns. The sustained firing rate of nigrostriatal neurons is low, and constrained to a limited range, below 10 spikes/sec, and it seems likely that much or most of the important functional variability in these neurons is carried by firing pattern rather than firing rate. The most numerous afferents to nigral DA neurons are GABAergic, and manipulation of GABA receptors on nigrostriatal neurons, principally $GABA_A$ receptors, produces dramatic effects on firing pattern, and more modest effects on firing rate, in vivo. The GABA afferent that seems to be most efficacious at modulating the firing pattern of nigrostriatal neurons comes from the axon collaterals of the SNr projection neuron. Many or most of the afferents to SN contact both the DA and the GABA neurons, providing the basis for a complex series of mono- and polysynaptic responses to both excitatory and inhibitory afferents.

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