Chapter 6
Basal Ganglia Control of Substantia Nigra Dopaminergic Neurons

Christian R Lee and James M Tepper

Abstract Although substantia nigra dopaminergic neurons are spontaneously active both in vivo and in vitro, this activity does not depend on afferent input as these neurons express an endogenous calcium-dependent oscillatory mechanism sufficient to drive action potential generation. However, afferents to these neurons, a large proportion of them GABAergic and arising from other nuclei in the basal ganglia, play a crucial role in modulating the activity of dopaminergic neurons. In the absence of afferent activity or when in brain slices, dopaminergic neurons fire in a very regular, pacemaker-like mode. Phasic activity in GABAergic, glutamatergic, and cholinergic inputs modulates the pacemaker activity into two other modes. The most common is a random firing pattern in which interspike intervals assume a Poisson-like distribution, and a less common pattern, often in response to a conditioned stimulus or a reward in which the neurons fire bursts of 2–8 spikes time-locked to the stimulus. Typically in vivo, all three firing patterns are observed, intermixed, in single nigrostriatal neurons varying over time. Although the precise mechanism(s) underlying the burst are currently the focus of intensive study, it is obvious that bursting must be triggered by afferent inputs.

Most of the afferents to substantia nigra pars compacta dopaminergic neurons comprise monosynaptic inputs from GABAergic projection neurons in the ipsilateral neostriatum, the globus pallidus, and the substantia nigra pars reticulata. A smaller fraction of the basal ganglia inputs, something less than 30%, are glutamatergic and arise principally from the ipsilateral subthalamic nucleus and pedunculopontine nucleus. The pedunculopontine nucleus also sends a cholinergic input to nigral dopaminergic neurons. The GABAergic pars reticulata projection neurons also receive inputs from all of these sources, in some cases relaying them disynaptically to the dopaminergic neurons, thereby playing a particularly significant role in setting and/or modulating the firing pattern of the nigrostriatal neurons.

Keywords Basal ganglia • Dopamine neuron • Electrophysiology • Parkinson's disease • Substantia nigra

Abbreviations

SK	Calcium-activated potassium
ChAT	Choline acetyltransferase
DA	Dopamine
EPSP	Excitatory postsynaptic potential
GPe	External part of the globus pallidus
GP	Globus pallidus
IPSP	Inhibitory postsynaptic potential
GPi	Internal part of the globus pallidus
M1	Muscarinic receptor 1
PD	Parkinson's disease
PPN	Pedunculopontine nucleus
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
VGluT	Vesicular glutamate transporter
TRP	Transient receptor potential

Introduction

The activity of substantia nigra pars compacta (SNc) dopaminergic neurons is influenced by the interactions between intrinsic membrane conductances and afferent input from other basal ganglia nuclei, as well as inputs from neurons outside the basal ganglia. When spontaneous activity is recorded in vitro where there is little afferent input, almost all nigral dopaminergic neurons exhibit a slow, very regular,

C.R. Lee
Department of Neurosurgery, New York University School of Medicine, New York, NY

J.M. Tepper (✉)
Center for Molecular and Behavioral Neuroscience, Rutgers, The State University of New Jersey, 197 University Avenue, Newark, NJ 07102
e-mail: jtepper@andromeda.rutgers.edu

G. di Giovanni et al. (ed.), *Birth, life and death of dopaminergic neurons in the Substantia Nigra*,
Journal of Neural Transmission. Supplementa, Vol. 73,
DOI 10.1007/978-3-211-92660-4_6,

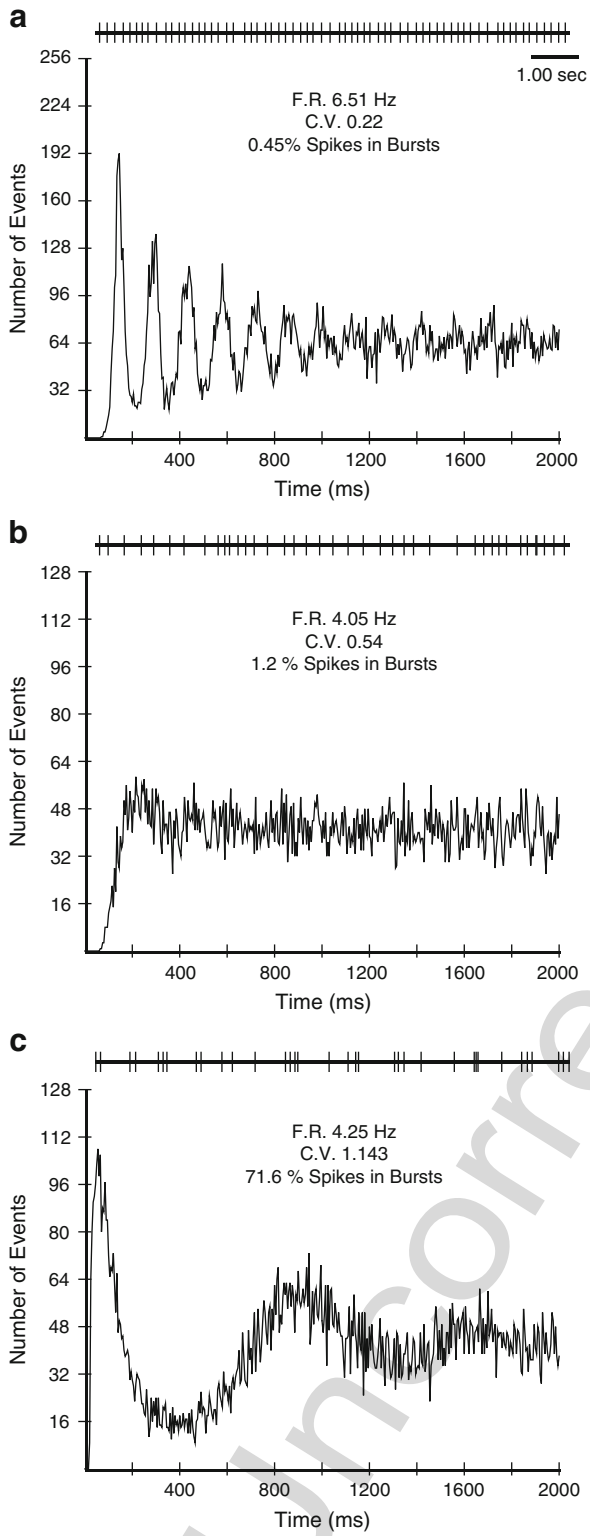

Fig. 1 Nigral dopaminergic neurons exhibit 3 distinct firing patterns or modes in vivo. (**a**) Pacemaker, (**b**) Random (**c**) Bursty. Each pattern gives rise to a characteristic autocorrelogram. Top insets show portions of the raw spike trains used to construct the autocorrelograms. Neurons exhibiting the pacemaker pattern with spikes occurring at fairly regular intervals produce autocorrelograms with three or more regularly occurring peaks (**a**). Neurons with spikes occurring more randomly produce autocorrelograms with an initial trough and a rise to a steady state (**b**) while neurons with many of their spikes occurring in bursts produce autocorrelograms with an initial peak which declines to steady state or a damped oscillation as in this case indicating rhythmic bursting (**c**). Note that the firing rates are largely similar between firing patterns while the coefficient of variation, defined as the standard deviation of the interspike interval divided by the mean interspike interval, exhibits a progressive increase from pacemaker to random and bursty neurons. *FR* Firing rate, *CV* Coefficient of variation

pacemaker-like firing pattern (Grace and Onn 1989; Yung et al. 1991; Richards et al. 1997; Paladini et al. 1999b; Gulácsi et al. 2003). However, when dopaminergic neurons are recorded in vivo, it becomes clear that dopaminergic neurons exhibit a variety of different firing patterns (Bunney et al. 1973; Wilson et al. 1977; Grace and Bunney 1984; Freeman et al. 1985; Tepper et al. 1995; Hyland et al. 2002; Fà et al. 2003). The firing patterns of dopaminergic neurons can be seen as existing along a continuum but can be classified into one of three more or less discrete firing patterns, regular or pacemaker, irregular or random, and bursty, based upon the shape of the autocorrelograms as illustrated in Fig. 1 (Tepper et al. 1995). Single neurons may shift among these different patterns and many classes of drugs, in particular agonists or antagonists of the neurotransmitters contained in the principal nigral afferents, GABA, and glutamate, exert potent and stereotyped effects on the firing pattern of dopaminergic neurons (Overton and Clark 1992; Engberg et al. 1993; Tepper et al. 1995; Paladini and Tepper 1999; Prisco et al. 2002; Blythe et al. 2007). The mean firing rates of neurons exhibiting these different firing patterns can be equal, suggesting that the mechanisms responsible for controlling firing pattern are largely independent of those modulating the firing rate in nigral dopaminergic neurons (Wilson et al. 1977; Tepper et al. 1995; Paladini and Tepper 1999; Tepper and Lee 2007).

In addition, the discharge of action potentials by dopaminergic neurons recorded in vivo is only loosely correlated between neurons under most conditions, suggesting that the different firing patterns are modified, but not directly driven by afferent inputs (Hyland et al. 2002).

Functionally, changes in the firing rate and more importantly the firing pattern of dopaminergic neurons are translated into changes in dopamine levels in terminal regions, with the bursty firing pattern being most efficacious in increasing terminal dopamine levels, especially in the nigrostriatal pathway (Gonon and Buda 1985; Gonon 1988; Bean and Roth 1991; Manley et al. 1992; Chergui et al. 1994b; Lee et al. 2004; but see Floresco et al. 2003). Similarly, afferent input can affect the release of dopamine from the somatodendritic region of dopaminergic neurons (Chen and Rice 2002; Cobb and Abercrombie, 2002, 2003a), sometimes independently of striatal dopamine release (Trent and Tepper 1991; Cobb and Abercrombie 2003b), which could

in turn modulate the strength of GABAergic input through presynaptic D1 dopamine receptors as well as the firing of SNc dopaminergic neurons through D2 autoreceptors (Cameron and Williams 1993; Seutin et al. 1994; Radnikow and Misgeld 1998; Misgeld et al. 2007). Thus, it is clear that an understanding of the afferent control of nigral dopaminergic neurons is an important prerequisite for understanding the complex interactions that take place both within the substantia nigra and throughout the basal ganglia network.

Afferent Inputs to SNc Dopaminergic Neurons

The basal ganglia are a collection of subcortical nuclei consisting of the neostriatum, the globus pallidus (GP), the subthalamic nucleus (STN), and the substantia nigra (Gerfen and Wilson 1996; Tepper et al. 2007), which is itself divided into the more dorsal pars compacta comprising primarily of dopaminergic neurons and the ventral substantia nigra pars reticulata (SNr) consisting primarily of GABAergic projection neurons (Lee and Tepper 2007b). Recently, some have argued that the pedunculopontine nucleus (PPN) should also be included as a basal ganglia nucleus (Mena-Segovia et al. 2004) and we include PPN afferents for the purposes of this review.

All of the basal ganglia nuclei project to the substantia nigra where they synapse on both dopaminergic and GABAergic neurons and most of the basal ganglia projections to the substantia nigra are GABAergic, with the exception of the projection from the STN, which is glutamatergic (Rinvik and Ottersen 1993) and the inputs from the PPN (Rye et al. 1987), some of which are glutamatergic and some of which are cholinergic (Futami et al. 1995; Takakusaki et al. 1996). In addition to the long-range projections from other basal ganglia nuclei, there is a significant inhibitory interaction between the GABAergic neurons in the SNr and the dopaminergic neurons in the SNc. As would be expected, the majority of the synapses formed on SNc dopaminergic neurons are GABAergic (Bolam and Smith 1990), although the majority of the afferents to dopaminergic neurons in the adjacent ventral tegmental area are not (Smith et al. 1996).

GABAergic Afferents

Neostriatum

The striatum is the principal input structure of the basal ganglia. Most striatal afferents are glutamatergic and excitatory and derive from the neocortex and intralaminar thalamic nuclei (Kemp and Powell 1971; Ingham et al. 1998). Most of the corticostriatal and thalamostriatal inputs terminate in the spiny regions of the principal neuron, the striatal spiny projection neuron, which also forms the only output of the nucleus. Striatal spiny neurons project to the GP as well as to the dopaminergic neurons of the SNc and the GABAergic projection neurons of the SNr (Grofová and Rinvik 1970; Grofová 1975; Somogyi et al. 1981; Totterdell et al. 1984; Williams and Faull 1985; Bolam and Smith 1990; Bevan et al. 1994). Striatal projections to dopaminergic neurons terminate relatively distally. The striatonigral projection colocalizes substance P and dynorphin in addition to GABA and has been called the direct pathway, in contrast to the striopallidal projections to the external GP that colocalize enkephalin and are termed the indirect pathway (Gerfen and Wilson 1996). Substance P immunoreactive terminals form symmetric synapses on the dendritic shafts of SNc dopaminergic neurons, with only a small proportion of boutons synapsing on dopaminergic perikarya (Bolam and Smith 1990).

Globus Pallidus

The globus pallidus (external globus pallidus in higher mammals) sends inhibitory GABAergic projections to the STN as well as to both segments of the substantia nigra, thereby directly innervating both dopaminergic and GABAergic nigral neurons (Grofová 1975; Hattori et al. 1975; Totterdell et al. 1984; Smith and Bolam 1989, 1990; Smith et al. 1990; Bevan et al. 1996; Sato et al. 2000). Pallidal terminals form GABA-immunoreactive symmetric synapses that terminate on both the somata and proximal dendrites of nigral neurons, occasionally forming pericellular baskets around somata in the substantia nigra (Smith and Bolam 1990).

Substantia Nigra Pars Reticulata

The SNr provides one of the most important, yet least-understood and -characterized inhibitory inputs to nigral dopaminergic neurons. In addition to their long-range projections to the thalamus and the superior colliculus (Rinvik 1975; Clavier et al. 1976; Faull and Mehler 1978; Tokuno and Nakamura 1987; Harting et al. 1988; Kemel et al. 1988; Williams and Faull 1988; Bickford and Hall 1992; Deniau and Chevalier 1992; Redgrave et al. 1992; Mana and Chevalier 2001; Sidibé et al. 2002; Lee and Tepper 2007b), they also issue local axon collaterals that mediate the inhibition of neighboring dopaminergic and GABAergic neurons

within the substantia nigra (MacNeil et al. 1978; Walters and Lakoski 1978; Grace and Bunney, 1979, 1985a,b; Waszczak et al. 1980; Deniau et al. 1982; Hajós and Greenfield 1994; Häusser and Yung 1994; Tepper et al. 1995; Lee et al. 2004; Saitoh et al. 2004)

Local axon collaterals of SNr GABAergic projection neurons arborize in both SNr and SNc and exhibit considerable variability from neuron to neuron in terms of the size, extent of the collateral field, and its position with respect to the dendritic tree of the cell of origin, and frequently bear varicosities resembling both terminal and *en passant* boutons (Deniau et al. 1982; Grofová et al. 1982; Kemel et al. 1988; Nitsch and Riesenberg 1988; Tepper et al. 2003; Mailly et al. 2003; Lee and Tepper 2007b; Figs. 2 and 3). Electron microscopic analysis has revealed that the varicosities are large boutons that form symmetric synapses with somata as well as proximal dendrites, often forming multiple pericellular contacts (Damlama 1994; Tepper et al. 2003; Boyes 2004; Fig. 3) similar to those originating from GP axon terminals (Smith and Bolam 1990).

Glutamatergic Afferents

Subthalamic Nucleus

Although GABAergic afferents account for the majority of the basal ganglia inputs to nigral dopaminergic neurons, there are significant glutamatergic inputs as well. The best-characterized basal ganglia glutamatergic input to substantia nigra is from the STN (Hammond et al 1978; Chang et al. 1984; Kita and Kitai 1987). Although injections of PHA-L into STN result in some labeling in SNc, the majority of labeled boutons are found in SNr. Subthalamonigral axons form boutons that contain small round vesicles and form asymmetric synapses on medium- and small-sized dendrites, mostly in SNr, and only rarely onto somata (Chang et al. 1984; Kita and Kitai 1987; Damlama 1994, Fig. 4). Most of these synapses are formed onto TH-immunonegative (presumably GABAergic) dendrites, with only about 10% of boutons originating from STN terminating on dopaminergic dendrites in SNr as shown in Fig. 4 (Damlama 1994).

Cholinergic Afferents

Pedunculopontine Nucleus

The projection from the PPN is neurochemically diverse and includes both glutamate and acetylcholine (Woolf and Butcher 1986; Gould et al. 1989; Clements and Grant 1990; Charara et al. 1996). This is the only source of cholinergic input to nigral dopaminergic neurons. At least some PPN terminals express both choline acetyltransferase (ChAT) and the vesicular glutamate transporter (VGluT) and thus may be both cholinergic and glutamatergic (Lavoie and Parent 1994). The majority of boutons labeled from the PPN contain small round synaptic vesicles and form asymmetric synapses as shown in Fig. 4 and are glutamate immunoreactive, while a smaller proportion exhibits immunoreactivity for GABA and forms symmetric synapses (Charara et al. 1996). As with glutamate, GABA and acetylcholine appear to be colocalized in some cell bodies in the PPN (Jia et al. 2003).

Cholinergic synapses can be found on dopaminergic perikarya and dendrites as well as on GABAergic neurons in the substantia nigra (Beninato and Spencer 1988; Martínez-Murillo et al. 1989; Bolam et al. 1991; Charara et al. 1996). Although the majority (65%) of boutons anterogradely labeled from the PPN synapse onto nondopaminergic neurons and dendrites, the 35% that do synapse onto dopaminergic dendrites is significantly greater than the proportion of terminals from the STN, of which only 10% synapse onto TH+ dendrites. Furthermore, the PPN boutons tend to form synapses onto larger diameter dendrites than the STN boutons (Damlama 1994), as illustrated in Fig. 4, perhaps suggesting that the PPN is a more potent source of direct excitation of dopaminergic neurons than the STN (see below).

Control of Nigral Dopaminergic Neurons by Afferent Input

The anatomical organization of the basal ganglia afferents to the substantia nigra, and the microcircuitry within the substantia nigra itself forms much of the basis necessary for understanding the effects observed in response to stimulation of afferents to SNc dopaminergic neurons on both short- and long-time scales. These responses are sometimes unexpected and in many cases suggest that an important part of the afferent input to SNc dopaminergic neurons is relayed and filtered through the axon collaterals of SNr GABAergic neurons.

Responses to GABAergic Input

Striatum

Early studies showed that electrical stimulation of the striatum in vivo in cats produced a monosynaptic inhibitory

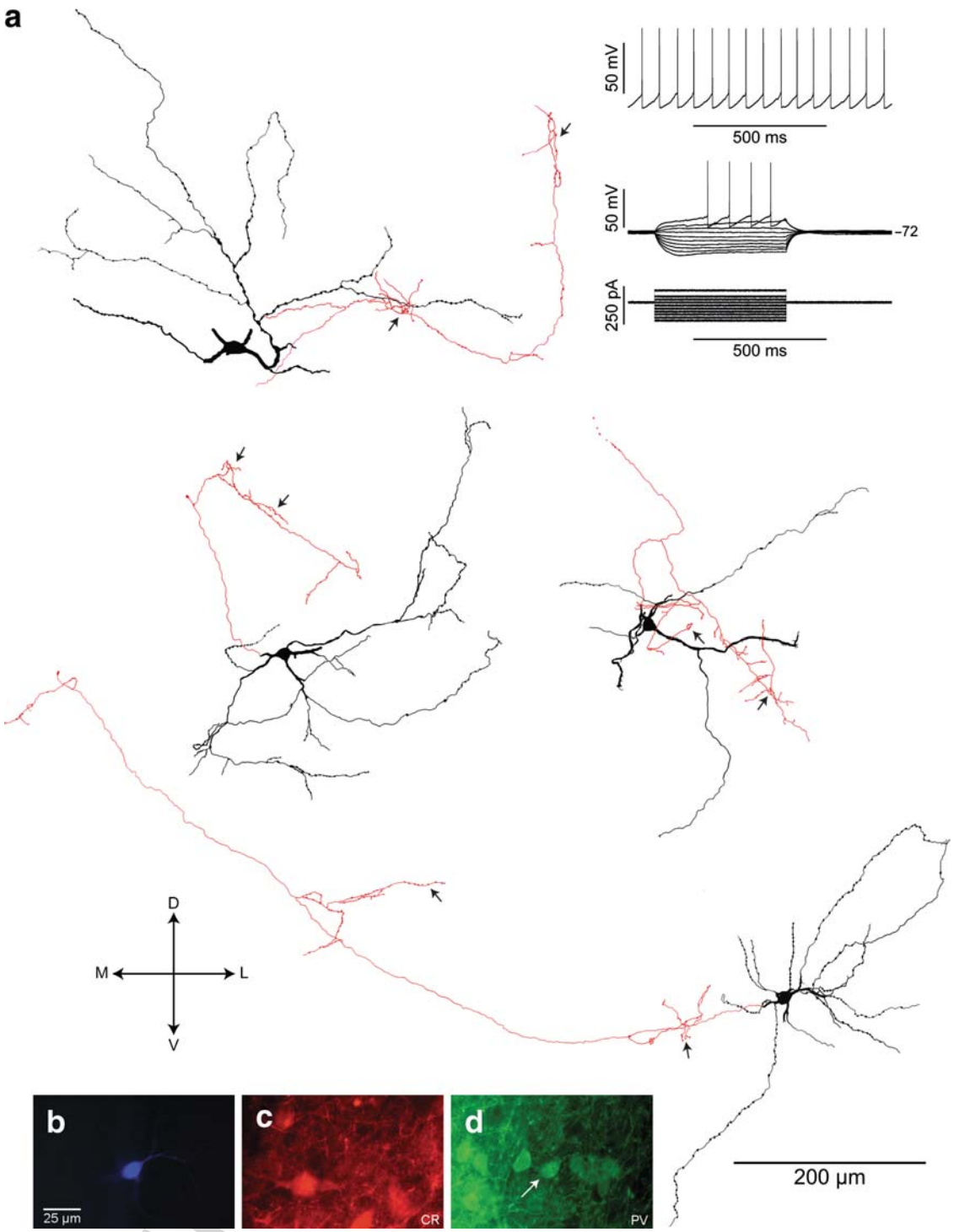

Fig. 2 Reconstructions of SNr GABAergic neurons filled with biocytin during whole- cell recording in vitro. (**a**) Representative examples of SNr GABAergic projection neurons recorded from coronal slices in vitro. Somata and dendrites are shown in black while axons are depicted in red. Note that all of the neurons issue local axon collaterals (*black arrows*) within the substantia nigra which in some cases can be observed to exhibit varicosities along their trajectories resembling *en passant* boutons as well as basket-like terminations with several large swellings characteristic of terminal boutons. Inset. Spontaneous activity and response to current injection (taken from bottom neuron) are typical for SNr GABAergic projection neurons. (**b–d**) Fluorescent images obtained from the bottom neuron show biocytin (**b**) calretinin (**c**) and parvalbumin (**d**). Note that the neuron exhibits immunoreactivity for parvalbumin (*white arrow*) but not calretinin. Other SNr GABAergic neurons containing calretinin as well as the small population containing both parvalbumin and calretinin similarly issue local axon collaterals. *CR* Calretinin, *PV* Parvalbumin, *D* Dorsal, *V* Ventral, *M* medial, *L* lateral. Orientation refers to reconstructed neurons. Modified from Lee and Tepper 2007b. Copyright 2007 Wiley-Liss, Inc

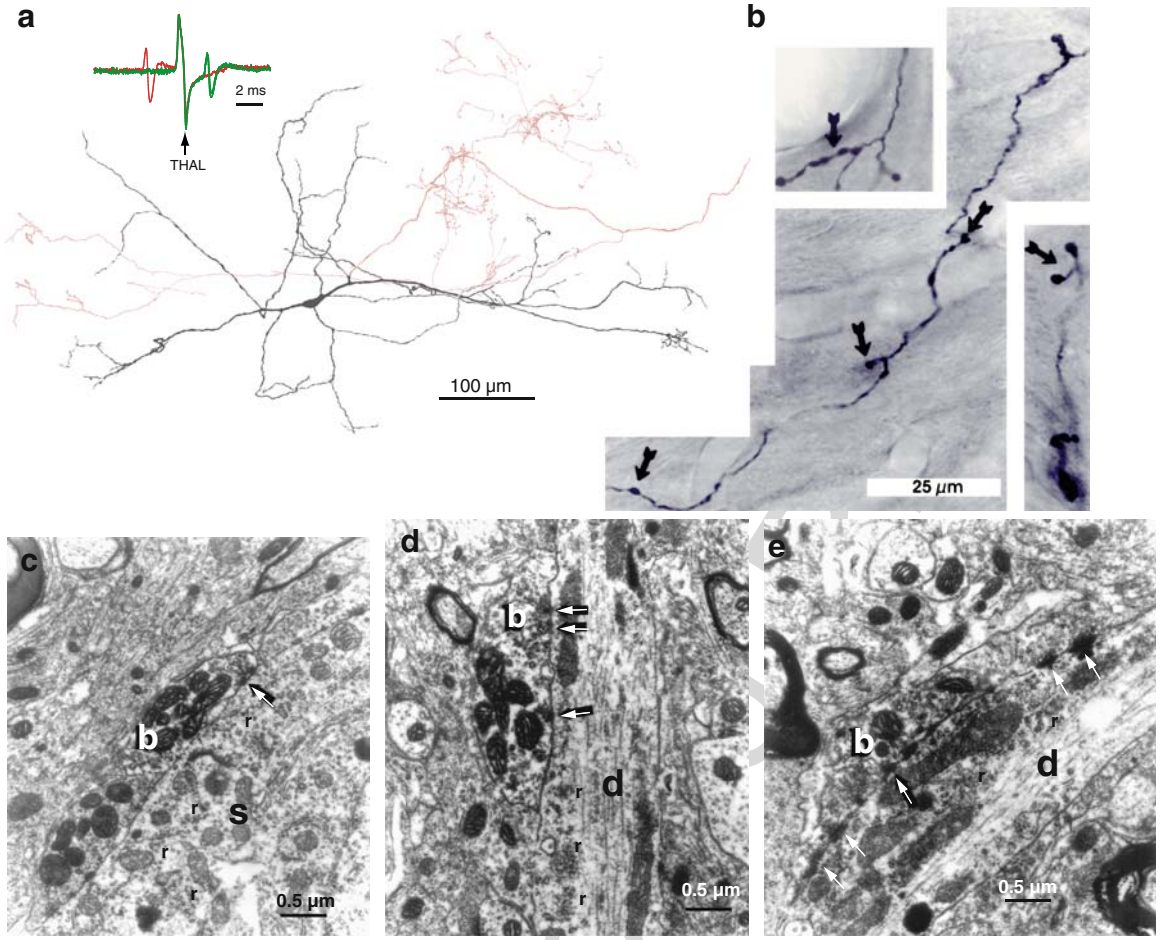

Fig. 3 Pars reticulata GABAergic projection neurons make synaptic contact with nigral dopaminergic neurons. (**a**) Reconstruction of an electrophysiologically identified rat nigrothalamic neuron juxtacellularly labeled with biocytin in vivo. The soma and dendrites are in black, the axon in red. Inset. 3 consecutive superimposed sweeps showing antidromic response of the nigrothalamic neuron following stimulation of the ventral thalamus (*arrow*). A collision is shown in the red trace. (**b**) High magnification light micrographs of portions of the local collateral arborization of a biocytin labeled nigrothalamic neuron. Note the varicosities (*arrows*) separated by long stretches of smooth axon. (**c**) Electron microscopic analysis of a biocytin filled varicosity shows that it is a large synaptic bouton (b) making a symmetric synapse (*white arrow*) onto the soma (s) of a dopaminergic neuron in pars compacta. Note the large number of free ribosomes (r) characteristic of dopaminergic neurons. (**d**) Large bouton (b) from a biocytin labeled nigrothalamic neuron makes a symmetric synapse onto a dopaminergic dendrite (d) in pars compacta. (**e**) Large biocytin-labeled bouton makes multiple symmetric contacts onto a large proximal dopaminergic dendrite in pars compacta

postsynaptic potential (IPSP) in unidentified nigral neurons that were almost certainly SNr GABAergic neurons (Precht and Yoshida 1971; Yoshida and Precht 1971) The IPSP had an onset latency of 14–20 ms and since an associated striatal-evoked field potential with the same latency was blocked by picrotoxin, this was considered to be a monosynaptic GABAergic response that we would today classify as being mediated by $GABA_A$ receptors. Subsequent in vivo studies in rats recording from electrophysiologically identified dopaminergic neurons revealed similar monosynaptic inhibitory responses following striatal stimulation (Collingridge and Davies 1981; Grace and Bunney 1985a; Tepper et al. 1990; Paladini and Tepper 1999). This effect would be expected, given the direct GABAergic projection from the striatum to SNc dopaminergic neurons (Bolam and Smith 1990).

However, when the stimulation intensity is decreased, SNc dopaminergic neurons respond with an increase in firing caused by the inhibition of SNr GABAergic neurons (Collingridge and Davies 1981; Grace and Bunney 1985a) that are more sensitive to GABAergic inhibition than dopaminergic neurons (Gulácsi et al. 2003; Fig. 5). Thus, under conditions of low to moderate levels of electrical stimulation, SNr GABAergic neurons are preferentially inhibited. The result is that SNc dopaminergic neurons are disinhibited from SNr GABAergic projection neurons and increase their firing rate (Grace and Bunney 1979, 1985a).

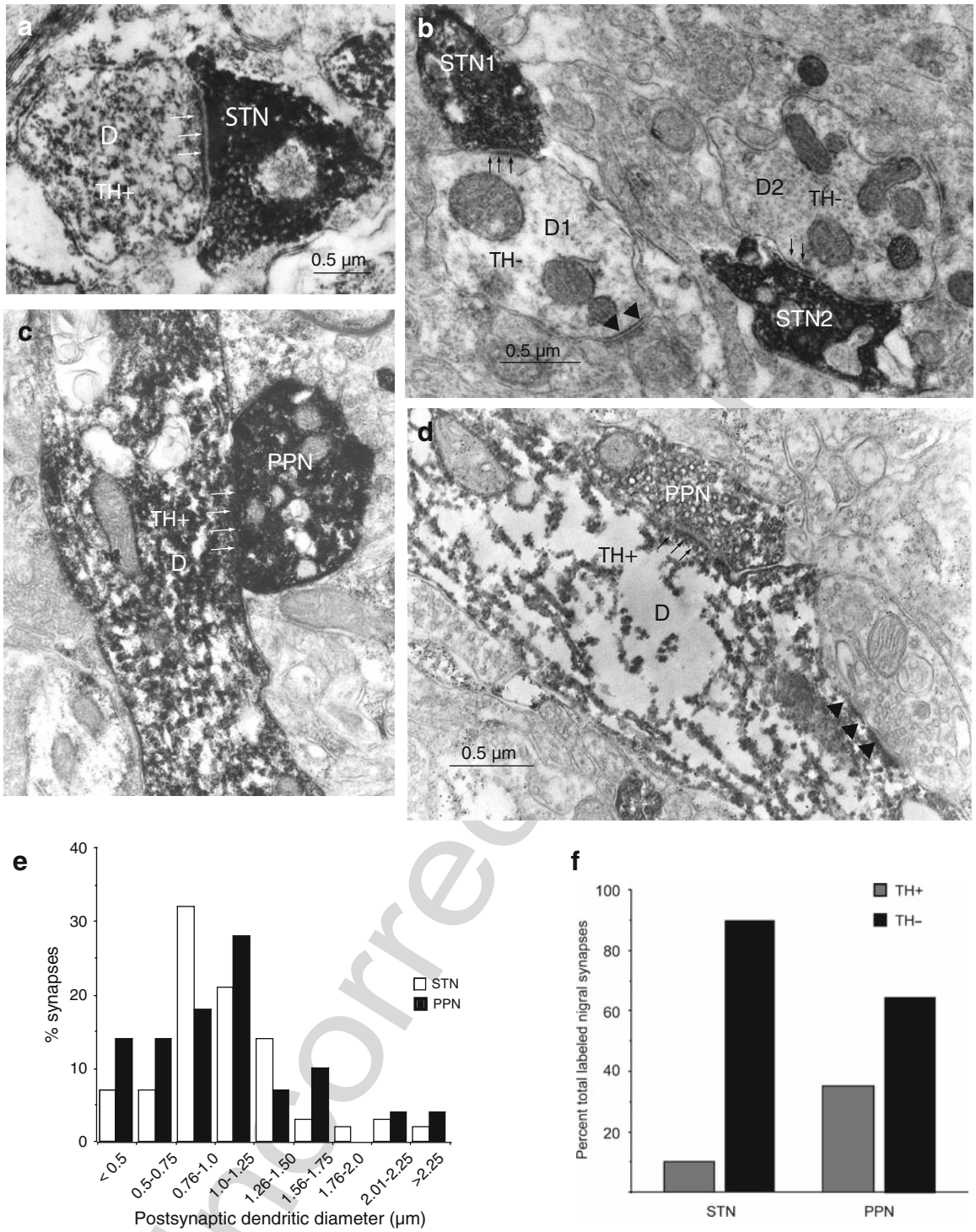

Fig. 4 Anterograde tracing of afferents from STN and PPN to substantia nigra. (**a**) A presynaptic bouton from STN labeled with PHA-L (STN) makes asymmetric synaptic contact (*arrows*) on TH-immunopositive (TH+) dopaminergic dendrite in pars compacta (D). (**b**) Two PHA-L labeled terminals from STN (STN1, STN2) make asymmetric synapses (*arrows*) onto medium-sized non-dopaminergic (TH-) dendrites (D1, D2) in pars reticulata. Note moderate postsynaptic thickenings that are much easier to see in the absence of TH immunolabeling. (**c**) Bouton (PPN) anterogradely labeled with PHA-L from PPN makes asymmetric synaptic contact (arrows) onto a medium sized dopaminergic (TH+) dendrite (D) in pars reticulata. (**d**) Another bouton labeled by PHA-L injection into the PPN makes a synapse onto a large proximal dopaminergic (TH+) dendrite in pars reticulata. (**e**) Histogram of the diameters of the dendrites at the site of synaptic contact made by afferents from STN and PPN showing that PPN afferents tend to make synapses with large, presumably more proximal dendrites than STN afferents. (**f**) Relative distribution of synaptic contacts in pars reticulata from STN and PPN afferents onto dopaminergic and non-dopaminergic dendrites. Note that the proportion of synapses made onto dopaminergic dendrites is much larger for boutons originating from PPN than from STN

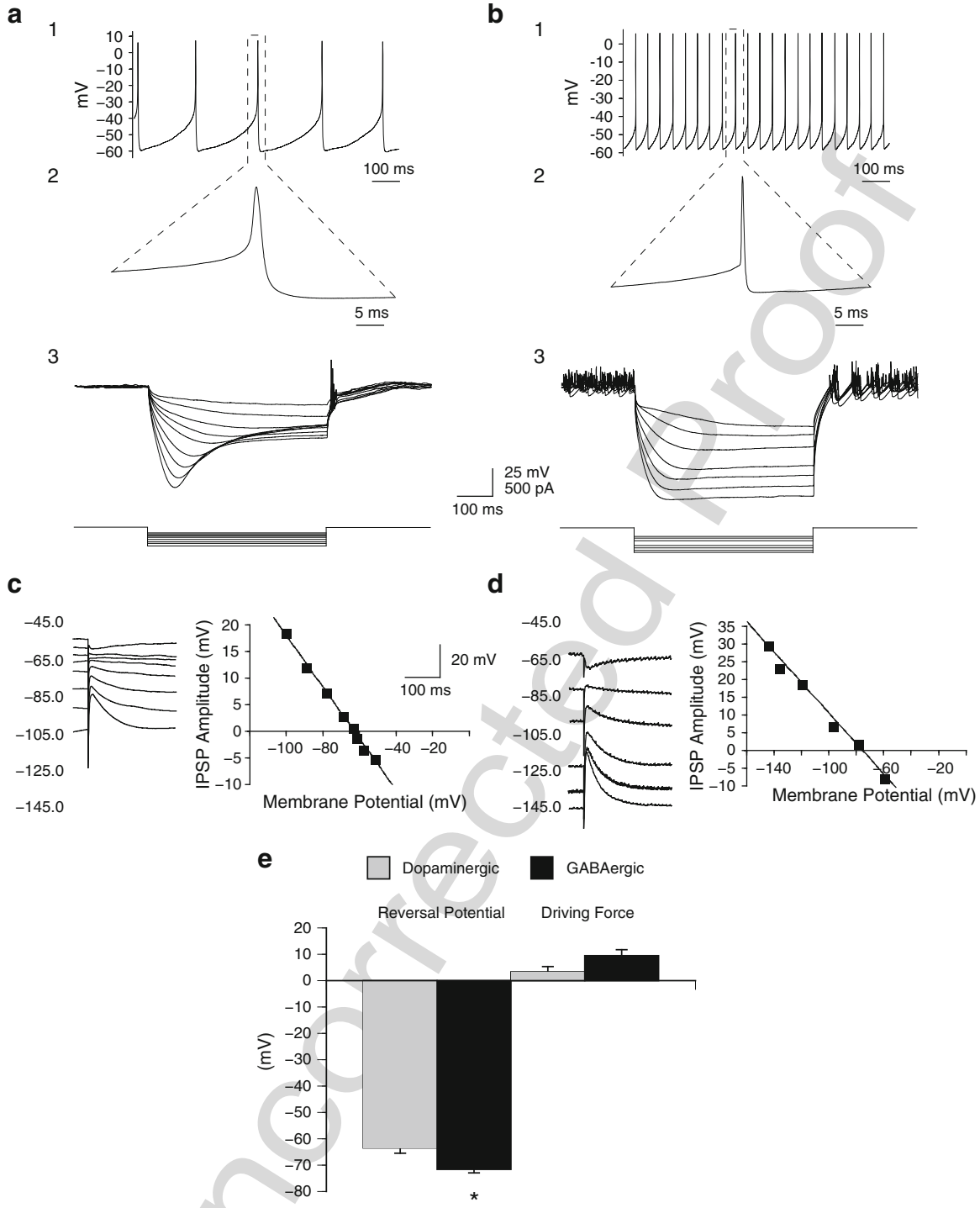

Fig. 5 The $GABA_A$ IPSP is less hyperpolarizing in SNc dopaminergic neurons than in SNr GABAergic neurons. (**a1, b1**) Spontaneous activity of a substantia nigra dopaminergic (**a1**) and GABAergic (**b1**) neuron in vitro. (**a2, b2**) The action potential width and afterhyperpolarization duration is greater for the dopaminergic neuron (**a2**) compared to the GABAergic neuron (**b2**). (**a3, b3**) Responses to hyperpolarizing current pulses delivered from rest exhibit a strong sag caused by I_h in a dopaminergic neuron (**a3**) but not in a GABAergic neuron (**b3**). These characteristics allow for identification of nigral dopaminergic and GABAergic neurons based on their physiological properties in vitro. (**c, d**) Gramicidin perforated-patch recording of an SNc dopaminergic neuron (**c**) and SNr GABAergic neuron (**d**) showing the IPSP recorded at varying membrane potentials following local stimulation of the SNr. Reversal potentials were determined from plots of the IPSP amplitude against the membrane potential. (**e**) The $GABA_A$ IPSP reversal potential was found to be less hyperpolarizing in dopaminergic neurons (-63.45 ± 2.02 mV) than in GABAergic neurons (-71.58 ± 1.37 mV). This corresponded to a greater hyperpolarizing driving force in GABAergic neurons (9.5 ± 2.2 mV) than in dopaminergic neurons (3.3 ± 2.0 mV). These findings indicate that nigral GABAergic neurons are more strongly hyperpolarized by GABA than the dopaminergic neurons, revealing an important mechanism underlying the seemingly paradoxical excitation of SNc dopaminergic neurons by GABAergic input and $GABA_A$ agonists through SNr projection neurons. $^*P < 0.01$. Modified from Gulácsi et al. 2003. Copyright 2003 the Society for Neuroscience

Globus Pallidus

Unlike afferents from the neostriatum the projection neurons of which fire slowly and episodically in vivo (Wilson 1993), the GP exerts a tonic inhibitory influence over SNc dopaminergic and SNr GABAergic neurons. Pallidal projection neurons fire spontaneously in vitro and exhibit very high spontaneous firing rates of ~10–100 Hz in vivo (DeLong 1971; Filion and Tremblay 1991; Nambu and Llinaś 1994; Celada et al. 1999; Cooper and Stanford 2000). The tonic inhibitory input generated by these high firing rates regularizes the firing pattern of SNc dopaminergic neurons in vivo. Electrical stimulation of the GP inhibits SNc dopaminergic neuron firing consistent with the monosynaptic innervation of SNc dopaminergic neurons by the GP (Paladini et al. 1999a). However, increasing pallidal neuronal activity by the local application of $GABA_A$ receptor antagonists paradoxically *increases* the number of SNc dopaminergic neurons exhibiting the bursty firing pattern and causes neurons exhibiting the random and pacemaker firing patterns to shift to the bursty firing pattern, rather than causing the expected inhibitory effects (Celada et al. 1999; Lee et al. 2004; Fig. 6). Functionally, the increase in burst firing caused by pallidal excitation leads to an increase in striatal dopamine levels (Lee et al. 2004; Fig. 6).

This is the same response that is observed when $GABA_A$ receptor antagonists are infused locally within the substantia nigra, suggesting that the chemical stimulation of the GP leads to a reduction in inhibitory drive to SNc dopaminergic neurons. The explanation for this seemingly paradoxical response is that while the chemical stimulation of the GP results in an asynchronous release of GABA in substantia nigra, electrical stimulation causes a synchronous release. Although the asynchronous release is sufficient to effectively inhibit the more sensitive SNr GABAergic projection neurons, it does not effectively inhibit the less sensitive dopaminergic neurons with the overall result being a GABAergic disinhibition. The electrical stimulus, however,

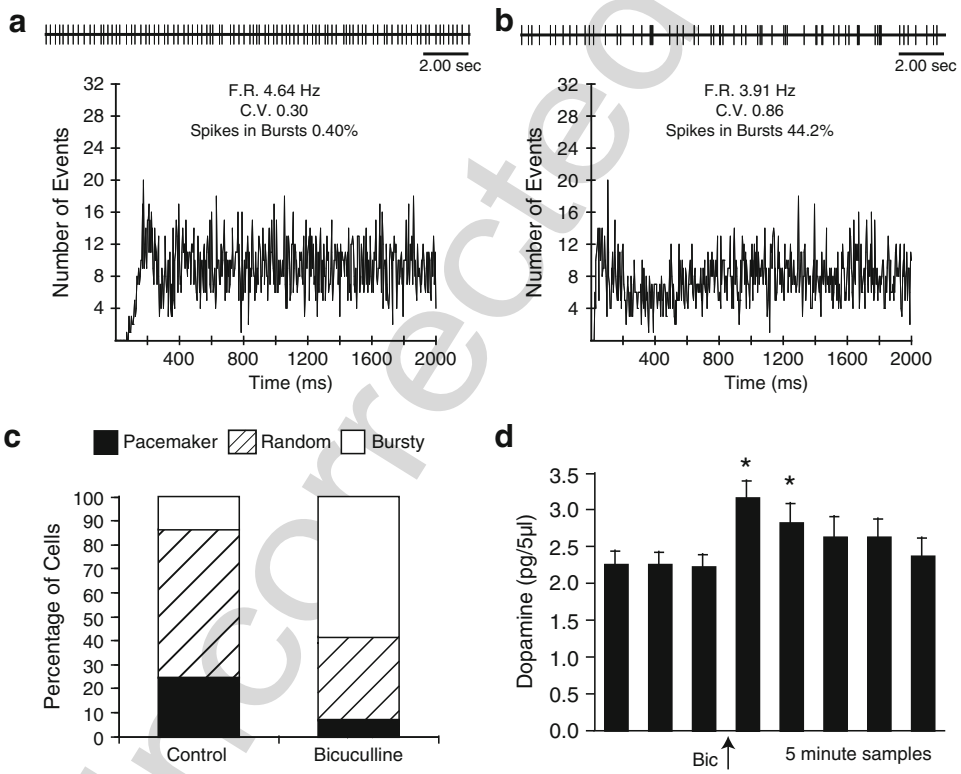

Fig. 6 Effects of pallidal excitation on SNc dopaminergic neuron firing pattern and striatal dopamine levels. (**a, b**) Autocorrelograms constructed from an extracellular recording of an SNc dopaminergic neuron in vivo. Portions of the raw spike train are shown above. This neuron was observed to exhibit a random firing pattern (**a**) which shifted to a bursty firing pattern following infusion of the $GABA_A$ receptor antagonist, bicuculline into the GP (**b**). Note that the firing rate (FR) was largely unchanged despite the significant increases in the coefficient of variation (CV) and overall percentage of total spikes fired in bursts. (**c**) The distribution of firing patterns exhibited by SNc dopaminergic neurons consisted mostly of the random firing pattern under control conditions, but pharmacological excitation of the GP with bicuculline shifted the distribution to one where the bursty firing pattern was most common. This is opposite to the effect that would be observed in response to a monosynaptic effect of the GP on SNc, demonstrating the important role of SNr GABAergic neurons in integrating synaptic input to the substantia nigra. (**d**) Simultaneous measurement of striatal dopamine levels with microdialysis revealed that pallidal excitation with bicuculline (*arrow*, Bic) led to a significant increase in striatal dopamine levels caused by the increase in burst firing. $^*P < 0.05$. Modified from Lee et al. 2004. Copyright 2004 IBRO

causes a massive synchronous release that directly inhibits both SNr projection neurons and dopaminergic neurons with the overall result being direct inhibition of the dopaminergic neuron (Celada et al. 1999; Paladini et al. 1999a; Lee et al. 2004; Tepper and Lee 2007; Brazhnik et al. 2008).

In contrast to the dramatic changes observed in firing pattern, the local application of $GABA_A$ antagonists or disinhibition caused by the chemical excitation of the GP produces less pronounced increases in the firing rate (Celada et al. 1999; Paladini and Tepper 1999; Lee et al. 2004). Conversely, inhibition of the GP results in a regularization of the firing of SNc dopaminergic neurons and a slight decrease in their firing rate as a result of reduced inhibition of SNr GABAergic neurons and the resultant increase in local inhibition (Celada et al. 1999).

Substantia Nigra Pars Reticulata

An important interaction between GABAergic SNr neurons and the overlying dopaminergic neurons was suggested by the finding of an inverse relationship between the spontaneous activity of some dopaminergic neurons and some pars reticulata nondopaminergic neurons in in vivo extracellular recordings (Grace and Bunney 1979). The study of this interaction has been complicated by the close proximity of the dopaminergic and GABAergic dendrites that are intermingled throughout SNr (Tepper et al. 1987). This precludes the direct stimulation of SNr GABAergic neurons and the recording of SNc dopaminergic neurons as has been used to study the afferent control exerted by other basal ganglia nuclei.

Although it has been postulated that intranigral inhibition might be carried out by specialized interneurons (Juraska et al. 1977; Francois et al. 1979; Grace and Bunney 1979, 1985a,b; Lacey et al. 1989; Johnson and North 1992; Bontempi and Sharp 1997; Hebb and Robertson 2000), the majority of the direct evidence suggests that the predominant sources of intranigral inhibition are the axon collaterals from SNr projection neurons (Deniau et al. 1982; Grofová et al. 1982; Tepper et al 1995; Celada et al. 1999; Paladini et al. 1999a; Lee and Tepper 2007b; Brazhnik et al. 2008).

The GABAergic output neurons of the SNr exhibit spontaneous, pacemaker-like firing at high rates both in vivo (~20–40 Hz) and in vitro (~10–40 Hz) (DeLong 1971; Deniau et al. 1978; Guyenet and Aghajanian 1978; Nakanishi et al. 1987b; Lacey et al. 1989; Yung et al. 1991; Richards et al. 1997; Celada et al. 1999; Gulácsi et al. 2003; Windels and Kiyatkin 2004; Atherton and Bevan 2005; Lee and Tepper 2007b) and are thus well suited to serve as a source of tonic inhibition and the mediators of disinhibition of dopaminergic neurons.

Spontaneous $GABA_A$ IPSPs are frequently encountered in SNc dopaminergic neurons in vitro, where afferent inhibitory projections from sources outside of the substantia nigra are disrupted, and local stimulation of the SNr in vitro elicits evoked IPSPs in dopaminergic neurons (Hajós and Greenfield, 1993, 1994; Häusser and Yung 1994; Fiorillo and Williams 1998; Saitoh et al. 2004; Gulácsi et al. 2003). Although these results are suggestive of the local inhibition of SNc dopaminergic neurons by SNr neurons, they could also be due to stimulus-evoked or spontaneous release of GABA from terminals arising from the striatum or GP (e.g., Iribe et al. 1999). The most definitive physiological evidence for the direct inhibition of SNc dopaminergic neurons by SNr projection neurons comes from the antidromic activation of local SNr axon collaterals by stimulating the thalamus or the superior colliculus in vivo, which produces powerful short latency inhibition of SNc dopaminergic neurons that cannot be mediated by anything other than monosynaptic synaptic connections made by the local axon collaterals of SNr projection neurons (Tepper et al. 1995; Paladini et al. 1999a; Brazhnik et al. 2008).

As mentioned earlier, SNr GABAergic neurons exhibit apparently greater sensitivity to inhibition by GABA than nigral GABAergic output neurons. This is due to different chloride regulatory mechanisms in the two cell types. The SNr projection neurons express KCC2, the typical potassium-chloride cotransporter found in most mature CNS neurons (Farrant and Kaila 2007) that keeps the intracellular chloride concentration low enough so that $GABA_A$ receptor stimulation results in a hyperpolarizing IPSP. Dopaminergic neurons, on the other hand, lack this cotransporter (although they do express a different, less efficient chloride exchanger) with the result that the opening of chloride channels by $GABA_A$ receptor activation produces a significantly smaller hyperpolarization that is responsible, at least in part, for the decreased sensitivity to GABAergic inhibition relative to the SNr output neurons (Gulácsi et al. 2003).

The increased sensitivity of SNr neurons to GABA and the resultant effects on the physiology of SNc dopaminergic neurons is manifest in several ways. SNc dopaminergic neurons respond to $GABA_A$ receptor agonists applied either locally in the SN or administered intravenously with an *increase* in firing (MacNeil et al. 1978; Walters and Lakoski 1978; Grace and Bunney 1979; Waszczak et al. 1980) concomitant to a decrease in the firing rate of SNr GABAergic neurons (MacNeil et al. 1978; Walters and Lakoski 1978; Grace and Bunney 1979; Waszczak et al. 1980). This unique property likely underlies, at least in part, the rewarding effects of many drugs with abuse potential that act as $GABA_A$ agonists such as ethanol, benzodiazepines, and barbiturates (Ross et al. 1982; Mereu et al. 1984; Mereu

and Gessa 1985; Tepper and Lee 2007). Further, the local infusion of a $GABA_A$ agonist within the substantia nigra results in *increased* striatal dopamine levels (Santiago and Westerink 1992), and dopaminergic neurons that lack μ opioid receptors are *excited* by μ agonists (Lacey et al. 1989; Johnson and North 1992). All of these seemingly paradoxical effects are likely to be caused by disinhibition mediated via the GABAergic SNr projection neurons.

Receptors Mediating GABAergic Inhibition of SNc Dopaminergic Neurons

Anatomical studies have demonstrated that SNc dopaminergic neurons possess both ionotropic $GABA_A$ and G-protein coupled $GABA_B$ receptors (Bowery et al. 1987; Nicholson et al. 1992; Charara et al. 2000; Boyes and Bolam 2003). $GABA_A$ receptors mediate a hyperpolarizing conductance that is carried mostly by chloride (Gulácsi et al. 2003; Farrant and Kaila 2007), while $GABA_B$ receptors activate a potassium conductance (Lacey et al. 1988). The activation of either $GABA_A$ or $GABA_B$ receptors produces hyperpolarization and/or suppression of firing in vitro and causes an additional regularization of firing pattern in vivo (Grace and Bunney 1979; Waszczak et al. 1980; Pinnock 1984; Lacey et al. 1988; Erhardt et al. 1998; Gulácsi et al. 2003).

However, the vast majority of the evidence from in vivo studies in rats has suggested that SNc dopaminergic neurons are subject to tonic suppression of burst firing and are phasically inhibited primarily through $GABA_A$ as opposed to $GABA_B$ receptors (Nakamura et al. 1979; Grace and Bunney 1985a; Tepper et al. 1995; Paladini and Tepper 1999). The inhibition produced by the stimulation of GABAergic afferents from the striatum, GP, or SNr in vivo was found to be blocked by $GABA_A$ but not $GABA_B$ receptor antagonists in rat (Paladini et al. 1999a). In fact, the local application of $GABA_B$ antagonists *potentiates* evoked inhibition and leads to the regularization of the firing pattern, suggesting that presynaptic $GABA_B$ autoreceptors, located on all the basal ganglia GABAergic nigral afferents, are tonically activated in vivo and suppress GABA release and reduce evoked inhibition of SNc dopaminergic neurons (Paladini et al. 1999a; Paladini and Tepper 1999; Boyes and Bolam 2003). Presynaptic $GABA_B$ receptors likely also suppress excitatory input to SNc dopaminergic neurons (Wu et al. 1999).

However, local electrical stimulation in vitro and especially high-frequency train stimulation can elicit slow, long-lasting, $GABA_B$-mediated IPSP and currents in SNc dopaminergic neurons, suggesting that $GABA_B$ receptor activation from synaptically released GABA does indeed occur, but for some reason is not detected in the in vivo experiments (Johnson and North 1992; Cameron and Williams 1993; Hajós and Greenfield, 1993, 1994; Häusser and Yung 1994; Saitoh et al. 2004). This is likely caused by the extrasynaptic location of $GABA_B$ receptors in relation to GABAergic synapses (Boyes and Bolam 2003). In this situation, GABA must overcome reuptake and diffuse from the synaptic cleft to activate the extrasynaptic receptors, as has been shown in the hippocampus (Scanziani 2000). In some cases, the rhythmic firing of GABAergic afferents can cause sufficient GABA release to overcome reuptake and activate the extrasynaptic $GABA_B$ receptors (Scanziani 2000), but this has not been observed following train stimulation of GABAergic afferents to SNc dopaminergic neurons in rat (Paladini et al. 1999a). The local application of $GABA_A$ but not $GABA_B$ receptor antagonists increases striatal dopamine levels, further indicating a tonic regulation by GABA through $GABA_A$ but not $GABA_B$ receptors (Santiago and Westerink 1992).

In recent in vivo experiments in mice, however, the stimulation of the striatum, GP, or SNr was shown to reliably induce inhibition with an early component mediated by $GABA_A$ receptors and a late protracted component mediated by $GABA_B$ receptors, even in response to single-pulse stimulation (Brazhnik et al. 2008). The late, $GABA_B$-mediated response was lengthened following the inhibition of GABA reuptake, suggesting that GABA reuptake mechanisms help to reduce $GABA_B$ receptor activation in vivo (Brazhnik et al. 2008). Interestingly, the application of a $GABA_B$ receptor antagonist in mice led to a slight decrease in the spontaneous firing rate and a slight regularization of the firing pattern of SNc dopaminergic neurons just as it does in rats (Tepper et al. 1995; Paladini and Tepper 1999) in the same neurons in which a blockade of postsynaptic $GABA_B$ receptors attenuated the late inhibition, as shown in Fig. 7. Thus, just as in rat, there appears to be a tonic presynaptic stimulation of $GABA_B$ autoreceptors without the tonic activation of postsynaptic $GABA_B$ receptors (Brazhnik et al. 2008). The appearance of the late, $GABA_B$-sensitive component in mice but not rats was attributed to the smaller size and greater packing density of neurons of the mouse brain resulting in similar stimuli evoking substantially greater GABA release that was able to escape reuptake and reach extrasynaptic $GABA_B$ receptors.

Responses to Glutamatergic Input

Subthalamic Nucleus

Subthalamic nucleus neurons fire spontaneously both in vivo and in vitro at ~6–30 Hz (Nakanishi et al. 1987a; Bergman

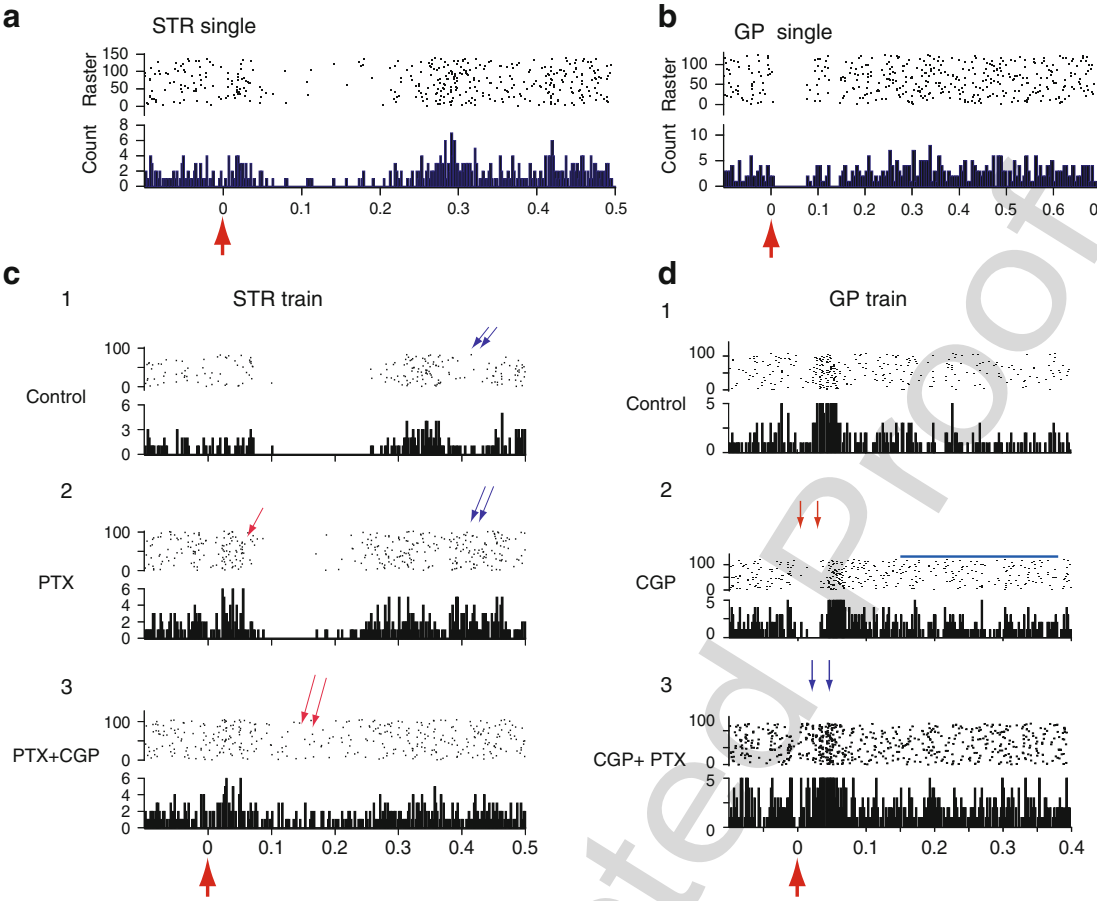

Fig. 7 GABAergic afferents to nigral dopaminergic neurons in mice exert both $GABA_A$ and $GABA_B$ receptor mediated effects. (**a**) Response of a substantia nigra dopaminergic neuron to single pulse stimulation of neostriatum (*arrow*). Note the rather long latency to the onset of the inhibitory response, the incomplete suppression of firing and the length of the inhibition that extends beyond 200 ms, all typical for striatal-evoked responses. (**b**) Similar stimulation of GP evokes an inhibitory response that exhibits a very short onset latency, a complete suppression of firing during the inhibition and shorter overall duration of inhibition than striatal-evoked responses (note different time scales in a and b). (**c**) The early and late components of the striatal-evoked inhibition of nigral dopaminergic neurons are mediated by different GABA receptors. (**c1**) Control recordings following trains of striatal stimulation (5 pulses of 300 μA at 100 Hz). Note the second period of inhibition seen at around 450 ms (*double blue arrows*). (**c2**) Local pressure application of $GABA_A$ receptor antagonist, picrotoxin (500 μM) completely blocks the early part of the inhibition (unmasking an excitatory response as well, *single red arrow*) and the delayed inhibition (*double blue arrows*) but does not affect the late component of the inhibition. (**c3**) Subsequent simultaneous application of picrotoxin and the $GABA_B$-selective antagonist, CGP-55845A (500 μ M) blocks both components of the evoked inhibition indicating that the early inhibition is due to $GABA_A$ receptor activation whereas the late inhibition is mediated by $GABA_B$ receptor stimulation. (**d**) Both presynaptic and postsynaptic $GABA_B$ effects can be seen in the same neuron. (**d1**) Control recordings of brief train stimuli delivered to GP at low intensity. (**d2**) Following application of CGP-55845A, the early inhibition is markedly strengthened due to increased $GABA_A$ receptor activation (*double red arrows*) as a result of the blockade of inhibitory $GABA_B$ autoreceptors on pallidonigral afferents. At the same time, CGP-55845A almost completely eliminates the late component of the inhibitory response (*horizontal blue line*) due to blockade of postsynaptic $GABA_B$ receptors. D3. Subsequent simultaneous application of picrotoxin and CGP-55845A eliminates all inhibition. Modified from (Brazhnik et al. 2008). Copyright 2008 by the Society for Neuroscience

et al. 1994; Wichmann et al. 1994; Bevan and Wilson 1999; Beurrier et al. 1999; Do and Bean 2003; Hallworth et al. 2003; Wilson et al. 2006), thus providing SNc dopaminergic neurons with a source of tonic glutamatergic input.

Glutamatergic input, particularly via NMDA receptor stimulation, induces burst firing in vivo while blocking NMDA receptors in vivo leads to a regularization of firing pattern (Grace and Bunney 1984; Charlety et al 1991; Overton and Clark 1992, 1997; Chergui et al. 1993). Similar results have been obtained in vitro (Johnson et al. 1992; Morikawa et al. 2003; Blythe et al. 2007). Lesions or pharmacological inhibition of the STN similarly decreases burst firing in SNc dopaminergic neurons (Smith and Grace 1992), most likely due to the decrease in NMDA receptor stimulation.

Burst firing can also be produced in vivo by the local blockade of $GABA_A$ receptors. The local application of bicuculline or picrotoxin produces intense burst firing

(Tepper et al. 1995; Paladini and Tepper 1999; Brazhnik et al. 2008) as does the disinhibition of the GABAergic input from SNr (Celada et al. 1999; Lee et al. 2004). Either $GABA_A$ or $GABA_B$ receptor stimulation can prevent NMDA-induced burst firing in vivo or in vitro (Engberg et al. 1993; Seutin et al. 1994; Paladini et al. 1999b; Erhardt et al. 2002): an effect explained in computational studies by alterations in the dynamical interaction among membrane potential, conductance, and dendritic coupling (Canavier 1999; Komendantov et al. 2004; Kusnetsov et al. 2006). Thus, although glutamatergic input to NMDA receptors promotes burst firing, this effect of glutamatergic input on bursting in dopaminergic neurons is powerfully modulated by GABAergic afferents.

Experimentally induced increases in the activity of the STN by electrical or chemical stimulation have led to mixed effects on SNc dopaminergic neurons. Early in vivo recordings revealed a short latency excitation of SNc dopaminergic neurons elicited by STN stimulation (Hammond et al 1978). Later experiments using either electrical or chemical stimulation of the STN in vivo revealed mixed excitatory and inhibitory responses, the latter being attributed to polysynaptic inhibition evoked by STN-induced excitation of pallidal or nigral GABAergic neurons (Robledo and Féger 1990; Féger and Robledo 1991; Smith and Grace 1992; Chergui et al. 1994a), with the initial short latency response consisting most often of inhibition (Smith and Grace 1992). However, longer duration pharmacological stimulation of the STN increased firing rate and induced burst firing in SNc dopaminergic neurons, which was at least partly due to the activation of NMDA receptors (Smith and Grace 1992; Chergui et al. 1994a). The explanation for these mixed effects was revealed to be a near simultaneous activation of a monosynaptic EPSP that was blocked by a non-NMDA receptor antagonist (although under certain conditions, an MK-801 sensitive component could be seen) and polysynaptic IPSP that was blocked by a $GABA_A$ receptor antagonist. The mixed EPSP/IPSP survived transection of striatonigral and pallidonigral pathways indicating that the IPSP was due, at least in part, to STN-evoked activation of the axon collaterals of pars reticulata projection neurons (Iribe et al. 1999).

Furthermore, glutamatergic input can modify the firing pattern of SNr GABAergic neurons and evoke burst firing in those neurons as well (Ibáñez-Sandoval et al. 2007; Lee and Tepper 2007a). Therefore, the STN likely controls both the timing and pattern of inhibition coming from the SNr.

Although many of the effects of glutamate on dopaminergic neurons are mediated by NMDA receptors (Johnson and North 1992; Johnson et al. 1992; Overton and Clark 1992, 1997; Chergui et al. 1993; Meltzer et al. 1997b; Paladini et al. 1999b) while others are mediated by non-NMDA receptors (Zhang et al. 1994; Blythe et al. 2007), glutamatergic input from the STN might affect SNc dopaminergic neurons through other mechanisms (Fiorillo and Williams 1998; Morikawa et al. 2003; Blythe et al. 2007). SNc dopaminergic neurons express both group I metabotropic glutamate receptors as well as ionotropic glutamate receptors (Martin et al. 1992; Ong et al. 1997; Paquet et al. 1997; Kosinski et al. 1998; Yung 1998; Chatha et al. 2000; Hubert et al. 2001; Kaneda et al. 2003). The actions of metabotropic glutamate receptors on the SNc dopaminergic neurons are complex. Group I receptor activation has been reported to cause an IPSP following brief agonist exposure in vitro that densensitizes following continued agonist exposure revealing an excitatory postsynaptic potential (EPSP) (Mercuri et al. 1993; Shen and Johnson 1997; Fiorillo and Williams 1998). The initial hyperpolarization is caused by calcium-activated potassium (SK) channel activation, while the depolarization is caused by activation of nonselective transient receptor potential (TRP) channels (Fiorillo and Williams 1998; Tozzi et al. 2003; Bengtson et al. 2004).

In vivo, and in vitro metabotropic glutamate receptor activation has been reported to potentiate burst firing and to exert mixed effects on the firing rate of SNc dopaminergic neurons. Similar to the $GABA_B$ receptors, metabotropic glutamate receptors are localized at extrasynaptic sites, suggesting that reuptake might serve as a significant barrier to their activation (Hubert et al. 2001). In addition, group II and III metabotropic glutamate receptors have been reported to suppress excitatory synaptic input to SNc dopaminergic neurons (Wigmore and Lacey 1998; Valenti et al. 2005; Wang et al. 2005), suggesting that glutamate can affect the strength of afferent input which might act at ionotropic receptors (Meltzer et al. 1997a; Prisco et al. 2002).

Therefore, glutamatergic input to the substantia nigra can directly excite SNc dopaminergic neurons, indirectly inhibit them by exciting SNr GABAergic neurons, and directly inhibit or excite them by activating metabotropic glutamate receptors on the dopaminergic neurons.

Responses to Cholinergic Input

Pedunculopontine Nucleus

Although there is some heterogeneity in the physiological properties of PPN neurons and the identity of the neurotransmitters the neurons are releasing is unclear due to the high degree of colocalization of acetylcholine with glutamate, given that these neurons fire spontaneously at ~0.5–20 Hz in vivo and in vitro (Scarnati et al. 1987; Takakusaki et al 1997), it seems reasonable to assume that SNc dopaminergic neurons receive tonic cholinergic and glutamatergic input

from the PPN. Consistent with this, the firing rate of SNc dopaminergic neurons decreases in response to the microinfusion of exogenous acetylcholinesterase, which decreases cholinergic tone to SNc dopaminergic neurons (Greenfield et al. 1981).

Electrical stimulation of the PPN either in vitro or in vivo produces excitatory responses in SNc dopaminergic neurons. Excitatory postsynaptic potentials elicited by PPN stimulation in vitro are partly blocked by glutamate receptor antagonists and wholly blocked by the addition of acetylcholine receptor antagonists (Futami et al. 1995). In vivo electrical stimulation of the PPN produces short latency activation of most neurons recorded, which is also blocked by glutamate (non-NMDA) and acetylcholine receptor antagonists (Scarnati et al. 1986; Scarnati et al. 1987; Di Loreto et al. 1992; Lokwan et al. 1999). It is possible that the glutamatergic input to SNc dopaminergic neurons from the PPN favors the activation of non-NMDA receptors (Di Loreto et al. 1992; Meltzer et al. 1997b), but the basis for this is unclear. Nevertheless, the activity seen in SNc dopaminergic neurons following electrical stimulation of the PPN frequently contains burst firing (Lokwan et al. 1999). Chemical stimulation of the PPN results in an increase in burst firing, but not the firing rate of ventral tegmental area dopaminergic neurons, which are similar but not identical to nigral dopaminergic neurons in their responses to afferent input (Floresco et al. 2003; Keath et al. 2007).

Receptors Mediating Cholinergic Actions on SNc Dopaminergic Neurons

Anatomical studies have demonstrated the presence of both ionotropic nicotinic receptors and G-protein coupled muscarinic receptors in the substantia nigra (Deutch et al. 1987; Nastuk and Graybiel 1991). Nicotinic agonists potentiate glutamatergic EPSPs (Yamashita and Isa 2004) and the firing rate of nigral dopaminergic neurons decreases in response to a nicotinic antagonist (Clarke et al. 1985). The infusion of a muscarinic antagonist into the SN reduces striatal dopamine levels (Miller and Blaha 2005). Thus, both nicotinic and muscarinic receptors contribute to the tonic cholinergic modulation of SNc dopaminergic neuron activity. In addition, there are likely presynaptic effects mediated by the cholinergic input as acetylcholine acts to decrease glutamatergic and GABAergic input to midbrain dopaminergic neurons through muscarinic receptors (Grillner et al. 2000; Grillner and Mercuri 2002; Zheng and Johnson 2003) and enhances both glutamatergic and GABAergic inputs through nicotinic receptors (Mansvelder et al. 2002, but see Grillner and Mercuri 2002).

Peripherally administered nicotine induces an increase in the firing rate as well as burst firing in SNc dopaminergic neurons in vivo (Lichtensteiger et al. 1976, 1982; Clarke et al. 1985; Grenhoff et al. 1986). In vitro, nicotinic receptor stimulation causes a depolarization and increase in firing rate, but not burst firing, in midbrain dopaminergic neurons as well as the subsequent activation of a calcium-activated nonselective cation conductance (Calabresi et al. 1989; Pidoplichko et al. 1997; Sorenson et al. 1998; Yin and French 2000; Matsubayashi et al. 2003; Yamashita and Isa 2003).

Muscarinic receptor stimulation causes an increase in firing rate and burst firing in ventral tegmental area neurons in vivo, but only the effect on firing rate, not burst firing is observed in SNc dopaminergic neurons (Gronier and Rasmussen 1998). In vitro, muscarinic (M1) receptor stimulation causes a depolarization of SNc dopaminergic neurons and an increase in their spontaneous firing rate and the frequency of oscillatory potentials underlying firing (Lacey et al. 1990; Scroggs et al. 2001). However, with varying durations of activation, muscarinic receptors have been observed to cause hyperpolarization with brief activation and depolarization with more prolonged activation (Fiorillo and Williams 2000; Blythe et al. 2007). The initial hyperpolarization is caused by the activation of an SK channel, while the depolarization is likely caused by the activation of a nonselective cation current (Lacey et al. 1990; Fiorillo and Williams 2000). Nevertheless, the main effect of PPN stimulation is an increase in striatal dopamine levels, suggesting that the main role of the mixed input from the PPN is to increase activity in SNc dopaminergic neurons (Forster and Blaha 2003).

Summary and Conclusions

Though receiving input from outside the basal ganglia, the afferents from within the basal ganglia play a major role in the control and modulation of the firing rate and the pattern of activity of substantia nigra dopaminergic neurons. Although these neurons do not require any synaptic input to generate spontaneous activity, a tonic glutamatergic input from the STN and PPN increases their firing rate and appears necessary for burst firing. Burst firing is powerfully suppressed by GABAergic input originating from striatum, globus pallidus, and substantia nigra pars reticulata projection neurons and modulated by cholinergic input through both nicotinic and muscarinic receptors, as well as metabotropic glutamate receptors. Glutamatergic and cholinergic G-protein coupled receptors have been shown to attenuate synaptically evoked activity in SNc dopaminergic neurons in vitro, suggesting that brief, synaptically evoked activation

of these receptors is generally inhibitory, but different responses could be expected with varying durations of activation as might occur in vivo. Therefore, GABAergic, cholinergic, and metabotropic glutamate receptors largely act as gain control mechanisms, decreasing and increasing the effect of glutamate acting through ionotropic receptors on the firing pattern of SNc dopaminergic neurons.

The interactions of afferent input that shape the activity of SNc dopaminergic neurons are complex and involve a multitude of ionotropic and metabotropic receptors acting directly on the neurons themselves, as well as presynaptically shaping the inputs to them. In addition, the neurons can modulate the input they receive on a local level through dendritic dopamine release leading to the activation of presynaptic dopamine receptors that affect GABA release, as well as their own responsiveness to afferent input by controlling dendritic excitability through D2 autoreceptors. The complex actions and interactions of afferent input to nigral dopaminergic neurons serve as the basis for the signaling repertoire displayed by these neurons, which through their effects on forebrain dopamine levels, influences much of the functioning of the basal ganglia as a whole.

Conflicts of interest statement We declare that we have no conflict of interest.

Acknowledgments Supported in part by NS034865 (JMT). We thank Fulva Shah for helpful comments on the manuscript.

References

Atherton JF, Bevan MD (2005) Ionic mechanisms underlying autonomous action potential generation in the somata and dendrites of GABAergic substantia nigra pars reticulata neurons in vitro. J Neurosci 25:8272–8281

Bean AJ, Roth RH (1991) Extracellular dopamine and neurotensin in rat prefrontal cortex in vivo: effects of median forebrain bundle stimulation frequency, stimulation pattern, and dopamine autoreceptors. J Neurosci 11:2694–2702

Bengtson CP, Tozzi A, Bernardi G, Mercuri NB (2004) Transient receptor potential-like channels mediate metabotropic glutamate receptor EPSCs in rat dopamine neurones. J Physiol 555: 323–330

Beninato M, Spencer RF (1988) The cholinergic innervation of the rat substantia nigra: a light and electron microscopic immunohistochemical study. Exp Brain Res 72:178–184

Bergman H, Wichmann T, Karmon B, DeLong MR (1994) The primate STN. II. Neuronal activity in the MPTP model of Parkinsonism. J Neurophysiol 72:507–520

Beurrier C, Congar P, Bioulac B, Hammond C (1999) STN neurons switch from single-spike activity to burst-firing mode. J Neurosci 19:599–609

Bevan MD, Wilson CJ (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J Neurosci 19:7617–7628

Bevan MD, Bolam JP, Crossman AR (1994) Convergent synaptic input from the neostriatum and the subthalamus onto identified nigrothalamic neurons in the rat. Eur J NeuroSci 6:320–334

Bevan MD, Smith AD, Bolam JP (1996) The substantia nigra as a site of synaptic integration of functionally diverse information arising from the ventral pallidum and the globus pallidus in the rat. Neuroscience 75:5–12

Bickford ME, Hall WC (1992) The nigral projection to predorsal bundle cells in the superior colliculus of the rat. J Comp Neurol 319:11–33

Blythe SN, Atherton JF, Bevan MD (2007) Synaptic activation of dendritic AMPA and NMDA receptors generates transient high-frequency firing in substantia nigra dopamine neurons in vitro. J Neurophysiol 97:2837–2850

Bolam JP, Smith Y (1990) The GABA and substance P input to dopaminergic neurones in the substantia nigra of the rat. Brain Res 529:57–78

Bolam JP, Francis CM, Henderson Z (1991) Cholinergic input to dopaminergic neurons in the substantia nigra: a double immunocytochemical study. Neuroscience 41:483–494

Bontempi B, Sharp FR (1997) Systemic morphine-induced Fos protein in the rat striatum and nucleus accumbens is regulated by mu opioid receptors in the substantia nigra and ventral tegmental area. J Neurosci 17:8596–8612

Bowery NG, Hudson AL, Price GW (1987) $GABA_A$ and $GABA_B$ receptor site distribution in the rat central nervous system. Neuroscience 20:365–383

Boyes J (2004) The Microcircuitry of the Substantia Nigra. Thesis, Lincoln College, Oxford University, D. Phil

Boyes J, Bolam JP (2003) The subcellular localization of $GABA_B$ receptor subunits in the rat substantia nigra. Eur J NeuroSci 18:3279–3293

Brazhnik E, Shah F, Tepper JM (2008) GABAergic afferents activate both $GABA_A$ and $GABA_B$ receptors in mouse substantia nigra dopaminergic neurons in vivo. J Neurosci 28(41):10386–10398

Bunney BS, Walters JR, Roth RH, Aghajanian GK (1973) Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. J Pharmacol Exp Ther 185:560–571

Calabresi P, Lacey MG, North RA (1989) Nicotinic excitation of rat ventral tegmental neurones in vitro studied by intracellular recording. Br J Pharmacol 98:135–140

Cameron DL, Williams JT (1993) Dopamine D1 receptors facilitate transmitter release. Nature 366:344–347

Canavier CC (1999) Sodium dynamics underlying burst firing and putative mechanisms for the regulation of the firing pattern in midbrain dopamine neurons: a computational approach. J Comput Neurosci 6:49–69

Celada P, Paladini CA, Tepper JM (1999) GABAergic control of rat substantia nigra dopaminergic neurons: role of globus pallidus and substantia nigra pars reticulata. Neuroscience 89:813–825

Chang HT, Kita H, Kitai ST (1984) The ultrastructural morphology of the subthalamic-nigral axon terminals intracellularly labeled with horseradish peroxidase. Brain Res 299:182–185

Charara A, Smith Y, Parent A (1996) Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: phaseolus vulgaris-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. J Comp Neurol 364:254–266

Charara A, Heilman TC, Levey AI, Smith Y (2000) Pre- and postsynaptic localization of $GABA_B$ receptors in the basal ganglia in monkeys. Neuroscience 95:127–140

Charlety PJ, Grenhoff J, Chergui K, De la Chapelle B, Buda M, Svensson TH, Chouvet G (1991) Burst firing of mesencephalic dopamine neurons is inhibited by somatodendritic application of kynurenate. Acta Physiol Scand 142:105–112

Chatha BT, Bernard V, Streit P, Bolam JP (2000) Synaptic localization of ionotropic glutamate receptors in the rat substantia nigra. Neuroscience 101:1037–1051

Chen BT, Rice ME (2002) Synaptic regulation of somatodendritic dopamine release by glutamate and GABA differs between substantia nigra and ventral tegmental area. J Neurochem 81: 158–169

Chergui K, Charléty PJ, Akaoka H, Saunier CF, Brunet JL, Buda M, Svensson TH, Chouvet G (1993) Tonic activation of NMDA receptors causes spontaneous burst discharge of rat midbrain dopamine neurons in vivo. Eur J NeuroSci 5:137–144

Chergui K, Akaoka H, Charléty PJ, Saunier CF, Buda M, Chouvet G (1994a) STN modulates burst firing of nigral dopamine neurones via NMDA receptors. NeuroReport 5:1185–1188

Chergui K, Suaud-Chagny MF, Gonon F (1994b) Nonlinear relationship between impulse flow, dopamine release and dopamine elimination in the rat brain in vivo. Neuroscience 62: 641–645

Clarke PB, Hommer DW, Pert A, Skirboll LR (1985) Electrophysiological actions of nicotine on substantia nigra single units. Br J Pharmacol 85:827–835

Clavier RM, Atmadja S, Fibiger HC (1976) Nigrothalamic projections in the rat as demonstrated by orthograde and retrograde tracing techniques. Brain Res Bull 1:379–384

Clements JR, Grant S (1990) Glutamate-like immunoreactivity in neurons of the laterodorsal tegmental and pedunculopontine nuclei in the rat. Neurosci Lett 120:70–73

Cobb WS, Abercrombie ED (2002) Distinct roles for nigral GABA and glutamate receptors in the regulation of dendritic dopamine release under normal conditions and in response to systemic haloperidol. J Neurosci 22:1407–1413

Cobb WS, Abercrombie ED (2003a) Relative involvement of globus pallidus and STN in the regulation of somatodendritic dopamine release in substantia nigra is dopamine-dependent. Neuroscience 119: 777–786

Cobb WS, Abercrombie ED (2003b) Differential regulation of somatodendritic and nerve terminal dopamine release by serotonergic innervation of substantia nigra. J. Neurochem 84: 575–584

Collingridge GL, Davies J (1981) The influence of striatal stimulation and putative neurotransmitters on identified neurones in the rat substantia nigra. Brain Res 212:345–359

Cooper AJ, Stanford IM (2000) Electrophysiological and morphological characteristics of three subtypes of rat globus pallidus neurone in vitro. J Physiol 527:291–304

Damlama M (1994) Subthalamic and pedunculopontine inputs to substantia nigra: a light and electron microscopic analysis. Ph.D. Thesis, Rutgers University University Microfilms International

DeLong MR (1971) Activity of pallidal neurons during movement. J Neurophysiol 34:414–427

Deniau JM, Chevalier G (1992) The lamellar organization of the rat substantia nigra pars reticulata: distribution of projection neurons. Neuroscience 46:361–377

Deniau JM, Hammond C, Riszk A, Féger J (1978) Electrophysiological properties of identified output neurons of the rat substantia nigra (pars compacta and pars reticulata): evidences for the existence of branched neurons. Exp Brain Res 32:409–422

Deniau JM, Kitai ST, Donoghue JP, Grofova I (1982) Neuronal interactions in the substantia nigra pars reticulata through axon collaterals of the projection neurons. An electrophysiological and morphological study. Exp Brain Res 47:105–113

Deutch AY, Holliday J, Roth RH, Chun LL, Hawrot E (1987) Immunohistochemical localization of a neuronal nicotinic acetylcholine receptor in mammalian brain. Proc Natl Acad Sci USA 84: 8697–8701

Di Loreto S, Florio T, Scarnati E (1992) Evidence that non-NMDA receptors are involved in the excitatory pathway from the pedunculopontine region to nigrostriatal dopaminergic neurons. Exp Brain Res 89:79–86

Do MT, Bean BP (2003) Subthreshold sodium currents and pacemaking of subthalamic neurons: modulation by slow inactivation. Neuron 39:109–120

Engberg G, Kling-Petersen T, Nissbrandt H (1993) $GABA_B$-receptor activation alters the firing pattern of dopamine neurons in the rat substantia nigra. Synapse 15:229–238

Erhardt S, Andersson B, Nissbrandt H, Engberg G (1998) Inhibition of firing rate and changes in the firing pattern of nigral dopamine neurons by gamma-hydroxybutyric acid (GHBA) are specifically induced by activation of $GABA_B$ receptors Naunyn Schmiedebergs. Arch Pharmacol 357:611–619

Erhardt S, Mathé JM, Chergui K, Engberg G, Svensson TH (2002) GABA(B) receptor-mediated modulation of the firing pattern of ventral tegmental area dopamine neurons in vivo Naunyn Schmiedebergs. Arch Pharmacol 65:173–80

Fá M, Mereu G, Ghiglieri V, Meloni A, Salis P, Gessa GL (2003) Electrophysiological and pharmacological characteristics of nigral dopaminergic neurons in the conscious, head-restrained rat. Synapse 48:1–9

Farrant M, Kaila K (2007) The cellular, molecular and ionic basis of $GABA_A$ receptor signalling. Prog Brain Res 160:59–87

Faull RL, Mehler WR (1978) The cells of origin of nigrotectal, nigrothalamic and nigrostriatal projections in the rat. Neuroscience 3:989–1002

Féger J, Robledo P (1991) The effects of activation or inhibition of the stn on the metabolic and electrophysiological activities within the pallidal complex and substantia nigra in the rat. Eur J NeuroSci 3:947–952

Filion M, Tremblay L (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 547:142–151

Fiorillo CD, Williams JT (1998) Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons. Nature 394:78–82

Fiorillo CD, Williams JT (2000) Cholinergic inhibition of ventral midbrain dopamine neurons. J Neurosci 20:7855–7860

Floresco SB, West AR, Ash B, Moore H, Grace AA (2003) Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 6:968–973

Forster GL, Blaha CD (2003) Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. Eur J NeuroSci 17:751–762

Francois C, Percheron G, Yelnik J, Heyner S (1979) Demonstration of the existence of small local circuit neurons in the Golgi-stained primate substantia nigra. Brain Res 172:160–164

Freeman AS, Meltzer LT, Bunney BS (1985) Firing properties of substantia nigra dopaminergic neurons in freely moving rats. Life Sci 36:1983–1994

Futami T, Takakusaki K, Kitai ST (1995) Glutamatergic and cholinergic inputs from the pedunculopontine tegmental nucleus to dopamine neurons in the substantia nigra pars compacta. Neurosci Res 21:331–342

Gerfen CR, Wilson CJ (1996) The basal ganglia. In: Swanson LW, Bjorklund A, Hokfelt T (eds) Handbook of Chemical Neuroanatomy (12th Edition). Elsevier, Amsterdam, pp 371–468

Gonon FG (1988) Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry. Neuroscience 24:19–28

Gonon FG, Buda MJ (1985) Regulation of dopamine release by impulse flow and by autoreceptors as studied by in vivo voltammetry in the rat striatum. Neuroscience 14:765–774

González-Hernández T, Rodriguez M (2000) Compartmental organization and chemical profile of dopaminergic and GABAergic neurons in the substantia nigra of the rat. J Comp Neurol 421:107–135

Gould E, Woolf NJ, Butcher LL (1989) Cholinergic projections to the substantia nigra from the pedunculopontine and laterodorsal tegmental nuclei. Neuroscience 28:611–623

Grace AA, Bunney BS (1979) Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata inhibitory neurons. Eur J Pharmacol 59:211–218

Grace AA, Bunney BS (1984) The control of firing pattern in nigral dopamine neurons: burst firing. J Neurosci 4:2877–2890

Grace AA, Bunney BS (1985a) Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Brain Res 333:271–284

Grace AA, Bunney BS (1985b) Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Brain Res 333:285–298

Grace AA, Onn SP (1989) Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded in vitro. J Neurosci 9:3463–3481

Greenfield SA, Stein JF, Hodgson AJ, Chubb IW (1981) Depression of nigral pars compacta cell discharge by exogenous acetylcholinesterase. Neuroscience 6:2287–2295

Grenhoff J, Aston-Jones G, Svensson TH (1986) Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol Scand 128:351–358

Grillner P, Mercuri NB (2002) Intrinsic membrane properties and synaptic inputs regulating the firing activity of the dopamine neurons. Behav Brain Res 130:149–169

Grillner P, Berretta N, Bernardi G, Svensson TH, Mercuri NB (2000) Muscarinic receptors depress GABAergic synaptic transmission in rat midbrain dopamine neurons. Neuroscience 96:299–307

Grofová I (1975) The identification of striatal and pallidal neurons projecting to substantia nigra. An experimental study by means of retrograde axonal transport of horseradish peroxidase. Brain Res 91:286–291

Grofová I, Rinvik E (1970) An experimental electron microscopic study on the striatonigral projection in the cat. Exp Brain Res 11:249–262

Grofová I, Deniau JM, Kitai ST (1982) Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP. J Comp Neurol 208:352–368

Gronier B, Rasmussen K (1998) Activation of midbrain presumed dopaminergic neurones by muscarinic cholinergic receptors: an in vivo electrophysiological study in the rat. Br J Pharmacol 124:455–464

Gulácsi A, Lee CR, Sík A, Viitanen T, Kaila K, Tepper JM, Freund TF (2003) Cell type-specific differences in chloride-regulatory mechanisms and $GABA_A$ receptor-mediated inhibition in rat substantia nigra. J Neurosci 23:8237–8246

Guyenet PG, Aghajanian GK (1978) Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra. Brain Res 150:69–84

Hajós M, Greenfield SA (1993) Topographic heterogeneity of substantia nigra neurons: diversity in intrinsic membrane properties and synaptic inputs. Neuroscience 55:919–934

Hajós M, Greenfield SA (1994) Synaptic connections between pars compacta and pars reticulata neurones: electrophysiological evidence for functional modules within the substantia nigra. Brain Res 660:216–224

Hallworth NE, Wilson CJ, Bevan MD (2003) Apamin-sensitive small conductance calcium-activated potassium channels, through their selective coupling to voltage-gated calcium channels, are critical determinants of the precision, pace, and pattern of action potential generation in rat STN neurons in vitro. J Neurosci 23: 7525–7542

Hammond C, Deniau JM, Rizk A, Féger J (1978) Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. Brain Res 151:235–244

Harting JK, Huerta MF, Hashikawa T, Weber JT, Van Lieshout DP (1988) Neuroanatomical studies of the nigrotectal projection in the cat. J Comp Neurol 278:615–631

Hattori T, Fibiger HC, McGeer PL (1975) Demonstration of a pallidonigral projection innervating dopaminergic neurons. J Comp Neurol 162:487–504

Häusser MA, Yung WH (1994) Inhibitory synaptic potentials in guinea-pig substantia nigra dopamine neurones in vitro. J Physiol 479:401–422

Hebb MO, Robertson HA (2000) Identification of a subpopulation of substantia nigra pars compacta gamma-aminobutyric acid neurons that is regulated by basal ganglia activity. J Comp Neurol 416: 30–44

Hubert GW, Paquet M, Smith Y (2001) Differential subcellular localization of mGluR1a and mGluR5 in the rat and monkey Substantia nigra. J Neurosci 21:1838–1847

Hyland BI, Reynolds JN, Hay J, Perk CG, Miller R (2002) Firing modes of midbrain dopamine cells in the freely moving rat. Neuroscience 114:475–492

Ibáñez-Sandoval O, Carrillo-Reid L, Galarraga E, Tapia D, Mendoza E, Gomora JC, Aceves J, Bargas J (2007) Bursting in substantia nigra pars reticulata neurons in vitro: possible relevance for Parkinson disease. J Neurophysiol 98:2311–2323

Ingham CA, Hood SH, Taggart P, Arbuthnott GW (1998) Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway. J Neurosci 18:4732–4743

Iribe Y, Moore K, Pang KC, Tepper JM (1999) Subthalamic stimulation-induced synaptic responses in substantia nigra pars compacta dopaminergic neurons in vitro. J Neurophysiol 82:925–933

Jia HG, Yamuy J, Sampogna S, Morales FR, Chase MH (2003) Colocalization of gamma-aminobutyric acid and acetylcholine in neurons in the laterodorsal and pedunculopontine tegmental nuclei in the cat: a light and electron microscopic study. Brain Res 992:205–219

Johnson SW, North RA (1992) Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J Physiol 450:455–468

Johnson SW, Seutin V, North RA (1992) Burst firing in dopamine neurons induced by N-methyl-D-aspartate: role of electrogenic sodium pump. Science 258:665–667

Juraska JM, Wilson CJ, Groves PM (1977) The substantia nigra of the rat: a Golgi study. J Comp Neurol 172:585–600

Kaneda K, Imanishi M, Nambu A, Shigemoto R, Takada M (2003) Differential expression patterns of mGluR1 alpha in monkey nigral dopamine neurons. NeuroReport 14:947–950

Keath JR, Iacoviello MP, Barrett LE, Mansvelder HD, McGehee DS (2007) Differential modulation by nicotine of substantia nigra versus ventral tegmental area dopamine neurons. J Neurophysiol 98:3388–3396

Kemel ML, Desban M, Gauchy C, Glowinski J, Besson MJ (1988) Topographical organization of efferent projections from the cat substantia nigra pars reticulata. Brain Res 455:307–323

Kemp JM, Powell TP (1971) The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi method. Philos Trans R Soc Lond B Biol Sci 262:429–439

Kita H, Kitai ST (1987) Efferent projections of the STN in the rat: light and electron microscopic analysis with the PHA-L method. J Comp Neurol 260:435–452

Komendantov AO, Komendantova OG, Johnson SW, Canavier CC (2004) A modeling study suggests complementary roles for $GABA_A$ and NMDA receptors and the SK channel in regulating the firing pattern in midbrain dopamine neurons. J Neurophysiol 91:346–357

Kosinski CM, Standaert DG, Testa CM, Penney JB Jr, Young AB (1998) Expression of metabotropic glutamate receptor 1 isoforms in the substantia nigra pars compacta of the rat. Neuroscience 86:783–798

Lacey MG, Mercuri NB, North RA (1988) On the potassium conductance increase activated by $GABA_B$ and dopamine D2 receptors in rat substantia nigra neurones. J Physiol 401:437–453

Lacey MG, Mercuri NB, North RA (1989) Two cell types in rat substantia nigra zona compacta distinguished by membrane properties and the actions of dopamine and opioids. J Neurosci 9:1233–1241

Lacey MG, Calabresi P, North RA (1990) Muscarine depolarizes rat substantia nigra zona compacta and ventral tegmental neurons in vitro through M1-like receptors. J Pharmacol Exp Ther 253:395–400

Lavoie B, Parent A (1994) Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra. J Comp Neurol 344:232–241

Lee CR, Tepper JM (2007a) A calcium-activated nonselective cation conductance underlies the plateau potential in rat substantia nigra GABAergic neurons. J Neurosci 27:6531–6541

Lee CR, Tepper JM (2007b) Morphological and physiological properties of parvalbumin- and calretinin-containing gamma-aminobutyric acidergic neurons in the substantia nigra. J Comp Neurol 500:958–972

Lee CR, Abercrombie ED, Tepper JM (2004) Pallidal control of substantia nigra dopaminergic neuron firing pattern and its relation to extracellular neostriatal dopamine levels. Neuroscience 129: 481–489

Lichtensteiger W, Felix D, Lienhart R, Hefti F (1976) A quantitative correlation between single unit activity and fluorescence intensity of dopamine neurones in zona compacta of substantia nigra, as demonstrated under the influence of nicotine and physostigmine. Brain Res 117:85–103

Lichtensteiger W, Hefti F, Felix D, Huwyler T, Melamed E, Schlumpf M (1982) Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 21:963–968

Lokwan SJ, Overton PG, Berry MS, Clark D (1999) Stimulation of the pedunculopontine tegmental nucleus in the rat produces burst firing in A9 dopaminergic neurons. Neuroscience 92:245–254

MacNeil D, Gower M, Szymanska I (1978) Response of dopamine neurons in substantia nigra to muscimol. Brain Res 154:401–403

Mailly P, Charpier S, Menetrey A, Deniau JM (2003) Three-dimensional organization of the recurrent axon collateral network of the substantia nigra pars reticulata neurons in the rat. J Neurosci 23:5247–5257

Mana S, Chevalier G (2001) The fine organization of nigro-collicular channels with additional observations of their relationships with acetylcholinesterase in the rat. Neuroscience 106:357–374

Manley LD, Kuczenski R, Segal DS, Young SJ, Groves PM (1992) Effects of frequency and pattern of medial forebrain bundle stimulation on caudate dialysate dopamine and serotonin. J Neurochem 58:1491–1498

Mansvelder HD, Keath JR, McGehee DS (2002) Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 33:905–919

Martin LJ, Blackstone CD, Huganir RL, Price DL (1992) Cellular localization of a metabotropic glutamate receptor in rat brain. Neuron 9:259–270

Martínez-Murillo R, Villalba RM, Rodrigo J (1989) Electron microscopic localization of cholinergic terminals in the rat substantia nigra: an immunocytochemical study. Neurosci Lett 96:121–126

Matsubayashi H, Amano T, Seki T, Sasa M, Sakai N (2003) Electrophysiological characterization of nicotine-induced excitation of dopaminergic neurons in the rat substantia nigra. J Pharmacol Sci 93:143–148

Meltzer LT, Serpa KA, Christoffersen CL (1997a) Metabotropic glutamate receptor-mediated inhibition and excitation of substantia nigra dopamine neurons. Synapse 26:184–193

Meltzer LT, Christoffersen CL, Serpa KA (1997b) Modulation of dopamine neuronal activity by glutamate receptor subtypes. Neurosci Biobehav Rev 21(4):511–518

Mena-Segovia J, Bolam JP, Magill PJ (2004) Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? Trends Neurosci 27:585–588

Mercuri NB, Stratta F, Calabresi P, Bonci A, Bernardi G (1993) Activation of metabotropic glutamate receptors induces an inward current in rat dopamine mesencephalic neurons. Neuroscience 56:399–407

Mereu G, Gessa GL (1985) Low doses of ethanol inhibit the firing of neurons in the substantia nigra, pars reticulata: a GABAergic effect? Brain Res 360:325–330

Mereu G, Fadda F, Gessa GL (1984) Ethanol stimulates the firing rate of nigral dopaminergic neurons in unanesthetized rats. Brain Res 292:63–69

Miller AD, Blaha CD (2005) Midbrain muscarinic receptor mechanisms underlying regulation of mesoaccumbens and nigrostriatal dopaminergic transmission in the rat. Eur J NeuroSci 21:1837–1846

Misgeld U, Drew G, Yanovsky Y (2007) Presynaptic modulation of GABA release in the basal ganglia. Prog Brain Res 160:245–259

Morikawa H, Khodakhah K, Williams JT (2003) Two intracellular pathways mediate metabotropic glutamate receptor-induced Ca2+ mobilization in dopamine neurons. J Neurosci 23:149–157

Naito A, Kita H (1994) The cortico-nigral projection in the rat: an anterograde tracing study with biotinylated dextran amine. Brain Res 637:317–322

Nakamura S, Iwatsubo K, Tsai CT, Iwama K (1979) Cortically induced inhibition of neurons of rat substantia nigra (pars compacta). Jpn J Physiol 29:353–357

Nakanishi H, Kita H, Kitai ST (1987a) Electrical membrane properties of rat subthalamic neurons in an in vitro slice preparation. Brain Res 437:35–44

Nakanishi H, Kita H, Kitai ST (1987b) Intracellular study of rat substantia nigra pars reticulata neurons in an in vitro slice preparation: electrical membrane properties and response characteristics to subthalamic stimulation. Brain Res 437:45–55

Nambu A, Llinaś R (1994) Electrophysiology of globus pallidus neurons in vitro. J Neurophysiol 72:1127–1139

Nastuk MA, Graybiel AM (1991) Pharmacologically defined M1 and M2 muscarinic cholinergic binding sites in the cat's substantia nigra: development and maturity. Brain Res Dev Brain Res 61:1–10

Nicholson LF, Faull RL, Waldvogel HJ, Dragunow M (1992) The regional, cellular and subcellular localization of $GABA_A$/benzodiazepine receptors in the substantia nigra of the rat. Neuroscience 50:355–370

Nitsch C, Riesenberg R (1988) Immunocytochemical demonstration of GABAergic synaptic connections in rat substantia nigra after different lesions of the striatonigral projection. Brain Res 461:127–142

Ong WY, He Y, Garey LJ (1997) Localisation of glutamate receptors in the substantia nigra pars compacta of the monkey. J Hirnforsch 38:291–298

Overton P, Clark D (1992) Iontophoretically administered drugs acting at the N-methyl-D-aspartate receptor modulate burst firing in A9 dopamine neurons in the rat. Synapse 10:131–140

Overton PG, Clark D (1997) Burst firing in midbrain dopaminergic neurons. Brain Res Brain Res Rev 25:312–334

Paladini CA, Tepper JM (1999) $GABA_A$ and $GABA_B$ antagonists differentially affect the firing pattern of substantia nigra dopaminergic neurons in vivo. Synapse 32:165–176

Paladini CA, Celada P, Tepper JM (1999a) Striatal, pallidal, and pars reticulata evoked inhibition of nigrostriatal dopaminergic neurons is mediated by GABA(A) receptors in vivo. Neuroscience 89:799–812

Paladini CA, Iribe Y, Tepper JM (1999b) $GABA_A$ receptor stimulation blocks NMDA-induced bursting of dopaminergic neurons in vitro by decreasing input resistance. Brain Res 832:145–151

Paquet M, Tremblay M, Soghomonian JJ, Smith Y (1997) AMPA and NMDA glutamate receptor subunits in midbrain dopaminergic neurons in the squirrel monkey: an immunohistochemical and in situ hybridization study. J Neurosci 17:1377–1396

Pidoplichko VI, DeBiasi M, Williams JT, Dani JA (1997) Nicotine activates and desensitizes midbrain dopamine neurons. Nature 390:401–404

Pinnock RD (1984) Hyperpolarizing action of baclofen on neurons in the rat substantia nigra slice. Brain Res 322:337–340

Precht W, Yoshida M (1971) Blockage of caudate-evoked inhibition of neurons in the substantia nigra by picrotoxin. Brain Res 32:229–233

Prisco S, Natoli S, Bernardi G, Mercuri NB (2002) Group I metabotropic glutamate receptors activate burst firing in rat midbrain dopaminergic neurons. Neuropharmacology 42:289–296

Radnikow G, Misgeld U (1998) Dopamine D1 receptors facilitate $GABA_A$ synaptic currents in the rat substantia nigra pars reticulata. J Neurosci 18:2009–2016

Redgrave P, Marrow L, Dean P (1992) Topographical organization of the nigrotectal projection in rat: evidence for segregated channels. Neuroscience 50:571–595

Richards CD, Shiroyama T, Kitai ST (1997) Electrophysiological and immunocytochemical characterization of GABA and dopamine neurons in the substantia nigra of the rat. Neuroscience 80:545–557

Rinvik E (1975) Demonstration of nigrothalamic connections in the cat by retrograde axonal transport of horseradish peroxidase. Brain Res 90:313–318

Rinvik E, Ottersen OP (1993) Terminals of subthalamonigral fibres are enriched with glutamate-like immunoreactivity: an electron microscopic, immunogold analysis in the cat. J Chem Neuroanat 6:19–30

Robledo P, Féger J (1990) Excitatory influence of rat subthalamic nucleus to substantia nigra pars reticulata and the pallidal complex: electrophysiological data. Brain Res 518:47–54

Ross RJ, Waszczak BL, Lee EK, Walters JR (1982) Effects of benzodiazepines on single unit activity in the substantia nigra pars reticulata. Life Sci 31:1025–1035

Rye DB, Saper CB, Lee HJ, Wainer BH (1987) Pedunculopontine tegmental nucleus of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. J Comp Neurol 259:483–528

Saitoh K, Isa T, Takakusaki K (2004) Nigral GABAergic inhibition upon mesencephalic dopaminergic cell groups in rats. Eur J NeuroSci 19:2399–2409

Santiago M, Westerink BH (1992) The role of GABA receptors in the control of nigrostriatal dopaminergic neurons: dual-probe microdialysis study in awake rats. Eur J Pharmacol 219:175–181

Sato F, Lavallée P, Lévesque M, Parent A (2000) Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. J Comp Neurol 417:17–31

Scanziani M (2000) GABA spillover activates postsynaptic $GABA_B$ receptors to control rhythmic hippocampal activity. Neuron 25:673–681

Scarnati E, Proia A, Campana E, Pacitti C (1986) A microiontophoretic study on the nature of the putative synaptic neurotransmitter involved in the pedunculopontine-substantia nigra pars compacta excitatory pathway of the rat. Exp Brain Res 62:470–478

Scarnati E, Proia A, Di Loreto S, Pacitti C (1987) The reciprocal electrophysiological influence between the nucleus tegmenti pedunculopontinus and the substantia nigra in normal and decorticated rats. Brain Res 423:116–124

Seutin V, Johnson SW, North RA (1994) Effect of dopamine and baclofen on N-methyl-D-aspartate-induced burst firing in rat ventral tegmental neurons. Neuroscience 58:201–206

Scroggs RS, Cardenas CG, Whittaker JA, Kitai ST (2001) Muscarine reduces calcium-dependent electrical activity in substantia nigra dopaminergic neurons. J Neurophysiol 86:2966–2972

Sesack SR, Deutch AY, Roth RH, Bunney BS (1989) Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J Comp Neurol 290:213–242

Shen KZ, Johnson SW (1997) A slow excitatory postsynaptic current mediated by G-protein-coupled metabotropic glutamate receptors in rat ventral tegmental dopamine neurons. Eur J NeuroSci 9: 48–54

Sidibé M, Paré JF, Smith Y (2002) Nigral and pallidal inputs to functionally segregated thalamostriatal neurons in the centromedian/parafascicular intralaminar nuclear complex in monkey. J Comp Neurol 447:286–299

Smith Y, Bolam JP (1989) Neurons of the substantia nigra reticulata receive a dense GABA-containing input from the globus pallidus in the rat. Brain Res 493:160–167

Smith Y, Bolam JP (1990) The output neurones and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat. J Comp Neurol 296:47–64

Smith ID, Grace AA (1992) Role of the STN in the regulation of nigral dopamine neuron activity. Synapse 12:287–303

Smith Y, Bolam JP, Von Krosigk M (1990) Topographical and synaptic organization of the GABA-Containing pallidosubthalamic projection in the rat. Eur J NeuroSci 2:500–511

Smith Y, Charara A, Parent A (1996) Synaptic innervation of midbrain dopaminergic neurons by glutamate-enriched terminals in the squirrel monkey. J Comp Neurol 364:231–253

Somogyi P, Bolam JP, Totterdell S, Smith AD (1981) Monosynaptic input from the nucleus accumbens–ventral striatum region to retrogradely labelled nigrostriatal neurones. Brain Res 217: 245–263

Sorenson EM, Shiroyama T, Kitai ST (1998) Postsynaptic nicotinic receptors on dopaminergic neurons in the substantia nigra pars compacta of the rat. Neuroscience 87:659–673

Takakusaki K, Shiroyama T, Yamamoto T, Kitai ST (1996) Cholinergic and noncholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. J Comp Neurol 371:345–361

Takakusaki K, Shiroyama T, Kitai ST (1997) Two types of cholinergic neurons in the rat tegmental pedunculopontine nucleus: electrophysiological and morphological characterization. Neuroscience 79:1089–1109

Tepper JM, Lee CR (2007) GABAergic control of substantia nigra dopaminergic neurons. Prog Brain Res 160:189–208

Tepper JM, Sawyer SF, Groves PM (1987) Electrophysiologically identified nigral dopaminergic neurons intracellularly labeled with HRP: Light microscopic analysis. J Neurosci 7:2794–2806

Tepper JM, Trent F, Nakamura S (1990) Postnatal development of the electrical activity of rat nigrostriatal dopaminergic neurons. Brain Res Dev Brain Res 54:21–33

Tepper JM, Martin LP, Anderson DR (1995) $GABA_A$ receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. J Neurosci 15:3092–3103

Tepper JM, Sun BC, Martin LP, Creese I (1997) Functional roles of dopamine D2 and D3 autoreceptors on nigrostriatal neurons analyzed by antisense knockdown in vivo. J Neurosci 17: 2519–2530

Tepper JM, Celada P, Iribe Y, Paladini C (2003) Afferent control of nigral dopaminergic neurons: the role of GABAergic inputs. In: Graybiel A et al (eds) The Basal Ganglia VI. Kluwer, New York, pp 641–651

Tepper JM, Abercrombie ED, Bolam JP (2007) Basal ganglia macrocircuits. Prog Brain Res 160:3–7

Tokuno H, Nakamura Y (1987) Organization of the nigrotectospinal pathway in the cat: a light and electron microscopic study. Brain Res 436:76–84

Totterdell S, Bolam JP, Smith AD (1984) Characterization of pallidonigral neurons in the rat by a combination of Golgi impregnation and retrograde transport of horseradish peroxidase: their monosynaptic input from the neostriatum. J Neurocytol 13:593–616

Tozzi A, Bengtson CP, Longone P, Carignani C, Fusco FR, Bernardi G, Mercuri NB (2003) Involvement of transient receptor potential-like channels in responses to mGluR-I activation in midbrain dopamine neurons. Eur J NeuroSci 18:2133–2145

Trent F, Tepper JM (1991) Dorsal raphé stimulation modifies striatal-evoked antidromic invasion of nigral dopaminergic neurons in vivo. Exp Brain Res 84:620–630

Valenti O, Mannaioni G, Seabrook GR, Conn PJ, Marino MJ (2005) Group III metabotropic glutamate-receptor-mediated modulation of excitatory transmission in rodent substantia nigra pars compacta dopamine neurons. J Pharmacol Exp Ther 313:1296–1304

Walters JR, Lakoski JM (1978) Effect of muscimol on single unit activity of substantia nigra dopamine neurons. Eur J Pharmacol 47:469–471

Wang L, Kitai ST, Xiang Z (2005) Modulation of excitatory synaptic transmission by endogenous glutamate acting on presynaptic group II mGluRs in rat substantia nigra compacta. J Neurosci Res 82: 778–787

Waszczak BL, Eng N, Walters JR (1980) Effects of muscimol and picrotoxin on single unit activity of substantia nigra neurons. Brain Res 188:185–197

Wichmann T, Bergman H, DeLong MR (1994) The primate STN. I. Functional properties in intact animals. J Neurophysiol 72:494–506

Wigmore MA, Lacey MG (1998) Metabotropic glutamate receptors depress glutamate-mediated synaptic input to rat midbrain dopamine neurones in vitro. Br J Pharmacol 123:667–674

Williams MN, Faull RL (1985) The striatonigral projection and nigrotectal neurons in the rat. A correlated light and electron microscopic study demonstrating a monosynaptic striatal input to identified nigrotectal neurons using a combined degeneration and horseradish peroxidase procedure. Neuroscience 14:991–1010

Williams MN, Faull RL (1988) The nigrotectal projection and tectospinal neurons in the rat. A light and electron microscopic study demonstrating a monosynaptic nigral input to identified tectospinal neurons. Neuroscience 25:533–562

Wilson CJ (1993) The generation of natural firing patterns in neostriatal neurons. Prog Brain Res 99:277–297

Wilson CJ, Young SJ, Groves PM (1977) Statistical properties of neuronal spike trains in the substantia nigra: cell types and their interactions. Brain Res 136:243–260

Wilson CL, Cash D, Galley K, Chapman H, Lacey MG, Stanford IM (2006) STN neurones in slices from 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-lesioned mice show irregular, dopamine-reversible firing pattern changes, but without synchronous activity. Neuroscience 143:565–572

Woolf NJ, Butcher LL (1986) Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. Brain Res Bull 16:603–637

Windels F, Kiyatkin EA (2004) GABA, not glutamate, controls the activity of substantia nigra reticulata neurons in awake, unrestrained rats. J Neurosci 24:6751–6754

Wu HQ, Schwarcz R, Shepard PD (1994) Excitatory amino acid-induced excitation of dopamine-containing neurons in the rat substantia nigra: modulation by kynurenic acid. Synapse 16:219–230

Wu YN, Shen KZ, Johnson SW (1999) Presynaptic inhibition preferentially reduces in NMDA receptor-mediated component of transmission in rat midbrain dopamine neurons. Br J Pharmacol 127: 1422–1430

Yamashita T, Isa T (2003) Fulfenamic acid sensitive, Ca(2+)-dependent inward current induced by nicotinic acetylcholine receptors in dopamine neurons. Neurosci Res 46:463–473

Yamashita T, Isa T (2004) Enhancement of excitatory postsynaptic potentials by preceding application of acetylcholine in mesencephalic dopamine neurons. Neurosci Res 49:91–100

Yin R, French ED (2000) A comparison of the effects of nicotine on dopamine and non-dopamine neurons in the rat ventral tegmental area: an in vitro electrophysiological study. Brain Res Bull 51: 507–514

Yoshida M, Precht W (1971) Monosynaptic inhibition of neurons of the substantia nigra by caudato-nigral fibers. Brain Res 32: 225–228

Yung KK (1998) Localization of ionotropic and metabotropic glutamate receptors in distinct neuronal elements of the rat substantia nigra. Neurochem Int 33:313–326

Yung WH, Häusser MA, Jack JJ (1991) Electrophysiology of dopaminergic and non-dopaminergic neurones of the guinea-pig substantia nigra pars compacta in vitro. J Physiol 436:643–667

Zhang J, Chiodo LA, Freeman AS (1994) Influence of excitatory amino acid receptor subtypes on the electrophysiological activity of dopaminergic and nondopaminergic neurons in rat substantia nigra. J Pharmacol Exp Ther 269:313–321

Zheng F, Johnson SW (2003) Dual modulation of gabaergic transmission by metabotropic glutamate receptors in rat ventral tegmental area. Neuroscience 119:453–460

Zhou FM, Wilson CJ, Dani JA (2002) Cholinergic interneuron characteristics and nicotinic properties in the striatum. J Neurobiol 53:590–605