CHAPTER

17

Neurophysiology of Substantia Nigra Dopamine Neurons: Modulation by GABA and Glutamate

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OUTLINE

I. INTRODUCTION

It has been more than four decades now since Bunney, Aghajanian, and their colleagues at Yale University published the first electrophysiological studies of midbrain dopamine (DA) neurons in vivo (Bunney et al., 1973a,b). These extracellular single unit recordings revealed that DA neurons in the substantia

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nigra (SN) pars compacta (SNc) and ventral tegmental area (VTA) of chloral hydrate-anesthetized rats fired spontaneously at low rates with occasional slow bursts. In addition, these investigators showed that DA neurons were powerfully inhibited by intravenous administration of compounds that enhance DA tone or activate DA receptors, amphetamine or apomorphine, effects that were completely reversed by administration of antipsychotic drugs. Moreover, the firing of DA neurons was also suppressed by iontophoretic application of DA directly to DA neurons themselves, suggesting the presence of "presynaptic" receptors for DA, now known as somatodendritic (SD) autoreceptors, on the DA neurons themselves. Subsequent studies revealed that the source of the DA that activated these autoreceptors was the dendrites of the DA neurons themselves (Geffen et al., 1976; Groves et al., 1975; Paden et al., 1976), and that these dendrites made synapses with other DA dendrites (Wilson et al., 1977a), thereby creating a self-inhibitory network of DA neurons. These pioneering studies were prompted, in large part, by a desire to understand the sites and mechanisms of action of antipsychotic drugs and provided the impetus for a myriad of subsequent electrophysiological and anatomical experiments by laboratories all over the world.

Over the succeeding 40 years, it has become clear that mesencephalic DA neurons and the DA innervation of the forebrain play crucial roles not only in the execution of voluntary movement and as sites of action for antipsychotic drugs and stimulant drugs of abuse, but also as core components of neuronal systems regulating reward, reinforcement, and addiction, as well as several types of higher cognitive function, including various forms of associative learning (Schultz, 2007; Schultz et al., 1997). The number of papers published on DA neurons exceeds 150,000 (PubMed, August 2015), far too many for any one review to even attempt to cover. This chapter will limit itself to a review of the basic anatomy of the SN and the electrophysiological and morphological characteristics of SN DA neurons, and the control of these neurons by known afferents, particularly GABA and glutamate inputs. Other aspects of the afferent control of DA neurons have been reviewed elsewhere (Kitai et al., 1999; Lee and Tepper, 2009; Morikawa and Paladini, 2011; Paladini and Roeper, 2014; Tepper and Lee, 2007). Various features of DA neuron anatomy, physiology, and pathophysiology are also reviewed in chapters The Neuroanatomical Organization of the Basal Ganglia, Subtypes of Midbrain Dopamine Neurons, Phasic Dopamine Signaling in Action Selection and Reinforcement Learning, and Determinants of Selective Vulnerability of Dopamine Neurons in Parkinson's Disease.

II. NEUROCYTOLOGY OF NIGROSTRIATAL DA NEURONS

Most of the DA cell bodies that project to the striatum (the nigrostriatal DA system) are located in a densely packed, relatively thin shell, 300–500 μm thick, the SNc (A9 in the terminology of Dahlstrom and Fuxe, 1964), dorsal to the larger and more diffuse SNr that comprises predominantly GABAergic projection neurons (Lee and Tepper, 2007). There are approximately 25,000 DA neurons bilaterally in the rat SN (Oorschot, 1996; Nair-Roberts et al., 2008). Smaller numbers of striatally projecting neurons are also found in the adjacent retrorubral field (A8) as well as in isolated patches in the SNr (Deutch et al., 1986). It is worth pointing out that many "nigrostriatal" DA neurons have been shown, by retrograde labeling, to collateralize to multiple regions, including the cingulate and the prefrontal cortex (Fallon, 1981; Takada and Hattori, 1986). The latter are distinct from prefrontal-projecting DA neurons identified in medial VTA (Lammel et al., 2008) (see chapter: Subtypes of Midbrain Dopamine Neurons).

Nigral DA neurons have been divided into dorsal and ventral tier groups (Fallon and Moore, 1978) (see also chapter: The Neuroanatomical Organization of the Basal Ganglia). The dorsal tier neurons express calbindin, whereas the ventral tier neurons do not (Gerfen et al., 1987a,b; but see also Neuhoff et al., 2002). It has been argued on the basis of retrograde tracing that the dorsal tier neurons preferentially innervate the striatal matrix compartment, whereas the ventral tier neurons innervate the striosome/patch compartment (Gerfen et al., 1987a). However, more recent studies using novel anterograde tracing techniques show quite clearly that single nigrostriatal neurons can innervate both patch and matrix compartments (Prensa and Parent, 2001; Matsuda et al., 2009). Similarly, it has been claimed that the dorsal tier neurons have dendrites oriented principally mediolaterally in SNc, whereas the ventral tier neurons extend dendrites ventrally into the SNr (Fallon and Moore, 1978). However, subsequent intracellular labeling studies suggest that many or most nigrostriatal neurons have dendrites that arborize within SNc as well as one or two ventrally directed dendrites (Grace and Onn, 1989; Kita et al., 1986; Tepper et al., 1987) (Fig. 17.1).

Nigral DA neurons are medium to large sized, 12–25 μm in diameter, and exhibit multipolar, fusiform, or polygonal somata that emit 3–5 thick, smooth dendrites that taper rapidly to about 1 μm or less in diameter. Dendrites are aspiny, but occasionally emit sparse thorn- or spine-like appendages. There are usually one or two ventrally directed dendrites that course through the SNr perpendicular to the surface of the

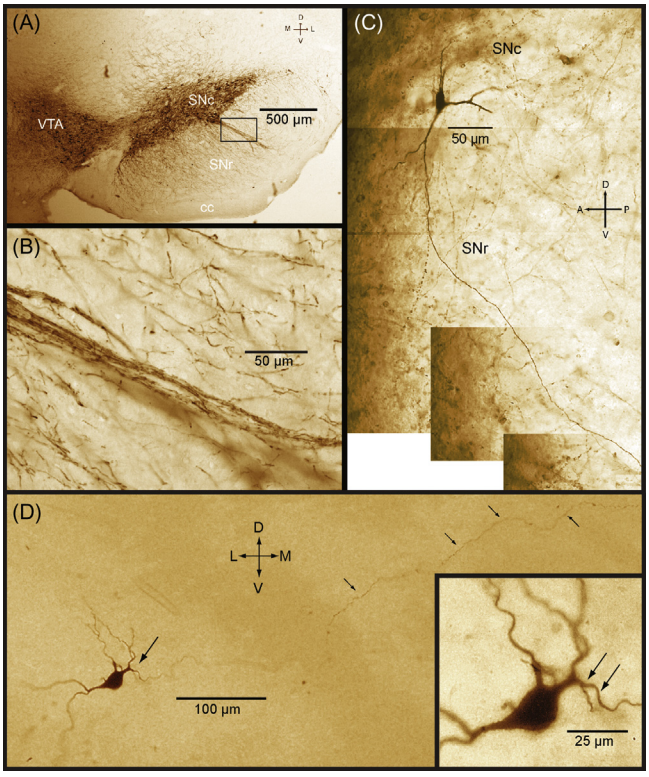

FIGURE 17.1 Neuroanatomical organization of the SN and neurocytology of nigral DA neurons. (A) Coronal section through rat midbrain immunostained for tyrosine hydroxylase, illustrating the densely packed DA neurons of the SNc and the adjacent VTA. Note the numerous DA fibers that penetrate deep into the SNr. The SN is bordered ventrally by the cerebral peduncles or crus cerebri (cc). (B) Higher magnification micrograph of the area within the box in (A), illustrating the fasciculation of some of the ventral dendrites coursing perpendicular to the surface of the SNc. Note that the dendrites are for the most part nonvaricose. (C) Photomontage of an electrophysiologically identified DA neuron in the SNc filled with biocytin after whole-cell recording in vitro. The dorsal dendrites arborize mostly within SNc, and the neuron extends one thick, smooth, and unbranched dendrite several hundred μm ventral through SNr. (D) Photomicrograph of an electrophysiologically identified DA neuron in SN in a 350 μm coronal section stained with biocytin following in vitro whole-cell recording. The axon (large arrow) could be followed (small arrows) as it coursed medially for several hundred μm in this single optical plane. Inset shows the axon emerging from a short, thick proximal dendrite approximately 25 μm from the center of the soma. *Source: (For C): Modified from Iribe, Y., Moore, K., Pang, K.C., Tepper, J.M., 1999. Subthalamic stimulation-induced synaptic responses in substantia nigra pars compacta dopaminergic neurons in vitro. J. Neurophysiol. 82, 925–933.*

SNc. These are often the largest and longest dendrites issued by the neuron, can exceed 1 mm in length, and extend throughout the entire dorsoventral extent of the SNr where they often form dendritic fascicles (Juraska et al., 1977; Kita et al., 1986; Tepper et al., 1994, 1987) (Fig. 17.1). Most of the dorsal dendrites are shorter than the ventrally directed dendrites but are similar in other respects, and arborize in, and sometimes extend beyond, SNc, in all directions.

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

It is sometimes claimed that the axon most commonly emerges from a dendrite at a relatively great distance from the soma (up to 240 μm) (Hausser et al., 1995). But this observation may have arisen from a selection artifact for the largest neurons in vitro where dendritic recording is easiest, since observations from several other studies indicate that the axon typically emerges from the soma or a proximal dendrite, usually within 30 μm of the soma (Grace and Bunney, 1983c; Grace and Onn, 1989; Matsuda et al., 2009; Tepper et al., 1987) (Fig. 17.1).

In marked contrast to the projection neurons of virtually all other basal ganglia nuclei, DA neurons of the SN do not emit local axon collaterals (Juraska et al., 1977; Matsuda et al., 2009; Tepper et al., 1987). After emerging from the cell and exhibiting an often initially tortuous and recurving trajectory, the axons course medially and rostral to SN, coalesce into a tract often referred to as the *medial forebrain bundle* that traverses the fields of Forel and projects into the forebrain. As they ascend, the axons arborize sparsely in the subthalamic nucleus (STN) (Cragg et al., 2004; Matsuda et al., 2009), and then continue rostrally, fanning out laterally through the globus pallidus external segment (GPe), where they form a small arborization (Lindvall and Bjorklund, 1979; Matsuda et al., 2009), before reaching their principal target, the striatum.

In the striatum, the axons from single cells branch profusely and form large, dense arborizations of varicose processes that occupy an average volume of approximately 0.5 mm^3 (Matsuda et al., 2009). Nigrostriatal axons form Gray's Type II symmetrical synapses, mainly on the dendrites or the necks of the dendritic spines of the striatal spiny projection neurons. Interestingly, although some of the DA synapses are made by terminal boutons or *en passant* varicosities, many of the synapses are very small and are formed by

thinner intervaricose segments of the axons (Freund et al., 1984; Groves et al., 1994; Pickel et al., 1981). These are easy to miss in single electron microscopic thin sections, especially if one is concentrating on varicosities, and almost certainly have contributed to the confusion about whether DA terminals actually form typical morphologically defined synapses in the striatum or not (see, for example, Descarries et al., 1996; Groves et al., 1994, for discussion).

III. ELECTROPHYSIOLOGICAL PROPERTIES OF NIGROSTRIATAL DA NEURONS

A. Extracellular Recordings

During in vivo extracellular recordings from anesthetized adult rats or mice, nigral DA neurons fire spontaneously between approximately 2 and 8 spikes/s, with a mean firing rate around 4 spikes/s (Bunney et al., 1973a,b). Estimates of the proportion of mesencephalic DA neurons that are spontaneously active in vivo in anesthetized rats vary widely, with some authors claiming that up to 50% of the neurons are normally silent (Chiodo, 1988; Floresco et al., 2003) to others who claim that the large majority of the neurons are spontaneously active under normal conditions (Dai and Tepper, 1998). This difference may depend on differences of depth of anesthesia. Spontaneous action potentials are unusually wide, between 2.5 and 4 ms long in duration depending on filter settings and electrode characteristics (Bunney et al., 1973a,b; Ungless and Grace, 2012).

Nigrostriatal DA neurons are readily identified by antidromic activation following stimulation of the striatum, GPe, or medial forebrain bundle. Like other monoaminergic neurons, nigrostriatal DA neurons exhibit slow conduction velocities in the range of 0.4–0.5 m/s as a result of their thin, unmyelinated axons. Antidromic responses of nigrostriatal DA neurons usually consist of a small spike, termed the initial segment (IS) spike, even when antidromically activated at low rates. Very often when the antidromic response is a "full" spike, consisting of both the IS and the SD spike, there is a marked delay between the IS and SD components causing a notch in the initial positive part of the extracellularly recorded waveform. The same IS–SD break is often observed in spontaneous action potentials as well (Bunney et al., 1973a,b; Deniau et al., 1978; Guyenet and Aghajanian, 1978; Grace and Bunney, 1983b,c, 1984a, b; Paladini et al., 1999; Tepper et al., 1982; Tepper et al., 1982, 1984a,b; Trent et al., 1991) (Fig. 17.2).

DA neurons recorded in vivo in anesthetized rodents exhibit three distinct modes or patterns of firing that are clearly distinguishable from inspection of their autocorrelation histograms (Tepper et al., 1995) (Fig. 17.2). The most common pattern of activity is a random, or irregular mode of firing, characterized by an initial prolonged trough in the autocorrelation function representing a long postfiring inhibition. The next most common firing pattern is a regular, pacemaker-like firing, characterized by constant interspike intervals, a low coefficient of variation, and a lack of bursting. The third and least common mode (but the one that has generated the most interest) is burst firing, characterized by stereotyped bursts of two to eight action potentials in which the first intraburst interspike interval is typically around 60 ms, followed by progressively increasing interspike intervals and progressively decreasing spike amplitudes (Brazhnik et al., 2008; Grace and Bunney, 1984a,b; Paladini et al., 1999a; Tepper et al., 1995) (Fig. 17.2).

The maximal instantaneous intraburst firing rate in anesthetized rodents is typically in the range of 12–15 Hz (Grace and Bunney, 1984a; Tepper et al., 1990), although significantly higher maximal intraburst firing rates have been observed in unanesthetized behaving rats (Hyland et al., 2002; Kiyatkin and Rebec, 1998). Thus, when the mean rate of firing and its overall variability in DA neurons increases (eg, during recordings in awake rodents, or when channels or receptors are modified (Herrik et al., 2010)), the traditional 80/160 template method for identifying bursts can become problematic. Alternative burst detection methods have been introduced more recently that relate bursts (and pauses) to the stochastic properties of the spike train and are independent of the absolute firing frequency (eg, distribution surprise methods, stochastic models (Bingmer et al., 2011; Ko et al., 2012)). Additionally, a phase function that identifies periodicity based on the phase relation of spikes, and is therefore also independent of firing rate, has been described recently (Dodla and Wilson, 2010).

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

The mechanisms controlling the firing patterns are of great interest to basal ganglia researchers for many

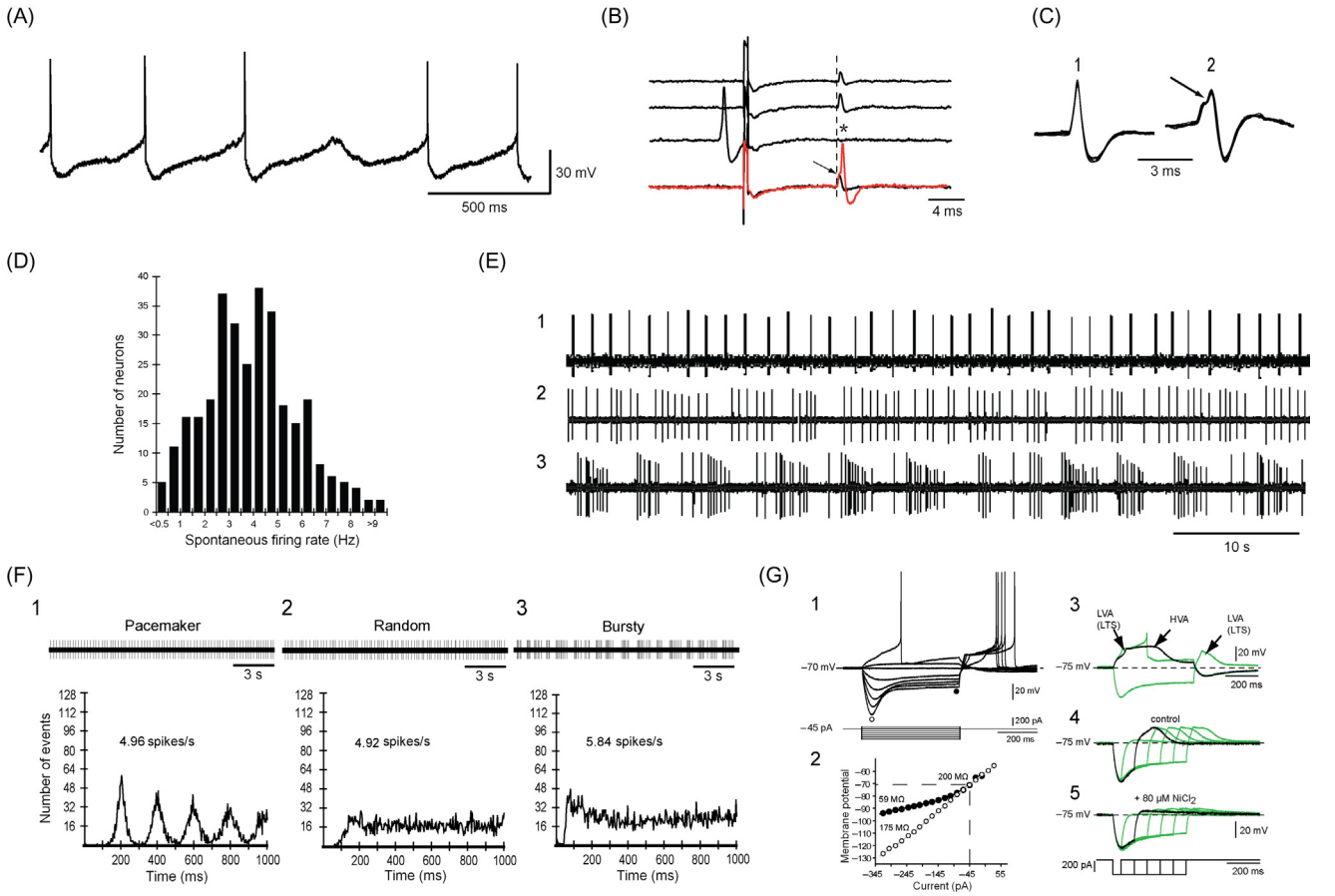

FIGURE 17.2 Basic electrophysiological characteristics of rodent nigral DA neurons. (A) In vivo intracellular recording of an antidromically identified nigrostriatal neuron in a urethane-anesthetized rat. Note long, slow spike afterhyperpolarization and regular spontaneous firing pattern. The 4th spike in the train misses, revealing the underlying LVA Ca^{2+} membrane potential oscillation that drives spontaneous pacemaker spiking. (B) Extracellularly recorded antidromic responses of a nigrostriatal neuron in a urethane-anesthetized rat. The asterisk marks a collision extinction in the 3rd sweep. Antidromic responses consist almost exclusively of the IS spike except for the red trace in the 4th sweep that is a full IS–SD spike. The arrow points to the IS–SD break. (C) Extracellularly recorded action potentials from two different nigrostriatal neurons in a chloral hydrate-anesthetized mouse illustrate the typical long duration spike and IS–SD break (arrow). Each spike is the overlay of 5 spikes averaged from 10 consecutive spontaneous action potentials. (D) Distribution of spontaneous firing rates of nigral DA neurons in a chloral hydrate-anesthetized rat. (E) Extracellularly recorded spontaneous spike trains from three different antidromically identified nigrostriatal neurons in chloral hydrate-anesthetized mice illustrating the three different patterns of spontaneous activity seen in vivo, pacemaker (E1), random (E2), and bursty (E3). (F) Autocorrelograms generated from spike trains (insets, top) of three different nigrostriatal neurons illustrating the distinct histogram shapes that characterize the three firing patterns in urethane-anesthetized rats. (G) In vitro whole-cell recordings from SNc DA neurons in mice. (G1) Hyperpolarizing current injections result in a slowly developing sag in the voltage response due to activation of I_h that results in a time-dependent inward rectification that reduces the input resistance of the neuron by about 67% (G2). (G3) Depolarizing current injection in a DA neuron hyperpolarized to −75 mV results in a low threshold spike (LTS) and subsequent high-voltage-activated (HVA) Ca^{2+} spike as well as a rebound LTS. (G4) Relaxation following hyperpolarizing current injections of varying durations shows that the rebound spike is all-or-none. (G5) Addition of a low concentration of Ni^{2+} blocks the rebound slow spike, identifying it as an LTS. LVA, low-voltage activated. *Source: (For C): Redrawn from Brazhnik, E., Shah, F., Tepper, J.M., 2008. GABAergic afferents activate both $GABA_A$ and $GABA_B$ receptors in mouse substantia nigra dopaminergic neurons in vivo. J. Neurosci. 28, 10386–10398 (For D) From Dai, M., Tepper, J.M., 1998. Do silent dopaminergic neurons exist in rat substantia nigra in vivo? Neuroscience 85, 1089–1099 (For F): Redrawn from Tepper, J.M., Martin, L.P., Anderson, D.R., 1995. $GABA_A$ receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. J. Neurosci. 15, 3092–3103.*

reasons. Different firing patterns could lead to qualitatively different effects with respect to dendritic release of DA in SN (Bjorklund and Lindvall, 1975; Cheramy et al., 1981; Groves et al., 1975) and/or release of DA in striatum. Experimentally induced burst firing (Lee et al., 2004; Suaud-Chagny et al., 1992) or electrical stimulation of the medial forebrain bundle that mimics burst firing (Bean and Roth, 1991; Chergui et al., 1994b; Gonon, 1988; Gonon and Buda, 1985; Manley et al., 1992) leads to increased extracellular DA levels in striatum and/or

cortex compared to pacemaker-like firing. This results from saturation of the DA transporter that is responsible for regulating extracellular DA levels (Chergui et al., 1994b; Miller and Abercrombie, 1999; but see also Rice and Cragg, 2008) (see chapter: Regulation of Extracellular Dopamine: Release and Uptake) rather than from increased release per pulse. Higher extracellular levels of DA could lead to qualitatively different effects than lower levels if, for example, a significant fraction of striatal D_1 receptors were located predominantly extra- or perisynaptically (Caille et al., 1996; Gonon, 1997). Under most conditions, firing rate and pattern appear to regulate SD and axon terminal DA release in parallel. Under some conditions however, IS and/or axonal and SD activity become dissociated (Onn et al., 2003; Trent and Tepper, 1991) leading to independent regulation of DA release in SN and axon terminal regions (Cobb and Abercrombie, 2003).

Perhaps most importantly, a number of studies have shown that DA neurons respond to reward, or stimuli that predict reward by firing a short burst (Schultz, 2007; Schultz et al., 1997) (see also chapter: Phasic Dopamine Signaling in Action Selection and Reinforcement Learning). This is becoming even more important, as recent optogenetic studies demonstrate that selective optical stimulation of SNc DA neurons in a burst pattern elicit reward-related learning, establishing a causal relationship between DA neuron firing pattern and reward-related behavior (Ilango et al., 2014; Rossi et al., 2013).

B. Intracellular and Whole-Cell Recordings

There have only been a handful of in vivo intracellular recording studies of nigral DA neurons due to substantial technical challenges, including the depth of the SN, the need to traverse several heavily myelinated regions, the anatomical organization of the SNc, and the responses of the neurons to intracellular penetration. As such, these recordings, mostly obtained by Grace and Bunney in the early to mid-1980s, represented a technical tour de force and were extremely valuable. The results from their earlier recordings confirm those from the earliest extracellular recordings described earlier. In addition they (1) revealed that nigral DA neurons exhibit a prolonged spike afterhyperpolarization and a slowly developing depolarizing sag in the membrane potential in response to strong hyperpolarizing current injections, (2) identified the presumed IS spike seen in extracellular recordings, and (3) showed the first intracellularly recorded synaptic responses in DA neurons (Grace and Bunney, 1983a,b, 1984a,b, 1985b; Tepper et al., 1987).

Almost all subsequent intracellular recordings of DA neurons have been obtained in vitro in acute midbrain slice preparations, first with sharp electrodes (Grace, 1990, 1991; Kita et al., 1986) and more recently with whole-cell recordings (Paladini et al., 2001). These have confirmed and extended the in vivo recordings and showed that the sag in nigrostriatal neurons is due to activation of a hyperpolarization-activated cation channel (HCN) that mediates the depolarizing current, I_h. The prolonged spike afterhyperpolarization and changes in firing pattern are due to activation of the apamin-sensitive calcium-activated K^+ channel, SK (Shepard and Bunney, 1991) mediated by mRNA encoding for the SK3 gene (Köhler et al., 1996; Stocker and Pedarzani, 2000; Wolfart et al., 2001). Seutin and colleagues were the first to demonstrate that SK channels control in vivo burst firing in DA neurons using the SK channel blocker *N*-methyl-laudano-sine (Waroux et al., 2005). Subsequent pharmacologically or genetically induced impairments of SK channels in DA neurons confirmed these initial findings and demonstrated that SK channel inhibition potentiated in vivo burst firing both in anesthetized and awake rodents (Herrik et al., 2010; Ji et al., 2009; Soden et al., 2013).

DA neurons also express ATP-sensitive potassium (K_{ATP}) channels (Schiemann et al., 2012). In contrast to SK channels, K_{ATP} channels are necessary for bursting in vivo for a medial subpopulation of SNc neurons. In vitro experiments demonstrated that selective opening of K_{ATP} channels in the presence of tonic *N*-methyl-D-aspartate (NMDA) receptor stimulation was sufficient to switch these DA neurons to a burst firing mode (Schiemann et al., 2012). While the biophysical mechanisms of how K_{ATP} channel opening enables burst firing— and which in vivo upstream mechanism controls K_{ATP} channel open probabilities— in DA neurons is not yet clear, its activity may be related to energy balance (Levin, 2000). Behavioral data suggest that K_{ATP} channel-mediated bursting in medial SN DA neurons is important for explorative behavior (Schiemann et al., 2012).

DA neurons also express a variety of calcium channels, in particular T-type and L-type, enabling both low and high threshold Ca^{2+} spikes, respectively, as well as a slow oscillatory potential that drives rhythmic single spiking in vitro and probably in vivo as well (Galarraga and Bargas, 1995; Kang and Kitai, 1993a,b; Nedergaard et al., 1993; Wilson and Callaway, 2000). Finally, nigrostriatal neurons also possess SD DA D_2 autoreceptors that hyperpolarize the neuron by opening an inwardly rectifying K^+ (GIRK) channel (Lacey et al., 1987, 1989). D_2 autoreceptors also mediate synaptic responses between midbrain DA neurons (Beckstead et al., 2004).

IV. NEUROANATOMY OF GABAergic AFFERENTS TO NIGRAL DA NEURONS

Most of the afferents to the SN are GABAergic, and at least 70% of the synapses formed on nigral DA neurons are GABAergic (Bolam and Smith, 1990; Gulley and Smithberg, 1971; Ribak et al., 1976; Rinvik and Grofova, 1970). Both $GABA_A$ and $GABA_B$ receptors have been identified on DA neurons (Lacey, 1993; Lacey et al., 1988; Sugita et al., 1992). Stimulation of each type, both in vivo and in vitro, produces an inhibitory response although with different time courses and ionic bases (Cameron and Williams, 1993; Engberg et al., 1993; Lacey et al., 1988).

In vivo studies show different $GABA_A$ and $GABA_B$ receptor-mediated effects on DA neurons (Engberg and Nissbrandt, 1993; Tepper et al., 1995). Due to the high chloride reversal potential ($E_{rev} = -60$ mV), $GABA_A$ receptor activation will not hyperpolarize the cell sufficiently enough to stop single spiking, although coordinated increase in activity from GABAergic afferents could be sufficient to prevent firing by increasing conductance to a point where action potentials fail. In contrast to $GABA_A$, $GABA_B$ receptor activation is expected to increase a potassium conductance ($E_{rev} = -110$ mV) via GIRK channels, and sufficiently hyperpolarize DA neurons to terminate spiking activity altogether, although unequivocal identification of an afferent activating postsynaptic $GABA_B$ receptors has proven elusive.

$GABA_A$ and $GABA_B$ receptors display regional segregation, with in situ hybridization and immunostaining showing that the GABA-B_{R1} and GABA-B_{R2} subunits (Charara et al., 2000) are expressed at significantly greater abundance in nigral DA neurons than in SNr GABAergic neurons, or in any other basal ganglia nucleus. Conversely, mRNA levels (Lu et al., 1999) and immunostaining for virtually all $GABA_A$ receptor subunits, particularly $alpha_1$ and $alpha_2$ subunits, are greater in the SNr than in the SNc. Most or all of the $GABA_A$ subunit immunostaining is constrained to postsynaptic specializations of symmetric synapses (Fujiyama et al., 2000), whereas $GABA_B$ subunits label both presynaptic terminals, where they serve as inhibitory GABAergic autoreceptors, as well as dendrites (for review, see Boyes and Bolam, 2007). Interestingly, a large proportion of the postsynaptic $GABA_B$ subunits appear to be located extrasynaptically (Boyes and Bolam, 2003). Although nigrostriatal DA and SNr GABAergic neurons express both $GABA_A$ and $GABA_B$ receptors, the responses of nigral neurons to GABA released from afferents is complex and varies depending on the nature of the afferent stimulation (Celada et al., 1999; Lee et al., 2004) (see also chapter: The Substantia Nigra Pars Reticulata).

A. Afferents from the Striatum

The densest and best-characterized GABAergic inputs arise from the spiny projection neurons of the striatum (Bolam and Smith, 1990; Grofova and Rinvik, 1970; Hattori et al., 1973a,b; Somogyi et al., 1981; Watabe-Uchida et al., 2012) and the GPe (Hattori et al., 1975; Smith and Bolam, 1990; Watabe-Uchida et al., 2012). Striatonigral efferents (the so-called direct pathway; see chapter: The Neuroanatomical Organization of the Basal Ganglia) colocalize substance P and dynorphin and arise from both the patch and matrix compartments (Gerfen and Young, 1988), which were proposed to preferentially or selectively innervate the SNc and SNr, respectively (Gerfen and Sawchenko, 1984).

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

B. Afferents from the GPe

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

C. Afferents from SNr Neurons

A third source of GABAergic inputs to nigrostriatal DA neurons arises locally (Grace and Bunney, 1979; Nitsch and Riesenberg, 1988) and is comprised of the local axon collaterals of the SNr GABAergic projection neurons (Tepper et al., 1995). These neurons (see chapter: The Substantia Nigra Pars Reticulata) emit a large diameter axon that issues several locally arborizing collaterals that exhibit varicosities *en passant* as well as terminal varicosities in SNr and SNc (Deniau et al., 1982; Grofova et al., 1982; Mailly et al., 2003) before ascending to their principal sites of termination in the thalamus and tectum. Electron microscopic analyses reveal that the varicosities are large boutons that form symmetric synapses with the somata and proximal dendrites of DA neurons in SNc and SNr. Individual collateral branches often form proximal multiple *en passant* synapses or pericellular baskets (Gulacsi et al., 2003; Lee and Tepper, 2007), similar to those formed by pallidal terminals (Smith and Bolam, 1990). SNr projection neurons typically fire spontaneously around 15–30 spikes/s in vivo and can exceed 100 spikes/s (Deniau et al., 2007) (see chapter: The Substantia Nigra Pars Reticulata). The SNr collateral input provides a crucial source of GABA to nigrostriatal neurons and plays a particularly important role in the modulation of their firing pattern and response to excitatory and inhibitory afferent inputs as described later.

D. Afferents from the Rostromedial Tegmental Nucleus

Finally, more recent studies show a robust source of GABAergic inputs to nigrostriatal neurons arising from the rostromedial tegmental nucleus (RMTg) (see chapters: The Tail of the Ventral Tegmental Area/Rostromedial Tegmental Nucleus: A Modulator of Midbrain Dopamine Systems, and the Rostromedial Tegmental Nucleus: Connections with the Basal Ganglia). RMTg projects bilaterally, but primarily ipsilaterally, to SNc DA neurons (Jhou et al., 2009a,b). The RMTg is located just caudal to the VTA and SNc, and the general region was originally termed "retroVTA" (Scammell et al., 2000) or the "tail of the VTA" (Perrotti et al., 2005). However, this nucleus is not considered to be simply an extension of the population of GABAergic neurons located within the VTA, since the RMTg constitutes neurons that display differential characteristics, including deltaFosB expression in response to aversive stimuli and psychostimulant drugs (Colussi-Mas et al., 2007; Geisler and Wise, 2008; Perrotti et al., 2005), sensitivity to μ-receptor activation (Matsui et al., 2014), and specific afferents from the lateral habenula (Barrot et al., 2012; Quina et al., 2015), that are not present in VTA GABAergic neurons (see chapters: The Tail of the Ventral Tegmental Area/Rostromedial Tegmental Nucleus: A Modulator of Midbrain Dopamine Systems, and the Rostromedial Tegmental Nucleus: Connections with the Basal Ganglia).

V. NEUROPHYSIOLOGY OF GABAergic AFFERENTS

A. Responses to Striatal Stimulation

Both DA and GABAergic SN neurons in vivo respond to ipsilateral striatal stimulation with monosynaptic inhibitory postsynaptic potentials (IPSPs) (Grace and Bunney, 1983a,b; Yoshida and Precht, 1971) that lead to inhibition of spontaneous activity (Collingridge and Davies, 1981; Tepper and Groves, 1990) (Fig. 17.3). The latency to the onset of striatal-evoked inhibition is relatively long (in rats and mice exceeding 10 ms; Brazhnik et al., 2008; Paladini et al., 1999a; Tepper et al., 1990), consistent with the relatively slow conduction velocity and long latency antidromic responses of striatonigral neurons (~10 ms) following nigral stimulation in rats (Ryan et al., 1986).

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

B. Responses to Pallidal Stimulation

Nigrostriatal neurons respond to stimulation of the ipsilateral GPe (see chapter: Organization of the Globus Pallidus) with short latency monosynaptic IPSPs (Tepper et al., 1986) and inhibition of spontaneous

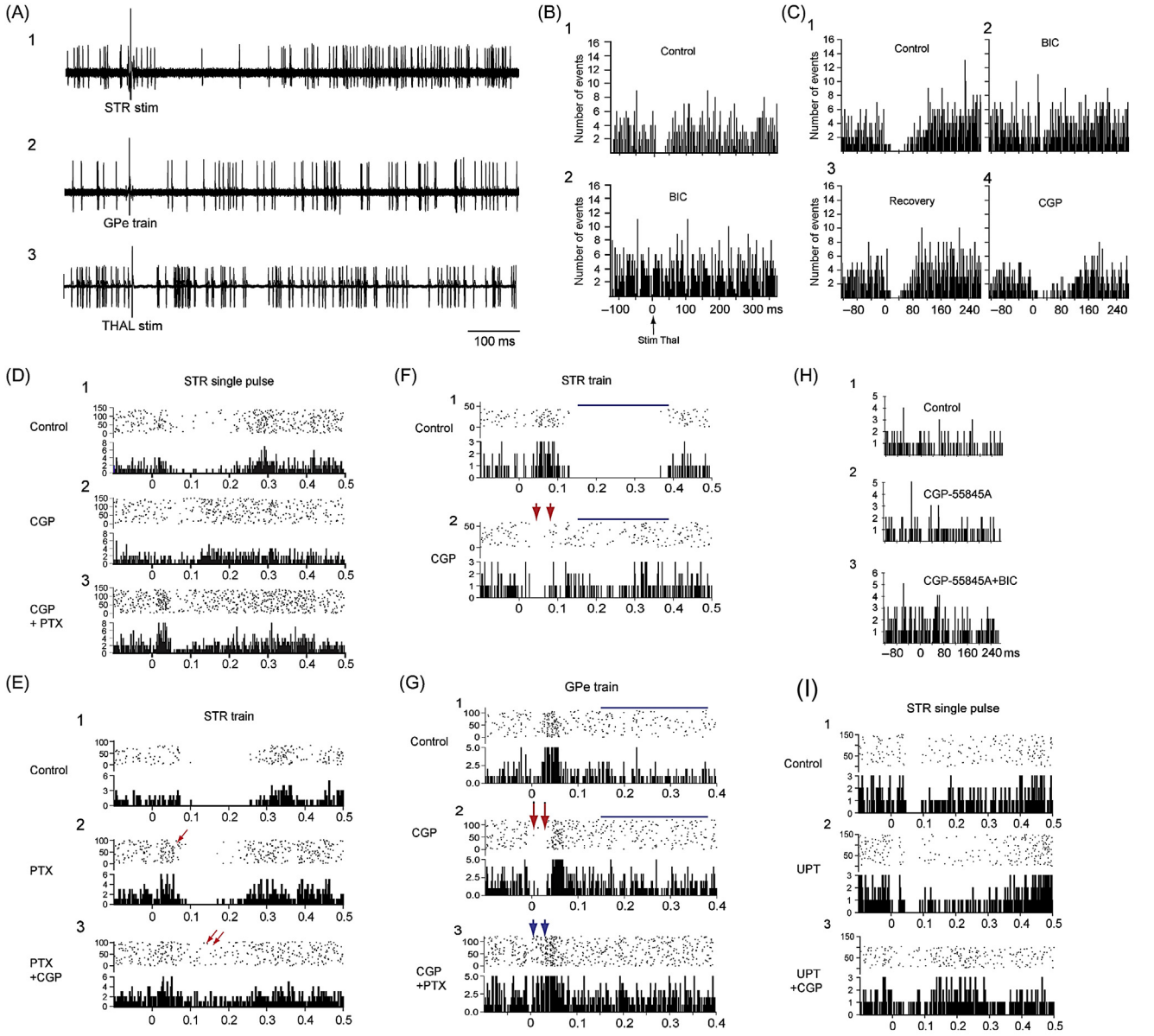

FIGURE 17.3 Inhibitory responses in nigral DA neurons following stimulation of GABAergic afferents. (A) Raw spike trains recorded extracellularly illustrating responses to single pulse electrical stimulation of dorsolateral striatum (STR) (A1), GPe (A2), and ventromedial thalamus (THAL) (A3) (which antidromically activates SNr GABAergic projection neurons) in mice. Each trace consists of the overlay of 25–37 consecutive sweeps at 0.67 Hz. Note the slow onset and long duration of the striatal-evoked inhibition compared to the rapid onset and shorter duration inhibition following activation of GPe and SNr afferents. (B) Typical peristimulus time histograms (PSTHs) showing that thalamic (*SNr*)-elicited inhibition (B1) is eliminated when the recording pipette contains the $GABA_A$-selective antagonist, bicuculline (BIC) (B2). (C) Inhibition elicited by single pulse GPe stimulation (C1) is completely blocked by pressure application of BIC using multibarrel pipettes (C2). After recovery from BIC (C3), subsequent pressure application of the $GABA_B$-selective antagonist, CGP55845A (CGP) not only fails to block inhibition, but actually produces a slight augmentation and prolongation of the inhibition as well as a slight reduction in spontaneous firing rate (see text for explanation). (D) PSTHs showing pharmacologically distinguishable early and late components of the inhibitory response of a nigral DA neuron to single pulse striatal stimulation in mice. (D1) Control stimulation (660 μA) elicits a long duration (>200 ms) inhibition with a delayed onset. (D2) Pressure application of CGP eliminates the late component of the inhibition but not the early component that is augmented by blockade of presynaptic $GABA_B$ autoreceptors. (D3) Subsequent simultaneous application of CGP plus the $GABA_A$ antagonist, picrotoxin (PTX), eliminates both components of the evoked inhibition except for the small postexcitation inhibition following the PTX-induced increased firing. (E) Same as D for a different cell, but the order of drug application is reversed. (E1) Striatal train stimulation elicits stronger inhibition than the single pulse stimulation in D1. (E2) Application of PTX eliminates the early part of the inhibition but has no effect on the later portion. (E3) Subsequent simultaneous application of PTX and CGP eliminates all inhibition. Note the presence of similar excitatory response to stimulation in the presence of PTX as seen in D3 (see Paladini, Celada, et al., 1999, for explanation). (F) Simultaneous pre- and postsynaptic $GABA_B$ effects. (F1) Striatal train stimulation elicits only a minimal early inhibition but a significant

activity (Paladini et al., 1999a), consistent with the anatomical findings (Fig. 17.3). However, if the GPe is stimulated chemically by local infusion of bicuculline ($GABA_A$ receptor antagonist) (which increases the mean firing rate of GPe neurons by 55%), nigrostriatal neurons respond with a modest but statistically significant *increase* in firing rate and a dramatic increase in burst firing (Celada et al., 1999; Lee et al., 2004) (Fig. 17.4). The opposite occurs if muscimol ($GABA_A$ receptor agonist) is infused into GPe. Under these conditions, GPe activity is almost completely suppressed and the nigrostriatal neurons respond with a modest decrease in firing rate and a shift away from bursty or random firing to a pacemaker-like firing pattern (Celada et al., 1999).

These effects are clearly opposite to what one expects from excitation or inhibition of a monosynaptic inhibitory input. The explanation for these seemingly incompatible results is the same as that for striatal-induced excitation of nigrostriatal neurons and depends again on the different sensitivities of DA and SNr GABA neurons to stimulation of $GABA_A$ receptors. When GPe neurons are activated by an electrical stimulus, all the neurons within the field of the stimulating electrode are depolarized and induced to fire simultaneously. This causes a massive and nearly synchronous release of GABA in the SN a few ms later. The synchronous nature of electrically stimulated release probably leads to greater extracellular levels of GABA than those that result from the chemical stimulation of the GPs which, although exciting large numbers of GPe neurons, does so in an asynchronous manner. Thus, the extracellular levels of GABA that are controlled almost exclusively by diffusion and uptake into presynaptic terminals and glia (Kirmse et al., 2008; Schousboe and Waagepetersen, 2007) are likely to be lower following chemical stimulation of GPe, where the asynchronous release allows the uptake mechanisms to clear the release GABA, than after electrical stimulation when all of the GABA is released simultaneously putting a much greater load on the uptake system. This leads to the situation where following chemical stimulation, there is a much greater inhibitory response from the SNr projection neurons than from the less sensitive DA neurons, resulting in a selective inhibition of the SNr GABAergic neurons and a consequent disinhibition of the DA neurons. Conversely, following electrical stimulation of GPe, the synchronous release of GABA is sufficient to inhibit both the nigrostriatal neurons and the SNr GABAergic neurons and so the monosynaptic inhibition of the DA neurons becomes apparent, although it is no doubt opposed by simultaneous disinhibition from the SNr neurons.

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

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

A similar sort of "paradoxical" response occurs in nigral DA neurons to activation of an extrabasal ganglia afferent, the lateral habenula. Stimulation of the lateral habenula produces potent inhibition in nigral

late inhibition (blue line). (F2) Following CGP application, the same stimuli now evoke a clear early inhibition (red arrows) and the late inhibition is substantially attenuated. (G) Facilitation of GABAergic inhibition is blocked by $GABA_A$ antagonists in mice. (G1) GPe train stimulation evokes inhibition with a weak early and strong late component. (G2) Local CGP application greatly strengthens the early inhibition while completely eliminating the late inhibition. (G3) Subsequent application of CGP and PTX eliminates all inhibitory responses. (H) Presynaptic effects of $GABA_B$ antagonists. (H1) Control PSTH with single pulse thalamic stimulation set to subthreshold current elicits no response. (H2) Local application of CGP unmasks a clear inhibitory response to the identical stimulus. Note that there is a slight decrease in background firing rate. (H3) Subsequent simultaneous application of the $GABA_B$ antagonist and the $GABA_A$ antagonist, bicuculline, eliminates the unmasked inhibition. (I) Blocking GABA uptake greatly enhances the late component of the evoked inhibition. (I1) Single pulse striatal stimulation elicits a strong early inhibition and a weaker late inhibition. (I2) Local application of the selective GABA uptake inhibitor, nipecotic acid (UPT), selectively augments the late inhibition. (I3) Subsequent application of CGP and UPT completely blocks the late component of the inhibition but not the early component. Data in (A), (D)–(G), and (I) are taken from extracellular recordings in chloral hydrate-anesthetized mice. Data in (B), (C), and (H) are taken from extracellular recordings in urethane-anesthetized rats. *Source: (For B): Redrawn from Tepper, J.M., Martin, L.P., Anderson, D.R., 1995. $GABA_A$ receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. J. Neurosci. 15, 3092–3103. (For C, H): Redrawn from Paladini, C.A., Celada, P., Tepper, J.M., 1999. Striatal, pallidal, and pars reticulata evoked inhibition of nigrostriatal dopaminergic neurons is mediated by GABA(A) receptors in vivo. Neuroscience 89, 799–812. (For D–G, I): Redrawn from Brazhnik, E., Shah, F., Tepper, J.M., 2008. GABAergic afferents activate both $GABA_A$ and $GABA_B$ receptors in mouse substantia nigra dopaminergic neurons in vivo. J. Neurosci. 28, 10386–10398.*

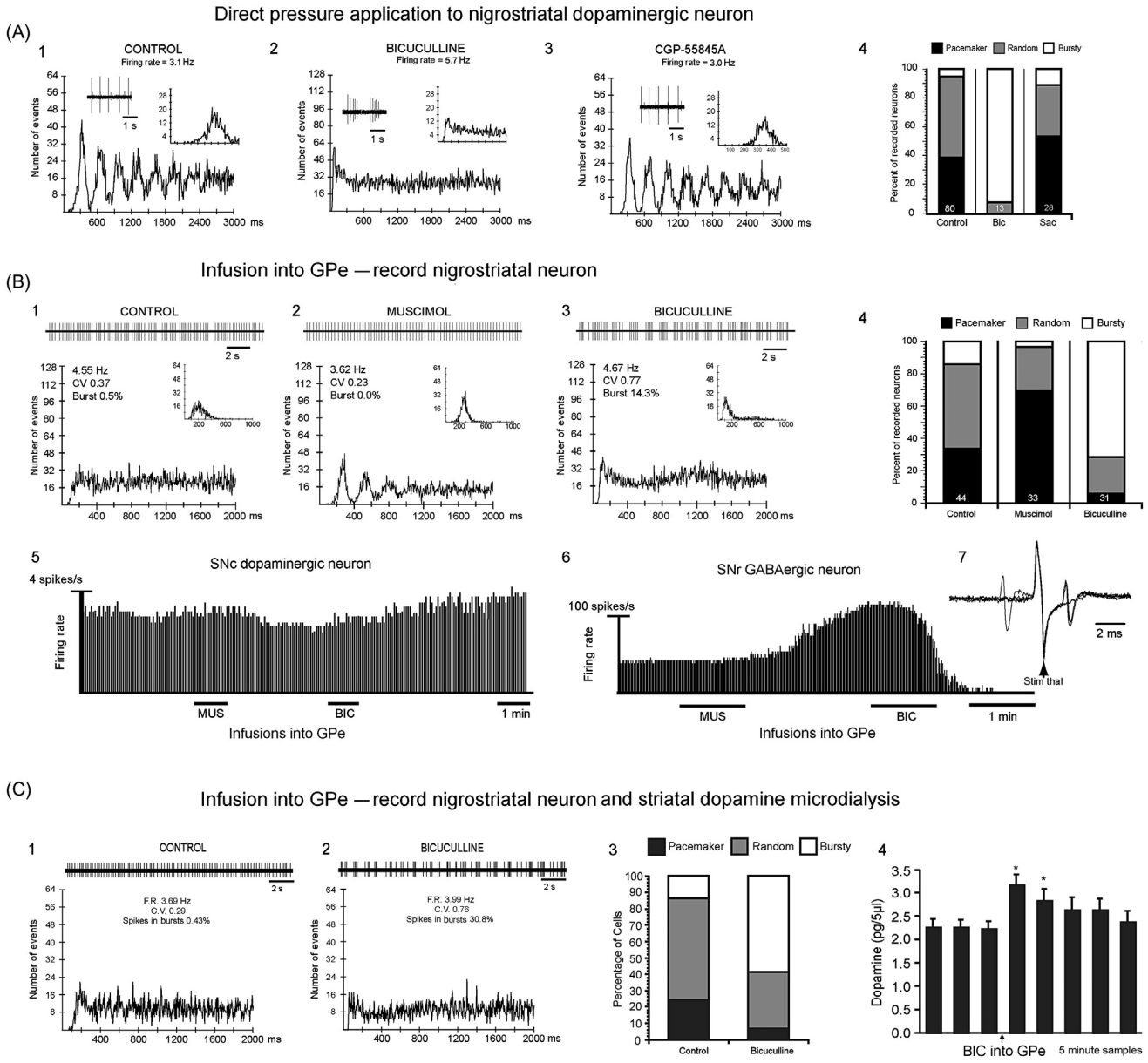

FIGURE 17.4 Blocking $GABA_A$ inputs to nigrostriatal DA neurons evokes bursty firing in vivo. (A1) Predrug control neuron exhibits pacemaker firing. (A2) Local application of the $GABA_A$ antagonist, bicuculline, produces a dramatic shift to a bursty firing pattern along with an increase in firing rate within a few seconds. (A3) The effects of bicuculline wear off in about 7 min and the subsequent application of the $GABA_B$ antagonist, CGP55845A, fails to elicit burst firing, and in fact contributes to increased regularity of firing as indicated by an increase in the number of peaks in the autocorrelogram (9) compared to that in the predrug control (7). (A4) Distribution of firing patterns of rat nigrostriatal neurons in vivo under control conditions, after local application of bicuculline (Bic), or the $GABA_B$ antagonist, 2-OH saclofen (Sac), through the recording pipette. (B) Manipulation of GPe firing rate by infusion of drugs exerts paradoxical effects on SNc activity. (B1) Control SNc neuron firing in the random mode. (B2) Following infusion of muscimol (MUS) into GPe that produced almost complete inhibition of GPe firing, the nigrostriatal neuron shifts to pacemaker firing accompanied by a small decrease in firing rate. (B3) GPe infusion of bicuculline (BIC) produced a 58% increase in GPe firing rate and caused the DA neuron to switch to bursty firing, accompanied by a slight increase in firing rate. (B4) Distribution of firing patterns for all SNc neurons following pallidal drug infusions. (B5) Ratemeter record of the SNc neuron in (B1–3) shows that the dramatic changes in firing pattern are accompanied by very modest changes in firing rate. Note that the changes in firing rate and pattern are opposite to what would result from monosynaptic pallidal input to SNc neurons. (B6) In contrast to the SNc neurons, the firing rate of one representative SNr projection neuron (B7) more than doubles following GPe MUS infusion, and its spontaneous activity is completely suppressed following GPe infusion of bicuculline, consistent with a powerful monosynaptic inhibitory pallidal input. (C) Simultaneous recording of nigrostriatal neuron activity and striatal DA levels measured by microdialysis. (C1) Control neuron firing randomly. (C2) GPe infusion of bicuculline causes neuron to shift to a bursty firing pattern with a modest increase in firing rate (F.R.), the typical response as shown in (C3). (C4) Simultaneous microdialysis in striatum reveals that the switch to the bursty firing pattern causes a 44% increase in extracellular DA levels. *Source: (For A1–3): Redrawn from Paladini, C.A., Tepper, J.M., 1999. GABA(A) and GABA(B) antagonists differentially affect the firing pattern of substantia nigra dopaminergic neurons in vivo. Synapse 32, 165–176. (For A4): Redrawn from Tepper, J.M., Martin, L.P., Anderson, D.R., 1995. $GABA_A$ receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. J. Neurosci. 15, 3092 -3103. (For B1–6): Redrawn from Celada, P., Paladini, C.A., Tepper, J.M., 1999. GABAergic control of rat substantia nigra dopaminergic neurons: role of globus pallidus and substantia nigra pars reticulata. Neuroscience 89, 813–825. (For C): Redrawn from Lee, C.R., Abercrombie, E.D., Tepper, J.M., 2004. Pallidal control of substantia nigra dopaminergic neuron firing pattern and its relation to extracellular neostriatal dopamine levels. Neuroscience 129, 481–489.*

DA neurons in rodent and monkey, whereas lesions of this area lead to increased forebrain DA release (Hikosaka et al., 2008; Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). The paradox arises from the fact that the output of the lateral habenula is glutamatergic and would be expected to produce excitation of nigral DA neurons. There are a number of possible explanations for this, but a disynaptic loop involving lateral habenular projections to RMTg neurons and feedforward inhibition of nigrostriatal neurons remains a likely explanation, as well as comprising a major candidate for a source of negative reward-related signals in DA neurons (Jhou et al., 2009b) (see also chapter: The Tail of the Ventral Tegmental Area/Rostromedial Tegmental Nucleus: A Modulator of Midbrain Dopamine Systems).

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

C. Responses to SNr Stimulation

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

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

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

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

The SNr GABAergic axon collaterals were subsequently carefully mapped (Mailly et al., 2003), and electron microscopic evidence was provided for the

existence of synapses formed by collaterals of SNr projection neurons onto nigrostriatal neurons (Gulacsi et al., 2003; Lee and Tepper, 2009). Results from a subsequent experiment where non-DA SNr neurons were recorded in vitro, stained with biocytin and reconstructed in order to compare their SD and axonal morphology with their electrophysiological characteristics revealed a morphologically and electrophysiologically homogenous population of neurons in SNr, differing only in co-expression of either parvalbumin or calretinin (Lee and Tepper, 2007).

Thus the SNr GABAergic input to nigrostriatal DA neurons arises predominantly or exclusively from the axon collaterals of the SNr principal cells, which play a dual role as both projection neurons and the source of intranigral GABAergic inhibition (Deniau et al., 2007).

D. Why Are SNr Neurons So Much More Sensitive to GABA Than Nigrostriatal Neurons?

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

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

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

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

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

However in vivo in rats, single pulse stimulation of striatum, GPe, or antidromic activation of SNr projection neurons with stimuli up to 1 mA produces inhibition of nigral DA neurons that is completely blocked by local application of $GABA_A$ antagonists (Paladini and Tepper, 1999; Tepper et al., 1995). The $GABA_B$ antagonists CGP35348 or CGP55845A not only fail to block the inhibition, but in many cases lead to an augmented inhibitory response (Fig. 17.3). Train stimuli similar to those used in the in vitro experiments elicited longer duration, more powerful inhibition from striatum or GPe. In some of these cases, bicuculline or PTX completely blocked the augmented inhibition. In other cases, only the early part of the inhibition was blocked and the later portion remained. However, as with single pulse stimulation the $GABA_B$ antagonists, saclofen or CG-55845A did not block any of inhibition resulting from train stimulation nor did the SK channel blocker, apamin, or the D_2 receptor antagonist, eticlopride (Paladini and Tepper, 1999).

If the stimulus intensity is adjusted to be just below threshold for evoking inhibition, application of $GABA_B$ antagonists unmasks an inhibitory response that can then be blocked by application of PTX or bicuculline (Paladini and Tepper, 1999) (Fig. 17.3). Thus in vivo in rats, inhibition in nigral DA neurons evoked from all three principal GABAergic afferents appears to be mediated predominantly or exclusively through stimulation of postsynaptic $GABA_A$ receptors. The potentiation of

the inhibition by application of $GABA_B$ antagonists arises from blockade of presynaptic inhibitory $GABA_B$ autoreceptors located on the terminals of striatal, pallidal, and SNr neurons that synapse onto DA neurons (Giralt et al., 1990; Hausser and Yung, 1994, see Misgeld et al., 2007, for review). This blockade results in increased stimulus-evoked GABA release that produces larger $GABA_A$ receptor-mediated inhibition that can be completely blocked by $GABA_A$ antagonists (Paladini and Tepper, 1999).

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

Indeed this seems to be the case. Recent experiments in vivo in mice reveal that stimulation of striatum, GPe, or antidromic activation of SNr projection neurons with single pulses delivered at amplitudes similar to those used in previous experiments in rats-evoked inhibitory responses of significantly greater duration than those observed in rats (Brazhnik et al., 2008). Furthermore, the inhibitory responses could be seen to be composed of two discrete components, an early inhibition that could be selectively blocked by $GABA_A$ receptor antagonists and a later component, not usually seen in rats, that was unaffected by bicuculline or PTX but that was blocked by the selective $GABA_B$ antagonist, CGP55845A. Although the late component could be blocked by CGP55845A, as in rats, there was no evidence for a tonic $GABA_B$-mediated inhibitory tone (Brazhnik et al., 2008) (Fig. 17.3).

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

GABA uptake blockers had relatively little effect on the early part of the evoked inhibition but greatly augmented the late component, an effect that was selectively antagonized by $GABA_B$ antagonists (Brazhnik et al., 2008; Fig. 17.3). Masked postsynaptic $GABA_B$ inhibitory effects that can be revealed by the application of GABA uptake blockade have also been shown to occur in striatum (Kirmse et al., 2008). In all other respects, the responses to GABAergic afferent inputs were identical in rats and mice.

F. Why Are Postsynaptic $GABA_B$ Effects in Response to Stimulation of GABAergic Afferents In Vivo Seen in Mice but Not in Rats?

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

There are observations that support this hypothesis. A study of the postnatal changes in nigrostriatal neurons in rats showed that striatal-evoked inhibition was especially potent in neonatal rat pups, lasting for several hundred ms, but by the time the rats had reached

21 days of age, the average duration of inhibition did not differ from that in adults (Tepper and Groves, 1990). Three weeks of age is well before the rat striatum has fully matured anatomically or physiologically (Tepper and Trent, 1993; Tepper et al., 1998), but is the period when the size of the brain is close to that of adult rats. Additional support comes from in vitro release studies where field stimulation of cortical or striatal slices released 80% more norepinephrine and 300% more DA in the mouse slices than in the rat slices using the same stimuli, indicating that identical stimuli released far more transmitter in mouse than in rat (Scholze et al., 2007). Finally, in the in vivo mouse studies just described, electrical stimulation of striatum, GPe, or thalamus evoked much longer duration inhibition than identical stimulation in rats (Brazhnik et al., 2008; Paladini and Tepper, 1999; Tepper et al., 1995).

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

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

In marked contrast to the relatively modest effects on nigrostriatal neuron firing rate, $GABA_A$ antagonists exerted consistent and dramatic effects on the firing patterns of SNc DA neurons. Local application of bicuculline methiodide produced a dramatic increase in the CV, the proportion of neurons firing in bursts, and the percentage of spikes fired in bursts (Paladini and Tepper, 1999; Tepper et al., 1995). Other $GABA_A$ antagonists that lack the SK channel blocking ability of bicuculline methiodide (Johnson and Seutin, 1997), PTX and gabazine, mimicked the potent effects of bicuculline at switching neurons from pacemaker or random firing to burst firing (Brazhnik et al., 2008; Paladini and Tepper, 1999) (Fig. 17.4). Regardless of the initial firing pattern, all the $GABA_A$ antagonists caused the majority of nigrostriatal neurons to shift to a bursty firing pattern. There was no correlation between the effects of $GABA_A$ antagonists on firing pattern and baseline firing rate or drug-induced changes in firing rate (Paladini and Tepper, 1999). This suggests that the mechanisms that modulate firing pattern and firing rate are different, and at least partially independent, and further, that altering GABAergic input to DA neurons has a greater effect on firing pattern than on firing rate.

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

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

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

The mechanism of the $GABA_A$-mediated burst suppression is not completely understood, but

NMDA-induced burst firing of nigral DA neurons in vitro can be blocked by the selective $GABA_A$ agonist, isoguvacine. The blockade is independent of membrane polarization but is associated with a high conductance state (Lobb et al., 2011a; Paladini et al., 1999b). This effect has been simulated in compartmental models of DA neurons by a few groups where it has been explained by alterations in the interactions of membrane potential and conductance (Canavier, 1999; Kuznetsov et al., 2006; Lobb et al., 2010).

In spite of the robust GABA tone, most DA neurons recorded *in vivo* actively fire spikes (Dai and Tepper, 1998; Grace and Bunney, 1983a; Paladini et al., 1999a; Paladini and Tepper, 1999; Wilson et al., 1977b), and tonic levels of DA are observed in target regions (Gonon, 1988; Floresco et al., 2003). Local application of NMDA, but not an AMPA, receptor antagonists, as well as genetic deletion of NMDA receptors specifically on DA neurons, significantly reduce spontaneous burst firing (Chergui et al., 1993; Overton and Clark 1992; see also Charlety et al., 1991; Zweifel et al., 2009).

VI. GLUTAMATE AFFERENTS TO NIGRAL DA NEURONS

A. Neuroanatomy of Glutamate Afferents

Watabe-Uchida et al. (2012) used cell-specific transsynaptic rabies constructs to identify the monosynaptic inputs to midbrain DA neurons. In combination with studies from Geisler and colleagues, we now know that nigrostriatal neurons receive their most prominent glutamate input from pedunculopontine nucleus (PPN; Hertel et al., 1997) and STN (Geisler et al., 2008; Watabe-Uchida et al., 2012).

B. Responses to PPN Activity

The PPN has a robust effect on DA neuron firing pattern. When the activity of the PPN is increased by blocking GABA transmission with bicuculline within the PPN in vivo, burst firing of putative DA neurons in the SN and VTA increases by 50% (% of spikes fired in bursts; Floresco et al., 2003). In contrast, muscimol/baclofen-induced PPN inhibition reduced burst firing by about 50%. These data, while obtained in anesthetized rodents, suggest that excitatory glutamatergic and/or cholinergic inputs from PPN serve as powerful positive modulators of burst firing in DA neurons. In awake behaving rats, lidocaine-induced PPN inactivation led to about a 50% reduction of maximal burst firing frequency of VTA and medial SN DA neurons in response to a conditioned reward-predicting sensory cue (tone or light) (Pan and Hyland, 2005). Thus, excitatory input from the rostral pons is important in controlling the maximal intraburst frequency of DA neurons in response to salient cues. More recent data from awake monkeys indicated the presence of distinct PPN subpopulations coding either for predicted or actual reward values (Okada et al., 2009). However, cue-dependent burst firing was still apparent after PPN inactivation (Pan and Hyland, 2005), indicating that additional synaptic inputs could have coincident activation on DA neurons to generate the full burst response for salient cues.

The mechanisms of PPN-induced bursting have not been fully resolved. PPN efferents projecting to the midbrain DA cell groups have been shown to have a significant cholinergic component that excites DA neurons through a nicotinic receptor (Dautan et al., 2014; Good and Lupica, 2009). However, pharmacological and genetic inactivation studies demonstrated an important contribution of postsynaptic NMDA receptors on bursting in DA neurons, enhancing spontaneous and stimulation-induced bursting and increase burst length but not intraburst frequencies (Overton and Clark, 1992; Tong et al., 1996; Zweifel et al., 2009).

C. Responses to STN Activity

In addition to excitatory pontine input, remaining excitatory synapses onto DA neurons result mainly from STN and less prominently from cortical inputs. Indeed, direct inputs to the SNc or VTA from cortex are sparse (Geisler and Zahm, 2005; Naito and Kita, 1994; Watabe-Uchida et al., 2012). Under some circumstances, bursts can be induced in SNc DA neurons by cortical stimulation, but these are apparently relayed through the STN (Overton and Clark, 1997). The STN is a spontaneously active glutamate afferent (Watabe-Uchida et al., 2012) that is likely a source of tonic glutamate (see chapter: The Subthalamic Nucleus).

Despite its clinical relevance in deep-brain stimulation for Parkinson disease (see chapter: Deep-Brain Stimulation for Neurologic and Neuropsychiatric Disorders), there are relatively few recent in vivo studies on the contribution of glutamatergic drive by the STN on bursting in DA neurons. GABA-mediated disinhibition of the STN leads to increased burst firing in a subpopulation of DA neurons in an NMDA-sensitive manner (Chergui et al., 1994b). In addition, electrolytic and neurotoxic STN lesions dramatically reduced burst firing mainly in lateral SN DA neurons in anesthetized rats (Smith and Grace, 1992).

This should not be surprising since the STN is a glutamatergic nucleus and sends a monosynaptic projection to the SN (Hammond et al., 1978). Remarkably, however, in both of the experiments just referred to,

the predominant *initial* response to chemical or electrical stimulation of STN was either no effect or inhibition of nigral neurons. Excitation and/or burst firing were only seen in a minority of the neurons. This was almost certainly due to preferential activation of SNr GABAergic projection neurons by the STN input, since 90% of the synapses made by STN afferents synapse onto GABAergic dendrites in SNr and only about 10% synapse directly onto DA dendrites (Lee and Tepper, 2009).

Subsequent in vitro intracellular recordings showed that nigral DA neurons respond to STN stimulation with a depolarizing postsynaptic potential (DPSP) that exhibits a reversal potential around −38 mV, a value very close to spike threshold (Iribe et al., 1999). Pharmacological dissection of the DPSP revealed it to be the result of near-simultaneous activation of a monosynaptic glutamatergic input with a reversal potential near 0 mV, presumably originating from STN, and a $GABA_A$ IPSP. The IPSP resulting from electrical stimulation of STN could have come from inadvertent activation of descending GABAergic fibers from striatum or GPe, but this was ruled out when the IPSP survived knife cuts just anterior to STN several days before the recordings, and by the demonstration that blocking the glutamatergic input pharmacologically completely eliminated the IPSP (Iribe et al., 1999).

These data showed that chemical or electrical stimulation of STN simultaneously activates a monosynaptic EPSP and a disynaptic $GABA_A$-mediated IPSP from the SNr projection neurons that together produce mixed, but initially inhibitory effects on DA neurons, as first reported by Robledo and colleagues (Robledo and Feger, 1990; Robledo et al., 1988). It also cannot be ruled out that the STN-elicited burst firing of nigrostriatal neurons is meditated in part through a monosynaptic excitation of GPe neurons that then preferentially inhibit SNr neurons and produce bursting in nigrostriatal neurons via disinhibition just as chemical stimulation of GPe does (Celada et al., 1999; Lee et al., 2004).

D. Afferent Regulation of Burst Firing in Nigrostriatal Neurons

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

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

There is little doubt that NMDA receptor stimulation increases or causes burst firing in DA neurons in vivo although the mechanism remains controversial. An early hypothesis for this action identified a sodium-based mechanism dependent on an electrogenic sodium pump (Johnson et al., 1992) that was subsequently simulated in a compartmental model (Canavier, 1999; Li et al., 1996). However, the experimental data and the simulations replicate sustained plateau depolarizations far better than they do the burst itself, and both the experimental data and the model result in prolonged bouts of high-frequency firing displaying reverse spike frequency adaptation riding on large plateau potentials that do not resemble in vivo bursts. Further, the hypothesis cannot explain why NMDA receptor stimulation specifically promotes burst firing, while depolarizations of the membrane by non-NMDA glutamatergic agonists or current injection do not.

With a large enough injection of constant current, DA neurons will increase firing but will also suffer rapid spike accommodation, presumably due to sodium channel inactivation that is initiated with depolarization of the neuron. However, computational models demonstrate that DA neurons are nonetheless capable of firing at burst rates as long as sodium channel inactivation is removed after each action potential (Canavier, 1999; Kuznetsov et al., 2006; Li et al., 1996).

Dynamic clamp experiments show that the NMDA receptor conductance is capable of following the activity of DA neurons at bursting rates and helps to

remove sodium channel inactivation by allowing full hyperpolarization of the membrane potential during the repolarization phase following each action potential within a burst. NMDA receptors are uniquely suited to do this due to the Mg^{2+} block when the membrane potential is hyperpolarized. Depolarization of the membrane potential removes the Mg^{2+} block and increases the conductance of the pore (Mayer et al., 1984; Nowak et al., 1984). Without this voltage-dependence, NMDA receptors would simply depolarize the membrane potential in response to ligand binding and the cell would enter into a state of depolarization block. Thus, following each action potential during a burst, the NMDA receptor undergoes Mg^{2+} block to allow full hyperpolarization and mitigate sodium channel inactivation. The NMDA receptor then unblocks during the depolarizing phase prior to the next action potential, increasing the speed of depolarization. Therefore, the voltage dependence of NMDA receptors allows DA neurons to fire at rates higher than those possible during sustained depolarization from constant current injection (Deister et al., 2009).

The rescue from depolarization block by NMDA receptor activation can also be explained by the receptor's nonlinear current–voltage relationship. The Mg^{2+} block imparts a negative slope conductance in the NMDA channel's current–voltage relationship (Lobb et al., 2010), and other channels with negative slope conductances (eg, Cav1.3) also enhance bursts in DA neurons (Putzier et al., 2009b). The L-type Ca^{2+}-mediated current likely provides the depolarizing current for the fast burst oscillation, as it does for the slow spontaneous oscillation in SNc DA neurons (Mercuri et al., 1994; Nedergaard et al., 1993).

Finally, although the hyperpolarizing phase of the burst oscillation arises from an unknown outward current, it is likely to be a voltage-sensitive, rather than a calcium-dependent, K^+ current or delayed rectifier. DA neurons are known to possess the subthreshold-activated A-type K^+ current, mediated by the Kv4.3 subunit, throughout its SD extent (Gentet and Williams, 2007; Liss and Roeper, 2001). This current, which has kinetics consistent with bursts, appears to be a powerful modulator of DA neuron pacemaking (Khaliq and Bean, 2008; Kuznetsova et al., 2010; Putzier et al., 2009a; Segev and Korngreen, 2007), but may also play a central role in burst firing. K-ATP channels that enable NMDA-mediated bursting of medial SN DA neuron in vitro and in vivo (Schiemann et al., 2012) might also act in this fashion. A deactivating potassium current similar to the one known to be present in DA neurons (Liss et al., 2001; Schiemann et al., 2012) allows for spiking currents as the origin of high-frequency bursts at the site of NMDA receptor activation.

Thus, it is apparent that intrinsic cellular dynamics are an important component of DA neuron bursting. The intraburst firing frequency is determined by the degree of NMDA receptor activation and the kinetics of the ionic channels underlying the burst mechanism. Glutamate also activates metabotropic glutamate receptors (mGluRs), mainly type 1 (mGluR1), in DA neurons (Hubert et al., 2001), and tonic activation of mGluRs by bath perfusion in vitro produces membrane potential depolarization that is mediated, at least partly, by opening of a nonselective cationic conductance (Guatteo et al., 1999; Tozzi et al., 2003). However, electrical stimulation of glutamate afferents results in rapid activation of mGluRs, which leads to a membrane potential hyperpolarization via opening of SK channels following Ca^{2+} release from intracellular stores (Fiorillo and Williams, 1998; Morikawa et al., 2003).

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

In summary, as a tentative hypothesis, assume that the glutamatergic afferents to nigrostriatal neurons, arising principally from the PPN and the STN, are tonically active and provide a more or less constant input to DA neurons, keeping them "primed" and burst-capable. They do not burst fire all the time

because of substantial $GABA_A$ tone provided by the GABAergic afferents (Lobb et al., 2011a), the most crucial of which may be the SNr and RMTg projections. The GABA tone suppresses NMDA-mediated bursting, keeping the DA neuron in a balanced, high chord conductance state, without a change in slope conductance (Lobb et al., 2010). The SNr neuronal activity is tightly controlled by input from the GPe. A transient increase in the activity of pallidonigral afferents will lead to a similarly timed transient decrease in SNr GABAergic output, thereby disinhibiting the nigrostriatal neuron and allowing a burst (Lobb et al., 2011b). In contrast, brief decreases in output of pallidonigral neurons will disinhibit the SNr neurons, thereby increasing their activity and their GABAergic output to reestablish burst suppression in nigrostriatal neurons. In this model the glutamatergic/NMDA inputs are absolutely essential for burst firing, but do not trigger it (Lobb et al., 2011a).

VII. CONCLUDING REMARKS

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

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References

Barrot, M., Sesack, S.R., Georges, F., Pistis, M., Hong, S., Jhou, T.C., 2012. Braking dopamine systems: a new GABA master structure for mesolimbic and nigrostriatal functions. J. Neurosci. 32, 14094–14101.

Bean, A.J., Roth, R.H., 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.

Beckstead, M.J., Grandy, D.K., Wickman, K., Williams, J.T., 2004. Vesicular dopamine release elicits an inhibitory postsynaptic current in midbrain dopamine neurons. Neuron. 42, 939–946.

Bingmer, M., Schiemann, J., Roeper, J., Schneider, G., 2011. Measuring burstiness and regularity in oscillatory spike trains. J. Neurosci. Methods. 201, 426–437.

Bjorklund, A., Lindvall, O., 1975. Dopamine in dendrites of substantia nigra neurons: suggestions for a role in dendritic terminals. Brain Res. 83, 531–537.

Blythe, S.N., Atherton, J.F., Bevan, M.D., 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, J.P., Smith, Y., 1990. The GABA and substance P input to dopaminergic neurones in the substantia nigra of the rat. Brain Res. 529, 57–78.

Bontempi, B., Sharp, F.R., 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.

Boyes, J., Bolam, J.P., 2003. The subcellular localization of GABA(B) receptor subunits in the rat substantia nigra. Eur. J. Neurosci. 18, 3279–3293.

Boyes, J., Bolam, J.P., 2007. Localization of GABA receptors in the basal ganglia. Prog. Brain Res. 160, 229–243.

Brazhnik, E., Shah, F., Tepper, J.M., 2008. GABAergic afferents activate both GABAA and GABAB receptors in mouse substantia nigra dopaminergic neurons in vivo. J. Neurosci. 28, 10386–10398.

Bunney, B.S., Aghajanian, G.K., Roth, R.H., 1973a. Comparison of effects of L-dopa, amphetamine and apomorphine on firing rate of rat dopaminergic neurones. Nat. New Biol. 245, 123–125.

Bunney, B.S., Walters, J.R., Roth, R.H., Aghajanian, G.K., 1973b. Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. J. Pharmacol. Exp. Ther. 185, 560–571.

Caille, I., Dumartin, B., Bloch, B., 1996. Ultrastructural localization of D1 dopamine receptor immunoreactivity in rat striatonigral neurons and its relation with dopaminergic innervation. Brain Res. 730, 17–31.

Cameron, D.L., Williams, J.T., 1993. Dopamine D1 receptors facilitate transmitter release. Nature. 366, 344–347.

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

Canavier, C.C., Landry, R.S., 2006. An increase in AMPA and a decrease in SK conductance increase burst firing by different mechanisms in a model of a dopamine neuron in vivo. J. Neurophysiol. 96, 2549–2563.

Canavier, C.C., Oprisan, S.A., Callaway, J.C., Ji, H., Shepard, P.D., 2007. Computational model predicts a role for ERG current in repolarizing plateau potentials in dopamine neurons: implications for modulation of neuronal activity. J. Neurophysiol. 98, 3006–3022.

Celada, P., Paladini, C.A., Tepper, J.M., 1999. GABAergic control of rat substantia nigra dopaminergic neurons: role of globus pallidus and substantia nigra pars reticulata. Neuroscience. 89, 813–825.

Charara, A., Heilman, T.C., Levey, A.I., Smith, Y., 2000. Pre- and postsynaptic localization of GABA(B) receptors in the basal ganglia in monkeys. Neuroscience. 95, 127–140.

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

Cheramy, A., Leviel, V., Glowinski, J., 1981. Dendritic release of dopamine in the substantia nigra. Nature. 289, 537–542.

Chergui, K., Akaoka, H., Charlety, P.J., Saunier, C.F., Buda, M., Chouvet, G., 1994a. Subthalamic nucleus modulates burst firing of nigral dopamine neurones via NMDA receptors. NeuroReport. 5, 1185–1188.

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

Chergui, K., Charlety, P.J., Akaoka, H., Saunier, C.F., Brunet, J.L., Buda, M., Svensson, T.H., 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.

Chiodo, L.A., 1988. Dopamine-containing neurons in the mammalian central nervous system: electrophysiology and pharmacology. Neurosci. Biobehav. Rev. 12, 49–91.

Cobb, W.S., Abercrombie, E.D., 2003. Differential regulation of somatodendritic and nerve terminal dopamine release by serotonergic innervation of substantia nigra. J. Neurochem. 84, 576–584.

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

Colussi-Mas, J., Geisler, S., Zimmer, L., Zahm, D.S., Berod, A., 2007. Activation of afferents to the ventral tegmental area in response to acute amphetamine: a double-labelling study. Eur. J. Neurosci. 26, 1011–1025.

Cragg, S.J., Baufreton, J., Xue, Y., Bolam, J.P., Bevan, M.D., 2004. Synaptic release of dopamine in the subthalamic nucleus. Eur. J. Neurosci. 20, 1788–1802.

Dahlstrom, A., Fuxe, K., 1964. Localization of monoamines in the lower brain stem. Experientia. 20, 398–399.

Dai, M., Tepper, J.M., 1998. Do silent dopaminergic neurons exist in rat substantia nigra in vivo? Neuroscience. 85, 1089–1099.

Dautan, D., Huerta-Ocampo, I., Witten, I.B., Deisseroth, K., Bolam, J. P., Gerdjikov, T., Mena-Segovia, J., 2014. A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. J. Neurosci. 34, 4509–4518.

Deister, C.A., Teagarden, M.A., Wilson, C.J., Paladini, C.A., 2009. An intrinsic neuronal oscillator underlies dopaminergic neuron bursting. J. Neurosci. 29, 15888–15897.

Deniau, J.M., Hammond, C., Riszk, A., Feger, 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, J.M., Kitai, S.T., Donoghue, J.P., 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.

Deniau, J.M., Mailly, P., Maurice, N., Charpier, S., 2007. The pars reticulata of the substantia nigra: a window to basal ganglia output. Prog. Brain Res. 160, 151–172.

Descarries, L., Watkins, K.C., Garcia, S., Bosler, O., Doucet, G., 1996. Dual character, asynaptic and synaptic, of the dopamine innervation in adult rat neostriatum: a quantitative autoradiographic and immunocytochemical analysis. J. Comp. Neurol. 375, 167–186.

Deutch, A.Y., Goldstein, M., Roth, R.H., 1986. The ascending projections of the dopaminergic neurons of the substantia nigra, zona reticulata: a combined retrograde tracer-immunohistochemical study. Neurosci. Lett. 71, 257–263.

Diana, M., Garcia-Munoz, M., Richards, J., Freed, C.R., 1989. Electrophysiological analysis of dopamine cells from the substantia nigra pars compacta of circling rats. Exp. Brain Res. 74, 625–630.

Dodla, R., Wilson, C.J., 2010. A phase function to quantify serial dependence between discrete samples. Biophys. J. 98, L5–7.

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

Engberg, G., Nissbrandt, H., 1993. Gamma-hydroxybutyric acid (GHBA) induces pacemaker activity and inhibition of substantia nigra dopamine neurons by activating GABAB-receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 348, 491–497.

Erhardt, S., Nissbrandt, H., Engberg, G., 1999. Activation of nigral dopamine neurons by the selective GABA(B)-receptor antagonist SCH 50911. J. Neural. Transm. 106, 383–394.

Fallon, J.H., 1981. Collateralization of monoamine neurons: mesotelencephalic dopamine projections to caudate, septum, and frontal cortex. J. Neurosci. 1, 1361–1368.

Fallon, J.H., Moore, R.Y., 1978. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J. Comp. Neurol. 180, 545–580.

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

Fiorillo, C.D., Williams, J.T., 1998. Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons. Nature. 394, 78–82.

Floresco, S.B., West, A.R., Ash, B., Moore, H., Grace, A.A., 2003. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nature Neuroscience. 6, 968–973.

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, A.S., Meltzer, L.T., Bunney, B.S., 1985. Firing properties of substantia nigra dopaminergic neurons in freely moving rats. Life Sci. 36, 1983–1994.

Freund, T.F., Powell, J.F., Smith, A.D., 1984. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience. 13, 1189–1215.

Fujiyama, F., Fritschy, J.M., Stephenson, F.A., Bolam, J.P., 2000. Synaptic localization of GABA(A) receptor subunits in the striatum of the rat. J. Comp. Neurol. 416, 158–172.

Galarraga, E., Bargas, J., 1995. Firing patterns in substantia nigra compacta identified neurons in vitro. Arch. Med. Res. 26, 191–199.

Geffen, L.B., Jessell, T.M., Cuello, A.C., Iversen, L.L., 1976. Release of dopamine from dendrites in rat substantia nigra. Nature. 260, 258–260.

Geisler, S., Marinelli, M., Degarmo, B., Becker, M.L., Freiman, A.J., Beales, M., Meredith, G.E., Zahm, D.S., 2008. Prominent activation of brainstem and pallidal afferents of the ventral tegmental area by cocaine. Neuropsychopharmacology. 33, 2688–2700.

Geisler, S., Wise, R.A., 2008. Functional implications of glutamatergic projections to the ventral tegmental area. Rev. Neurosci. 19, 227–244.

Geisler, S., Zahm, D.S., 2005. Afferents of the ventral tegmental area in the rat-anatomical substratum for integrative functions. J. Comp. Neurol. 490, 270–294.

Gentet, L.J., Williams, S.R., 2007. Dopamine gates action potential backpropagation in midbrain dopaminergic neurons. J. Neurosci. 27, 1892–1901.

Gerfen, C.R., Baimbridge, K.G., Thibault, J., 1987a. The neostriatal mosaic: III. Biochemical and developmental dissociation of patch–matrix mesostriatal systems. J. Neurosci. 7, 3935–3944.

Gerfen, C.R., Herkenham, M., Thibault, J., 1987b. The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. J. Neurosci. 7, 3915–3934.

Gerfen, C.R., Sawchenko, P.E., 1984. An anterograde neuroanatomical tracing method that shows the detailed morphology of neurons, their axons and terminals: immunohistochemical localization of an axonally transported plant lectin, *Phaseolus vulgaris* leucoagglutinin (PHA-L). Brain Res. 290, 219–238.

Gerfen, C.R., Young III, W.S., 1988. Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: an in situ hybridization histochemistry and fluorescent retrograde tracing study. Brain Res. 460, 161–167.

Giralt, M.T., Bonanno, G., Raiteri, M., 1990. GABA terminal autoreceptors in the pars compacta and in the pars reticulata of the rat substantia nigra are GABAB. Eur. J. Pharmacol. 175, 137–144.

Goetz, T., Arslan, A., Wisden, W., Wulff, P., 2007. GABA(A) receptors: structure and function in the basal ganglia. Prog. Brain Res. 160, 21–41.

Gonon, F., 1997. Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. J. Neurosci. 17, 5972–5978.

Gonon, F.G., 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, F.G., Buda, M.J., 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.

Good, C.H., Lupica, C.R., 2009. Properties of distinct ventral tegmental area synapses activated via pedunculopontine or ventral tegmental area stimulation in vitro. J. Physiol. 587, 1233–1247.

Grace, A.A., 1990. Evidence for the functional compartmentalization of spike generating regions of rat midbrain dopamine neurons recorded in vitro. Brain Res. 524, 31–41.

Grace, A.A., 1991. Regulation of spontaneous activity and oscillatory spike firing in rat midbrain dopamine neurons recorded in vitro. Synapse. 7, 221–234.

Grace, A.A., Bunney, B.S., 1979. Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata inhibitory neurons. Eur. J. Pharmacol. 59, 211–218.

Grace, A.A., Bunney, B.S., 1980. Nigral dopamine neurons: intracellular recording and identification with L-dopa injection and histofluorescence. Science. 210, 654–656.

Grace, A.A., Bunney, B.S., 1983a. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—3. Evidence for electrotonic coupling. Neuroscience. 10, 333–348.

Grace, A.A., Bunney, B.S., 1983b. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—2. Action potential generating mechanisms and morphological correlates. Neuroscience. 10, 317–331.

Grace, A.A., Bunney, B.S., 1983c. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—1. Identification and characterization. Neuroscience. 10, 301–315.

Grace, A.A., Bunney, B.S., 1984a. The control of firing pattern in nigral dopamine neurons: burst firing. J. Neurosci. 4, 2877–2890.

Grace, A.A., Bunney, B.S., 1984b. The control of firing pattern in nigral dopamine neurons: single spike firing. J. Neurosci. 4, 2866–2876.

Grace, A.A., Bunney, B.S., 1985a. Low doses of apomorphine elicit two opposing influences on dopamine cell electrophysiology. Brain Res. 333, 285–298.

Grace, A.A., Bunney, B.S., 1985b. Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. Brain Res. 333, 271–284.

Grace, A.A., Onn, S.P., 1989. Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded in vitro. J. Neurosci. 9, 3463–3481.

Grofova, 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.

Grofova, I., Deniau, J.M., Kitai, S.T., 1982. Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP. J. Comp. Neurol. 208, 352–368.

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

Groves, P.M., Linder, J.C., Young, S.J., 1994. 5-Hydroxydopamine-labeled dopaminergic axons: three-dimensional reconstructions of axons, synapses and postsynaptic targets in rat neostriatum. Neuroscience. 58, 593–604.

Groves, P.M., Wilson, C.J., Young, S.J., Rebec, G.V., 1975. Self-inhibition by dopaminergic neurons. Science. 190, 522–528.

Guatteo, E., Mercuri, N.B., Bernardi, G., Knopfel, T., 1999. Group I metabotropic glutamate receptors mediate an inward current in rat substantia nigra dopamine neurons that is independent from calcium mobilization. J. Neurophysiol. 82, 1974–1981.

Gulacsi, A., Lee, C.R., Sik, A., Viitanen, T., Kaila, K., Tepper, J.M., Freund, T.F., 2003. Cell type-specific differences in chloride-regulatory mechanisms and GABA(A) receptor-mediated inhibition in rat substantia nigra. J. Neurosci. 23, 8237–8246.

Gulley, R.L., Smithberg, M., 1971. Synapses in the rat substantia nigra. Tissue Cell. 3, 691–700.

Gulley, R.L., Wood, R.L., 1971. The fine structure of the neurons in the rat substantia nigra. Tissue Cell. 3, 675–690.

Guyenet, P.G., Aghajanian, G.K., 1978. Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra. Brain Res. 150, 69–84.

Hajos, M., Greenfield, S.A., 1993. Topographic heterogeneity of substantia nigra neurons: diversity in intrinsic membrane properties and synaptic inputs. Neuroscience. 55, 919–934.

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

Hammond, C., Deniau, J.M., Rizk, A., Feger, J., 1978. Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. Brain Res. 151, 235–244.

Hattori, T., Fibiger, H.C., McGeer, P.L., 1975. Demonstration of a pallido-nigral projection innervating dopaminergic neurons. J. Comp. Neurol. 162, 487–504.

Hattori, T., Fibiger, H.C., McGeer, P.L., Maler, L., 1973a. Analysis of the fine structure of the dopaminergic nigrostriatal projection by electron microscopic autoradiography. Exp. Neurol. 41, 599–611.

Hattori, T., McGeer, P.L., Fibiger, H.C., McGeer, E.G., 1973b. On the source of GABA-containing terminals in the substantia nigra.

Electron microscopic autoradiographic and biochemical studies. Brain Res. 54, 103–114.
Hausser, M., Stuart, G., Racca, C., Sakmann, B., 1995. Axonal initiation and active dendritic propagation of action potentials in substantia nigra neurons. Neuron. 15, 637–647.
Hausser, M.A., Yung, W.H., 1994. Inhibitory synaptic potentials in guinea-pig substantia nigra dopamine neurones in vitro. J. Physiol. 479, 401–422.
Hebb, M.O., Robertson, H.A., 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.
Herrik, K.F., Christophersen, P., Shepard, P.D., 2010. Pharmacological modulation of the gating properties of small conductance Ca^{2+}-activated K^+ channels alters the firing pattern of dopamine neurons in vivo. J. Neurophysiol. 104, 1726–1735.
Hertel, A., Weppner, M., Baas, H., Schreiner, M., Maul, F.D., Baum, R.P., Fischer, P.A., Hor, G., 1997. Quantification of IBZM dopamine receptor SPET in de novo Parkinson patients before and during therapy. Nucl. Med. Commun. 18, 811–822.
Hikosaka, O., Bromberg-Martin, E., Hong, S., Matsumoto, M., 2008. New insights on the subcortical representation of reward. Curr. Opin. Neurobiol. 18, 203–208.
Hubert, G.W., 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, B.I., Reynolds, J.N., Hay, J., Perk, C.G., Miller, R., 2002. Firing modes of midbrain dopamine cells in the freely moving rat. Neuroscience. 114, 475–492.
Ilango, A., Kesner, A.J., Keller, K.L., Stuber, G.D., Bonci, A., Ikemoto, S., 2014. Similar roles of substantia nigra and ventral tegmental dopamine neurons in reward and aversion. J. Neurosci. 34, 817–822.
Iribe, Y., Moore, K., Pang, K.C., Tepper, J.M., 1999. Subthalamic stimulation-induced synaptic responses in substantia nigra pars compacta dopaminergic neurons in vitro. J. Neurophysiol. 82, 925–933.
Jhou, T.C., Fields, H.L., Baxter, M.G., Saper, C.B., Holland, P.C., 2009a. The rostromedial tegmental nucleus (RMTg), a GABAergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses. Neuron. 61, 786–800.
Jhou, T.C., Geisler, S., Marinelli, M., Degarmo, B.A., Zahm, D.S., 2009b. The mesopontine rostromedial tegmental nucleus: a structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. J. Comp. Neurol. 513, 566–596.
Ji, H., Hougaard, C., Herrik, K.F., Strobaek, D., Christophersen, P., Shepard, P.D., 2009. Tuning the excitability of midbrain dopamine neurons by modulating the Ca^{2+} sensitivity of SK channels. Eur. J. Neurosci. 29, 1883–1895.
Ji, H., Shepard, P.D., 2007. Lateral habenula stimulation inhibits rat midbrain dopamine neurons through a GABA(A) receptor-mediated mechanism. J. Neurosci. 27, 6923–6930.
Johnson, S.W., North, R.A., 1992a. Two types of neurone in the rat ventral tegmental area and their synaptic inputs. J. Physiol. 450, 455–468.
Johnson, S.W., North, R.A., 1992b. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12, 483–488.
Johnson, S.W., Seutin, V., 1997. Bicuculline methiodide potentiates NMDA-dependent burst firing in rat dopamine neurons by blocking apamin-sensitive Ca^{2+}-activated K^+ currents. Neurosci. Lett. 231, 13–16.
Johnson, S.W., Seutin, V., North, R.A., 1992. Burst firing in dopamine neurons induced by *N*-methyl-D-aspartate: role of electrogenic sodium pump. Science. 258, 665–667.
Juraska, J.M., Wilson, C.J., Groves, P.M., 1977. The substantia nigra of the rat: a Golgi study. J. Comp. Neurol. 172, 585–600.
Kang, Y., Kitai, S.T., 1993a. Calcium spike underlying rhythmic firing in dopaminergic neurons of the rat substantia nigra. Neurosci. Res. 18, 195–207.
Kang, Y., Kitai, S.T., 1993b. A whole cell patch-clamp study on the pacemaker potential in dopaminergic neurons of rat substantia nigra compacta. Neurosci. Res. 18, 209–221.
Khaliq, Z.M., Bean, B.P., 2008. Dynamic, nonlinear feedback regulation of slow pacemaking by A-type potassium current in ventral tegmental area neurons. J. Neurosci. 28, 10905–10917.
Kirmse, K., Dvorzhak, A., Kirischuk, S., Grantyn, R., 2008. GABA transporter 1 tunes GABAergic synaptic transmission at output neurons of the mouse neostriatum. J. Physiol. 586, 5665–5678.
Kita, H., 2007. Globus pallidus external segment. Prog. Brain Res. 160, 111–133.
Kita, T., Kita, H., Kitai, S.T., 1986. Electrical membrane properties of rat substantia nigra compacta neurons in an in vitro slice preparation. Brain Res. 372, 21–30.
Kitai, S.T., Shepard, P.D., Callaway, J.C., Scroggs, R., 1999. Afferent modulation of dopamine neuron firing patterns. Curr. Opin. Neurobiol. 9, 690–697.
Kiyatkin, E.A., Rebec, G.V., 1998. Heterogeneity of ventral tegmental area neurons: single-unit recording and iontophoresis in awake, unrestrained rats. Neuroscience. 85, 1285–1309.
Ko, D., Wilson, C.J., Lobb, C.J., Paladini, C.A., 2012. Detection of bursts and pauses in spike trains. J. Neurosci. Methods. 211, 145–158.
Köhler, M., Hirschberg, B., Bond, C.T., Kinzie, J.M., Marrion, N.V., Maylie, J., Adelman, J.P., 1996. Small-conductance, calcium-activated potassium channels from mammalian brain. Science. 273, 1709–1714.
Kuznetsov, A.S., Kopell, N.J., Wilson, C.J., 2006. Transient high-frequency firing in a coupled-oscillator model of the mesencephalic dopaminergic neuron. J. Neurophysiol. 95, 932–947.
Kuznetsova, A.Y., Huertas, M.A., Kuznetsov, A.S., Paladini, C.A., Canavier, C.C., 2010. Regulation of firing frequency in a computational model of a midbrain dopaminergic neuron. J. Comp. Neurosci. 28, 389–403.
Lacey, M.G., 1993. Neurotransmitter receptors and ionic conductances regulating the activity of neurones in substantia nigra pars compacta and ventral tegmental area. Prog. Brain Res. 99, 251–276.
Lacey, M.G., Mercuri, N.B., North, R.A., 1987. Dopamine acts on D2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. J. Physiol. 392, 397–416.
Lacey, M.G., Mercuri, N.B., North, R.A., 1988. On the potassium conductance increase activated by GABAB and dopamine D2 receptors in rat substantia nigra neurones. J. Physiol. 401, 437–453.
Lacey, M.G., Mercuri, N.B., North, R.A., 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.
Lammel, S., Hetzel, A., Hackel, O., Jones, I., Liss, B., Roeper, J., 2008. Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron. 57, 760–773.
Lee, C.R., Abercrombie, E.D., Tepper, J.M., 2004. Pallidal control of substantia nigra dopaminergic neuron firing pattern and its relation to extracellular neostriatal dopamine levels. Neuroscience. 129, 481–489.
Lee, C.R., Tepper, J.M., 2007. Morphological and physiological properties of parvalbumin- and calretinin-containing gamma-aminobutyric acidergic neurons in the substantia nigra. J. Comp. Neurol. 500, 958–972.
Lee, C.R., Tepper, J.M., 2009. Basal ganglia control of substantia nigra dopaminergic neurons. J. Neural. Transm. Suppl.71–90.

Levin, B.E., 2000. Glucose-regulated dopamine release from substantia nigra neurons. Brain Res. 874, 158–164.
Li, Y.X., Bertram, R., Rinzel, J., 1996. Modeling *N*-methyl-D-aspartate-induced bursting in dopamine neurons. Neuroscience. 71, 397–410.
Lindvall, O., Bjorklund, A., 1979. Dopaminergic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. Brain Res. 172, 169–173.
Liss, B., Franz, O., Sewing, S., Bruns, R., Neuhoff, H., Roeper, J., 2001. Tuning pacemaker frequency of individual dopaminergic neurons by Kv4.3L and KChip3.1 transcription. EMBO J. 20, 5715–5724.
Liss, B., Roeper, J., 2001. A role for neuronal K(ATP) channels in metabolic control of the seizure gate. Trends Pharmacol. Sci. 22, 599–601 [Discussion 601–602].
Liu, T., Soong, S.J., Wilson, N.P., Craig, C.B., Cole, P., Macaluso, M., Butterworth Jr., C.E., 1993. A case control study of nutritional factors and cervical dysplasia. Cancer Epidemiol. Biomark. Prev. 2, 525–530.
Lobb, C.J., Troyer, T.W., Wilson, C.J., Paladini, C.A., 2011a. Disinhibition bursting of dopaminergic neurons. Front. Syst. Neurosci. 5, 25.
Lobb, C.J., Wilson, C.J., Paladini, C.A., 2011b. High-frequency, short-latency disinhibition bursting of midbrain dopaminergic neurons. J. Neurophysiol. 105, 2501–2511.
Lobb, C.J., Wilson, C.J., Paladini, C.A., 2010. A dynamic role for GABA receptors on the firing pattern of midbrain dopaminergic neurons. J. Neurophysiol. 104, 403–413.
Lu, X.Y., Ghasemzadeh, M.B., Kalivas, P.W., 1999. Regional distribution and cellular localization of gamma-aminobutyric acid subtype 1 receptor mRNA in the rat brain. J. Comp. Neurol. 407, 166–182.
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, J.M., 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.
Manley, L.D., Kuczenski, R., Segal, D.S., Young, S.J., Groves, P.M., 1992. Effects of frequency and pattern of medial forebrain bundle stimulation on caudate dialysate dopamine and serotonin. J. Neurochem. 58, 1491–1498.
Martin, G.E., Haubrich, D.R., 1978. Striatal dopamine release and contraversive rotation elicited by intranigrally applied muscimol. Nature. 275, 230–231.
Matsuda, W., Furuta, T., Nakamura, K.C., Hioki, H., Fujiyama, F., Arai, R., Kaneko, T., 2009. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J. Neurosci. 29, 444–453.
Matsui, A., Jarvie, B.C., Robinson, B.G., Hentges, S.T., Williams, J.T., 2014. Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. Neuron. 82, 1346–1356.
Matsumoto, M., Hikosaka, O., 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 447, 1111–1115.
Mayer, M.L., Westbrook, G.L., Guthrie, P.B., 1984. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature. 309, 261–263.
Mena-Segovia, J., Winn, P., Bolam, J.P., 2008. Cholinergic modulation of midbrain dopaminergic systems. Brain Res. Rev. 58, 265–271.
Mercuri, N.B., Bonci, A., Calabresi, P., Stratta, F., Stefani, A., Bernardi, G., 1994. Effects of dihydropyridine calcium antagonists on rat midbrain dopaminergic neurones. Br. J. Pharmacol. 113, 831–838.
Mereu, G., Gessa, G.L., 1985. Low doses of ethanol inhibit the firing of neurons in the substantia nigra, pars reticulata: a GABAergic effect? Brain Res. 360, 325–330.
Miller, D.W., Abercrombie, E.D., 1999. Role of high-affinity dopamine uptake and impulse activity in the appearance of extracellular dopamine in striatum after administration of exogenous L-DOPA: studies in intact and 6-hydroxydopamine-treated rats. J. Neurochem. 72, 1516–1522.
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, J.T., 2003. Two intracellular pathways mediate metabotropic glutamate receptor-induced Ca^{2+} mobilization in dopamine neurons. J. Neurosci. 23, 149–157.
Morikawa, H., Paladini, C.A., 2011. Dynamic regulation of midbrain dopamine neuron activity: intrinsic, synaptic, and plasticity mechanisms. Neuroscience. 198, 95–111.
Nair-Roberts, R.G., Chatelain-Badie, S.D., Benson, E., White-Cooper, H., Bolam, J.P., Ungless, M.A., 2008. Stereological estimates of dopaminergic, GABAergic and glutamatergic neurons in the ventral tegmental area, substantia nigra and retrorubral field in the rat. Neuroscience. 152, 1024–1031.
Naito, A., Kita, H., 1994. The cortico-pallidal projection in the rat: an anterograde tracing study with biotinylated dextran amine. Brain Res. 653, 251–257.
Nedergaard, S., Flatman, J.A., Engberg, I., 1993. Nifedipine- and omega-conotoxin-sensitive Ca^{2+} conductances in guinea-pig substantia nigra pars compacta neurones. J. Physiol. 466, 727–747.
Neuhoff, H., Neu, A., Liss, B., Roeper, J., 2002. I(h) channels contribute to the different functional properties of identified dopaminergic subpopulations in the midbrain. J. Neurosci. 22, 1290–1302.
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.
Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., Prochiantz, A., 1984. Magnesium gates glutamate-activated channels in mouse central neurones. Nature. 307, 462–465.
Okada, K., Toyama, K., Inoue, Y., Isa, T., Kobayashi, Y., 2009. Different pedunculopontine tegmental neurons signal predicted and actual task rewards. J. Neurosci. 29, 4858–4870.
Onn, S.P., Fienberg, A.A., Grace, A.A., 2003. Dopamine modulation of membrane excitability in striatal spiny neurons is altered in DARPP-32 knockout mice. J. Pharmacol. Exp. Ther. 306, 870–879.
Oorschot, D.E., 1996. Total number of neurons in the neostriatal, pallidal, subthalamic, and substantia nigral nuclei of the rat basal ganglia: a stereological study using the cavalieri and optical dissector methods. J. Comp. Neurol. 366, 580–599.
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, P.G., Clark, D., 1997. Burst firing in midbrain dopaminergic neurons. Brain Res. Brain Res. Rev. 25, 312–334.
Paden, C., Wilson, C.J., Groves, P.M., 1976. Amphetamine-induced release of dopamine from the substantia nigra in vitro. Life Sci. 19, 1499–1506.
Paladini, C.A., Celada, P., Tepper, J.M., 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, C.A., Iribe, Y., Tepper, J.M., 1999b. GABAA receptor stimulation blocks NMDA-induced bursting of dopaminergic neurons in vitro by decreasing input resistance. Brain Res. 832, 145–151.
Paladini, C.A., Fiorillo, C.D., Morikawa, H., Williams, J.T., 2001. Amphetamine selectively blocks inhibitory glutamate transmission in dopamine neurons. Nat. Neurosci. 4, 275–281.

Paladini, C.A., Roeper, J., 2014. Generating bursts (and pauses) in the dopamine midbrain neurons. Neuroscience. 282C, 109–121.
Paladini, C.A., Tepper, J.M., 1999. GABA(A) and GABA(B) antagonists differentially affect the firing pattern of substantia nigra dopaminergic neurons in vivo. Synapse. 32, 165–176.
Pan, W.X., Hyland, B.I., 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. J. Neurosci. 25, 4725–4732.
Perrotti, L.I., Bolanos, C.A., Choi, K.H., Russo, S.J., Edwards, S., Ulery, P.G., Wallace, D.L., Self, D.W., Nestler, E.J., Barrot, M., 2005. DeltaFosB accumulates in a GABAergic cell population in the posterior tail of the ventral tegmental area after psychostimulant treatment. Eur. J. Neurosci. 21, 2817–2824.
Pickel, V.M., Beckley, S.C., Sumal, K.K., Joh, T.H., Reis, D.J., Miller, R.J., 1981. Light and electron microscopic localization of enkephalin and tyrosine hydroxylase in neostriatum of fetal and adult rat brain. Acta Histochem. Suppl. 24, 97–105.
Prensa, L., Parent, A., 2001. The nigrostriatal pathway in the rat: a single-axon study of the relationship between dorsal and ventral tier nigral neurons and the striosome/matrix striatal compartments. J. Neurosci. 21, 7247–7260.
Putzier, I., Kullmann, P.H., Horn, J.P., Levitan, E.S., 2009a. Dopamine neuron responses depend exponentially on pacemaker interval. J. Neurophysiol. 101, 926–933.
Putzier, I., Kullmann, P.H., Horn, J.P., Levitan, E.S., 2009b. Cav1.3 channel voltage dependence, not Ca^{2+} selectivity, drives pacemaker activity and amplifies bursts in nigral dopamine neurons. J. Neurosci. 29, 15414–15419.
Quina, L.A., Tempest, L., Ng, L., Harris, J.A., Ferguson, S., Jhou, T. C., Turner, E.E., 2015. Efferent pathways of the mouse lateral habenula. J. Comp. Neurol. 523, 32–60.
Ribak, C.E., Vaughn, J.E., Saito, K., Barber, R., 1976. Immunocytochemical localization of glutamate decarboxylase in the substantia nigra of the rat. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 55, 205–211.
Rice, M.E., Cragg, S.J., 2008. Dopamine spillover after quantal release: rethinking dopamine transmission in the nigrostriatal pathway. Brain Res. Rev. 58, 303–313.
Rinvik, E., Grofova, I., 1970. Observations on the fine structure of the substantia nigra in the cat. Exp. Brain Res. 11, 229–248.
Rivera, C., Voipio, J., Payne, J.A., Ruusuvuori, E., Lahtinen, H., Lamsa, K., Pirvola, U., Saarma, M., Kaila, K., 1999. The K^+/Cl^- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. Nature. 397, 251–255.
Robledo, P., Feger, J., 1990. Excitatory influence of rat subthalamic nucleus to substantia nigra pars reticulata and the pallidal complex: electrophysiological data. Brain Res. 518, 47–54.
Robledo, P., Vezole, I., Feger, J., 1988. Excitatory effect of subthalamo-nigral and subthalamo-pallidal efferent pathways in the rat. C. R. Acad. Sci. 307, 133–138.
Rossi, M.A., Sukharnikova, T., Hayrapetyan, V.Y., Yang, L., Yin, H. H., 2013. Operant self-stimulation of dopamine neurons in the substantia nigra. PLoS One. 8, e65799.
Ryan, L.J., Tepper, J.M., Young, S.J., Groves, P.M., 1986. Frontal cortex stimulation evoked neostriatal potentials in rats: intracellular and extracellular analysis. Brain Res. Bull. 17, 751–758.
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, B.H., 1992a. 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.
Santiago, M., Westerink, B.H., 1992b. Simultaneous recording of the release of nigral and striatal dopamine in the awake rat. Neurochem. Int. 20 (Suppl.), 107S–110S.
Scammell, T.E., Estabrooke, I.V., McCarthy, M.T., Chemelli, R.M., Yanagisawa, M., Miller, M.S., Saper, C.B., 2000. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J. Neurosci. 20, 8620–8628.
Scanziani, M., 2000. GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. Neuron. 25, 673–681.
Schiemann, J., Schlaudraff, F., Klose, V., Bingmer, M., Seino, S., Magill, P.J., Zaghloul, K.A., Schneider, G., Liss, B., Roeper, J., 2012. K-ATP channels in dopamine substantia nigra neurons control bursting and novelty-induced exploration. Nat. Neurosci. 15, 1272–1280.
Scholze, P., Orr-Urtreger, A., Changeux, J.P., McIntosh, J.M., Huck, S., 2007. Catecholamine outflow from mouse and rat brain slice preparations evoked by nicotinic acetylcholine receptor activation and electrical field stimulation. Br. J. Pharmacol. 151, 414–422.
Schousboe, A., Waagepetersen, H.S., 2007. GABA: homeostatic and pharmacological aspects. Prog. Brain Res. 160, 9–19.
Schultz, W., 2007. Behavioral dopamine signals. Trends Neurosci. 30, 203–210.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science. 275, 1593–1599.
Schwyn, R.C., Fox, C.A., 1974. The primate substantia nigra: a Golgi and electron microscopic study. J. Hirnforsch. 15, 95–126.
Segev, D., Korngreen, A., 2007. Kinetics of two voltage-gated K^+ conductances in substantia nigra dopaminergic neurons. Brain Res. 1173, 27–35.
Shepard, P.D., Bunney, B.S., 1988. Effects of apamin on the discharge properties of putative dopamine-containing neurons in vitro. Brain Res. 463, 380–384.
Shepard, P.D., Bunney, B.S., 1991. Repetitive firing properties of putative dopamine-containing neurons in vitro: regulation by an apamin-sensitive Ca(2+)-activated K^+ conductance. Exp. Brain Res. 86, 141–150.
Smith, I.D., Grace, A.A., 1992. Role of the subthalamic nucleus in the regulation of nigral dopamine neuron activity. Synapse. 12, 287–303.
Smith, Y., Bevan, M.D., Shink, E., Bolam, J.P., 1998. Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience. 86, 353–387.
Smith, Y., Bolam, J.P., 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, J.P., 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, 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.
Soden, M.E., Jones, G.L., Sanford, C.A., Chung, A.S., Guler, A.D., Chavkin, C., Lujan, R., Zweifel, L.S., 2013. Disruption of dopamine neuron activity pattern regulation through selective expression of a human KCNN3 mutation. Neuron. 80, 997–1009.
Somogyi, P., Bolam, J.P., Totterdell, S., Smith, A.D., 1981. Monosynaptic input from the nucleus accumbens—ventral striatum region to retrogradely labelled nigrostriatal neurones. Brain Res. 217, 245–263.
Stocker, M., Pedarzani, P., 2000. Differential distribution of three Ca (2+)-activated K(+) channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. Mol. Cell Neurosci. 15, 476–493.
Suaud-Chagny, M.F., Chergui, K., Chouvet, G., Gonon, F., 1992. Relationship between dopamine release in the rat nucleus accumbens and the discharge activity of dopaminergic neurons during local in vivo application of amino acids in the ventral tegmental area. Neuroscience. 49, 63–72.

Sugita, S., Johnson, S.W., North, R.A., 1992. Synaptic inputs to GABAA and GABAB receptors originate from discrete afferent neurons. Neurosci. Lett. 134, 207–211.

Takada, M., Hattori, T., 1986. Collateral projections from the substantia nigra to the cingulate cortex and striatum in the rat. Brain Res. 380, 331–335.

Tepper, J.M., Bolam, J.P., 2004. Functional diversity and specificity of neostriatal interneurons. Curr. Opin. Neurobiol. 14, 685–692.

Tepper, J.M., Damlama, M., Trent, F., 1994. Postnatal changes in the distribution and morphology of rat substantia nigra dopaminergic neurons. Neuroscience. 60, 469–477.

Tepper, J.M., Groves, P.M., 1990. In vivo electrophysiology of central nervous system terminal autoreceptors. Ann. N.Y. Acad. Sci. 604, 470–487.

Tepper, J.M., Koos, T., Wilson, C.J., 2004. GABAergic microcircuits in the neostriatum. Trends Neurosci. 27, 662–669.

Tepper, J.M., Lee, C.R., 2007. GABAergic control of substantia nigra dopaminergic neurons. Prog. Brain Res. 160, 189–208.

Tepper, J.M., Martin, L.P., Anderson, D.R., 1995. GABAA receptor-mediated inhibition of rat substantia nigra dopaminergic neurons by pars reticulata projection neurons. J. Neurosci. 15, 3092–3103.

Tepper, J.M., Nakamura, S., Spanis, C.W., Squire, L.R., Young, S.J., Groves, P.M., 1982. Subsensitivity of catecholaminergic neurons to direct acting agonists after single or repeated electroconvulsive shock. Biol. Psychiatry. 17, 1059–1070.

Tepper, J.M., Nakamura, S., Young, S.J., Groves, P.M., 1984a. Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of striatal drug infusions. Brain Res. 309, 317–333.

Tepper, J.M., Young, S.J., Groves, P.M., 1984b. Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of increases in impulse flow. Brain Res. 309, 309–316.

Tepper, J.M., Paladini, C.A., Celada, P., 1998. GABAergic control of the firing pattern of substantia nigra dopaminergic neurons. Adv. Pharmacol. 42, 694–699.

Tepper, J.M., Sawyer, S.F., Groves, P.M., 1987. Electrophysiologically identified nigral dopaminergic neurons intracellularly labeled with HRP: light-microscopic analysis. J. Neurosci. 7, 2794–2806.

Tepper, J.M., Sawyer, S.F., Young, S.J., Groves, P.M., 1986. Autoreceptor-mediated changes in dopaminergic terminal excitability: effects of potassium channel blockers. Brain Res. 367, 230–237.

Tepper, J.M., Trent, F., 1993. In vivo studies of the postnatal development of rat neostriatal neurons. Prog. Brain Res. 99, 35–50.

Tepper, J.M., 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, J.M., Wilson, C.J., Koos, T., 2008. Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons. Brain Res. Rev. 58, 272–281.

Tong, Z.Y., Overton, P.G., Clark, D., 1996. Antagonism of NMDA receptors but not AMPA/kainate receptors blocks bursting in dopaminergic neurons induced by electrical stimulation of the prefrontal cortex. J. Neural. Transm. 103, 889–904.

Totterdell, S., Bolam, J.P., Smith, A.D., 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.

Tower, D.B., 1954. Structural and functional organization of mammalian cerebral cortex; the correlation of neurone density with brain size; cortical neurone density in the fin whale (*Balaenoptera physalus* L.) with a note on the cortical neurone density in the Indian elephant. J. Comp. Neurol. 101, 19–51.

Tozzi, A., Bengtson, C.P., Longone, P., Carignani, C., Fusco, F.R., Bernardi, G., Mercuri, N.B., 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., Nakamura, S., Tepper, J.M., 1991. Amphetamine exerts anomalous effects on dopaminergic neurons in neonatal rats in vivo. Eur. J. Pharmacol. 204, 265–272.

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

Ungless, M.A., Grace, A.A., 2012. Are you or aren't you? Challenges associated with physiologically identifying dopamine neurons. Trends Neurosci. 35, 422–430.

Walters, J.R., Lakoski, J.M., 1978. Effect of muscimol on single unit activity of substantia nigra dopamine neurons. Eur. J. Pharmacol. 47, 469–471.

Waroux, O., Massotte, L., Alleva, L., Graulich, A., Thomas, E., Liegeois, J.F., Scuvee-Moreau, J., Seutin, V., 2005. SK channels control the firing pattern of midbrain dopaminergic neurons in vivo. Eur. J. Neurosci. 22, 3111–3121.

Waszczak, B.L., Eng, N., Walters, J.R., 1980. Effects of muscimol and picrotoxin on single unit activity of substantia nigra neurons. Brain Res. 188, 185–197.

Waszczak, B.L., Hume, C., Walters, J.R., 1981. Supersensitivity of substantia nigra pars reticulata neurons to GABAergic drugs after striatal lesions. Life Sci. 28, 2411–2420.

Watabe-Uchida, M., Zhu, L., Ogawa, S.K., Vamanrao, A., Uchida, N., 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. Neuron. 74, 858–873.

Wilson, C.J., Callaway, J.C., 2000. Coupled oscillator model of the dopaminergic neuron of the substantia nigra. J. Neurophysiol. 83, 3084–3100.

Wilson, C.J., Groves, P.M., Fifkova, E., 1977a. Monoaminergic synapses, including dendro-dendritic synapses in the rat substantia nigra. Exp. Brain Res. 30, 161–174.

Wilson, C.J., Young, S.J., Groves, P.M., 1977b. Statistical properties of neuronal spike trains in the substantia nigra: cell types and their interactions. Brain Res. 136, 243–260.

Wolfart, J., Neuhoff, H., Franz, O., Roeper, J., 2001. Differential expression of the small-conductance, calcium-activated potassium channel SK3 is critical for pacemaker control in dopaminergic midbrain neurons. J. Neurosci. 21, 3443–3456.

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

Yung, W.H., Hausser, M.A., Jack, J.J., 1991. Electrophysiology of dopaminergic and non-dopaminergic neurones of the guinea-pig substantia nigra pars compacta in vitro. J. Physiol. 436, 643–667.

Zhang, H., Lee, T.H., Ellinwood Jr., E.H., 1992. The progressive changes of neuronal activities of the nigral dopaminergic neurons upon withdrawal from continuous infusion of cocaine. Brain Res. 594, 315–318.

Zhang, J.F., Randall, A.D., Ellinor, P.T., Horne, W.A., Sather, W.A., Tanabe, T., Schwarz, T.L., Tsien, R.W., 1993. Distinctive pharmacology and kinetics of cloned neuronal Ca^{2+} channels and their possible counterparts in mammalian CNS neurons. Neuropharmacology. 32, 1075–1088.

Zweifel, L.S., Parker, J.G., Lobb, C.J., Rainwater, A., Wall, V.Z., Fadok, J.P., Darvas, M., Kim, M.J., Mizumori, S.J., Paladini, C.A., Phillips, P.E., Palmiter, R.D., 2009. Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. Proc. Natl. Acad. Sci. U.S.A. 106, 7281–7288.