

Published in final edited form as:

*Neuroscience*. 2011 December 15; 198: 69–94. doi:10.1016/j.neuroscience.2011.07.061.

## Intrinsic and integrative properties of substantia nigra pars reticulata neurons

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### Abstract

The GABA projection neurons of the substantia nigra pars reticulata (SNr) are output neurons for the basal ganglia and thus critical for movement control. Their most striking neurophysiological feature is sustained, spontaneous high frequency spike firing. A fundamental question is: what are the key ion channels supporting the remarkable firing capability in these neurons? Recent studies indicate that these neurons express tonically active TRPC3 channels that conduct a Na-dependent inward current even at hyperpolarized membrane potentials. When the membrane potential reaches  $-60$  mV, a voltage-gated persistent sodium current ( $I_{NaP}$ ) starts to activate, further depolarizing the membrane potential. At or slightly below  $-50$  mV, the large transient voltage-activated sodium current ( $I_{NaT}$ ) starts to activate and eventually triggers the rapid rising phase of action potentials. SNr GABA neurons have a higher density of ( $I_{NaT}$ ), contributing to the faster rise and larger amplitude of action potentials, compared with the slow-spiking dopamine neurons.  $I_{NaT}$  also recovers from inactivation more quickly in SNr GABA neurons than in nigral dopamine neurons. In SNr GABA neurons, the rising phase of the action potential triggers the activation of high-threshold, inactivation-resistant Kv3-like channels that can rapidly repolarize the membrane. These intrinsic ion channels provide SNr GABA neurons with the ability to fire spontaneous and sustained high frequency spikes. Additionally, robust GABA inputs from direct pathway medium spiny neurons in the striatum and GABA neurons in the globus pallidus may inhibit and silence SNr GABA neurons, whereas glutamate synaptic input from the subthalamic nucleus may induce burst firing in SNr GABA neurons. Thus, afferent GABA and glutamate synaptic inputs sculpt the tonic high frequency firing of SNr GABA neurons and the consequent inhibition of their targets into an integrated motor control signal that is further fine-tuned by neuromodulators including dopamine, serotonin, endocannabinoids, and  $H_2O_2$ .

### Keywords

action potential; basal ganglia; ion channel; Parkinson's disease; substantia nigra; synapse

## 1. Introduction

The basal ganglia are a group of interconnected subcortical nuclei that include the caudate nucleus and putamen (the striatum), the globus pallidus external and internal segments (GPe

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and GPi), the subthalamic nucleus (STN), and the substantia nigra pars compacta and pars reticulata (SNc and SNr) (Fig. 1A; Parent et al., 2000; Gerfen and Bolam, 2010). The SNr and GPi (or entopeduncular nucleus in rodents) carry out an important role in basal ganglia physiology in that they are the output neurons for the basal ganglia network. Their projection neurons release GABA and subserve the important function of inhibiting and disinhibiting neurons in the main target nuclei which are the thalamus and superior colliculus. The spiking activity of SNr GABA neurons is shaped by a combination of intrinsic conductances that generate the tonic, high frequency, regular firing that is characteristic of these neurons under most conditions, and extrinsic influences that can increase or decrease their firing rate and in some cases change their firing pattern. Thus, an understanding of the intrinsic and extrinsic factors that influence the firing of nigral GABA neurons is central to elucidating how the basal ganglia control movement and other behaviors. Here we review the key anatomical and physiological characteristics of SNr GABA neurons that underlie the ability of these neurons to control target neurons and integrate input from other basal ganglia nuclei and elsewhere in the brain.

## 2. Key anatomical features of SNr GABA projection neurons

The substantia nigra is located in the ventral midbrain and bordered dorsally by the medial lemniscus and ventrally by the cerebral peduncle. It is divided into the more dorsal SNc with primarily dopamine neurons and the more ventral SNr with primarily GABA neurons (Fig. 1B). There is, however, some intermixing of dopamine neurons within the SNr (González-Hernández and Rodríguez, 2000). SNr GABA neurons are medium-to large-sized and have mostly ovoid or fusiform somata that emit 2–6 primary dendrites which branch frequently (Grofová et al., 1982; Cebrián et al., 2007; Lee and Tepper, 2007a). A single main axon typically arises from the soma or a primary dendrite and courses through the substantia nigra issuing one or more local axon collaterals before leaving the nucleus (Deniau et al., 1982; Grofová et al., 1982; Kemel et al., 1988; Mailly et al., 2003).

One primary target of SNr GABA neurons is the thalamus (Fig. 1A, D) where they form most of their synapses in the ventromedial and intralaminar thalamic nuclei in rodents (Beckstead et al., 1979; Di Chiara et al., 1979; Herkenham, 1979; Nishimura et al., 1997) and the ventral anterior and ventral lateral nuclei in primates (Carpenter et al., 1976; Hazrati and Parent, 1991; François et al., 2002). Axons from SNr GABA neurons form synapses on the proximal dendrites and somata of relay neurons in the thalamus of both rodents and primates, thus forming a structural basis for nigral inhibition of thalamic neurons (Bodor et al., 2008). Indeed, electrical stimulation of nigrothalamic neurons produces a short latency, short duration inhibition of thalamic neurons (Deniau et al., 1978; MacLeod et al., 1980; Tanibuchi et al., 2009a,b). Conversely, inhibition of the SNr leads to increases in the spontaneous discharge of thalamic neurons demonstrating a tonic inhibition of those neurons by SNr GABA cells (MacLeod et al., 1980; Deniau and Chevalier, 1985). The other main target of SNr GABA neurons is the superior colliculus (Fig. 1C) (Beckstead et al., 1979; Di Chiara et al., 1979; Beckstead and Frankfurter, 1982; Williams and Faull, 1988; Hikosaka et al., 2000) where stimulation of SNr GABA neurons induces short latency inhibition of neurons in that structure (Chevalier et al., 1981; Hikosaka and Wurtz, 1983b; Hikosaka and Wurtz, 1985a,b). Although commonly projecting to one primary target nucleus, some SNr GABA neurons send axon collaterals to multiple targets (Anderson and Yoshida, 1980; Beckstead, 1983; Parent et al. 1983; Cebrián et al., 2005). There are also less well characterized projections from SNr GABA neurons to multiple brainstem and midbrain structures (e.g. Takakusaki et al., 2003, 2004). SNr GABA neurons also issue local axon collaterals that carry out an important role of inhibition within the substantia nigra itself. These local axon collaterals arborize throughout both segments of the substantia nigra and frequently have varicosities resembling both *en passant* and terminal boutons (Deniau et al.,

1982; Grofová et al., 1982; Kemel et al., 1988; Maily et al., 2003; Lee and Tepper, 2007a). Both SNr GABA neurons and SNc dopamine neurons are locally inhibited via axon collaterals from SNr GABA neurons (Deniau et al., 1982, Tepper et al., 1995; Saitoh et al., 2004). These efferent connections in combination with afferent inputs (discussed in sections on individual synaptic inputs) provide the anatomical bases for SNr GABA neurons to affect multiple aspects of movement control under physiological and pathological conditions.

### 3. SNr GABA projection neurons fire sustained autonomous high frequency spikes

A striking neurophysiological feature of SNr GABA neurons is their sustained high frequency spike firing (Fig. 2A). SNr GABA neurons fire spikes of short duration (~ 1 ms) spontaneously at very high frequencies (Fig. 2A–D) (around 25–30 Hz in awake rodents: Gulley et al., 1999; Gulley et al., 2004; Maurice et al., 2003; Windels and Kiyatkin, 2006a,b; Walters et al., 2007; around 65 Hz in awake primates: DeLong et al., 1983; Hikosaka and Wurtz, 1983a; Schultz, 1986; Wichmann et al., 1999; Nevet et al., 2004; Wichmann and Kliem, 2004). In contrast, nigral dopamine neurons fire low frequency (often at 1–4 Hz) and long duration spikes (about 2.5 ms) (Lacey et al., 1989; Yung et al., 1991; Richards et al., 1997; Hyland et al., 2002; Zhou et al., 2006; Guzman et al., 2009). After blockade of ionotropic receptor-mediated synaptic inputs *in vitro*, the spiking activity of SNr GABA neurons remains strikingly different from their neighboring dopamine neurons (Fig. 2B–D). *In vitro*, SNr GABA neurons fire around 10–15 Hz while dopamine neurons fire spontaneously around 2 Hz (Lacey et al., 1989; Richards et al., 1997; Yung et al., 1991; Blythe et al., 2007; Lee and Tepper, 2007b; Zhou et al., 2006; Seutin and Engel, 2010; Ding et al., 2011; Lee et al., 2011). The lower firing rate *in vitro* is largely due to low recording temperatures (commonly room temperature to 30 °C). Additionally, when compared with nigral dopamine neurons, the action potentials of SNr GABA neurons have a more negative threshold, a larger amplitude, and faster rise rate. Also, SNr GABA neurons show no or little adaptation in both firing frequency and spike amplitude, whereas nigral dopamine neurons are adaptive in both parameters. These striking differences in spike waveform and pattern indicate qualitative and/or quantitative differences in intrinsic ion channels in SNr GABA neurons and nigral dopamine neurons.

### 4. Key ion channels supporting the sustained autonomous high frequency firing in SNr GABA neurons

Several recent studies indicate that multiple ion channels are critical to the sustained high frequency firing in SNr GABA neurons, including a tonically active transient receptor potential (TRP) channel, voltage-gated sodium ( $Na_V$ ), potassium ( $K_V$ ), and calcium ( $Ca_V$ ) channels, and calcium-activated potassium (KCa) channels (Atherton and Bevan, 2005; Zhou et al., 2008; Ding and Zhou, 2010; Seutin and Engel, 2010; Ding et al., 2011). The sections below summarize some key recent findings and discuss the functional importance of these intrinsic ion channels in SNr GABA neurons.

#### 4.1. Constitutively active classical type 3 transient receptor potential (TRPC3) channels depolarize SNr GABA neurons

SNr GABA neurons have a depolarized, non-oscillating membrane potential, unlike nigral DA neurons that have  $Ca^{2+}$ -mediated membrane potential oscillations (Wilson and Callaway, 2000; Chan et al., 2007). Based on experiments using the  $Na_V$  channel blocker tetrodotoxin (TTX) and Na replacement, Atherton and Bevan (2005) detected a Na-dependent, TTX-insensitive background cation conductance contributing to a tonic depolarization in SNr GABA neurons, but the molecular nature of this background

conductance was not identified. Recent data indicate that TRPC3 channels are a potential candidate (Zhou et al., 2008). TRP channels are a class of depolarizing cation channels with mammals having at least 28 different TRP channel types (Hardie, 2007; Nilius et al., 2007; Birnbaumer, 2009; Clapham, 2009). Among these TRP channels, the TRPC3 channel is unique in that it has substantial constitutive activity (Dietrich et al., 2003; Albert et al., 2006; Eder et al., 2007). The constitutive activity is further stimulated by diacylglycerol (DAG) in response to phospholipase C (PLC) activation (Hofmann et al., 1999; Albert and Large, 2006). Therefore, neurons expressing TRPC3 channels may have a depolarized membrane potential. Also, neurotransmitter stimulation of the  $G_{q/11}$ -PLC signaling pathway may ultimately enhance TRPC3 channels, providing a molecular basis for TRPC3 channels to serve as an effector channel for G-protein coupled neurotransmitter receptors.

A combined molecular and electrophysiological analysis (Zhou et al., 2008) has provided evidence that the TRPC3 channel contributes to depolarization of SNr GABA neurons. Single cell reverse transcription polymerase chain reaction (scRT-PCR) consistently detected TRPC3 but not other TRP mRNA in SNr GABA neurons (Zhou et al., 2008), suggesting that TRPC3 channels are expressed at a relatively high level in these neurons. After blocking voltage-dependent Na currents with TTX, flufenamic acid (FFA), a broad spectrum TRP channel blocker, resulted in a non-desensitizing hyperpolarization (Fig. 3A). When voltage-clamped at  $-70$  mV, FFA induced an apparent outward current, or reduced a *tonic* inward current accompanied by decreased whole-cell conductance (Fig. 3B). This FFA-sensitive inward current was linear and reversed its polarity around  $-35$  mV (Fig. 3C,D). These I-V characteristics and FFA-sensitivity together with the detection of TRPC3 mRNA indicate a potentially TRPC3 channel-mediated, tonic cation current in SNr GABA neurons. The tonic FFA-sensitive depolarization and inward current are also dependent on extracellular  $Na^+$ . Furthermore, infusion of a TRPC3 antibody known to inhibit these channels (Albert et al., 2006; Amaral and Pozzo-Miller, 2007) into SNr GABA neurons substantially reduced the firing frequency and increased firing irregularity (Fig. 3E). Taken together, these recent studies suggest that SNr GABA neurons express a constitutively active, TRPC3 channel-mediated,  $Na^+$ -dependent, voltage-independent inward current at membrane potentials negative to the action potential threshold. Because of their activity at hyperpolarized membrane potentials, these channels are particularly important in depolarizing SNr GABA neurons when voltage-dependent depolarizing ion channels are not active.

## 4.2. Voltage-activated sodium ( $Na_V$ ) channels in SNr GABA neurons

$Na_V$  channels are the most important ion channel in the generation of action potentials (Hille, 2001; Bean, 2007). The remarkable capability of SNr GABA neurons to fire sustained high frequency action potentials indicates that their  $Na_V$  channels must have suitable properties that meet this functional requirement. Recent studies indicate that SNr GABA neurons express a persistent sodium current ( $I_{NaP}$ ) that induces subthreshold depolarization and a classical transient sodium current ( $I_{NaT}$ ) that is larger and faster than  $I_{NaT}$  in the slow-spiking DA neurons (Atherton and Bevan, 2005; Ding and Zhou, 2010; Seutin and Engel, 2010).

**4.2.1. A persistent sodium current ( $I_{NaP}$ ) depolarizes SNr GABA neurons—**The constitutively active TRPC3 channels can depolarize SNr GABA neurons at very negative membrane potentials. But since the TRPC3 current reversal potential is around  $-35$  mV, the current becomes smaller as the neuron gets close to the action potential threshold, a situation that is not ideal for reliable spike generation. So other cation channels may join in depolarizing the membrane potential. The voltage-dependent  $I_{NaP}$  is an ideal candidate.  $I_{NaP}$  is generated when a small fraction of  $Na_V$  channels remain open for long periods of time

(Patlak and Ortiz, 1986; Alzheimer et al., 1993; Bant and Raman, 2010). Although the amplitude of  $I_{NaP}$  is only a fraction of  $I_{NaT}$ , its duration is much longer such that it can enhance neuronal excitability and contribute to the autonomous pacemaking activity (Crill, 1996; Do and Bean, 2003; Mercer et al., 2007; Khaliq and Bean, 2010).

Atherton and Bevan (2005) performed a detailed study on the  $I_{NaP}$  contribution to spontaneous spike firing in SNr GABA neurons. They found that spontaneous spiking continued almost unabated after blocking fast GABAergic and glutamatergic synaptic transmission, indicating that spontaneous high frequency firing is generated by intrinsic ion channels. They also found that blocking  $I_h$  at the native membrane potentials did not alter the firing, suggesting that the contribution of  $I_h$  is small under normal conditions. Using a voltage step protocol ranging from  $-80$  mV to  $-50$  mV, they detected a TTX-sensitive  $I_{NaP}$  that started to activate around  $-60$  mV and peaked around  $-50$  mV, indicating that  $I_{NaP}$  can depolarize the cell when it reaches  $-60$  mV or more positive potentials and contributes to the generation of spontaneous firing in SNr GABA neurons.

**4.2.3. The transient voltage-gated sodium current ( $I_{NaT}$ ) is strong and fast in SNr GABA neurons**—When a sufficient amount of the classical  $I_{NaT}$  is activated by subthreshold depolarization induced by TRPC3 channels and  $I_{NaP}$ , the regenerative fast rising phase of the action potential is triggered (Hille 2001; Bean 2007). SNr GABA neurons fire high frequency, short duration action potentials, whereas SNc DA neurons fire low frequency, long duration action potentials. The action potential threshold tends to be a few mV more negative in SNr GABA neurons than in nigral DA neurons, while action potential amplitude is about 10 mV larger in SNr GABA neurons than in nigral DA neurons (Richards et al., 1997; Ding et al., 2011). These observations indicate that  $I_{NaT}$  is different in these two cell types. Recent studies suggest that this is indeed the case (Ding and Zhou, 2010; Seutin and Engel, 2010). These studies showed that  $I_{NaT}$  has a higher density in SNr GABA neurons than in DA neurons (Fig. 2E–G), contributing to the faster rise and larger amplitude of action potentials in SNr GABA neurons. Additionally, the kinetics of  $I_{NaT}$  may also be different in these two neuron types (Ding and Zhou, 2010). Specifically,  $I_{NaT}$  has a steeper voltage-dependent activation and a faster deactivation in SNr GABA neurons than in nigral DA neurons, indicating that  $I_{NaT}$  in SNr GABA neurons can be activated more readily than those in nigral DA neurons, contributing to the fast rise and short duration of spikes in SNr GABA neurons. Equally important,  $I_{NaT}$  recovers more quickly from inactivation in SNr GABA neurons than in SN DA neurons, leading to less cumulative inactivation in SNr GABA neurons. Consequently, more functional  $Na_V$  channels are available in SNr GABA neurons than in nigral DA neurons (Ding and Zhou, 2010). The different recovery from inactivation may contribute to the fact that spike firing either is not or is only slightly adaptive in amplitude and frequency in SNr GABA neurons even at very high frequency, whereas it is strongly adaptive in nigral DA neurons when the frequency is above 10 Hz. Similarly, Martina and Jonas (1997) found that rapid recovery of  $I_{NaT}$  from inactivation is important for the fast spiking properties in hippocampal GABA interneurons, indicating that there may be common ionic mechanisms among fast spiking neurons in different brain areas.

#### 4.3. Voltage-activated potassium (Kv) currents in SNr GABA neurons

Kv currents are mainly responsible for repolarizing the membrane after the action potential has reached its peak and can activate even slightly before the peak (Hille, 2001; Bean, 2007). Therefore, a robust Kv current that activates quickly to rapidly repolarize the membrane and resists inactivation for continued availability is essential for sustained high frequency firing. A recent combined molecular and electrophysiological study indicates that SNr GABA neurons express a strong Kv3-like current with fast activation and slow

inactivation kinetics that is required for the sustained high frequency firing capability in these neurons (Ding et al., 2011).

**4.3.1. A robust Kv3-like fast delayed rectifier ( $I_{DR-fast}$ ) current in SNr GABA neurons**—Tissue level studies have detected Kv3.1, Kv3.2, Kv3.3 and Kv3.4 mRNAs and also Kv3.1, Kv3.2, and Kv3.3 proteins in the SNr region, whereas these Kv channel signals are very low in SNc (Perney et al., 1992; Weiser et al., 1994, 1995; Ozaita et al., 2002; Chang et al., 2007). Kv4.3 mRNA is prominently expressed in the SNc region (Tsauro et al., 1997; Serodio et al., 1998). Since the main cell type in SNr and SNc are the GABA neurons and DA neurons, respectively, the Kv3 mRNAs are likely in SNr GABA neurons, whereas Kv4.3 mRNA is likely in SNc DA neurons. Recently, Ding et al. (2011) performed qRT-PCR analysis on the expression of Kv1.1–6, Kv2.1–2, Kv3.1–4, and Kv4.1–3 in immunohistochemically identified, laser capture-microdissected SNr GABA neurons and nigral DA neurons. They found that in comparison with slow-spiking nigral DA neurons, fast-spiking SNr GABA neurons express more Kv3.1 and Kv3.4 mRNAs that can form the fast delayed rectifier type K channels and conduct  $I_{DR-fast}$ . In contrast, nigral DA neurons express more Kv4.2 and Kv4.3 mRNAs that may form  $I_A$  type channels. Voltage clamp data showed that SNr GABA neurons express a prominent  $I_{DR-fast}$  current that starts to activate near  $-30$  mV, above the spike threshold (Fig. 4A). The activation was fast but the decay or inactivation was slow (Fig. 4A). These properties of this  $I_{DR-fast}$  current are reminiscent of the currents mediated by cloned heteromeric Kv3.1 and Kv3.4 channels (Weiser et al., 1994; Rudy and McBain, 2001), indicating Kv3-like channels. The kinetic and pharmacological properties of the Kv3-like  $I_{DR-fast}$  current in fast-spiking SNr GABA neurons are also similar to the Kv3-like  $I_{DR-fast}$  currents in fast-spiking GABA neurons in other brain areas (Martina et al., 1998; Baranauskas et al., 2003; Lien and Jonas, 2003).

**4.3.2. Inhibition of Kv3-like  $I_{DR-fast}$  current impairs high frequency spiking in SNr GABA neurons**—In other neuron types that are capable of high frequency firing, pharmacological inhibition (by 1 mM TEA) or genetic inactivation of members of Kv3 channel family has been shown to impair the ability of neurons to fire high frequency spikes (Wang et al., 1998; Erisir et al., 1999; Lau et al., 2000; Lien and Jonas, 2003; Macica et al., 2003). Similarly, Ding et al. (2011) found that blocking the Kv3-like  $I_{DR-fast}$  also impaired the ability of SNr GABA neurons to fire high frequency spikes. As illustrated in Fig. 4B1, upon intracellular injection of depolarizing currents, SNr GABA neurons are able to fire sustained high frequency spikes, above the spontaneous firing frequency. The rise rate and the peak amplitude of these spikes are largely sustained, indicating that the Kv currents are able to quickly repolarize the cell and thus allow  $Na_V$  channels to recover from inactivation. Bath application of 1 mM TEA progressively reduced the spike amplitude, eventually leading to a complete cessation of firing (Fig. 4B2), indicating that SNr GABA neurons are unable to fire sustained high frequency spikes when  $I_{DR-fast}$  is blocked (Fig. 4A, B). As indicated by the delayed and shallow repolarization, blocking  $I_{DR-fast}$  likely causes cumulative inactivation of  $Na_V$  channels and eventual loss of spiking capability. Taken together, these results provide strong evidence that the Kv3-containing  $I_{DR-fast}$ , due to its fast activation and slow inactivation kinetics, is critical for SNr GABA neurons to rapidly repolarize and fire sustained high frequency spikes.

**4.3.3. The subthreshold  $I_A$  is weak in SNr GABA neurons**—In addition to the prominent  $I_{DR-fast}$ , SNr GABA neurons also express small amounts of the classic subthreshold-activating, subthreshold-inactivating, and transient  $I_A$  type current likely mediated by Kv4.2 and/or Kv4.3-containing channels (Ding et al., 2011). In contrast, nigral DA neurons express a robust  $I_A$ . While a strong subthreshold  $I_A$  can keep the firing of DA

neurons at low rates, a weak  $I_A$  allows SNr GABA neurons to fire at high frequencies (Liss et al., 2001; Koyama and Appel, 2006; Ding et al., 2011).

#### 4.4. Voltage-gated calcium ( $Ca_V$ ) channels and calcium-activated potassium ( $K_{Ca}$ ) channels in SNr GABA neurons

**4.4.1.  $Ca_V$  channels**— $Ca_V$  channels are among the intrinsic membrane channels influencing the excitability of the SNr neuronal membrane.  $Ca_V$  channels have been shown to influence both spontaneous activity in these neurons, as well as more complex behaviors such as burst firing (Atherton and Bevan, 2005; Ibáñez-Sandoval et al., 2007; Lee and Tepper, 2007b). Activation of  $Ca_V$  channels can lead to either increases or decreases in SNr neuron excitability. Calcium entry through N-type calcium channels ( $Ca_V2.2$ ) causes activation of  $K_{Ca}$  channels that decrease the firing rate and increase the regularity of firing in SNr GABA neurons (Atherton and Bevan, 2005; Yanovsky et al., 2005). Blockade of  $Ca_V2.2$  channels with  $\omega$ -conotoxin GVIA exerts effects similar to blockade of  $K_{Ca}$  with apamin including loss of the medium afterhyperpolarization, an increase in firing rate, and an increase in firing irregularity (Atherton and Bevan, 2005; Yanovsky et al., 2005). The role of  $K_{Ca}$  channels in the regulation of nigral GABA neuron activity is discussed in more detail in the next section.

Other calcium channels contribute to depolarization of SNr GABA neurons, either directly or by activating another calcium-activated depolarizing conductance. Some SNr GABA neurons exhibit a depolarizing plateau potential following depolarization from a hyperpolarized membrane potential (Matsuda et al., 1987; Nakanishi et al., 1987; Lee and Tepper, 2007b). This plateau potential can be abolished in calcium-free conditions or by the L-type  $Ca_V$  channel ( $Ca_V1$ ) blockers nimodipine or nifedipine (Fig. 5A,B) (Lee and Tepper, 2007b). Conversely, the L-type  $Ca_V$  channel activator, Bay K 8644 can evoke a plateau potential in response to depolarization if the neuron did not exhibit a plateau under control conditions (Fig. 5C) (Lee and Tepper, 2007b). The plateau potential can also be activated by calcium entry through ligand gated channels, such as those mediated by NMDA receptors, suggesting that the plateau potential is caused by a calcium-activated conductance rather than carried by L-type channels directly (Lee and Tepper, 2007b). The conductance underlying the plateau potential is carried primarily by sodium (Fig. 5D) and it can be blocked by FFA (Fig. 5E, F), suggesting that the conductance underlying the plateau is mediated by a TRP channel (Lee and Tepper, 2007b).

Under certain conditions, basal ganglia output neurons can exhibit oscillatory burst firing that is observed *in vivo* most commonly in pathological conditions including Parkinson's disease in humans (Wichmann and DeLong, 2006) and following dopamine denervation in animal models of the disease (Wichmann et al., 1999; Raz et al., 2000; Ruskin et al., 2002). Burst firing can also be observed during application of NMDA *in vitro* (Ibáñez-Sandoval et al., 2007). NMDA-induced burst firing in SNr GABA neurons appears to require activation of  $Ca_V$  channels, specifically T-type  $Ca_V$  channels ( $Ca_V3.2$ ), as burst firing is abolished by their pharmacological blockade (Ibáñez-Sandoval et al., 2007). Blockade of presumed T-type  $Ca_V$  channels also results in a decrease in firing rate and firing regularity in SNr GABA neurons as well as an attenuation of the afterhyperpolarization suggesting that T-type  $Ca_V$  channels might both depolarize the neurons and also contribute to activation of  $K_{Ca}$  channels (Yanovsky et al., 2005).

**4.4.2. Calcium-activated potassium ( $K_{Ca}$ ) channels**—SNr GABA neurons express  $K_{Ca}$  channels, likely consisting of SK2 subunits (Stocker and Pedarzani, 2000), that play a role in regulating the spontaneous firing rate and regularity of firing in these neurons.  $K_{Ca}$  channels are active during spontaneous activity *in vitro*, as blocking them with apamin

reduces the amplitude of the spike afterhyperpolarization (AHP) and increases the firing rate of SNr GABA neurons (Atherton and Bevan, 2005; Yanovsky et al., 2005).  $K_{Ca}$  channel activity also contributes to firing regularity as the coefficient of variation, and thus firing irregularity is increased when these channels are blocked (Atherton and Bevan, 2005), whereas the firing rate decreases but regularity increases when  $K_{Ca}$  channels are pharmacologically activated (Yanovsky et al., 2006).

The source of the calcium entry required to activate  $K_{Ca}$  channels during spontaneous activity has been shown to be primarily N-type ( $Ca_v2.2$ ) Ca channels (Atherton and Bevan, 2005; Yanovsky et al., 2005). There might also be a lesser contribution from T-type  $Ca_v$  channels as well (Yanovsky et al., 2005).  $K_{Ca}$  channels can also be activated by release of calcium from intracellular stores through ryanodine receptors, leading to a decrease firing rate following intracellular release of calcium induced by caffeine (Yanovsky et al., 2005). However, the release of intracellular calcium does not play a role in activation of  $K_{Ca}$  channels during spontaneous activity (Yanovsky et al., 2005). In addition to having an effect on firing rate and regularity, activation of  $K_{Ca}$  channels also prevents SNr GABA neurons from exhibiting burst firing, and it has been reported that burst firing can emerge following blockade of these channels with apamin (Yanovsky et al., 2005).

#### 4.5. Summary of key intrinsic ion channels supporting sustained high frequency firing in SNr GABA neurons

Based on the above discussion, we can outline the key mechanisms underlying the autonomous high frequency spike firing in SNr GABA neurons. First, tonically active TRPC3 channels can depolarize these neurons even when they are at very negative membrane potentials. When the membrane potential reaches  $-60$  mV,  $I_{NaP}$  starts to activate, further depolarizing the membrane potential. At or slightly below  $-50$  mV,  $I_{NaT}$  starts to activate and eventually triggers the rapid rising phase of action potentials. SNr GABA neurons have a higher density of  $I_{NaT}$ , contributing to the faster rise and larger amplitude of action potentials, compared with the slow-spiking DA neurons.  $I_{NaT}$  also recovers from inactivation quickly in SNr GABA neurons, enabling the sustained high frequency firing in SNr GABA neurons. The rising phase of the action potential triggers the activation of high-threshold, inactivation-resistant  $Kv3$ -like channels in SNr GABA neurons that can rapidly repolarize the membrane, further supporting the sustained high frequency firing. Calcium contributes to the excitability of SNr GABA neurons by directly depolarizing the neuron or by activating other channels which either hyperpolarize and regularize firing of the neuron, as in the case of  $K_{Ca}$  channels, or depolarize the neuron by activating one or more TRP channels, inducing a plateau depolarization. Whether calcium entry causes activation of  $K_{Ca}$  channels or TRP channels appears to be dictated by the calcium channel with primarily N-type calcium channels activating  $K_{Ca}$  channels while calcium entry through L-type channels leads to activation of TRP channels. Together, these intrinsic ion channels provide SNr GABA neurons with the capabilities to fire autonomous, sustained high frequency spikes, the default mode of operation for these basal ganglia output neurons.

### 5. Synaptic inputs to SNr GABA projection neurons and their regulation

The autonomous high frequency firing in SNr GABA neurons, driven by intrinsic ion channels, provides a default tonic inhibitory signal to its targets. SNr GABA neurons also receive an array of synaptic inputs that sculpt SNr GABA neuron activity and hence its output. The discussion below seeks to highlight key recent advances in the field of synaptic regulation of SNr GABA neurons. For more comprehensive reviews, readers are referred to Misgeld (2004) and Deniau et al. (2007). For metabotropic glutamate receptors in SNr, see a comprehensive review by Conn et al. (2005).



## 5.1. GABA input and its regulation

**5.1.1. GABAergic striatonigral input**—Anatomical studies have established that dopamine D1 receptor (D1R)-expressing medium spiny neurons (D1-MSNs) but not D2 receptor-expressing D2-MSNs in the striatum project strongly and largely exclusively to the SNr, forming the direct striatonigral pathway (Alexander and Crutcher, 1990; Gerfen et al., 1990; DeLong and Wichmann, 2007; Gerfen and Bolam, 2010). These D1-MSN axons may also give off limited collaterals and innervate structures on its passage (Parent et al., 2000; Lévesque and Parent, 2005; Fujiyama et al., 2011). This D1-MSN-originated striatonigral projection is readily demonstrated with immunostaining for D1R protein (Fig. 6A) (Huang et al., 1992; Levey et al., 1993; Yung et al., 1995). Further confirming the direct striatonigral projection, in mice expressing D1R promoter-controlled green fluorescent protein (GFP) or red fluorescent protein (RFP), a prominent GFP or RFP-labeled axon projection to SNr can be easily seen (Gong et al., 2003; Shuen et al., 2008).

Early electrophysiological recordings in intact animals have suggested that direct pathway MSNs inhibit SNr GABA neurons (see Hikosaka et al., 2000; Galvan and Wichmann, 2007 for review). Recordings in freely moving rats (Windels and Kiyatkin, 2004, 2006a) showed that SNr GABA neurons are sensitive to local application of the GABA<sub>A</sub> receptor blocker bicuculline, indicating that SNr GABA neurons are under the influence of tonic GABA inhibition. However, these electrophysiological recordings could not distinguish D1- or D2-MSNs or origins of the GABA inputs to SNr GABA neurons. Therefore, until recently, direct evidence for D1-MSN inhibition of SNr GABA neurons was lacking. Newly developed optogenetic techniques enable selective activation of specific groups of neurons by introducing light-sensitive ion channels (channelrhodopsin-2) into either D1-MSNs or D2-MSNs. Using this strategy, a recent study provides strong evidence that activation of D1-MSNs inhibits the spontaneous firing of SNr GABA projection neurons, whereas activation of D2-MSNs has the opposite effect (Kravitz et al., 2010). These new results confirm the classical basal ganglia model that the direct pathway D1-MSNs inhibit and the indirect pathway D2-MSNs excite GPi and SNr GABA neurons, respectively (Albin et al., 1989; DeLong, 1990).

**5.1.2. Dopamine D1 receptor facilitation of GABAergic striatonigral axon terminals**—Studies have established that striatonigral axon terminals strongly express D1Rs, providing the anatomical and molecular bases for dopamine regulation of the direct pathway MSN outputs (Fig. 6A) (Huang et al., 1992; Mansour et al., 1992; Levey et al., 1993; Yung et al., 1995; Smith and Kieval, 2000; Kliem et al., 2007; Kliem et al., 2010). These axons terminate mostly in SNr and generally do not innervate the neighboring areas. Due to its coupling to cAMP production that in turn increases neurotransmitter release (Missale et al., 1998; Yao and Sakaba, 2010), D1R activation should increase GABA release from striatonigral axon terminals, a prediction supported by microdialysis studies (Rosales et al., 1997; Trevitt et al., 2002; Kliem et al., 2007). However, despite these clear anatomical features and the neurochemical signaling pathway, functional physiological determination of presynaptic D1R-mediated facilitation of GABA release from striatonigral axon terminals had been controversial until recently. Cameron and Williams (1993) first reported that D1R activation enhanced GABA<sub>B</sub> receptor-mediated inhibitory postsynaptic potentials (IPSPs) in ventral tegmental dopamine neurons by presynaptically facilitating GABA release from forebrain afferents, although D1R expression is much weaker in VTA than in SNr. In 1998, two studies from 2 laboratories reached opposite conclusions. Radnikow and Misgeld (1998) reported that the D1-like agonist SKF38393 substantially increased the amplitude of evoked GABA<sub>A</sub> receptor-mediated inhibitory postsynaptic currents (IPSCs) in SNr GABA neurons. The frequency but not amplitude of the miniature IPSCs in the presence of TTX and Cd<sup>2+</sup> (to block sodium spikes and Ca<sup>2+</sup> channels, respectively) was also increased by the D1-like

agonist SKF38393. These effects were blocked by the D1-like antagonist SCH23390, leading to the conclusion that D1R activation facilitates vesicular GABA release from striatonigral axon terminals. In contrast, Miyazaki and Lacey (1998) reported that D1-like receptor activation inhibited GABA<sub>A</sub> IPSCs in SNr GABA neurons by decreasing GABA release from striatonigral axon terminals. Which conclusion is correct? A recent study (Chuhma et al., 2011) provides an answer to this question. In this study, the authors used transgenic mice with conditional channelrhodopsin-2 (ChR2) expression restricted to striatal MSNs. Consequently, MSNs including striatonigral neurons and their axon terminals can be selectively photo-activated. Using this strategy, Chuhma et al. (2011) demonstrated unambiguously that D1-like ligand stimulation increased IPSC amplitude when these axon terminals were selectively photo-stimulated locally in the SNr (Fig. 6B). Another recent study has confirmed the presynaptic enhancement of striatonigral IPSCs by D1R activation, and has extended those findings by demonstrating a concentration-dependent shift from D1R-mediated IPSC enhancement to nonspecific inhibition with increasing concentrations of D1R agonist (de Jesús Aceves et al., 2011). These new neurophysiological data overwhelmingly support the original hypothesis, based on the intense D1R expression at striatonigral axon terminals, that D1R activation facilitates GABA release from striatonigral axon terminals. In hindsight, what led to the different conclusions of these two early studies were probably nonspecific effects of agonists and/or different stimulating methods used in these two studies. Radnikow and Misgeld (1998) used minimal stimulation with a patch pipette, whereas Miyazaki and Lacey (1998) used a much larger twisted wire bipolar stimulating electrode, likely leading to activation of unintended targets.

The intense D1R expression at striatonigral axon terminals underscores the physiological importance of D1R-mediated facilitation of this synapse. By directly enhancing GABA release, SNc DA neurons, via dendritically released DA, may decrease the activity of SNr GABA neurons and promote motor activity. Simultaneously in the striatum, dopamine released from SNc DA neurons increases D1-MSN activity and impulse output (West and Grace, 2002; Liang et al., 2008), thus increasing GABA output to SNr GABA neurons. These DA effects at D1-MSN somata and axon terminals may synergistically inhibit SNr GABA neurons.

### 5.1.3. Cannabinoid CB1 receptor inhibition of striatonigral axon terminals—

The pioneering autoradiographic studies by Herkenham et al. (1990, 1991a,b) and subsequent immunohistochemical studies have established that cannabinoid CB1 receptors are intensely expressed on striatonigral axon terminals (Fig. 6C) (Tsou et al., 1998; Fukudome et al., 2004; Mátyás et al., 2006; see Freund et al., 2003 and Kano et al., 2009 for review). These CB1 receptors, together with the minor member CB2 of the cannabinoid receptor family, are coupled to Gi/o proteins. An established mode of operation is that CB1 receptor activation stimulates Gi/o that in turn inhibits Ca channels and Ca influx, leading to reduced neurotransmitter release. Evidence indicates that this mechanism operates at striatonigral axon terminals where CB agonists decrease the amplitude of GABA<sub>A</sub> IPSCs in SNr neurons (Fig. 6D) (Wallmichrath and Szabo, 2002a,b). At the same time, the paired pulse ratio is increased, indicating decreased vesicular GABA release. The presynaptic action of cannabinoids has been further confirmed by showing that CB receptor agonists neither affect the response of SNr neurons to exogenously applied GABA or a GABA<sub>A</sub> receptor agonist (Tersigni and Rosenberg, 1996; Chan et al., 1998; Wallmichrath and Szabo, 2002a,b) nor change the amplitude of Ca<sup>2+</sup>-independent miniature IPSCs (Wallmichrath and Szabo, 2002b).

More important, CB receptor antagonists have been reported to increase evoked IPSC amplitude, suggesting tonic presynaptic modulation of GABAergic input by endogenous cannabinoids (Wallmichrath and Szabo, 2002a; Yanovsky et al., 2003). Interestingly, IPSCs

evoked in SNr neurons in mouse brain slices were insensitive to antagonist treatment in the absence of direct depolarization of postsynaptic SNr neurons (Wallmichrath and Szabo, 2002b). This finding indicates that postsynaptic SNr neurons are a source of endogenous cannabinoids and that depolarization augments endogenous cannabinoid signaling (Wallmichrath and Szabo, 2002b). Endogenous cannabinoids are also released from SNc dopamine neurons (Yanovsky et al., 2003). Since SNr GABA neurons are spontaneously active, their intrinsic activity might support endogenous cannabinoid production (Romo-Parra et al., 2009; Kano et al., 2009) resulting in an endogenous cannabinoid tone in the nucleus. The endogenous cannabinoid functioning at striatonigral synapses has been suggested to be 2-arachidonoylglycerol (Szabo et al., 2006). The functional importance of cannabinoid signaling in SNr is demonstrated by the fact that local or peripheral administration of CB agonists increases the spontaneous firing rate of nigral GABA neurons *in vivo* (Miller and Walker, 1995; Tersigni and Rosenberg, 1996). Conversely, local application of a cannabinoid receptor antagonist leads to a decrease in firing rate implicating endogenous cannabinoids as tonic modulators of basal ganglia output (Tersigni and Rosenberg, 1996).

**5.1.2. GABA input from the globus pallidus external segment (GPe)**—Another major GABAergic afferent to SNr GABA neurons is the GPe-SNr projection. Anatomical studies using axon tracing techniques have established that SNr GABA projection neurons receive GABA input from GPe neurons (Smith and Bolam, 1989, 1991; Bevan et al., 1994, 1996). GPe afferent terminals make large symmetrical synapses preferentially on the cell body and proximal dendrites, forming perisomatic baskets on SNr GABA neurons, whereas striatal afferents make smaller but apparently more numerous synapses preferentially on more distal dendrites. These anatomical data suggest that GPe input may powerfully influence SNr GABA neuron activity (Smith and Bolam, 1989, 1991), although physiologically demonstrating this idea was complicated by the difficulty in separately stimulating striatonigral axons and pallidonigral axons. To minimize this technical problem, a recent study used a sagittal brain slice preparation that allows stimulation of the striatum and GPe separately (Connelly et al., 2010). This study convincingly demonstrated that activation of even a single GPe neuron evoked large IPSCs in SNr GABA neurons, confirming the original prediction based on anatomical data. Equally important, Connelly et al. (2010) found that while the striatonigral synapse facilitates during repetitive activation (Fig. 7A), the pallidonigral synapse depresses (Fig. 7B). Thus, when the usually silent D1-MSNs activate and produce repetitive output upon receiving strong, converging glutamate inputs from cortical and thalamic areas (Kincaid et al., 1998; Zheng and Wilson 2002; Smith et al. 2004), D1-MSNs may induce robust IPSPs and effectively inhibit SNr GABA neurons. Weak glutamate inputs are less likely to activate D1-MSN somata and the facilitatory mechanism at the axon terminal may also not engage. Therefore, both the D1-MSN cell body and axon terminal allow only strong signals to pass, serving as a high-pass filter (Connelly et al., 2010). In contrast, due to the depressing nature of the pallidonigral synapse and the high frequency spontaneous firing of GPe neurons, the pallidonigral synapse is most effective in inhibiting SNr GABA neurons after a brief pause that allows the synapse to recover from the tonic depression (Connelly et al., 2010). Because of the powerful GPe-SNr projection, activation of D2-MSNs can increase SNr GABA activity by inhibiting GPe neurons (Chuhma et al., 2011; Kravitz et al., 2010).

It is also necessary to point out that the axon terminal release properties of the fast-spiking GPe neurons are different from those of the fast-spiking SNr GABA neurons that can maintain almost constant release during high frequency repetitive stimulation (Kaneda et al., 2008) (Fig. 7C). Thus, the striatonigral, pallidonigral and nigrotectal synapses are endowed with distinct capabilities that serve their respective functions. The direct striatonigral input serves to inhibit the high frequency spontaneous firing of SNr GABA neurons and therefore

release the thalamocortical motor circuit and brainstem motor nuclei from tonic inhibition, allowing movement to occur (Chevalier and Deniau, 1990; Hikosaka, 2000). Under basal conditions, striatonigral neurons are largely silent, and asynchronized, sporadic inhibitory output to SNr GABA neurons is probably not effective in inhibiting these neurons, especially given that striatonigral synapses are often at distal dendrites, allowing SNr GABA neurons to fire at high frequency. When behaviorally important, convergent glutamate input from the cortex and thalamus strongly activates striatonigral neurons, the synchronized inhibitory output to SNr GABA neurons is more effective in inhibiting these neurons. The facilitating nature of the striatonigral synapse further enhances this inhibition. The precise function of the GPe input and role of the indirect pathway is less clear. However, it seems that the powerful pallidonigral synapse is normally depressed to allow SNr GABA neurons to fire high frequency spikes. The pallidonigral synapse is further weakened by tonic activation of D2 class dopamine receptors that presynaptically decrease GABAergic pallidonigral input (de Jesús Aceves et al., 2011). When behaviorally necessary, however, the pallidonigral synapse is turned on to inhibit SNr GABA neurons. Indeed, Connelly et al. (2010) found that after a brief (~ 2 s) pause that is known to occur to GPe neurons in motor-related events, the pallidonigral synapse recovered to its full strength. Therefore, it appears that the pallidonigral synapse is normally in a depressed state that allows high frequency firing of SNr neurons, but can exert a powerful influence upon either increased activation of GPe (Celada et al., 1999) or immediately following phasic inhibition of GPe (Connelly et al., 2010). The recent finding demonstrating regulation of the pallidonigral synapse by dopamine (de Jesús Aceves, et al., 2011) sets the stage to investigate the role of other neuromodulators at this synapse as well.

## 5.2. Glutamate input and its regulation by dopamine

**5.2.1. Excitatory glutamate input to SNr**—The best characterized excitatory afferents to SNr GABA neurons are from glutamate-containing neurons in the neighboring subthalamic nucleus (STN) (Fig. 1A, Fig. 6A) (Smith and Parent, 1988; Deniau et al., 2007; Ammari et al., 2010). Anatomical studies show that both in rodents and primates, glutamatergic neurons in STN project heavily to SNr, forming excitatory, asymmetric synapses with SNr GABA neurons (Kanazawa et al., 1976; Kita and Kitai, 1987; Smith et al., 1990; Bevan et al., 1994; Sato et al., 2000). Axon tracing studies indicate that striatonigral axons making symmetric synapses and subthalamonigral axons making asymmetric synapses converge onto SNr GABA projection neurons (Bevan et al., 1994).

Electrophysiological recordings have demonstrated that STN neuron activation induces excitatory postsynaptic currents or potentials in SNr GABA neurons (Nakanishi et al. 1987; Bosch et al., 2011). Excitation of STN neuronal activity by local injection of the GABA<sub>A</sub> receptor blocker bicuculline increased metabolism in the SNr (Féger et al., 1991). Additionally, STN neurons apparently innervate neighboring STN glutamate neurons, causing recurrent excitation, and often producing polysynaptic EPSCs and burst spiking in SNr GABA neurons (Fig. 8A,B,C) (Shen and Johnson 2006, 2008; Ammari et al., 2010). Thus, STN neuron excitation may drive SNr GABA neurons into burst firing (Murer et al., 1997; Tseng et al., 2000, 2001; Shen and Johnson, 2006). Electrophysiological recordings in patients with Parkinson's disease and in animal models indicate an excessive oscillatory burst firing in STN neurons (Bevan et al., 2006; Walters et al., 2000, 2007). STN lesion and functional inhibition reduce oscillatory firing and normalize the firing pattern in SNr GABA neuron in rat models of Parkinson's disease, further demonstrating the influence of STN on SNr GABA neuron activity (Ryan and Sanders, 1993; Murer et al., 1997; Tseng et al., 2001).

### 5.2.2. Presynaptic dopamine regulation of excitatory glutamate input—

Dopamine may affect glutamate release by acting on subthalamonigral axon terminals. Electrophysiological studies have shown that D1-like agonist SKF38393 increased STN-evoked EPSC in SNr GABA neurons, whereas the D2-like receptor agonist quinpirole had the opposite effect (Ibanez-Sandoval et al., 2006). SKF38393 also decreased the paired pulse ratio whereas quinpirole increased it, indicating that D1 class receptor activation facilitates and D2-like receptor activation inhibits glutamate vesicle release at subthalamonigral axon terminals (Rosales et al., 1997; Ibanez-Sandoval et al., 2006). It is not clear why subthalamonigral axon terminals express both D1-like receptors and D2-like receptors that have opposing effects. One possibility is that these dopamine receptor subtypes have different affinity to dopamine resulting in differential activation by ambient dopamine levels. Thus, by acting on subthalamonigral axon terminals, dopamine can regulate the intensity and pattern of glutamate synaptic input to SNr GABA neurons.

## 5.3. Dopamine input

**5.3.1. Dopamine dendrites in SNr—**As shown in Fig. 1B, a prominent anatomical feature in SNr is the dopamine dendrites originating from SNc dopamine neurons (Bjorklund and Lindvall, 1975; Cheramy et al., 1981; Wassef et al., 1981). Evidence from fast cyclic voltammetry studies and other approaches indicates that nigral dopamine cell somata and dendrites may release DA largely via vesicular exocytosis (Groves et al., 1975; Geffen et al., 1976; Jaffe et al., 1998; Beckstead et al., 2004; Chen and Rice, 2001; John et al., 2006; Patel et al., 2009; Ford et al., 2010). Somatodendritic dopamine release can be triggered by action potential-evoked  $\text{Ca}^{2+}$  influx via voltage-activated Ca channels (Ford et al., 2010), but other mechanisms such as pacemaking activity-driven, L-type  $\text{Ca}^{2+}$  channel-mediated  $\text{Ca}^{2+}$  oscillation (Chan et al., 2007) and  $\text{Ca}^{2+}$  release from intracellular stores may also contribute to or facilitate dopamine release from dopamine neuron dendrites (Patel et al., 2009). Together, these release mechanisms may lead to an ambient extracellular dopamine level that is further regulated by reuptake (Cragg et al., 2001). Indeed, somatodendritically released dopamine induces a tonic autoinhibition of nigral dopamine neurons via the inhibitory  $\text{D}_2$  autoreceptors (Lacey et al., 1987; Pucak and Grace, 1994; Werkman et al., 2001). Endogenously released dopamine may also activate  $\text{D}_1$ -like receptors on GABA and glutamate afferent terminals in the nigral areas (Misgeld et al., 2004; Ibanez-Sandoval et al., 2006).

**5.3.2. Direct dopamine depolarization of SNr GABA neurons—**Can dendritically released dopamine directly act on SNr GABA output neurons and influence their firing rate and pattern? Based on anatomical data, Cheramy et al. (1981) first suggested the possibility that dendritically released dopamine might directly act on SNr GABA neurons. Two iontophoretic studies also indicated that DA may exert an excitatory effect on SNr neurons in intact animals (Ruffieux and Schultz, 1980; Waszczak and Walters, 1983). However, these studies used extracellular recordings, did not remove synaptic inputs, and consequently could not determine if the effect was a direct excitation in SNr neurons or local circuit-mediated effect.

Recently, Zhou et al. (2009) have examined this question. scRT-PCR detected mRNAs for  $\text{D}_1\text{R}$  and  $\text{D}_5\text{R}$  in SNr GABA neurons, providing evidence that these basal ganglia output neurons may express  $\text{D}_1\text{R}$  and  $\text{D}_5\text{R}$ . These new results are consistent with two immunoelectron microscopy studies (Huang et al., 1992; Khan et al., 2000). Huang et al. (1992) detected  $\text{D}_1\text{Rs}$  in the dendrites in SNr, even though the origin of the dendrites was not identified. However, other EM studies have reported no  $\text{D}_1\text{R}$  signal in SNr neurons (Yung et al. 1995; Kliem et al. 2010).  $\text{D}_5\text{R}$  has been detected in SNr GABA neurons (Khan et al., 2000; Kliem et al., 2010). Based on these different results, it is reasonable to conclude that

the expression levels of D1R and D5R in SNr GABA neurons are probably low. However, even low levels of D1R and D5R may significantly influence basal ganglia output, because SNr GABA neurons are normally depolarized close to spike threshold such that their activity may be affected by even a small depolarization. Indeed, Zhou et al. (2009) found that the D<sub>1</sub>-like blocker SKF83566 induced a significant decrease in SNr GABA neuron firing frequency after blocking GABA<sub>A</sub> and ionotropic glutamate receptors and induced a clear hyperpolarization in SNr GABA neurons after blocking sodium spikes (Zhou et al., 2009). These results indicate that spontaneously released dopamine from dopamine dendrites induces tonic activation of D<sub>1</sub>-like receptors and exerts a tonic excitatory influence on SNr GABA neurons.

Direct excitation of SNr GABA neurons is readily observed with exogenous dopamine which increases the firing rate of SNr GABA neurons (Zhou et al., 2009) (Fig. 9A,B). After action potentials were blocked with TTX, bath application of exogenous dopamine induced a clear depolarization (Fig. 9C). When voltage clamped at  $-70$  mV, dopamine also induced an inward current in a dose-dependent manner (Fig. 9D). Whole cell conductance was increased. Voltage ramp experiments show that the net dopamine-induced current  $I-V$  was linear with a reversal potential around  $-35$  mV. These results suggest that dopamine was opening or enhancing a tonically active, mixed cation channel. Since D1R and D5R do not directly gate any ion channel, an important question is: what are the effector ion channels that mediate the depolarization? The fact that the dopamine current  $I-V$  curve was linear with a reversal potential around  $-35$  mV suggested involvement of a constitutively active, mixed cation channel, similar to the  $I-V$  relationship of the TRPC3 channel-mediated current in SNr GABA neurons (Zhou et al. 2008, 2009). Indeed, blocking TRPC3 channels by intracellular infusion of an antibody known to inhibit TRPC3 channels also blocked the D<sub>1</sub>-like excitation (Zhou et al., 2009). The mechanisms coupling dopamine receptor activation to TRPC3 channel activation is unknown, but lipid signaling mechanisms may be involved. D<sub>1</sub>-like receptor agonists have been shown to stimulate PLC that in turn produces lipid signaling molecules including DAG, and this effect was eliminated in D5R null mice (Sahu et al., 2009). DAG is known to enhance TRPC3 channel activity (Hoffmann et al. 1999). It is reasonable to conclude that the apparent D<sub>1</sub>-D<sub>5</sub> receptor activation in SNr GABA neurons may enhance the tonically active TRPC3 channels and that TRPC3 channels are the effector channel of direct dopamine excitation in these basal ganglia output neurons.

The direct postsynaptic excitatory dopamine effect appears to counter the effects of presynaptic D1R facilitation of GABA release from striatonigral terminals. Why does dopamine need to have two opposing effects via pre- and post-synaptic mechanisms? One possibility is that the postsynaptic dopamine effect in SNr GABA neurons may prevent possible presynaptically mediated over-inhibition of SNr GABA neurons and the consequent over-disinhibition of the targets of SNr GABA neurons. A balance between the D1R-mediated presynaptic inhibition of SNr GABA neurons and the D<sub>1</sub>-like direct postsynaptic excitation of SNr GABA neurons, in concert with intrinsic ion channels and other synaptic inputs, may be important in maintaining the proper activity of SNr GABA neurons suitable for movement control.

#### 5.4. Serotonin (5-HT) input

Histochemical studies have established that SNr receives dense 5-HT innervation originating from 5-HT neurons in raphe nuclei (Fig. 10A) (Steinbusch, 1981; Moukhles et al., 1997; Wallman et al., 2011), providing a rich anatomical basis for the 5-HT system to affect the motor control system (Hikosaka et al., 2006; Scholtissen et al., 2006; Nakamura et al., 2008; Fox et al., 2009). 5-HT neurons fire spontaneously at 1–2 Hz (Jacobs and Azmitia, 1992), leading to tonic 5-HT release and activation of 5-HT receptors (Rueter et al., 1997; Zhou et al., 2005). Over a dozen 5-HT receptors have been identified (Hannon and Hoyer, 2008).

With the exception of 5-HT<sub>3</sub> receptors coupling to a cation channel, all other 5-HT receptors are G-protein-coupled receptors (Barnes and Sharp, 1999; Zhou and Hablitz, 1999). SNr GABA neurons express multiple types of 5-HT receptors, particularly 5-HT<sub>2C</sub> receptors (5-HT<sub>2C</sub>-Rs) (Eberle-Wang et al., 1997; Clemett et al., 2000). 5-HT<sub>2C</sub>-Rs couple to G<sub>q/11</sub> protein and stimulate phospholipase C (PLC) that in turn generates diacylglycerol (DAG) and other lipid signaling molecules, providing a molecular basis for 5-HT<sub>2C</sub>-Rs to interact with other receptors and ion channels.

Studies indicate that exogenous 5-HT, via activating 5-HT<sub>2C</sub>-R, strongly excites SNr GABA neurons by inducing a linear inward current with a reversal potential around -30 mV (Fig. 10C) (Rick et al., 1995; Stanford and Lacey, 1996a; Zhou, unpublished data). This inward current is accompanied by an increased whole cell conductance, indicating an opening of cation channels that produces a net influx of cations and also excluding closing of K channels as the underlying ionic mechanism. Other excitatory 5-HT receptors (5-HT<sub>2A</sub>-R, 5-HT<sub>4</sub>-R) have also been detected in SNr, though the levels appear to be lower (Cornea-Hébert et al., 1999; Vilaró et al., 2005). The dense 5-HT axon terminals in the SNr release 5-HT spontaneously and induce tonic activation of 5-HT<sub>2C</sub>-Rs in SNr GABA neurons. Thus, blocking 5-HT reuptake induces excitation (Fig. 10B) and blocking 5-HT<sub>2C</sub>-R induces a hyperpolarization and decreases the firing rate in SNr GABA neurons (Zhou, unpublished data).

Since 5-HT<sub>2C</sub>-Rs do not directly gate any ion channels, a fundamental question is: what ion channels mediate the 5-HT<sub>2C</sub>-R activation-evoked inward current in SNr GABA neurons? As discussed above, constitutively active TRPC3 channels conduct a linear inward current with a reversal potential around -35 mV in SNr GABA neurons (Zhou et al., 2008). Unpublished data of Zhou indicate that the TRP channel blocker FFA inhibits 5-HT<sub>2C</sub>-R response. The I-V curves for 5-HT<sub>2C</sub>-R current and TRPC3 current are remarkably similar (Compare Fig. 3C,D with Fig. 10C). Generation of the 5-HT<sub>2C</sub>-R current is accompanied by increased conductance (Stanford and Lacey, 1996a; Zhou, unpublished data). Based on these data, it appears that TRPC3 channels may mediate the 5-HT<sub>2C</sub>-R activation-evoked inward current and excitation in SNr GABA neurons. This is entirely possible because 5-HT<sub>2C</sub>-R activation stimulates G<sub>q/11</sub> protein that in turn activates PLC, leading to the generation of DAG which enhances TRPC3 channel activity (Hofmann et al., 1999; Large et al., 2009). TRPC3 channels may thus serve as a common effector channel for 5-HT<sub>2C</sub>-Rs and potentially other G-protein coupled receptors that interact with lipid signaling mechanisms (Zhou, 2010).

### 5.5. Acetylcholine (ACh) input

Neurons in the SNr express nicotinic and muscarinic ACh receptors (nAChRs and mAChRs) (Nastuk and Graybiel, 1991; Klink et al., 2001; Woollorton et al., 2003; Michel et al., 2004; Poisik et al., 2008). Locally applied ACh causes excitation of SNr GABA neurons *in vivo* (Collingridge and Davies, 1981; Pinnock and Dray, 1982). Application of ACh to SNr GABA neurons *in vitro* induces an inward current when mAChRs are blocked, indicating the presence of functional nAChRs on these neurons (Klink et al., 2001; Woollorton et al., 2003; Poisik et al., 2008). Muscarinic stimulation similarly causes an increase in the firing rate of midbrain GABA neurons *in vitro* (Michel et al., 2004) via M3 receptor activation of protein kinase C followed by activation of a nonselective cationic conductance possibly mediated by TRPC channels (Michel et al., 2005).

Modulation of SNr GABA neuron activity by nAChRs plays a role in changes that result from nicotine exposure. nAChRs containing  $\alpha 4$  subunits are up-regulated by chronic nicotine exposure in midbrain GABA neurons including SNr GABA neurons (Nashmi et al., 2007). Recorded *in vitro*, SNr GABA neurons exposed to chronic nicotine exhibit an

increased tonic firing rate and a potentiated nicotine-induced increase in firing rate in response to further nicotine exposure when compared to control neurons (Nashmi et al., 2007). In contrast, midbrain dopamine neurons do not show a change in nAChR density in response to chronic nicotine exposure (Nashmi et al., 2007). Strikingly, SNc dopamine neurons exposed to chronic nicotine exhibit a decreased tonic firing rate and a muted response to further nicotine exposure *in vitro* possibly resulting from increased GABAergic input from neighboring SNr neurons (Nashmi et al., 2007).

In addition to being affected by exogenous ACh receptor agonists, SNr GABA neurons receive endogenous cholinergic input. The main cholinergic input to SN arises from the pedunculopontine nucleus (PPN) which also contains a significant number of glutamatergic and GABAergic neurons (Woolf and Butcher, 1986; Gould et al., 1989; Clements and Grant, 1990; Oakman et al., 1995; Charara et al., 1996; Wang and Morales, 2009). The PPN sends a dense projection to SNc suggesting preferential innervation of DA neurons (Saper and Loewy, 1982; Jackson and Crossman, 1983; Bolam et al., 1991), however there is also a projection to SNr (Saper and Loewy, 1982) and SNr GABA neurons receive synaptic contacts from PPN neurons (Lee and Tepper, 2009). Consistent with a direct innervation of SNr GABA neurons by the PPN, stimulation of the PPN *in vivo* most often produces short latency excitation of SNr GABA neurons (Scarnati et al., 1984; 1987). Further, PPN stimulation in organotypic cultures evokes EPSPs in SN GABA neurons that are attenuated by both Ach and glutamate receptor antagonists (Rohrbacher et al., 2000).

Surprisingly, lesioning the PPN increases SNr GABA neuron firing, but this effect is likely due to alterations in the basal ganglia network rather than a consequence of removing the monosynaptic projection from the PPN to the SNr (Breit et al., 2005). In addition, ACh might presynaptically alter afferent input to SNr through both mAChRs and nAChRs (Kayadjanian et al., 1994a,b; Michel et al., 2004) further complicating the interpretation of results obtained *in vivo*. In animals with dopaminergic lesion, however, additional lesion of the PPN leads to a decrease in SNr GABA neuron firing rate possibly suggesting an increased effect of the monosynaptic excitatory projection in Parkinsonian states, though the involvement of polysynaptic pathways is likely (Breit et al., 2006). The discovery of the PPN as an effective site of deep brain low frequency stimulation for the treatment of impaired gait and postural imbalance in Parkinson's disease (Gubellini et al. 2009; Hamani et al., 2010) heightens the importance of studying the role and mechanisms of input from the PPN in the modulation of SNr GABA neuron activity, although the descending projection of PPN is also likely to be important.

## 5.6. Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>)

H<sub>2</sub>O<sub>2</sub> is emerging as an important neuromodulator in the substantia nigra where it affects both SNc dopamine (Rice, 2011) and SNr GABA neurons (Lee et al., 2011). Elevated H<sub>2</sub>O<sub>2</sub> achieved by either exogenous application of H<sub>2</sub>O<sub>2</sub> or by increasing endogenous levels by inhibiting the metabolizing enzyme glutathione peroxidase, increases the spontaneous firing rate of guinea-pig SNr GABA neurons recorded *in vitro* (Fig. 11A, B) and induces a decrease in input resistance (Lee et al., 2011). Conversely, depleting endogenous H<sub>2</sub>O<sub>2</sub> with catalase decreases the spontaneous firing rate of these neurons and increases firing irregularity (Fig. 11C) (Lee et al., 2011). Thus, H<sub>2</sub>O<sub>2</sub> plays a role in maintaining the spontaneous activity of SNr GABA neurons. The source of H<sub>2</sub>O<sub>2</sub> involved in neuronal signaling is likely the electron transport chain in mitochondria, whose main role is the production of ATP during the process of oxidative phosphorylation (Boveris and Chance, 1973; Peuchen et al., 1997; Liu et al., 2002; Bao et al., 2009). Mitochondrial production of H<sub>2</sub>O<sub>2</sub> increases when neuronal activity increases (Kann et al., 2003; Avshalumov et al., 2005, 2008), and the spontaneous activity of SNr GABA neurons is sufficient to drive



modulatory H<sub>2</sub>O<sub>2</sub> production, resulting in tonic H<sub>2</sub>O<sub>2</sub> regulation of SNr neurons (Lee et al., 2011).

H<sub>2</sub>O<sub>2</sub> exerts its excitatory effects on guinea-pig SNr GABA neurons by activating a FFA-sensitive channel which is likely to be a TRP channel (Fig. 11A, B) (Lee et al., 2011). The increase in firing rate induced by either exogenous H<sub>2</sub>O<sub>2</sub> or elevated endogenous H<sub>2</sub>O<sub>2</sub> is reversed by FFA (Lee et al., 2011). In fact, when FFA is applied in the continued presence of elevated H<sub>2</sub>O<sub>2</sub>, the firing rate falls below control levels (Fig. 11B), possibly reflecting a loss of tonic depolarization by presumed TRP channels or the additional activation of a hyperpolarizing channel by H<sub>2</sub>O<sub>2</sub>. These possibilities were examined by first blocking presumed TRP channels with FFA, and then elevating H<sub>2</sub>O<sub>2</sub> levels in the continued presence of FFA. When this was done, SNr GABA neurons exhibited a decrease in firing rate in response to FFA, reflecting removal of a tonic depolarization mediated by TRP channels, followed by a suppression of firing when H<sub>2</sub>O<sub>2</sub> levels were elevated demonstrating that H<sub>2</sub>O<sub>2</sub> also activates a hyperpolarizing channel (Fig. 11 D , E) (Lee et al., 2011). H<sub>2</sub>O<sub>2</sub> hyperpolarizes SNc dopamine neurons by activating ATP-sensitive potassium (K<sub>ATP</sub>) channels (Avshalumov et al., 2005) that are also present on SNr GABA neurons (Schwanstecher and Panten, 1993; Stanford and Lacey, 1996b; Dunn-Meynell et al., 1998). When H<sub>2</sub>O<sub>2</sub> was increased in the presence of both a TRP channel and K<sub>ATP</sub> channel blocker, H<sub>2</sub>O<sub>2</sub> did not suppress the firing of SNr GABA neurons (Fig. 11F), indicating that H<sub>2</sub>O<sub>2</sub> can activate TRP channels as well as K<sub>ATP</sub> channels in guinea-pig SNr GABA neurons (Lee et al., 2011). Other experiments showed that the H<sub>2</sub>O<sub>2</sub>-induced increase in firing rate was only modestly enhanced when K<sub>ATP</sub> channels were blocked, suggesting that the main effect of H<sub>2</sub>O<sub>2</sub> on guinea-pig SNr GABA neurons is to increase their firing rate.

It is likely that H<sub>2</sub>O<sub>2</sub> plays a role in modulating the spontaneous firing rate of individual SNr GABA neurons and might also recruit increased activity in neighboring neurons given its ability to act as a diffusible messenger (Avshalumov et al., 2008). Further, as a part of abnormal reactive oxygen species production that may occur in Parkinson's disease (Lin and Beal, 2006; Rice, 2011), increased H<sub>2</sub>O<sub>2</sub> could contribute to pathological changes in basal ganglia output by increasing SNr GABA neuron activity.

## 6. Summary

The most striking neurophysiological feature of SNr GABA neurons is their sustained, spontaneous high frequency spike firing. Tonicly active TRPC3 channels and a subthreshold I<sub>NaP</sub> together depolarize the membrane potential toward spike threshold. The large and fast I<sub>NaT</sub> triggers the rapid rising phase of action potentials that in turn activates high-threshold, inactivation-resistant Kv3-like channels that can rapidly repolarize the membrane. The combination of these intrinsic ion channels provides these neurons with a remarkable spiking capability. Additionally, SNr GABA neurons receive and integrate excitatory, inhibitory and modulatory inputs that sculpt the default tonic high frequency firing into a meaningful motor control signal.

### Highlights

- SNr GABA projection neurons fire sustained autonomous high frequency spikes
- SNr GABA neurons have a higher density of Na currents than dopamine neurons
- Kv3-like current is essential for sustained fast spiking in SNr GABA neurons
- Dopamine D1 receptors facilitates the inhibitory striatonigral synapse

## Acknowledgments

This work was supported by NIH grants R01NS058850 and R01DA021194 to FMZ and F32NS063656 to CRL.

## Abbreviations

<b>ACh</b>	Acetylcholine
<b>DA</b>	dopamine
<b>D1R</b>	dopamine D1 receptor
<b>D2R</b>	dopamine D2 receptor
<b>5-HT<sub>2C</sub>-R</b>	serotonin 5-HT <sub>2C</sub> receptor
<b>GABA</b>	$\gamma$ -aminobutyric acid
<b>GPe</b>	globus pallidus external segment
<b>MSN</b>	medium spiny neuron
<b>Ca<sub>v</sub> channel</b>	voltage-activated calcium channel
<b>EPSC</b>	excitatory postsynaptic current
<b>IPSC</b>	inhibitory postsynaptic current
<b>FFA</b>	flufenamic acid
<b>GP</b>	globus pallidus
<b>I<sub>A</sub></b>	transient A-type potassium current
<b>I<sub>DR-fast</sub></b>	fast, delayed rectifier type potassium current
<b>I<sub>h</sub></b>	hyperpolarization-activation cation current
<b>I<sub>NaP</sub></b>	persistent sodium current
<b>I<sub>NaT</sub></b>	transient sodium current
<b>K<sub>ATP</sub> channel</b>	ATP-sensitive potassium channel
<b>KCa channel</b>	calcium-activated potassium channel
<b>Kv channel</b>	voltage-activated potassium channel
<b>Na<sub>v</sub> channel</b>	voltage-activated sodium channel
<b>PPN</b>	pedunculopontine nucleus
<b>PLC</b>	phospholipase C
<b>scRT-PCR</b>	single cell reverse transcription polymerase chain reaction
<b>SNr</b>	substantia nigra pars reticulata
<b>SNc</b>	substantia nigra pars compacta
<b>STN</b>	subthalamic nucleus
<b>TRP channel</b>	transient receptor potential channel
<b>TEA</b>	tetraethylammonium

**TTX**                      tetrodotoxin

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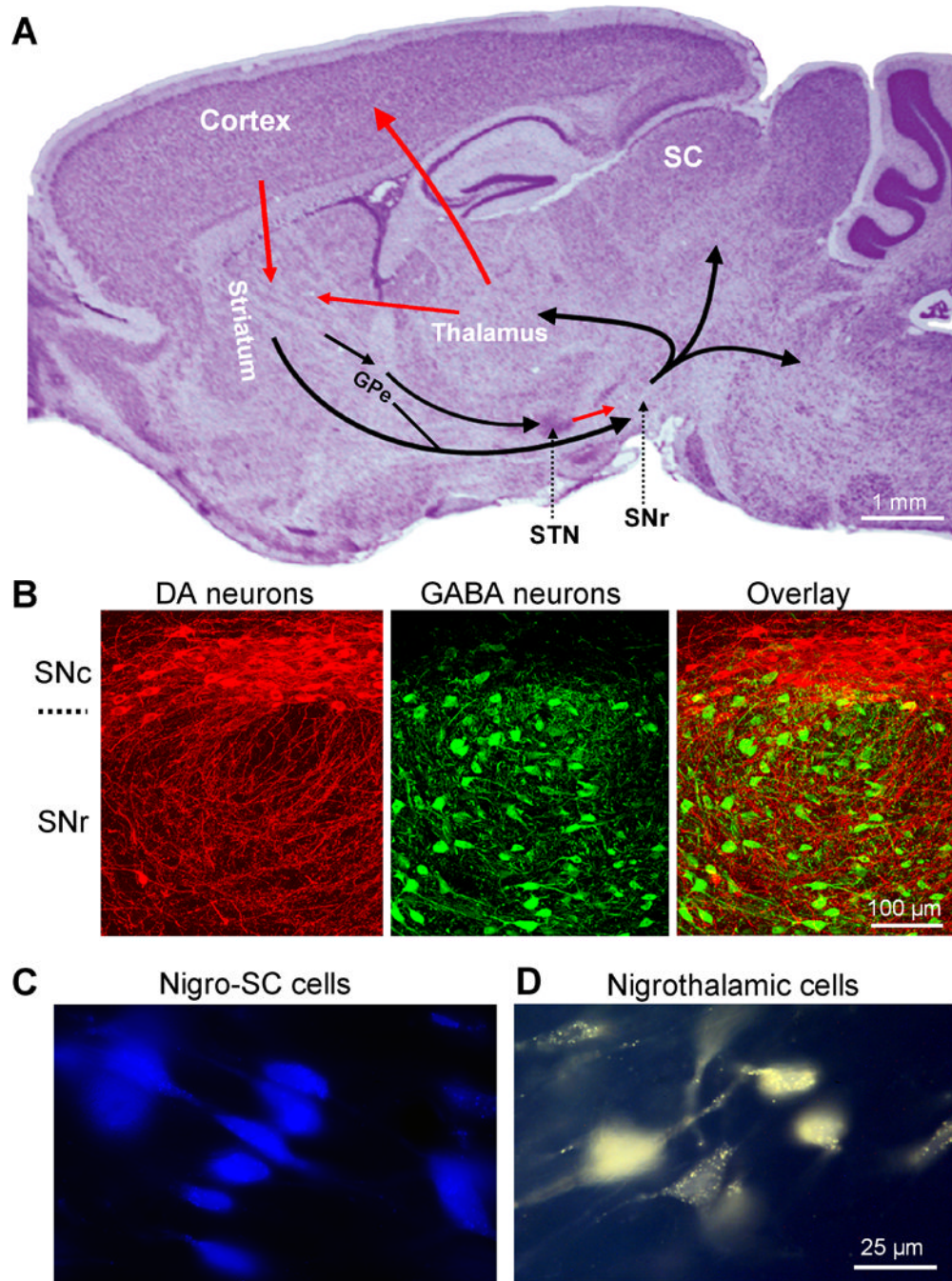
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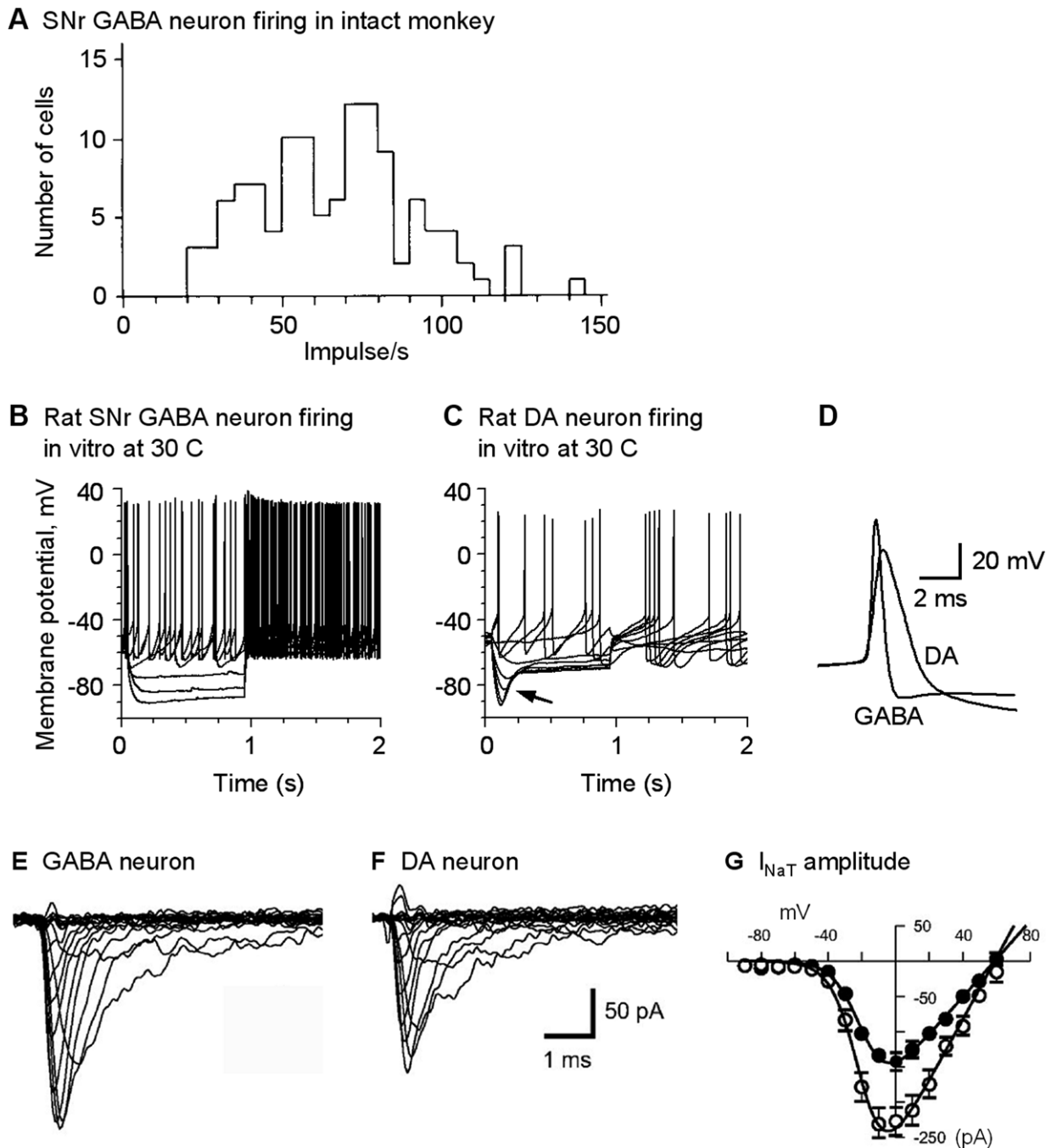
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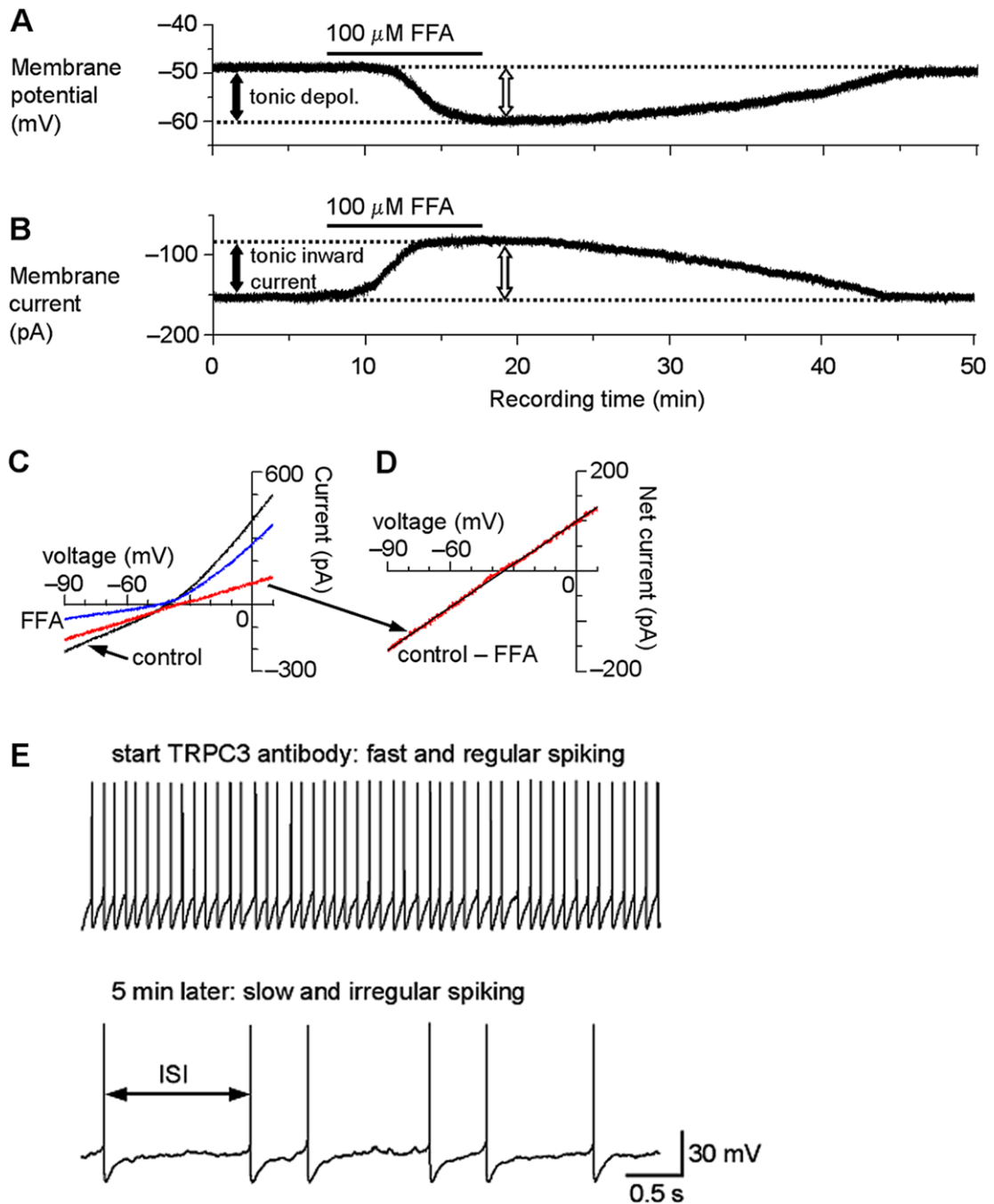
**Fig. 1.** The substantia nigra pars reticulata (SNr) is a key output nucleus of the basal ganglia. **(A)** A Nissl-stained sagittal mouse brain section showing the location of SNr and other major components of the basal ganglia. Arrows indicate information flow directions. The SNr receives information from several components of the basal ganglia and sends output to the thalamus, superior colliculus (SC), and brainstem motor structures. Unpublished data of FMZ. **(B)** Confocal images of double immunohistochemical staining for tyrosine hydroxylase (TH, red, a key enzyme for dopamine synthesis) and parvalbumin (PV, green, expressed only in GABA neurons). Most TH-positive dopamine neurons are in SNc with their dendrites extending into SNr where most neurons are PV-positive GABA neurons.

Modified from Zhou et al. 2009 with permission. **(C)** Examples of retrogradely labeled SNr neurons projecting to the superior colliculus (SC). Blue is a pseudocolor in this image for easier visualization. **(D)** Examples of retrogradely labeled SNr neurons projecting to the thalamus. **C** and **D** are modified from Lee and Tepper, 2007a with permission. Copyright 2006 Wiley-Liss, Inc.



**Fig. 2.** SNr GABA neurons fire sustained spontaneous high frequency spikes. **(A)** In intact primates, SNr GABA neurons fire tonic high frequency spikes. Modified from Schultz 1986 with permission. **(B, C)** In isolated preparations with fast synaptic inputs blocked and compared with nigral dopamine neurons, SNr GABA neurons still fire sustained high frequency spikes. In SNr GABA neurons, the  $I_h$  is weak whereas it is strong in nigral DA neurons as indicated by the arrow. Modified from Ding et al. 2011 with permission. **(D)** Spikes in SNr GABA neurons are larger in amplitude and shorter in duration than nigral DA neurons. **(E, F, G)** SNr GABA neurons have a higher density of the transient voltage-

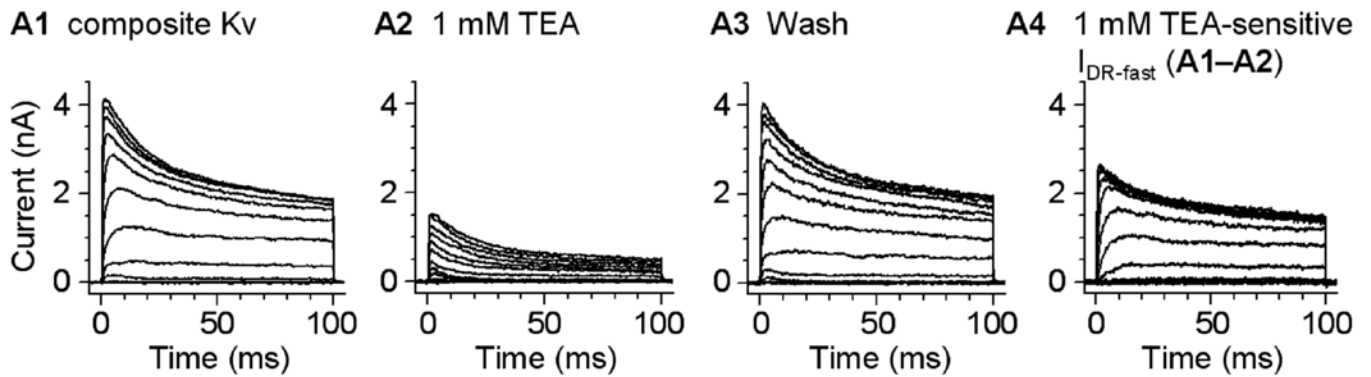
activated sodium current  $I_{NaT}$  than nigral DA neurons. **E–G** are modified from Seutin and Engel, 2010 with permission.



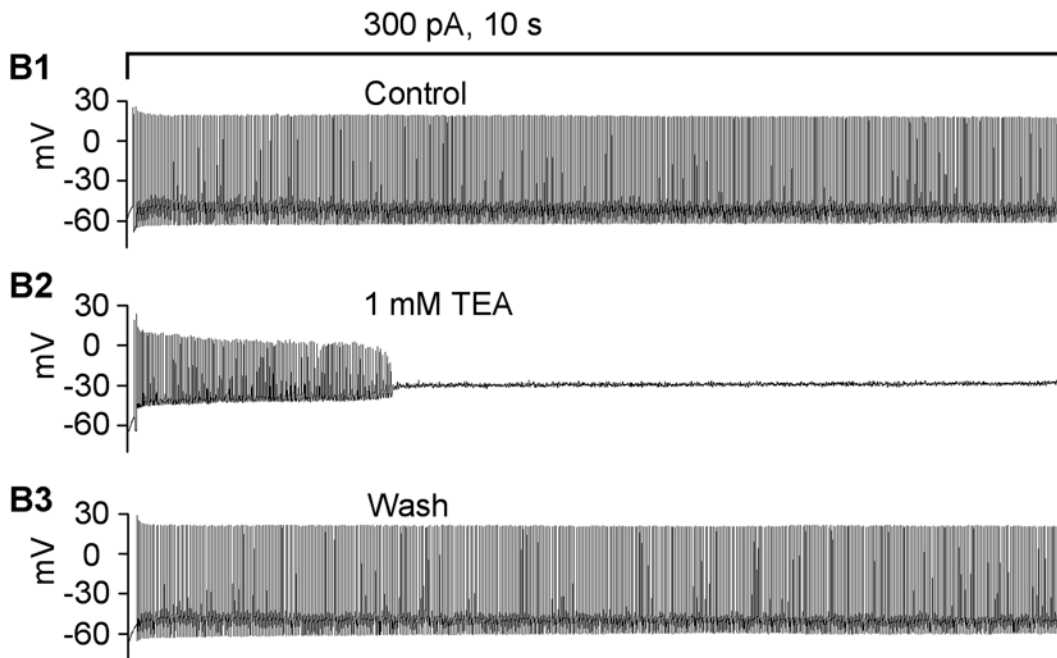
**Fig. 3.** TRP channels mediate a tonic inward current and depolarization in SNr GABA neurons. **(A)** After blocking  $\text{Na}_V$  channels with 1  $\mu\text{M}$  TTX and under current clamp recording condition, bath application of 100  $\mu\text{M}$  flufenamic acid (FFA) induced a hyperpolarization of about 10 mV (open arrow), indicating an FFA-sensitive tonic depolarization (depol., filled arrow). **(B)** When voltage clamped at  $-70$  mV, 100  $\mu\text{M}$  FFA induced an outward current (open arrow), or reduced a potential tonic inward current, as reflected by the apparent reduction of the holding current (filled arrow). **(C)** A linear voltage ramp from  $-90$  mV to  $10$  mV was applied under control condition (black trace) and during 100  $\mu\text{M}$  FFA application (blue trace). Digital subtraction (control - FFA) revealed the current inhibited by FFA (red trace)

and its I–V relationship. The decreased current also indicates an increased input resistance or decreased whole cell conductance. **(D)** The FFA-inhibited current in **C** displayed at an enhanced scale. The I–V relationship is clearly linear with no signs of voltage-dependent activation or inactivation and reversed its polarity around  $-35$  mV on average (intercept on X-axis in linear regression analysis as indicated by the black straight line). **(E)** Intracellular application of a TRPC3 antibody decreases the firing rate and increases the firing irregularity in SNr GABA neurons. Within the first minute of recording when the antibody was not likely to have diffused sufficiently into the cell, the firing was fast around 10 Hz and had a regular inter-spike interval (ISI). During the fifth minute of recording when a considerable amount of the antibody was likely to have diffused into the cell, the spontaneous firing became much slower and had an irregular ISI. Modified from Zhou et al., 2008 with permission.

## A Robust 1 mM TEA-sensitive $I_{DR}$ in SNr GABA neurons



## B Blocking $I_{DR}$ current impairs firing capability

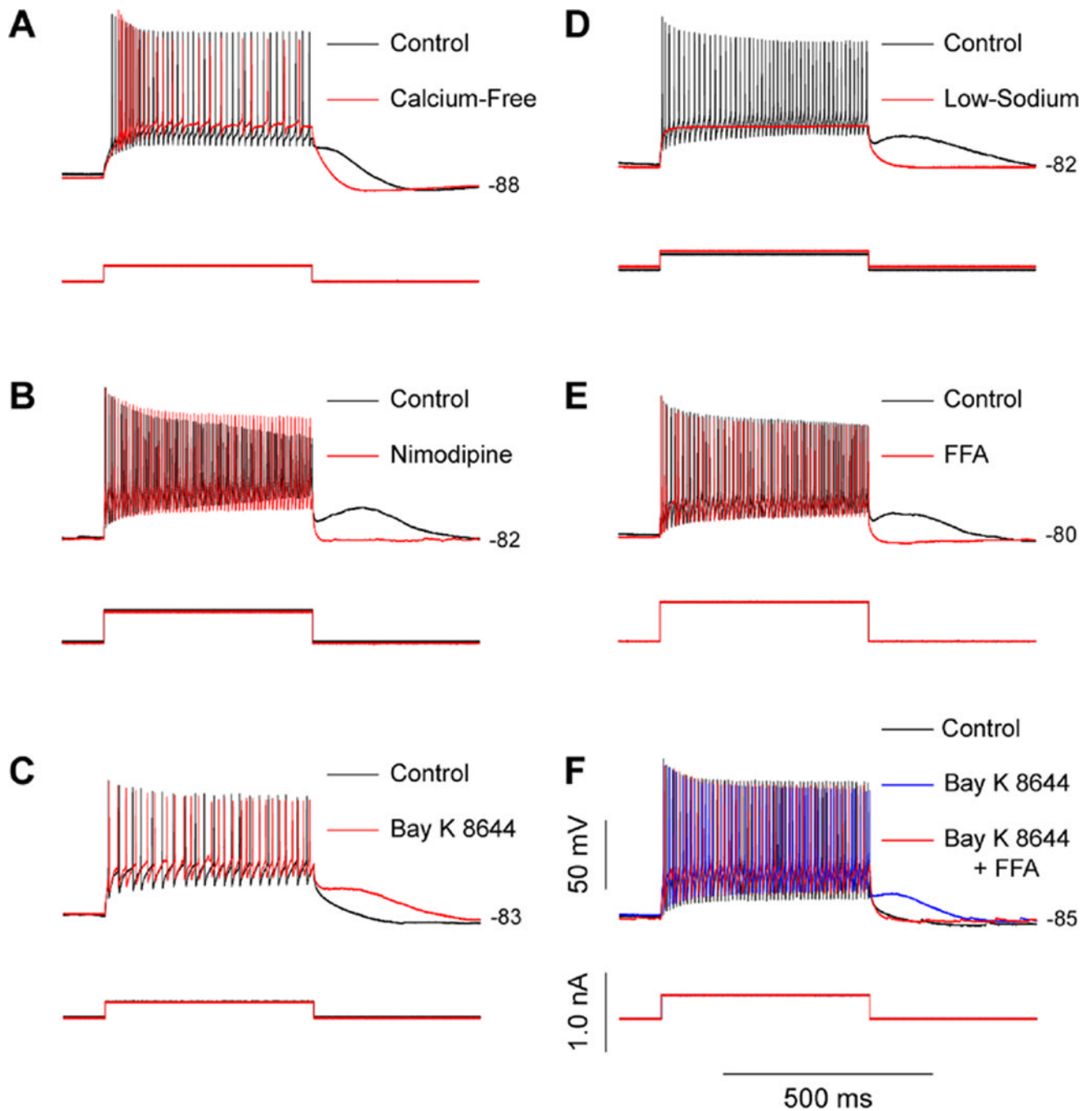


**Fig. 4.**

A robust, 1 mM TEA-sensitive  $I_{DR-fast}$  current is critical to the sustained high frequency firing in SNr GABA neurons. (A) Representative traces of Kv currents in a nucleated membrane patch isolated from a GABA neuron under control condition (A1), in the presence of 1 mM TEA (A2) and after washing out 1 mM TEA (A3). The 1 mM TEA-sensitive  $I_{DR-fast}$  was obtained by subtraction and displayed in A4. Holding potential was  $-100$  mV, the first depolarizing step was to  $-80$  mV and the last one was to  $+50$  mV, and each step increment was 10 mV. (B) Inhibition of Kv3 channel-mediated  $I_{DR-fast}$  by 1 mM TEA impairs the sustained high frequency firing in SNr GABA neurons. An example SNr GABA neuron was able to fire sustained high frequency (around 45 Hz) fast spikes upon injection of 300 pA current for 10 s (B1). In the presence of 1 mM TEA that blocks  $I_{DR-fast}$ , the same 10 s 300 pA injection induced spike firing only for about 3 s or less (B2). Note the spike amplitude decreased progressively. The SNr neuron regained its sustained high

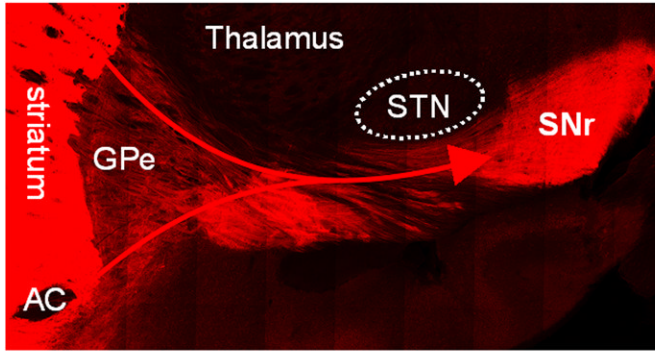
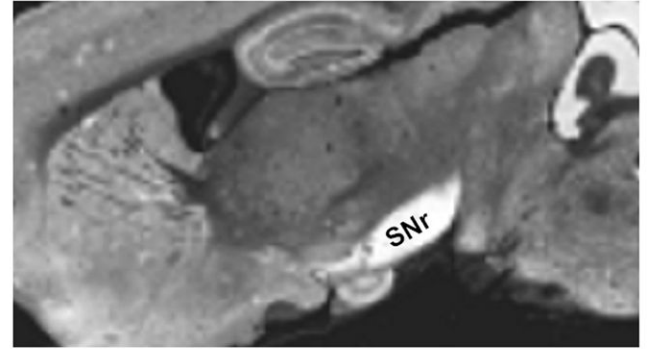
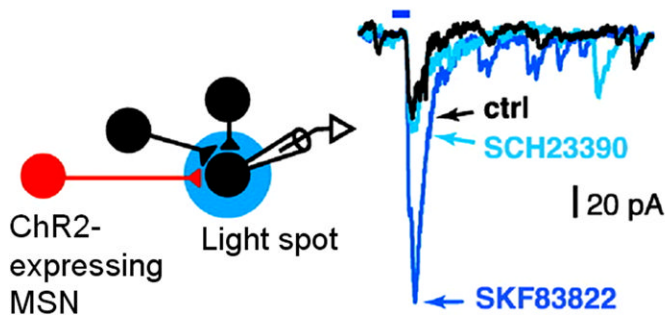
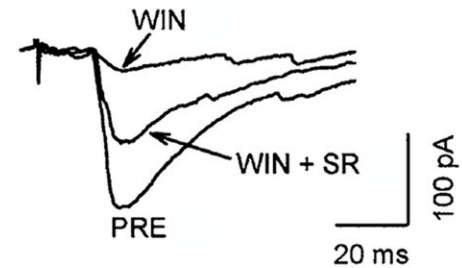
frequency firing capability after washing out 1 mM TEA (**B3**). Modified from Ding et al. 2011 with permission.



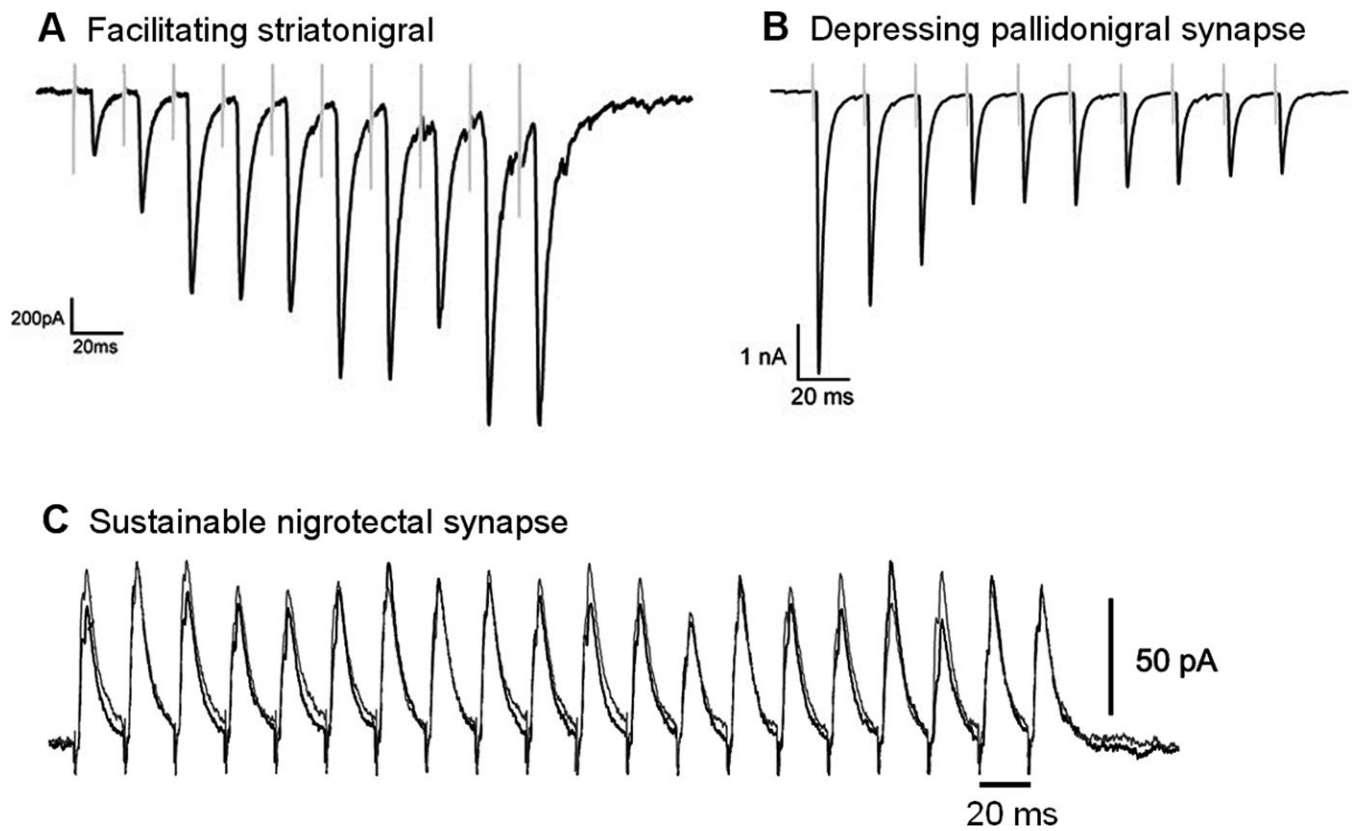


**Fig. 5.** SNr GABA neurons have a calcium-activated plateau potential. **(A)** A representative SNr GABA neuron exhibiting a plateau potential that manifests as a prolonged membrane depolarization following a depolarizing current pulse delivered while the neuron is held hyperpolarized (black trace). The plateau potential is abolished in calcium-free conditions (red trace). **(B)** Another SNr GABA neuron exhibits a plateau potential under control conditions (black trace) that is abolished by nimodipine (10  $\mu$ M; red trace) indicating the involvement of L-type calcium channels in plateau potential generation. **(C)** A SNr GABA neuron without a plateau potential under control conditions (black trace) is made to exhibit a plateau potential after activation of L-type calcium channels with Bay K 8644 (5  $\mu$ M; red

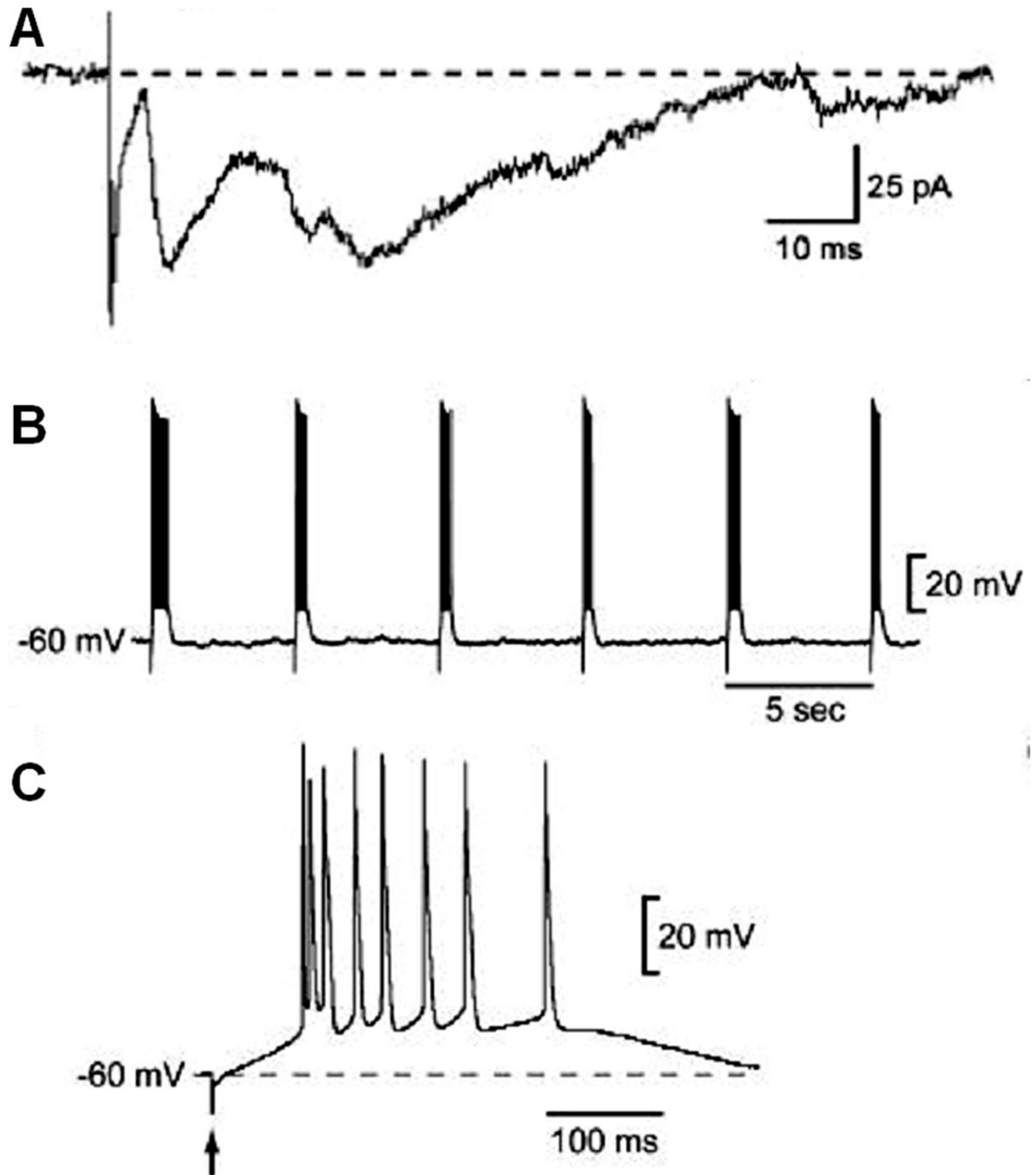
trace). **(D)** The plateau potential (black trace) is abolished in low-sodium conditions (red trace) suggesting that the conductance underlying the plateau potential is a calcium-activated nonselective cation conductance. **(E)** The plateau potential observed under control conditions (black trace) is abolished by the TRP channel blocker flufenamic acid (FFA; 200  $\mu$ M; red trace). **(F)** A neuron not exhibiting a plateau potential under control conditions (black trace) exhibits a plateau potential in the presence of Bay K 8644 (blue trace). The evoked plateau potential is similarly abolished by FFA (red trace). Modified from Lee and Tepper, 2007b with permission. Copyright 2007 Society for Neuroscience.

**A** D1R expression on striatonigral axons**C** CB1R expression on striatonigral axons**B** D1R activation increases GABA release from striatonigral axons**D** CB1R activation decreases GABA release from striatonigral axons**Fig. 6.**

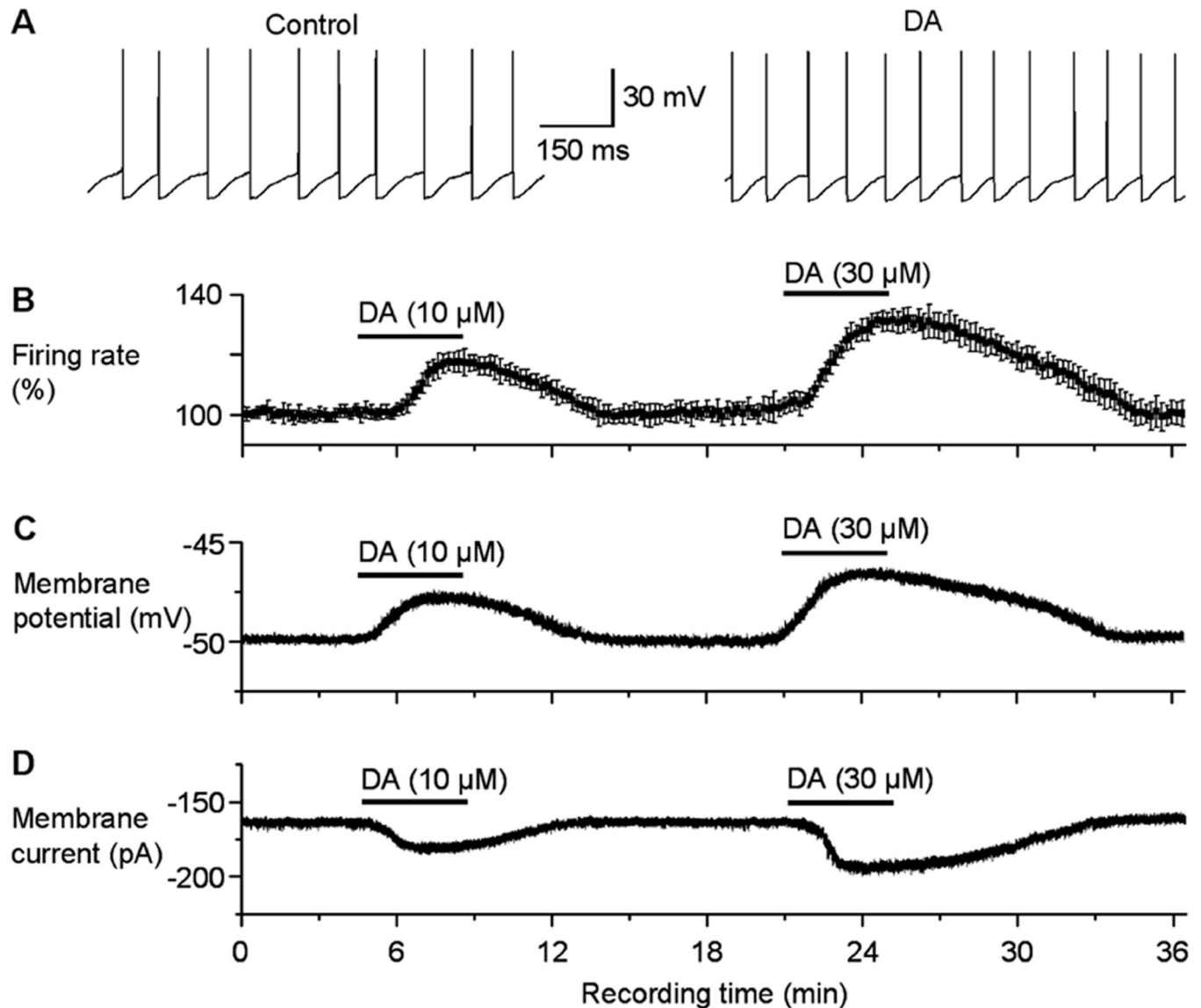
D1 receptor facilitation and CB1 receptor inhibition of the striatonigral axon terminals. **(A)** Immunostaining for D1 receptor protein reveals an intense expression of D1 receptors on striatonigral axons. Due to the curvature of the fibers in this sagittal section, only part of the projection is captured in this image. AC: anterior commissure. Unpublished data of FMZ. **(B)** Selective photoactivation of ChR2-expressing MSN axons in SNr evoked IPSCs in SNr GABA neurons that was enhanced by a D1-like agonist SKF83822. This enhancing effect was blocked by the D1-like antagonist SCH23390. Adapted from Chuhma et al. 2011 with permission. **(C)** Immunostaining for CB1 receptor protein reveals an intense expression of CB1 receptors on striatonigral axons. Adapted from Fukudome et al. 2004 with permission. **(D)** The cannabinoid agonist WIN55212-2 (WIN) depressed striatum stimulation-evoked IPSCs in SNr GABA neurons and this effect was largely reversed by cannabinoid antagonist SR141716A (SR). PRE indicates pre-drug control. Adapted from Wallmichrath and Szabo, 2002b with permission.



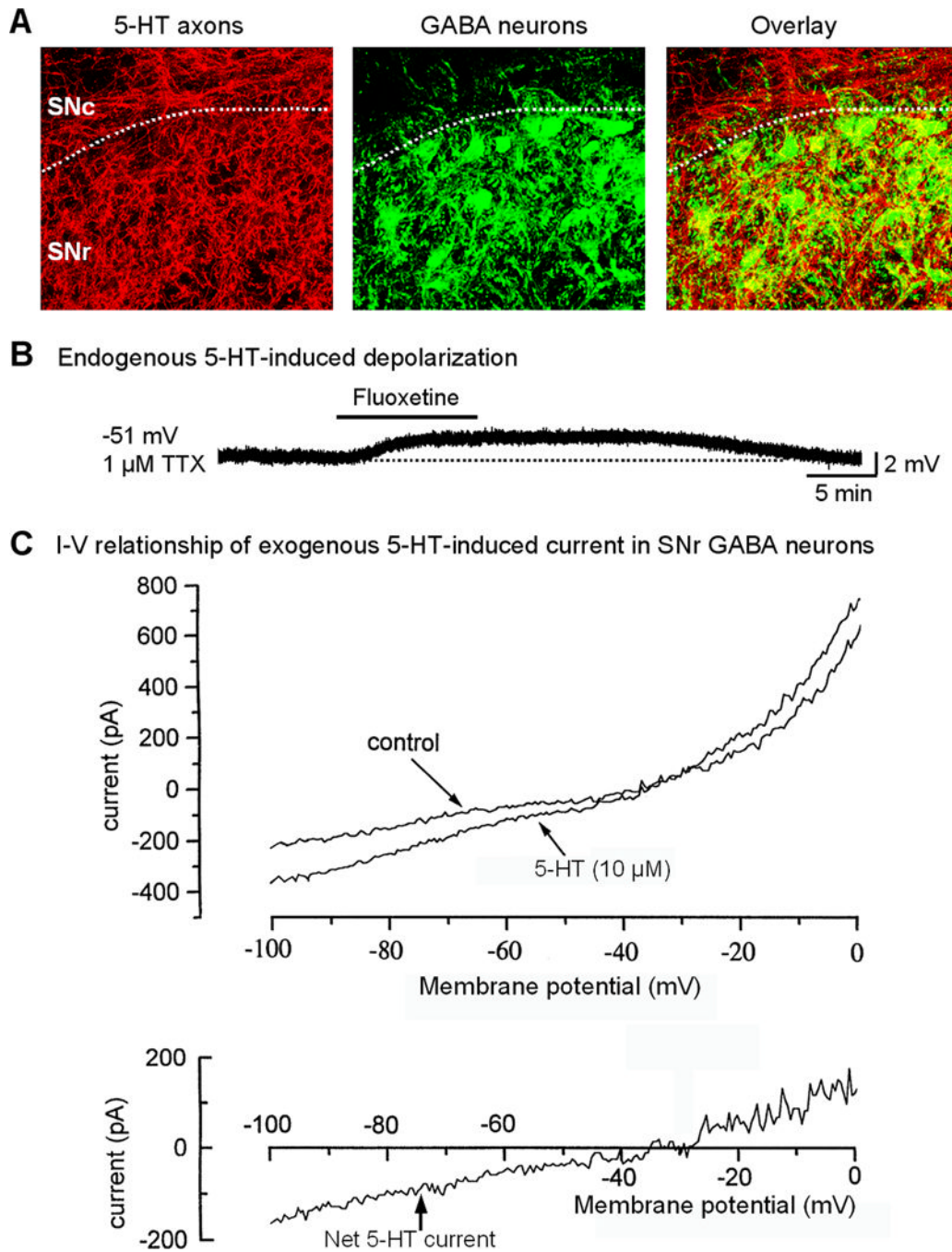
**Fig. 7.** Striatonigral, pallidonigral, and nigrotectal synapses have different functional properties. The striatonigral synapse is facilitating (**A**), the pallidonigral synapse is depressing (**B**), and the nigrotectal synapse is sustainable or constant (**C**). **A** and **B** are adapted from Connelly et al. 2010 and **C** is adapted from Kaneda et al. 2008 with permission.



**Fig. 8.** Excitatory synaptic input from STN neurons affects the firing of SNr GABA neurons. STN stimulation evokes complex polysynaptic EPSCs under voltage clamp at  $-70$  mV (A) and burst spike firing in SNr GABA neurons (B, C). Adapted from Shen and Johnson 2006 with permission.



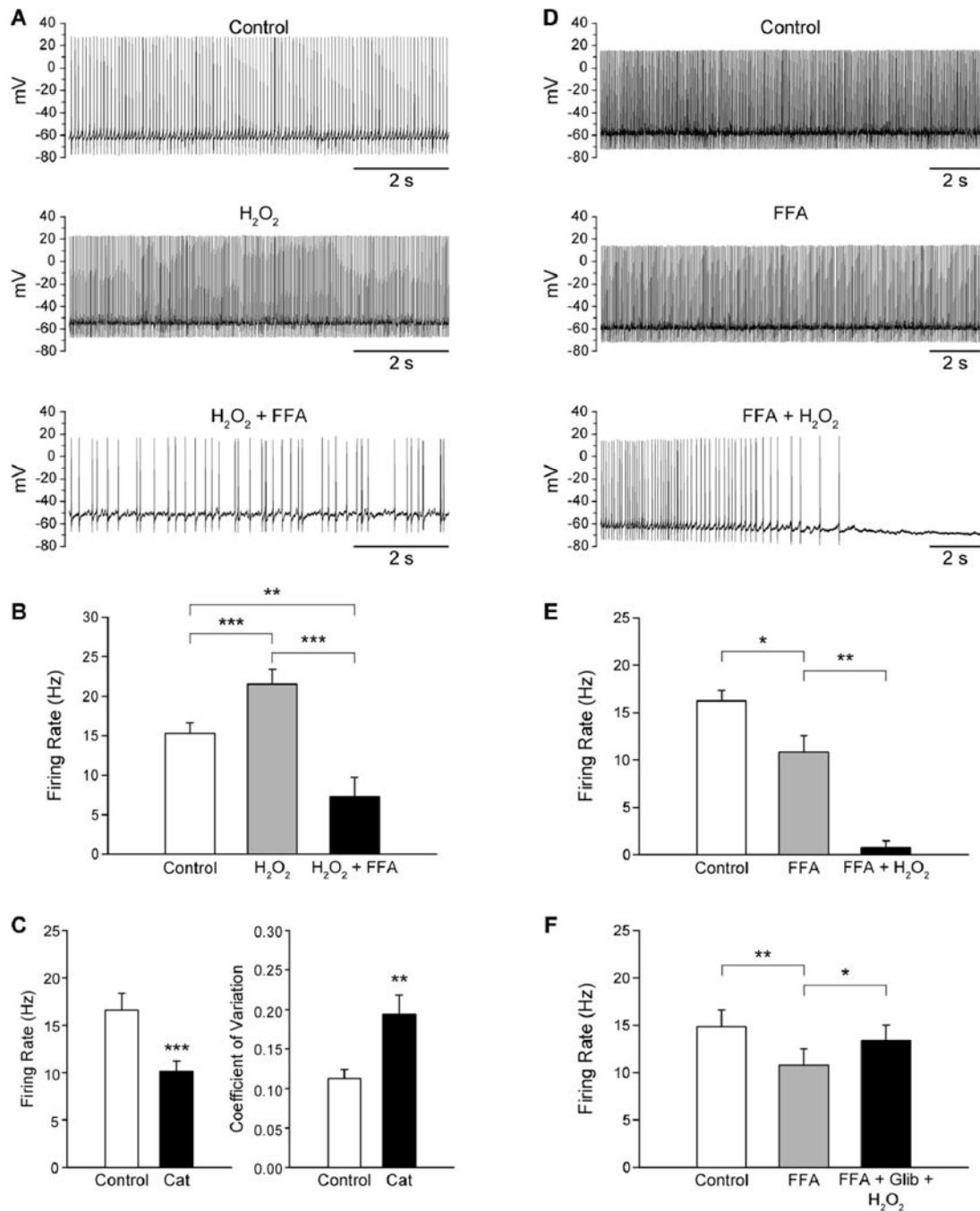
**Fig. 9.** Direct dopamine excitation in SNr GABA neurons. All recordings were made in the presence of picrotoxin, D-AP5 and CNQX to block fast synaptic transmission. Sulpiride was present to prevent potential complications from D<sub>2</sub> autoinhibition of DA neurons. **(A)** Examples of spontaneous spikes under control conditions (left) and during 10  $\mu$ M DA application (right). **(B)** Group data of DA enhancement of spiking. **(C)** An example recording showing that, after blocking spikes with 1  $\mu$ M TTX, DA induced a clear depolarization. **(D)** An example recording showing that, when voltage clamped at -70 mV, DA induced an inward current in the presence of 1  $\mu$ M TTX. Note that SNr GABA neurons are normally depolarized and have a large holding current when clamped at -70 mV. Modified from Zhou et al., 2009 with permission.

**Fig. 10.**

Direct 5-HT excitation in SNr GABA neurons. **(A)** Immunostaining for 5-HT transporter protein reveals a very dense 5-HT axonal network that intermingles with PV-positive GABA neurons in SNr. **(B)** Endogenous 5-HT induces a tonic depolarization in SNr GABA neurons that is enhanced by blocking 5-HT re-uptake with 2  $\mu\text{M}$  fluoxetine. Action potentials were blocked by 1  $\mu\text{M}$  TTX. Ionotropic glutamate receptors and GABA<sub>A</sub> receptors were blocked. **(C)** bath applied 5-HT induced a linear, voltage-independent inward current below action potential threshold. The whole cell conductance was increased during 5-HT application, indicating an opening of ion channels (e.g. TRPC3 channels), not a closing of background K channels. Note the remarkable similarity between this 5-HT current and the TRP current

shown in Fig. 3C,D. **A** and **B** are unpublished data of FMZ. **C** is adapted from Stanford and Lacey, 1996a, with permission.



**Fig. 11.**

Modulation of guinea-pig SNr GABA neuron firing rate by H<sub>2</sub>O<sub>2</sub>. (A) Spontaneous activity of a SNr GABA neuron under control conditions, in the presence of H<sub>2</sub>O<sub>2</sub> (1.5 mM), and with flufenamic acid (FFA; 20 μM) in the continued presence of H<sub>2</sub>O<sub>2</sub>. (B) H<sub>2</sub>O<sub>2</sub> causes an increase in SNr GABA neuron firing rate that is reversed by the TRP channel blocker FFA, with the resulting firing rate falling below control levels. (C) Depletion of endogenous H<sub>2</sub>O<sub>2</sub> with catalase (Cat; 500 U/mL) results in a decrease in firing rate and an increase in the coefficient of variation indicating that basal H<sub>2</sub>O<sub>2</sub> levels play a role in maintaining the tonic firing of SNr GABA neurons. (D) Spontaneous activity of another SNr GABA neuron under control conditions, in the presence of FFA, and with H<sub>2</sub>O<sub>2</sub> in the continued presence of

FFA. **(E, F)** Blockade of TRP channels with FFA causes a decrease in SNr GABA neuron firing rate. Addition of H<sub>2</sub>O<sub>2</sub> when TRP channels are blocked results in a suppression of firing, indicating activation of a hyperpolarizing conductance by H<sub>2</sub>O<sub>2</sub> **(E)**. The H<sub>2</sub>O<sub>2</sub>-induced suppression of firing is prevented by the K<sub>ATP</sub> channel blocker glibenclamide (Glib; 3μM) **(F)**. \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001. Modified from Lee et al., 2011 with permission.