Quantifying the Neural Elements Activated and Inhibited by Globus Pallidus Deep Brain Stimulation

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Johnson MD, McIntyre CC. Quantifying the neural elements activated and inhibited by globus pallidus deep brain stimulation. J Neurophysiol 100: 2549–2563, 2008. First published September 3, 2008; doi:10.1152/jn.90372.2008. Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) is an effective therapy option for controlling the motor symptoms of medication-refractory Parkinson’s disease and dystonia. Despite the clinical successes of GPi DBS, the precise therapeutic mechanisms are unclear and questions remain on the optimal electrode placement and stimulation parameter selection strategies. In this study, we developed a three-dimensional computational model of GPi-DBS in nonhuman primates to investigate how membrane channel dynamics, synaptic inputs, and axonal collateralization contribute to the neural responses generated during stimulation. We focused our analysis on three general neural elements that surround GPi-DBS electrodes: GPi somatodendritic segments, GPi efferent axons, and globus pallidus pars externa (GPe) fibers of passage. During high-frequency electrical stimulation (136 Hz), somatic activity in the GPi showed interpulse excitatory phases at 1–3 and 4–5.5 ms. When including stimulation-induced GABA_A and AMPA receptor dynamics into the model, the somatic firing patterns continued to be entrained to the stimulation, but the overall firing rate was reduced (78.7 to 25.0 Hz, P < 0.001). In contrast, axonal output from GPi neurons remained largely time-locked to each pulse of the stimulation train. Similar entrainment was also observed in GPe efferents, a majority of which have been shown to project through GPi en route to the subthalamic nucleus. The models suggest that pallidal DBS may have broader network effects than previously realized and the modes of therapy may depend on the relative proportion of GPi and/or GPe efferents that are directly affected by the stimulation.

INTRODUCTION

Multiple movement disorders, including Parkinson’s disease and dystonia, are characterized by abnormal neuronal activity in the globus pallidus pars interna (GPi) (Hutchinson et al. 1994, 1997; Vitek et al. 1999). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys, for instance, parkinsonian symptoms are present with altered GPi neuronal firing rates (Filion and Tremblay 1991), firing patterns (Wichmann and Soares 2006), oscillations (Nini et al. 1995), and receptive fields (Filion et al. 1988). Since the GPi is a primary output nucleus of the basal ganglia sending GABAergic projections to the ventral tier of thalamus, the centromedian-parafascicular nucleus of thalamus, and the pedunculopontine tegmental nucleus (PPN) (Baron et al. 2001; Kuo and Carpenter 1973; Parent et al. 2001; Shink et al. 1997; Sidibe et al. 1997), pathophysiological activity within the GPi can have widely distributed network effects (Mitchell et al. 1989).

Surgical ablation of the posteroverentral GPi is one approach to control the motor signs of Parkinson’s disease (Bakay et al. 1992) and primary generalized dystonia (Lozano et al. 1997). Chronic high-frequency electrical stimulation (HFS) of the same region is another approach to achieve equally therapeutic effects (Krauss et al. 2004; Volkmann 2004). Unlike the immutable effects of GPi lesioning, however, GPi deep brain stimulation (DBS) enables the clinician to tailor stimulation parameter settings postoperatively to maximize efficacy and minimize the induction of undesirable side effects (Kumar 2002; Volkmann et al. 2006). The juxtaposition of therapeutic outcomes generated by DBS and lesioning led to the hypothesis that HFS effectively silences the stimulated nucleus and thereby mitigates excessive GABAergic input into the motor thalamus and brain stem (Toth and Tomka 1968). Several modeling studies have argued that although HFS may inhibit local somatic activity, action potentials can be elicited in the axonal processes of the neuron, leading paradoxically to stimulus-driven output activity (McIntyre et al. 2004; Miocinovic et al. 2006). Most experimental studies investigating Gpi-HFS support these predictions showing that Gpi-HFS reduces somatic firing rates in the GPi (Boraud et al. 1996; Dostrovsky et al. 2000; Wu et al. 2001) as well as in one of its downstream targets, the ventrolateral nucleus of thalamus, with inhibitory latencies in the latter case consistent with monosynaptic GABAergic signaling (Anderson et al. 2003). Gpi-HFS has also been shown to induce more regular firing patterns in downstream thalamic nuclei (Montgomery 2006; Pralong et al. 2003). Moreover, similar changes in somatic firing patterns have been observed in the Gpi during Gpi-HFS (Bar-Gad et al. 2004) with modulatory effects propagating to regions of the Gpi that exceed predictions for the spread of suprathreshold current (Wu et al. 2001).

In this study, we developed an anatomically and physiologically realistic computational model of Gpi-DBS to investigate how membrane dynamics, synaptic input, and axonal collateralization contribute to these observed changes. The model simulates DBS with scaled clinical electrodes implanted in the caudal (sensorimotor) Gpi of a nonhuman primate. Three-dimensional (3-D) morphologies of individual pallidal neurons were positioned within the context of a reconstructed volume of the basal ganglia. We used the model system to first investigate what membrane channel and synaptic properties contribute to the experimentally observed somatic responses to HFS. We then evaluated the Gpi axonal output induced by clinically relevant stimulation parameters. Finally, we incor-

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ported globus pallidus pars externa (GPe) projection neurons, of which a majority course through and at times collateralize within GPi en route to the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr) (Parent and Parent 2002; Sato et al. 2000a), and tested the hypothesis that GPI-DBS can also excite these fibers of passage. The model provides a tool to examine how various stimulation paradigms affect the neural output of the pallidum and to make predictions in terms of stimulation-induced network effects within the basal ganglia. Preliminary results from this work have been presented in abstract form (Johnson et al. 2007).

METHODS

Neuron morphologies

Our model system used a 3-D reconstruction of the basal ganglia from a Cynomolgus monkey (Macaca fascicularis) (Martin and Bowden 2000) to define the boundaries of individual nuclei of interest (i.e., GPi and GPe) (Miocinovic et al. 2007). Biotinylated dextran amine (BDA) labeled GPi and GPe neurons from Cynomolgous monkeys were reconstructed in 3-D using Neurolucida (MicroBrightField, Williston, VT) as shown in Fig. 4 of Parent et al. (2001) and Fig. 5 of Sato et al. (2000a). Somatodendritic processes of GPi neurons were verified by counterstaining with cytochrome oxidase and the BDA labeling was sufficient to easily follow the axonal processes through each sagittal section. These GPi neurons consisted of ovoid, spindle-shaped, or triangular cell bodies with two to five long, but poorly branched, primary dendrites with dendritic fields typically spanning ≤1 mm along the rostrocaudal and/or dorsoventral planes but <300 µm along the mediolateral plane. Their neuronal morphologies (Fig. 1A) were distributed within the atlas-based reconstruction according to anatomically realistic orientations and axonal trajectories that followed dorsally along the lenticular fasciculus (LF) on leaving the GPi (Baron et al. 2001; Parent and Parent 2004). GPe neuron morphologies (Fig. 1B) were similarly distributed within the basal ganglia framework and oriented in 3-D such that their axonal processes extended through and collateralized within GPi and subsequently targeted STN (Sato et al. 2000a; Smith et al. 1994). Since it is unknown whether these axons preferentially follow the LF or the more ventral ansa lenticularis (AL) fiber tract on exiting the GPI, GPe axonal trajectories were given a random dorsoventral distribution (Fig. 1C). An iterative algorithm developed in MATLAB (The MathWorks, Natick, MA) converted truncated versions of these morphology files into segments with length and thickness parameters defined individually for the soma, dendrites, and axons in the case of GPi cells (Fig. 1C) and only the axons and associated collaterals in the case of GPe cells. Multicompartment cable models of GPi neurons and GPe axons were simulated within NEURON v6.1 (Hines and Carnevale 1997). The model scripts are available on the ModelDB website (http://senselab.med.yale.edu/modeldb).

Membrane properties

Based on in vitro electrical properties, two distinct types of neurons are known to exist within the entopeduncular nucleus (EP), which is the rat homolog of monkey GPI (Nakanishi et al. 1990, 1991). Type I neurons exhibit anomalous rectification typical of $I_h$ currents and the capacity for producing high-frequency activity with minimal spike adaptation. Given that the majority of EP neurons (80%) display these membrane characteristics, type I cells are thought to constitute the GABAergic projection neurons that target thalamic and brain stem nuclei. In contrast, type II neurons display small anomalous rectification, robust spike adaptation, and a steady repolarization after a hyperpolarizing pulse indicative of transient A-current. For the purposes of this study, however, we modeled only type I cells.

All somatic and dendritic compartments of the GPI neuron model were assigned a series of passive membrane properties (Table 1) (Kita et al. 2002). These neurons were oriented within a 3-D atlas-based reconstruction of monkey pallidum containing a DBS lead with electrode contacts positioned primarily in GPi. $D$: from the neuron reconstructions, GPi membrane model compartments were created for axonal, somatic, and dendritic segments and instantiated with physiologically relevant passive properties, ion channels, and distributions of AMPA and GABAA receptors. $E$: the 3-D position of each compartment was then transformed into polar coordinate space with respect to the DBS lead. Extracellular stimulus amplitudes applied to each compartment were defined according to potential distributions simulated in an axisymmetric finite element model of neural tissue, which consisted of a 250 µm layer of encapsulation tissue (0.1 S/m) between the DBS lead and the bulk tissue (0.30 S/m), 3-D, 3-dimensional; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DBS, deep brain stimulation; GABA, γ-aminobutyric acid type A; GPe, globus pallidus pars externa; GPI, globus pallidus pars interna.
The action potential threshold ($\text{AP}_\text{th}$) for these cells was identified as the voltage at which the derivative of the membrane voltage ($dV_m/dt$) was 2SDs larger than its mean during the interspike interval (Atherton and Bevan 2005). Since rat EP neurons are spontaneously active, the resting membrane potential was defined as the point halfway between the action potential repolarization trough and the $\text{AP}_\text{th}$ (Shin et al. 2007). Inclusion of ion channel mechanisms was based on previous reports of rat EP neurons as well as functionally related neurons in the substantia nigra pars reticulata (SNr) (Atherton and Bevan 2005). Ion channels were placed in both somatic and dendritic compartments since it has been reported previously that APs generated in the soma can backpropagate into the dendrites (Atherton and Bevan 2005; Haussler et al. 1995). In cases where ion channel activation and inactivation functions have not yet been characterized for EP or SNr neurons, channel kinetic equations were modeled from those reported in other brain regions (Table 2). Parameter values determined from these in vitro experiments were scaled with $Q_{10}$ values to match in vivo conditions at 36°C (see the APPENDIX).

Channel conductances were then adjusted manually to match the model’s somatic activity to specific electrophysiological behaviors of rat EP neurons (Nakanishi et al. 1990) (see Fig. 2).

Myelinated axons used in the GPi neuron simulations consisted of a double-cable model that included representations of the nodes of Ranvier (diameter, 1.4 μm), paranodal (1.4 μm) and internodal (1.6 μm) segments of the axon, and a myelin sheath (outer diameter, 2.0 μm) (McIntyre et al. 2002, 2004; Miocinovic et al. 2006). Nodal compartments were instantiated with nonlinear fast Na⁺ channels, persistent sodium channels, slow K⁺ channels, and a leakage current. The paranodal segment included a slow K⁺ current, whereas the internodal and myelin segments contained only passive mechanisms (membrane capacitance of 2 μF/cm², axoplasmic resistivity of 70 Ω·cm). These axonal properties were also used to model GPi axons that collateralized en passant through GPi. However, histological studies have suggested that axonal collaterals making synaptic boutons within the pallidum may be unmyelinated and of a smaller diameter than the primary efferent processes (Fox et al. 1975; Galvan et al. 2005; Kita and Kitai 1987; Korotchenko 1979). Given these unknowns in the GPi model, we investigated how collateral myelination and diameter affect the response of fibers of passage to deep brain stimulation. Unmyelinated axon compartments (100 μm in length) were modeled with modified Hodgkin–Huxley membrane dynamics (“hh” mechanism in NEURON) as described by Grill et al. (2008). The sodium channel conductance was increased from 0.24 to 0.35 S/cm² to generate a stable resting membrane potential and facilitate antidromic and orthodromic action potential propagation through the axonal branches. All simulations were run at 36°C.

### Synaptic properties

Anatomical tracing studies have shown that GPi cells are innervated by glutamatergic afferents arising from the subthalamic nucleus (STN) (Carpenter et al. 1981) and GABAergic afferents originating from the striatum and GPe (Percheron et al. 1984), thereby forming sites of convergent integration (Bolam and Smith 1992). More specifically, in primates, GPi neurons are richly innervated by dense baskets of GABAergic terminals around both the soma and the dendrites (Hazarati et al. 1990). γ-Aminobutyric acid (GABA)-positive boutons from the striatum account for about 32% of the axosomatic terminals and 80% of the axodendritic terminals in GPi (Shink and Smith 1995). Indirect pathway GABAergic afferents from the GPi represent an additional 48% of axosomatic boutons, whereas these processes make little to no contact with dendritic segments in GPi (Shink and Smith 1995). Glutamatergic afferents from the STN also target GPi neurons making sporadic synapses on both soma and dendrite compartments (~10% of all terminals) (Bolam and Smith 1992; Clarke and Bolam 1998; Shink and Smith 1995). The substantially higher proportion of GABAergic compared with glutamatergic synapses is thought to facilitate strong gating effects by striatal and GPe neurons on GPi output (Kita 2001).

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and GABA_A receptors were incorporated into the GPi neuron models with both sets of receptors randomly distributed along the somatic and dendritic arbors according to their relative ratios (Fig. 1D). In total, receptors were present in 7/15 somatic compartments (1 AMPA and 6 GABA_A) and 38/60 dendritic compartments (4 AMPA and 34 GABA_A). To simulate a synaptic event, an intracellular current pulse was generated in a virtual presynaptic terminal triggering the delivery of a fixed pulse (1 mM) of transmitter occurring over 1 ms to a postsynaptic compartment that used a minimal kinetic first-order model of either a glutamate-based AMPA receptor or GABA-based GABA_A receptor (Destexhe et al. 1994). The postsynaptic current generated by these models was dependent on the synaptic conductances ($g_{\text{AMPA}}$ and $g_{\text{GABA_A}}$). Synaptic conductances were tuned to reproduce firing rate and bursting features consistent with GPi spike recordings performed in monkeys treated with MPTP. This process involved generating synaptic events based on a representative set of input spike raster scans from extracellular microelectrode recordings in the putamen, GPe, and STN in the same MPTP-treated monkeys. This tuning process was simplified by using a single combination of recordings for each simulation and applying those spike patterns to all afferent axonal compartments of the same subtype. A collection of these simulations ($n = 10$ different sets of recorded raster scans) was then used to tune the synaptic conductances.

### Neuronal recordings in parkinsonian monkeys

Female rhesus macaque monkeys (Macaca mulatta, ~15 yr old) were treated with intracarotid injections of MPTP and evaluated behaviorally for parkinsonian contralateral limb rigidity and bradykinesia. For more methodological details, see Hashimoto et al. (2003).
DBS electric field model

Within the 3-D model, a monkey-scaled version of a human DBS lead was positioned along the coronal plane at an angle of 15° and along the sagittal plane at an angle of 25° such that most of the electrode contacts were present in the caudal portion of GPi (see Fig. 1C) (Gross et al. 1997; Siegfried and Liptitz 1994). The scaled DBS lead consisted of four cylindrical electrodes, each with a diameter of 750 μm and height of 500 μm (Elder et al. 2005). These dimensions were consistent with the relative volume of the Medtronic 3387 DBS lead in the human GPi. Briefly, the human GPi (478 mm³) (Yelnik 2002) is about 9.6-fold larger than the atlas-based reconstruction of the Cynomolgus monkey GPi used in this study (50 mm³). The volume ratio consumed by one of the cylindrical DBS electrodes was a comparable 8.6 (1.90 mm³ in the human and 0.22 mm³ in the monkey), although it should be noted that the proportional surface area for the scaled DBS electrode was slightly higher than that of a Medtronic 3387 DBS electrode (6.0 mm² in the human and 2.4 mm² in the monkey). Model neurons with segments that overlapped with any part of the DBS lead were removed from the analysis. This modeling criterion resulted in a remaining population of 63 GPi and 83 GPe neurons.

An axisymmetric finite-element model (FEM) of neural tissue was constructed around the DBS lead using COMSOL Multiphysics v3.3 (COMSOL, Burlington, MA). The FEM consisted of a mesh of tetrahedral elements within a 30 × 30-mm surface with the outside boundary set to a ground potential. Electrical properties of neural tissue were defined as homogeneous and isotropic (0.3 S/m) (Miocinovic et al. 2006), except for a 0.25-mm-thick section of encapsulation tissue at the electrode surface (0.1 S/m) (Grill and Mortimer 1994; Haberler et al. 2000; Moss et al. 2004). The stimulated metal contact boundaries were given a voltage and the potential distribution generated in the tissue was calculated using a frontal solution method of the Laplace equation (Fig. 1E). The model assumed ideal electrode behavior (i.e., no voltage drop at the electrode–tissue interface) and that the electric fields scaled linearly through the bulk tissue with increasing stimulation amplitude. Electrode impedances were calculated to be 3.4 kΩ (Butson et al. 2006).

The stimulus pulse train was based on experimentally recorded waveforms generated by a voltage-controlled implantable pulse generator (IPG; Medtronic, Minneapolis, MN). The stimulus waveform from the IPG had a pseudomonophasic profile consisting of a 90-μs cathodic phase followed by a 3-ms anodic phase separated by a 400-μs interphase delay. The waveform was then filtered according to a Fourier FEM simulation to incorporate the capacitive properties of the electrode–tissue interface (Butson and McIntyre 2005). The filtered waveform (Fig. 1E, top) was then applied to each neuron membrane compartment with peak cathodic amplitude defined by the FEM potential distribution during monopolar stimulation.

RESULTS

Characterization of membrane properties of GPi model neurons

The GPi neuron model faithfully replicated several electrophysiological features of EP neurons reported in brain function.
slices (Nakanishi et al. 1990, 1991; Shin and Carlen 2008; Shin et al. 2007) (Fig. 2). For these simulations, synaptic currents were excluded from the somatodendritic compartments and extracellular ion concentrations for Na\(^+\), K\(^+\), and Ca\(^{2+}\) were consistent with those described experimentally. Action potential height (model: 88.2 mV; in vitro: 94.6 mV) depended on the fast Na\(^+\) channel (NaF) conductance, whereas the fast K\(^+\) rectifying channel (Kv3.1) conductance had a large effect on action potential duration (0.73 ms, half-height width). The model also demonstrated a spontaneous firing rate of 18.0 Hz on average, which was similar to that observed for type I EP neurons in vitro (2–30 Hz) (Nakanishi et al. 1990). A sodium leakage current (NaL) has been implicated in the generation of spontaneous, rhythmic activity of SNr neurons (Atherton and Bevan 2005). Given the functional similarity of firing properties between SNr and EP neurons, somatic (g\(_{\text{NaL}} = 18 \mu S/cm^2\)) and dendritic (g\(_{\text{NaL}} = 0.1 \mu S/cm^2\)) compartments in the GPi neuron model were instantiated with this type of leakage current. Increasing the somatic NaL conductance resulted in a linear augmentation to the baseline firing rate (Fig. 2B). For somatic conductances <15 \mu S/cm\(^2\), however, model GPi neurons were no longer spontaneously active.

Neurons in the entopeduncular nucleus have been reported to exhibit unique responses to depolarizing and hyperpolarizing intracellular current injections. Robust depolarizing current pulses elicited high-frequency discharge rates (>200 Hz) in model neurons (Fig. 2C) with minimal spike adaptation (Fig. 2D). This generalized membrane feature was important to replicate since some neurons recorded in the GPs of our MPTP-treated monkeys fired at rates >100 Hz with intraburst rates exceeding 300 Hz. In addition to fast spikes, type I EP neurons when continuously hyperpolarized and on switching to a depolarizing potential also evoked slow spikes (Fig. 2E; compare with Fig. 2 in Nakanishi et al. 1990). In the model, the fast spikes were dependent on the NaF current, whereas the slow spikes required the presence of calcium currents and were more pronounced with the addition of tetraethylammonium (TEA; simulated as a 100-fold decrease in K\(^+\) channel conductance). Anomalous rectification, involving a decrease in the membrane potential shift following an intracellular hyperpolarizing current pulse, was incorporated into the model as a \(I_\text{h}\) current with hyperpolarization-activated cation (HCN) channels in both somatic and dendritic compartments (Fig. 2F) (Shin and Carlen 2008). Current–voltage plots demonstrated that the final HCN channel conductance used in the model generated an anomalous rectification, especially at more hyperpolarizing current levels, which closely followed experimental data (Fig. 2G). Input resistance was calculated as 101 M\(\Omega\) from the model’s current–voltage plot, which was similar to that reported in brain slices (112 ± 38 M\(\Omega\)) (Nakanishi et al. 1990). Moderate rebound responses at the cessation of a hyperpolarizing intracellular pulse were observed by Nakanishi et al. (1990); however, no detectable levels of transcripts of the low-threshold Ca\(^{2+}\) T-type channel family were reported with in situ hybridization (Talley et al. 1999) and, consequently, T-type calcium channels were not included in the model.

**Characterization of synaptic properties of GPi model neurons**

Raster scans of single-unit activity recorded in MPTP-treated monkeys were incorporated into the GPi neuron models as input signals for tuning synaptic conductance values of GABA\(_{\Lambda}\) and AMPA receptors. Extracellular spike recordings were performed in the sensorimotor regions of putamen (n = 35, 12.9 ± 7.5 Hz), GPe (n = 46, 49.9 ± 21.8 Hz), and STN (n = 13, 55.3 ± 13.0 Hz) while the monkeys were awake, but quietly resting. Representative raster scans with firing rates near population mean levels from each nucleus drove the pulsatile activity of dendritic GABA\(_{\Lambda}\) (putamen), somatic GABA\(_{\Lambda}\) (GPe), and somatodendritic AMPA (STN) synapses (Fig. 3A). Increasing the AMPA conductance alone was not sufficient to generate baseline firing rates consistent with those recorded in the parkinsonian GPi in vivo (n = 38, 77.7 ± 38.0 Hz). Although changing NaF, KDRf, or KDRs channel conductance could increase the GPi neuron model’s discharge rate, key properties of the action potential would no longer be consistent with in vitro experimental recordings. To compensate for the difference in baseline firing rates, we made the assumption that the sodium leakage current was higher in the in vivo state (i.e., g\(_{\text{NaL}}\) increased from 18 to 28 \mu S/cm\(^2\)). However, it should be noted that the work of Hanson et al. (2004) addressing similar issues in GPe neurons suggests that clustering of sodium channels at sites of excitatory synapses also facilitates increased pallidal firing.

Synaptic conductances were estimated by simulating the response of GPi neurons to 10 different combinations of recorded raster scans and evaluating the model output in terms of its ability to capture overall firing rate and burstiness (Fig. 3B). Bursts within the spike train were determined according to the Poisson surprise method (Hahn et al. 2008; Legendy and Salcman 1985) and evaluated in terms of the percentage of total spikes within bursts and the frequency of bursts. Although multiple combinations of AMPA and GABA\(_{\Lambda}\) synaptic conductances could generate firing rates comparable to those observed in our in vivo recordings in GPs (Fig. 3C), the set of parameter values was constrained when also accounting for burstiness (Fig. 3, D and E). Strengthening the conductances of both types of synapses increased both spike train burst measures, which underlined the intrinsic burst activity present in the input raster scans. Independently increasing the AMPA conductance resulted in prolonged bursts with greater than five spikes per burst, whereas increasing GABA\(_{\Lambda}\) conductance produced longer hyperpolarized pauses between bursts. The final AMPA and GABA\(_{\Lambda}\) conductances for each synapse used in the model were 0.005 and 0.0015 \mu S, respectively. The mean firing rate of the model neurons was 83.1 ± 10.9 Hz (n = 10), which was not significantly different from the firing rates recorded in vivo (P > 0.05, ANOVA) or from those observed in other studies (Boruda et al. 2002; Wichmann and Soares 2006). As shown in Fig. 3, D and E, the percentage of spikes in bursts and frequency of bursts calculated from the GPi neuron model population’s spike trains (36.2 ± 14.7% and 285.8 ± 128.2 Hz, respectively) were within the 95% confidence intervals of the same measures calculated for the in vivo GPi spike trains (33.8 ± 13.9% and 280.0 ± 146.5 Hz, respectively).
Somatic firing patterns during GPi-HFS depend on membrane properties

Initially, we used a GPi neuron model lacking synaptic inputs to investigate the intrinsic response of GPi cells to high-frequency extracellular stimulation (Fig. 4A). For suprathreshold stimulus pulses, model neurons exhibited a high probability of firing an action potential in their soma before the next stimulus pulse (i.e., within the 7.4-ms interpulse window) as shown for a representative GPi cell (Fig. 4B). The overall somatic firing rate of the GPi population, which lacked synaptic input, was only slightly above the baseline rate during stimulation (from 62 to 78.7 ± 14.4 Hz, \( n = 63 \)). Notably, however, the firing pattern during stimulation developed a nonuniform distribution during the interstimulus period with an excitatory crest between 1 and 3 ms (Fig. 4C). On increasing the stimulation intensity to −5 V, the initial excitatory phase became more pronounced at a latency of 1.5 ms and another excitatory phase developed between 4 and 5.5 ms (Fig. 4D).

Both of these time-locked responses depended on the conductance of specific ion channels (Fig. 4, E–L). The sodium leakage channel conductance (\( g_{\text{NaL}} \)) played an important role in the somatic firing rate during the stimulus train. Decreasing \( g_{\text{NaL}} \) reduced the probability of a spike occurring between stimulus pulses and, with very low \( g_{\text{NaL}} \) levels, HFS would no longer elicit somatic spikes. The excitatory phases of the peristimulus time histogram (PSTH) were dominated by the interplay between the fast \( \text{Na}^+ \) and the \( \text{Kv}3.1/\text{Kv}2.1 \) delayed rectifier \( \text{K}^+ \) currents (Fig. 4, E–L). Decreasing \( g_{\text{NaL}} \) by 33% resulted in a sharpening of the initial excitatory phase as well as the emergence of an inhibitory phase from 3.5 to 7.4 ms. Increasing either \( g_{\text{KDRf}} \) or \( g_{\text{KDRs}} \) generated similar augmentations to the initial excitatory phase. The second excitatory phase became more pronounced when reducing either \( g_{\text{KDRf}} \) or \( g_{\text{SK}} \).

Changing other ion channel currents smoothed the excitatory phases for some cells in the population, but it did not disrupt the overall ability of the neuron to become entrained to the stimulus. Whereas the average PSTH across the population exhibited a time-locked response, only neurons sufficiently close to the electrode responded with this type of behavior. For the stimulation configuration shown in Fig. 4C (−2 V), somatic entrainment was observed for the majority of somata within 700 μm of the electrode. When the stimulus amplitude was increased to −5 V (Fig. 4D), nearly all GPi neurons in our model population exhibited some degree of somatic entrainment.

Overall somatic firing rate during GPi-HFS depends on input from synaptic afferents

Integrating stimulation-evoked synaptic afferents into the GPi neuron model resulted in an overall reduction in somatic activity, but axonal output continued to be entrained to each electrical pulse of the stimulus train (Fig. 5A). A single stimulation pulse could transiently hyperpolarize the cell membrane with latencies dependent on the scaling of the synaptic conductances. The representative cell’s response (Fig. 5B) had a delay of 17.5 ms following a single stimulation pulse with a peak cathodic amplitude of −2 V and with synaptic weights set according to those trained by the in vivo afferent raster scans. Decreasing both AMPA and GABA_\(_A\) receptor conductances by 50% resulted in a decrease in the delay to 11.6 ms. On the other hand, increasing the conductances of both receptor types by factors of 2 and 4 augmented the delay to 22.4 and 27.0 ms.
respectively. In other words, increasing the overall extent of synaptic afferent input into the GPi model neurons increased the duration of the hyperpolarized response. For pulse trains using the same stimulus amplitude as in Fig. 5B, somatic spikes occurred during HFS, but did not appear after every stimulus pulse (Fig. 5C). For simulations with stronger afferent input, somatic activity during HFS was completely suppressed.

Population responses to HFS demonstrated variability in somatic firing patterns. Similar to the models lacking afferent synaptic input, these more detailed models exhibited interpulse somatic responses with peaks centered at 1 and 4–5 ms (Fig. 6A). The addition of synaptic afferents into the model significantly reduced the population’s mean somatic firing rate for both −2-V stimulation (25.0 ± 17.2 Hz, −70%, ANOVA, P < 0.001) and −5-V stimulation (45.3 ± 24.4 Hz, −45%, ANOVA, P < 0.001). Four different somatic responses to HFS were observed across the population: complete inhibition, inhibition with a sharply locked response (width <1 ms), inhibition with a broadly locked response (width >1 ms), and inhibition without locking (Fig. 6B). The population responded in approximately equal proportions within these classifications for monopolar stimulation (−2 V) through contact 1. At higher stimulus voltages, a greater number of model neurons exhibited inhibition with a broad, time-locked response (49 vs. 25%).

In terms of GPi output during HFS, the averaged PSTH showed a prominent peak at 1 ms and an attenuated secondary response from 5 to 6 ms (Fig. 6C). In most cases, the latter response derived from early somatic discharge within the interstimulus period, which in turn augmented the output firing rate (172.2 ± 42.7 Hz) beyond the stimulation frequency (136 Hz) for those axons with stimulus-driven activity. For the −2 V stimulation configuration, the overall GPi population output rate was 108.2 ± 79.0 Hz, which was not significantly different from the model’s baseline rate (ANOVA, P = 0.32). However, on increasing the stimulation amplitude to −5 V, the population’s output rate increased significantly above baseline (158.6 ± 62.1 Hz, P < 0.001). As shown in Fig. 6D, the percentage of GPi afferents entrained at or above the stimulation frequency similarly increased from −2 to −5 V (64–92%), which paralleled a decrease in the number of cells influenced by synaptic input from afferent collaterals, but located in a subthreshold potential distribution for direct axonal efferent excitation.

**Activation of GPe fibers of passage during GPi-HFS**

The GPi is by no means a homogeneous input–output structure; it contains numerous axonal fibers passing through from putamen, GPe, STN, as well as nigral and brain stem

![Computation Modeling of GPi-DBS](http://jn.physiology.org/)

**FIG. 4.** GPi-DBS models lacking afferent synaptic input exhibited somatic spikes time-locked to the electrical stimulation train. A: a population of 63 GPi model neurons was distributed within the posterior GPi such that their axons followed the lenticular fasciculus on exiting the pallidum. B: high-frequency stimulation induced somatic action potentials following most stimulus pulses. The example somatic response is from the GPi neuron is labeled in green in A and indicated by the arrow. C: a peristimulus time histogram of the population’s response to monopolar stimulation at contact 1 (shown in yellow in A) at 136 Hz, 90-μs pulse width, and −2 V peak cathodic amplitude showed an overall increase in firing rate between 1 and 3 ms. D: by increasing the peak cathodic stimulation amplitude to −5 V, the population’s response developed a sharper response at 1.5 ms and an additional excitatory peak at 5 ms. E–I: individually varying the membrane channel conductances of NaL, NaF, KDRf, KDRs, and SK by 33% affected the amplitude and relative ratio of excitatory peaks in the PSTH population responses. J–L: in contrast, changes in HCN, CaL, and CaN conductances resulted in little to no adaptations to the PSTH population responses. Bin widths on the PSTH plots were 0.05 ms and smoothed with a 5-point averaging window. CaL, L-type high-voltage–activated calcium current; CaN, N-type high-voltage–activated calcium current; HCN, hyperpolarization-activated cation; HFS, high-frequency stimulation; KDRf, fast deactivating potassium current; KDRs, slowly deactivating potassium current; NaF, fast-acting sodium current; NaL, sodium leakage current; PSTH, peristimulus time histogram; SK, calcium-activated potassium current.
fully recovering before the next stimulus pulse. Since the amplitude of the hyperpolarizing potential prevented the neuron from similar increases in synaptic conductances led to complete somatic inhibition of the in vivo GPi spike recordings. Using these parameter values in the context of the 3-D GPi-DBS model resulted in little to no somatic response. The total number of fibers showing activated output (H11022 80% and H11002 80%) at H11002 2 V stimulation intensities through contact 2 produced the largest percentage activation (34.9 and 68.7%, respectively) (Fig. 8A). On the other hand, the population responses of GPi efferents had a more spatially tuned profile at H11002 2 V, but a more uniform activation profile when increasing the stimulation amplitude to H11002 5 V (Fig. 8B). In the former case, stimulation through contact 1 at H11002 2 V produced the highest percentage activation (65.1%), whereas contact 3, which was located in part outside the GPi, elicited the smallest percentage activation (15.9%). Comparing these activation percentages to those simulated from the GPi neuron population (28.9 and 20.5%, respectively) showed markedly different activation ratios that depended on the precise location of the active contact within the pallidum (GPe;GPe of 2.25 for contact 1 and 0.78 for contact 2, respectively) (Fig. 8C). On increasing the stimulus amplitude to H11002 5 V, this spatially distinct profile of GPi to GPe activation ratios largely disappeared.

**DISCUSSION**

High-frequency stimulation of the GPi is a promising therapy for individuals with Parkinson’s disease (Volkmann 2004) and dystonia (Krauss et al. 2004). Despite its well-documented clinical successes, the therapeutic mechanisms and optimal targets remain a matter of debate (Bejjani et al. 1997; Wu et al. 2001). Our computational models of pallidal DBS provide new tools to investigate how membrane channel dynamics, synaptic inputs, and axonal collateralization contribute to neuronal responses during stimulation.

Generating parkinsonian-like activity in computational models of GPi neurons

The GPi neuron model reproduced many of the electrophysiological attributes of recordings in the rat entopeduncular nucleus, the homolog of primate GPi. Although the ion channel kinetics, conductances, and distributions are unlikely to be unique, the final parameter set did capture the signature features of EP type I neurons. These attributes included an inward regions (Charara and Parent 1994; Parent and Parent 2002). To investigate the hypothesis that GPi-HFS not only activates GPi efferents but also these fibers of passage, anatomical reconstructions of GPe fibers were simulated with axonal branches collateralizing en passant within GPi (Fig. 7A). The example GPe neuron reconstruction consisted of two primary branches that projected primarily along the parasagittal plane (Sato et al. 2000a). Clinically relevant DBS settings entrained GPe axonal activity to the stimulation frequency when membrane compartments exceeded threshold. These action potentials not only developed along the primary axon, but they also could be generated in the branches (Fig. 7B). The latter occurrence suggested that DBS could lead to substantial release of neurotransmitters as assumed in our previous analysis.

Several studies have suggested that collaterals within the pallidum are unmyelinated and of a smaller diameter than the primary fibers of passage (Fox et al. 1975; Galvan et al. 2005; Kita and Kitai 1987; Korotchenko 1979). We evaluated how collateral myelination affects the ability of electrical stimulation to influence the activity of GPe fibers of passage (Fig. 7C). The total number of fibers showing activated output (>80% entrainment to the stimulation) was similar for populations with myelinated and unmyelinated branches, which reflects the fact that most action potentials developed in the primary axon (66–84% of the population). The percentage of fibers in which the action potential first developed in one of the branches was reduced for unmyelinated collaterals at higher stimulus intensities. For fibers of passage with unmyelinated branches, the extent of activation depended on the diameter of those collaterals such that populations with larger-diameter collaterals showed higher activation ratios (Fig. 7D). Increasing the collateral diameter also augmented the percentage of activated fibers of passage that had action potentials first develop in their branches (Fig. 7E). This variability in the site of action potential initiation was found to generate a slight temporal delay (0–1.5 ms) for orthodromic and/or antidromic action potential innervation of the branch terminals (Fig. 7F). Thus depending on the spatial separation of the branches, the timing of stimulus-induced afferent input into GPi neurons may not be temporally uniform across GPi.

Whereas the previous analysis examined the responses of single GPe projection neurons during GPi-DBS using contact 1, we next asked how the population would respond if the electrode contact and stimulation voltage were varied. The likelihood of activating the output of GPe efferents was for the most part nonuniform across contact sites. For GPe fibers of passage with 0.8-µm-diameter unmyelinated collaterals, high-frequency stimulation at both −2 and −5 V intensities produced the largest percentage activation (34.9 and 68.7%, respectively) (Fig. 8A). On the other hand, the population responses of GPi efferents had a more spatially tuned profile at −2 V, but a more uniform activation profile when increasing the stimulation amplitude to −5 V (Fig. 8B). In the former case, stimulation through contact 1 at −2 V produced the highest percentage activation (65.1%), whereas contact 3, which was located in part outside the GPi, elicited the smallest percentage activation (15.9%). Comparing these activation percentages to those simulated from the GPi neuron population (28.9 and 20.5%, respectively) showed markedly different activation ratios that depended on the precise location of the active contact within the pallidum (GPe;GPe of 2.25 for contact 1 and 0.78 for contact 2, respectively) (Fig. 8C). On increasing the stimulus amplitude to −5 V, this spatially distinct profile of GPi to GPe activation ratios largely disappeared.
rectifying current, calcium spikes in the presence of TEA, and the capacity for following high-frequency intracellular current stimulation with minimal spike adaptation. Whether these characteristics translate to neurons in the primate GPi and whether the underlying membrane channel properties differ between normal and pathological states require further investigation. Such experiments, however, are technically challenging to perform in primates and especially in primates with neurological disorders. As such, computational models are useful to test how membrane channel properties might contribute to the pathological activity observed in the GPi of human and nonhuman primates.

Pathological activity observed in GPi neurons in parkinsonian or dystonic primates may indeed be a product of changes in expression level and distribution of certain membrane channels, but could also derive from alterations in synaptic input from afferent fibers, or a combination of the two. Our simulations suggest that certain ion channels may facilitate higher firing rates (NaL, NaF, KV3.1, KV3.2) and burstiness (HCN, SKCa, Cal) in GPi neuronal activity. Whereas the NaL current was used to augment the baseline firing rate to match that observed in vivo, other mechanisms are possible, including an elevated leak reversal potential, a nonspecific cation conductance (Lee and Tepper 2007), or clustering of sodium channels at excitatory synapses (Hanson et al. 2004). By instantiating synaptic inputs (AMPA and GABA_B) with release probabilities derived from in vivo recordings in afferent nuclei, the models demonstrated that the increased burstiness observed in the parkinsonian state could be produced entirely from pathological network activity (i.e., abnormal putamen, GPe, and STN input). Other receptor types are known to exist within the logical network activity (i.e., abnormal putamen, GPe, and the parkinsonian state could be produced entirely from pathological network activity (i.e., abnormal putamen, GPe, and STN input). Other receptor types are known to exist within the logical network activity (i.e., abnormal putamen, GPe, and the parkinsonian state could be produced entirely from pathological network activity (i.e., abnormal putamen, GPe, and STN input).

Effects of intrinsic membrane properties on somatic activity during GPi-HFS

A consistent observation with electrophysiological recordings in GPi during GPi-HFS is the regularization of somatic activity (Bar-Gad et al. 2004; Boraud et al. 1996; Dostrovsky et al. 2000; Wu et al. 2001). Bar-Gad et al. (2004) showed that the majority of pallidal neurons in nonhuman primates (70%) were time-locked during high-frequency stimulation with latencies for the first and second excitatory phases ranging from 1.5 to 3.5 and from 5.5 to 7 ms, respectively, with inhibitory phases in between. Similar temporal locking, although not specifically analyzed, has also been observed in the raw recordings of human GPi cells during 300-Hz stimulation [2.0 –2.6 ms, Fig. 4B (Wu et al. 2001) and ~2.4–2.7 ms, Fig. 1B (Dostrovsky et al. 2000)]. These time-locked responses were also consistent with observations from MPTP-treated parkinsonian monkeys in which GPi-HFS was shown to decrease somatic bursting in GPi (Boraud et al. 1996). Our models reproduced time-locked somatic activity with two excitatory phases and inhibitory phases in between during GPi-HFS (Fig. 6). The first excitatory phase had an interpulse latency of 1 ms, which paralleled that found in vivo. The second excitatory time-locked response (4–5 ms) emerged at higher stimulation amplitudes and appeared slightly earlier than inhibition with stimulation applied through contact 1. Bin widths on the PSTH plots were 0.05 ms and smoothed with a 5-point averaging window.

![Diagram](http://jn.physiology.org/)

**FIG. 6.** Models that incorporated synaptic afferent responses during DBS exhibited time-locked behavior overall, but also showed inhibition and a substantial degree of response variability across the spatially distributed population. A: averaged somatic responses to GPi-DBS from a population of model GPi neurons under baseline conditions (n = 10) and during HFS (n = 63). Somatic responses to HFS exhibited a time-locked excitatory phase at 1 and 4–5 ms and an overall decrease in firing frequency across the remainder of the interpulse interval. B: the population, however, exhibited nuanced differences in the somatic response to HFS, which depended on the potential distribution around a particular neuron. C: despite the inhibitory and time-locked behavior within the soma, HFS drove efferent activity through the axons with a prominent excitatory peak at 1 ms and a secondary peak from 5 to 6 ms. D: population responses in the axons similarly depended on stimulation amplitude. These simulations were derived from the GPi neuron population shown in Fig. 4A with stimulation applied through contact 1. Bin widths on the PSTH plots were again 0.05 ms and smoothed with a 5-point averaging window.
than that observed experimentally (Bar-Gad et al. 2004), which may reflect deviations in certain membrane channel properties from the actual biophysical values. Our models showed that the time-locked responses of GPi neurons during HFS depended on the direct activation of Na\(^+\) channels and an interplay between Na\(^+\) channels and Kv3.1/Kv2.1 channels. Decreasing the sodium conductance or increasing the potassium conductance sharpened the initial time-locked PSTH response. In turn, varying the conductances of either the Kv3.1 or SK channels could augment the second excitatory phase within the PSTH.

Effects of afferent input on somatic activity during GPi-HFS

The models demonstrated that afferent stimulation of both AMPA and GABA\(_A\) receptors resulted in overall inhibition of GPi spike rates as predicted by (Wu et al. 2001). Our models showed a range of inhibitory periods following a stimulus pulse (12–27 ms) that depended on the intensity of synaptic input. These durations were comparable to the inhibitory periods observed following suprathreshold stimulation in humans (10–25 ms at 50% recovery) (Dostrovsky et al. 2000) and were consistent with a dependence on stimulation intensity. For example, Wu et al. (2001) found that GPi spike activity in humans resumed after 15 to 40 ms for stimulation using 50- to 100-μA levels, respectively. One explanation could be that more intense electrical stimulation induces a disproportionate increase in GABA release from striatal and pallidal afferents, which in turn augments the activation of extrasynaptic GABA\(_A\) and especially GABA\(_B\) receptors (Galvan et al. 2005).

However, the lower somatic firing rates observed experimentally during GPi-HFS do not necessarily indicate that inhibitory afferents from putamen or GPe or collaterals from other GPi neurons were excited more than those from STN. It is possible that the relatively higher proportion of GABAergic inputs fibers and their dense perisomal and dendritic baskets predispose GPi neurons toward inhibitory responses during HFS. For instance, Kita et al. (2005) observed that neuronal firing rates in GPi during STN stimulation were influenced more by the GPe–GPi pathway than the STN–GPi pathway. Studies have also indicated that GABA\(_A\) and GABA\(_B\) receptors are up-regulated in the GPi after unilateral dopaminergic denervation (Pan et al. 1985; Robertson et al. 1990). An up-regulation of GABA receptors in GPi may implicate a compensatory mechanism to decreased GABAergic transmission along the direct pathway and increased GABAergic signaling along the indirect pathway (Johnston and Duty 2003). Thus loss of dopaminergic signaling in Parkinson’s disease may further “prime” GPi somata for inhibitory responses to HFS. Whether these changes, and the models’ assumptions of constant distributions and conductances of AMPA and GABA\(_A\) synapses, persist with long-term stimulation of the GPi will require further investigation.

The entrained firing patterns during HFS remained even after including the synaptic mechanisms in the models. Models that incorporated AMPA and GABA\(_A\) receptors showed variability in firing pattern responses that depended on the potential distribution around the neuron. For instance, time-locked responses were present in 42 and 70% of the GPi population for stimulation amplitudes at −2 and −5 V, respectively. The latter of these values was comparable to that observed experimentally in nonhuman primates (70%) (Bar-Gad et al. 2004). This study also noted that a small fraction of cells demonstrated overall excitation during HFS. Our GPi-DBS models suggest that these responses could have resulted from a preferential activation of excitatory input (e.g., activation of STN afferents) or an altogether lack of afferent input, which in the nonsynaptic neuron models showed neuronal entrainment to the stimulation coupled with a slight increase in the overall firing probability.
We observed elevated GPi axonal entrainment with higher stimulation voltages, which in turn resulted in a decrease in the number of cells completely inhibited (25 to 8%). Dostrovsky et al. (2000) estimated that the currents used in their experiments would be subthreshold to activate somata or axons located >250–600 µm from the stimulating electrode. Nevertheless, they observed neuronal inhibition following HFS at recording distances >600 µm. They hypothesized that HFS could activate afferent fibers, which collateralized beyond the activation volume and thus influenced GPi activity, a phenomenon that our GPi-DBS models reproduced. In turn, GABA signaling may have important implications in the therapeutic mechanisms of DBS. Penn et al. (1998), for example, demonstrated that local injection of muscimol (a GABA<sub>A</sub> agonist) into the GPi of a patient with Parkinson's disease significantly reduced the parkinsonian motor signs.

Mechanistic implications of axonal collateralization within GPi

The models predicted that a substantial number of GPi axonal efferents were driven during HFS despite their complex and variable somatic activity. These results suggest that the pallidal receiving areas of thalamus and brain stem are inhibited during GPi-HFS. Experimental recordings in the pallidal-receiving areas of thalamus support this prediction, demonstrating reduced firing rates during GPi-HFS (Anderson et al. 2003; Montgomery 2006) with spikes time-locked to the stimulation pulse train (Pralong et al. 2003). An overall decrease in neuronal activity has also been reported in the PPN during GPi-HFS in a parkinsonian monkey (J Zhang, D Ghosh, and J Vitek, personal communication).

The GPi contains a rich set of fibers of passage, many of which form collaterals en passant (Parent and Parent 2002). The models predicted that a substantial number of GPe projection neurons were excited by direct stimulation of their primary axons and/or axon collaterals extending through GPi. Although not explicitly investigated, other fibers of passage through GPi (including efferents from the STN and putamen) may also be activated by GPi-HFS. Imaging studies support the concept of activating multiple pathways during GPi-HFS. For example, Davis et al. (1997) found a statistically significant increase in regional cerebral blood flow (rCBF) in the ipsilateral lentiform nuclei (LN, which includes the GPe and putamen) during therapeutic GPi-HFS. Similarly, Fukuda et al. (2001) observed an augmented positron emission tomographic (PET) response in the ipsilateral LN during GPi-HFS. Although orthodromic activation of STN afferents that project to pallidum could account for the larger rCBF response in GPe, the increased response in putamen is likely due to a different mechanism since STN only sparsely innervates the putamen (Parent and Parent 2002). Our models suggest that the PET results derived from antidromic activation of GPe and putamen fiber projections passing through or near the GPi and the subsequent synaptic activity induced within their collateral networks.

Activation profiles for GPe fibers of passage were nonuniform across the different electrode contacts at lower stimulation voltages. Consequently, for dorsal contacts stimulated at lower stimulation voltages, the models predicted that GPe axonal collaterals could be activated in equal or greater numbers than GPi axonal efferents. Activation of GPe fibers would be expected not only to inhibit GPi directly, but also to suppress STN, which would in turn weaken the excitatory effects of STN on both GPe and GPi. Clinical data has suggested that dorsal contacts in GPi-DBS implants were more effective than the ventral contacts at relieving bradykinesia, but ventral contacts improved levodopa-induced dyskinesias more successfully (Bejjani et al. 1997; Krack et al. 1998; Yelnik et al. 2000). According to these reports, the dorsal contacts were likely in GPe or along the medullary lamina separating GPe and GPi. Others have reported that intraoperative high-frequency stimulation through a lesioning probe putatively targeting the GPe improved bradykinesia and, at high stimulation amplitudes, produced dyskinesias (Vitek et al. 2004). Relieving certain motor symptoms may thus require balancing the activation of GPi and GPe efferents. Similar to the predicted effects of activating GPi efferents, entrainment of GPi output could also have far-reaching network effects. Its inhibitory effect on STN somatic activity could disrupt recurrent signaling of GPi, SNr, PPN, and GPe neurons not directly activated by the stimulation.

Other fibers of passage may also be activated during GPi-DBS. For example, the majority of STN axons project through GPi en route to the GPe (Sato et al. 2000b), striatofugal fibers course through GPi en route to the SNr (Parent et al. 1995), and bundles of dopaminergic fibers from the substantia nigra pars compacta, serotonergic fibers from the dorsal raphe nucleus,
using the Arrhenius equation (KDRf: Kv3.1), enable a rapid recovery of Na+ channel conductance and kinetic rates were adjusted to those present at 36°C using a Q10 value of 1.58, which led to a scaling value of 1.78 channel conductance and kinetic rates were adjusted to those present et al. (1988). Since data in these experiments were collected at 23°C, GPi somatodendritic sodium currents (NaF, NaL) benefit provided by DBS. for determining which neural elements underlie the therapeutic passage activation can be an important factor to incorporate these fibers of passage are beyond the scope of this study. GPi somatodendritic potassium delayed rectifier currents (KDRf and KDRs) are robustly expressed in GP and substantia nigra and appear to be present in EP as well (Vega-Saenz de Miera 2004). Kinetic rate equations were derived from Chan et al. (2007), with a Q10 of 4 and described as follows

\[ I_{KDRf} = g_{KDRf} f(v)(v - E_k) \] (8)

\[ f_s(v) = \frac{1}{1 + \exp[-(v + 16.2)/8.6]} \] (9)

Kv2.1 potassium channels, which are thought to produce the slowly deactivating potassium current (KDRs), are robustly expressed in GP and substantia nigra and appear to be present in EP as well (Vega-Saenz de Miera 2004). Kinetic rate equations were derived from Chan et al. (2007), with a Q10 of 4 and described as follows

\[ I_{KDRs} = g_{KDRs} f(v)s(v)(v - E_k) \] (10)

\[ r_s(v) = \frac{1}{1 + \exp[-(v + 22.0)/8.2]} \] (11)

\[ \tau_s(v) = \frac{5}{\exp[(v + 30)/14] + \exp[-(v + 30)/20]} + 5 \] (12)

\[ S_s(v) = \frac{0.74 \exp[(v + 25)/12] + 0.26}{1 + \exp[(v - 50)/20] + \exp[(50 - v)/20] + 800} \] (13)

\[ C_s(v) = \frac{0.81 \exp[-\log([Ca^{2+}]) + 0.46]}{1 + \exp[-\log([Ca^{2+}]) + 0.46]} \] (14)

GPi somatodendritic small conductance calcium-activated potassium current (SK)

Neurons in the entopeduncular nucleus (and in the SNr) express small conductance calcium-activated potassium channels (SK), which are thought to produce the slowly deactivating potassium current (KDRs), are robustly expressed in GP and substantia nigra and appear to be present in EP as well (Vega-Saenz de Miera 2004). Kinetic rate equations were derived from Chan et al. (2007), with a Q10 of 4 and described as follows

\[ I_{SK} = g_{SK} f(v)(v - E_k) \] (15)

HCN channels, which are thought to regulate the rate and uniformity of spontaneous activity, are expressed in entopeduncular nucleus neurons (Chan et al. 2004). Kinetics for these channels were modeled according to Huguenard and McCormick (1992). No Q10 adjustment was necessary since their experiments were performed at 36°C

\[ I_{HCN} = g_{HCN} f(v)(v - E_h) \] (16)
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\[ b_a(v) = \frac{1}{1 + \exp(v + 75)/5.5} \]

\[ \tau_d(v) = \frac{1}{\exp(-14.59 - 0.086v) + \exp(-1.87 + 0.0701v)} \]

(16)

**GPi somatodendritic high-voltage–activated calcium currents (CaN, CaL)**

High-voltage–activated (HVA) calcium channels with N- and L-type subunits are expressed in the EP (Cole et al. 2005; Ludvig et al. 1997). The kinetic rate equations for both currents were reproduced as described in Gillies and Willshaw (2006), with a Q10 of 1.95.

\[ I_{CaN} = g_{CaN}q(V)u(V)\kappa(V) \]

\[ I_{CaL} = g_{CaL}q(V)^2w(Ca^{2+})\kappa(V) \]

(17)

(18)

\[ q_a(V) = \frac{1}{1 + \exp(-(v + 16.4)/11.3)} \]

\[ \tau_a(v) = \frac{1.25}{\cosh[-0.031(v + 28.9)]} \]

(19)

\[ \tau_d(v) = 98 + \cosh[0.021(24.8 - v)] \]

(20)

\[ w_a(Ca^{2+}) = 0.53 + \frac{0.47}{1 + \exp([Ca^{2+}]_o - 0.7)/0.15} \]

\[ \tau_o([Ca^{2+}]_o) = 1.220 \]

(21)

\[ \kappa(v) = \frac{v}{[Ca^{2+}]_o \exp(-2vF/RT)} \]

\[ (1 - \exp(-2vF/RT)) \]

(22)

where \( F \) is Faraday’s constant, \( R \) is the gas constant, and \( T \) is the temperature in Kelvin. Intracellular calcium concentrations were modeled as a submembrane shell as reported by Gillies and Willshaw (2006), with buffering and diffusion mechanisms determined by

\[ [Ca^{2+}]_o = -I_{CaL} + I_{CaN}c \frac{[Ca^{2+}]_o - [Ca^{2+}]}{\tau_{Ca}} \]

where \( c \) is the conversion constant, \( \tau_{Ca} \) is the time constant (185.7 ms for these simulations), and \([Ca^{2+}]_o \) is the basal intracellular calcium concentration.

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