Membrane Channel Interactions Underlying Rat Subthalamic Projection Neuron Rhythmic and Bursting Activity

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INTRODUCTION

The subthalamic nucleus (STN) plays a pivotal role in the dynamics and function of the basal ganglia, a group of subcortical nuclei implicated in a variety of motor, association and limbic functions (Alexander et al. 1990). It is the only glutamatergic nucleus in the basal ganglia with projections to the substantia nigra reticulata, entopeduncular nucleus (rat analogue to the primate internal segment of the globus pallidus), and globus pallidus (Bevan et al. 1994; Kita and Kitai 1987; Kita et al. 1983a; Parent and Smith 1987; Smith et al. 1998). It receives a direct glutamatergic cortical input (Fujimoto and Clark 1991; Shink et al. 1996;). The STN also receives an input from the substantia nigra containing tyrosine hydroxylase-positive terminals (Hassani et al. 1997; Prensa et al. 2000).

STN projection neurons are considered to have an important role in both the manifestation of key symptoms of Parkinson’s disease (Albin et al. 1989; Crossman 2000) and in their treatment (Ashkan et al. 2004; Filho et al. 2001). Periodicity in local field potential recordings from the STN is observed to be dominated by two frequencies (6 and 20 Hz) in human Parkinson’s patients (Brown et al. 2001). On levodopa treatment, the low-frequency components are reduced. Activity in the primate STN is increased in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson’s disease (Bergman et al. 1994; Delong 1990). This co-occurs with an increase in the STN population of neurons exhibiting slow periodic bursting activity (4–8 Hz) (Bergman et al. 1994). In rat, increases in STN neuron activity are also observed in the 6-hydroxydopamine (6-OHDA) model of Parkinson’s disease (Hassani et al. 1996; Kreiss et al. 1997). A move from regular to bursting activity in the STN is also seen in this model (Ni et al. 2001).

Rat STN projection neurons have several distinguishing characteristics. In vitro STN cells fire in a slow rhythmic manner in the absence of external input yet do not exhibit a subthreshold oscillation in the absence of action potentials. A persistent sodium current is demonstrated to contribute to this regular rest firing pattern (Bevan and Wilson 1999; Do and Bean 2003). In early studies, depolarizing current applied to continuously hyperpolarized cells revealed both “slow action potentials” and “slow depolarizing potentials” (Nakanishi et al. 1987). Both are forms of a plateau potential, where the former consists of an all-or-none calcium dependent slow action potential lasting around 30 ms, the latter a depolarization long outlasting the duration of the depolarizing stimulus.

Physiological differences within the rat STN projection neuron population have been recently observed. Releasing a cell from hyperpolarization (induced either via current injection or GABAergic afferent stimulation) leads to a calcium-dependent rebound burst of spikes in a majority of cells (Bevan et al. 2002). This rebound can be either short (<100 ms) or long, often having a duration of many hundreds of milliseconds (Bevan et al. 2002). The duration of the short bursts can be extended with the application of apamin (an antagonist of calcium-activated potassium channels).

Sustained hyperpolarization of a subpopulation of rat STN cells can induce a slow rhythmic bursting (Beurrier et al. 1999). It is argued that constant hyperpolarization together with the application of apamin is required for the generation of slow rhythmic bursts (Hallworth et al. 2003; Wilson et al. 2000).
Similar low-frequency rhythmic bursting is also observed with the application of N-methyl-D-aspartate (NMDA) (Wilson et al. 2004; Zhu et al. 2004). Multiple bursting modes have been reported, from pure modes (consisting of long-lasting bursts of constant duration) to mixed modes (alternating short and long bursts) (Beurrer et al. 1999). The recorded frequencies of in vitro rhythmic bursting range from 0.1 to 0.5 Hz (Beurrer et al. 1999; Hallworth et al. 2003).

Many of the defining characteristics of the STN neuron are observed under hyperpolarized conditions. Bevan et al. (2002) demonstrate a subset of these characteristics by inducing inhibitory postsynaptic potentials (IPSP) acting on GABA receptors. As the STN has a large GABAergic input, it is possible that many of these characteristics have a functional role in the information processing of these neurons.

The aim of this paper is to present a new model of single rat STN neurons that enables us to look at the interactions of key channel types. The model reveals a consistent set of mechanisms underlying the wide range of behaviors exhibited by these neurons. We also use the model to explore how changes in channel density or distribution can lead to diversity in the observed behaviors among STN neurons. The model provides a number of testable predictions arising from the proposed mechanisms.

METH O D S

We construct a multi-compartmental model of the rat STN projection neuron with the following aims: 1) we wish the model to exhibit many of the well-known and characteristic features of STN neurons employing a reduced or minimized parameter set. In the outline of the model in the following text, we describe explicit assumptions that are made to reduce the model complexity. 2) For many neuron models of this type, there is an issue of how to deal with unknown parameter values. Although increasingly the STN is becoming of interest to many research labs, there is still a limited amount of data available. We would like to adopt a method to compensate for absent data that does not degrade our first aim by increasing model complexity through adding arbitrary free parameters. And 3) we make explicit the procedure used for choosing specific parameter values in the simulations.

Morphology

The dendritic fields of most rat STN projection neurons are flat and oval, their long axis lying parallel to the long axis of the nucleus (Afsharpour 1985). Dendrites can extend over 500 µm, and on average three to four primary dendrites extend from the soma. Therefore it is possible for a dendritic field to extend across 1,000 µm (Kita et al. 1983a). The morphology of the STN cell model is based on schematic trees described by Kita et al. (1983a) and Afsharpour (1985), consisting of a soma and three identical trees (Fig. 1). Distal dendrites are reported to have sparse numbers of spines, contributing their small surface area to the overall surface area (Afsharpour 1985). This is incorporated into the morphological model via a small surface area shunt. The STN cell morphology has an important role in the function of these neurons. Their enormity should allow for a wide collection of potentially diverse cortical and pallidal input (Nambu et al. 1996).

The effects on the electrical properties of the cell by possible volume under- or overestimation (for example, due to shrinkage in the preparations) are considered in the following text in the derivation of the passive properties. The morphology is split into smaller compartments where the length of each compartment ranges from 5 to 22% of the electrotonic length (the number of compartments consequently ranged from 440 to 95). Spatial simulation accuracy was varied to speed the parameter search procedure.

Passive properties

Examples of passive property measurements in rat STN projection neurons are given in Table 1. Extracting passive properties from electrophysiological data is a difficult task (Major et al. 1994; Thurbon et al. 1998). The procedure we follow here is similar to protocols previously reported (Thurbon et al. 1998) and is two pronged. We aim to find a passive model that both is consistent with the properties in Table 1 and exhibits the passive characteristics of transients commonly observed in in vitro intracellular experiments (e.g., Nakamishi et al. 1987). It is not possible within the given constraints to determine exact values of the key passive properties of STN cells. However, we can sufficiently represent the passive characteristics of these cells to provide a framework to explore the interaction of active properties.

To aid our selection of passive membrane properties we construct an initial model that excludes active channels. The membrane potential of a compartment j is described by

\[ \frac{dv_j}{dt} = \frac{v_{j-1} - v_j}{r_{j-1}} - \frac{v_j - v_{j+1}}{r_{j+1}} - I_{ion} - I_{shunt} \]  

where \( c_m \) is the membrane capacitance for compartment j (given by the specific membrane capacitance multiplied by surface area, \( C_m A_j \)), \( v_j \) is the membrane potential of compartment j, \( r_{j-1} \) and \( r_{j+1} \) are the axial resistances between compartments. Axial resistance is given by the specific cytoplasmic resistance \( R_c \), length and cross-sectional areas of the joining compartments. This, and Eq. 1, take different forms depending on the branching arrangement. \( I_j \) is the stimulus current applied to compartment j (usually 0 unless the compartment represents the soma). \( I_{ion} \) is the ionic currents flowing across the membrane of compartment j. In the passive model, this is a leak current only \( (I_{Leak}) \) given by the specific membrane resistance \( R_m \), membrane surface area \( A_j \) and the reversal potential of the passive channels \( (E_l) \)

\[ I_{Leak} = \frac{v_j - E_l}{R_c/A_j} \]  

An additional shunt is added to the soma compartment with the conductance of the shunt given by \( G_{shunt} \). The shunt represents a change of \( R_m \) at the soma generally influenced by the experimental setup and recording equipment.

We assume a specific membrane capacitance of \( C_m = 1 \mu F \ cm^{-2} \). It is likely that the membrane capacitance is slightly different from this value. However, as capacitance and morphology errors trade off with each other, we only explore the effects of one of these. Making this assumption, and assuming the morphology given in Fig. 1, we...
lished intracellular data. Assuming a particular morphology and for the comparison of the simulation of the experiments with the published on a per experiment basis (accounting for potential differences directly recorded values as in Table 1. Compared with a recorded possible combinations of passive model parameters that we could arrangements. As we have highlighted, there are inevitably other recording. The calculated shunt was small in the other experimental difference from the recorded

1983b; Nakanishi et al. 1987). Different values of

membrane properties. The selected parameter set should be considered simply as being consistent with observed STN passive membrane properties.

Active properties

Active membrane properties are added to the passive model by modifying the membrane ionic currents \( I_{\text{ion}} \) in Eq. 1. In the active model this is given by

\[
I_{\text{ion}} = I_{\text{Na}} + I_{\text{KCa}} + I_{\text{KCa}} + I_{\text{Ca}} + I_{\text{Cl}} + I_{\text{Ca}} + I_{\text{Na}} + I_{\text{Na}}
\]  

where the current components correspond to currents through specific channel types as listed in Table 3. Full equations and parameters for these currents are given in the APPENDIX.

Active membrane properties involve a significantly increased parameter uncertainty compared with the passive properties in the preceding text. Not only must we identify what channels are likely to underlie the behaviors of the rat STN projection neuron, but we must also address the myriad of parameters describing individual channel kinetics. Taken together with nonuniform distributions of certain channel types over the dendritic tree and the limited data available from the rat subthalamus, this makes the process of modeling the active properties of these cells enormously underdetermined.

We could proceed by declaring the key parameters underlying each of the channels kinetic properties as free and allow ourselves the luxury of choosing parameters that yield the behaviors in which we are interested. This has the limitation that many combinations of parameter values may yield the same behaviors, providing little information about the key channel interactions and phenomena underlying these characteristics.

We take an alternative approach and exploit the fact that a significant number of active channel properties have been characterized in other areas of the rat brain (for example, thalamus and cortex). Assuming that channel properties vary little across brain areas, we use the kinetic parameter values of these channels in the subthalamic model. This assumption certainly may not be correct. For example, channel subunit constituency can vary across structures. However, if we fix the kinetic parameterization as experimentally recorded for particular channels (apart from \( Q_{10} \) temperature adjustments, see the APPENDIX), then we dramatically reduce the parameter space within which to explore characteristic STN behaviors. It may now be unrealistic to expect a perfect match to distinguishing STN neuron behaviors. However, if we capture the broad classes of observed STN behaviors in the model, we have a better chance of identifying the key active membrane components that underlie these behaviors.

Table 3 lists the nine channel types included in the model. The choice of channels is based on studies revealing certain channel types or classes in the STN (Baufreton et al. 2003; Bevan and Wilson 1999; Do and Bean 2003; Song et al. 2000; Wigmore and Lacey 2000; Zhu et al. 2004). In a similar manner to passive properties, our goal is not to provide a complete and definitive definition of STN active membrane properties but rather to provide a realistic set of channels within a modeling framework to reveal how key STN behaviors can arise from their interaction. Although the kinetic descriptions and properties of each channel are taken from the associated descriptions (see Table 3), we must align the descriptions to compensate for the differences in experimental recording temperature. We do this by using a combination of restricted voltage shifts of activation/inactivation curves and rate scale factors (reflecting \( Q_{10} \) modifications).

The locations and densities of active channels across the membrane can play an important role in the behaviors exhibited by the cell. However, apart from evidence that the low–voltage-activated calcium channel (CaT) is not located proximally on the STN projection neuron (Song et al. 2000), there is very little data on the distributions of the

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### Table 1. Examples of recorded passive properties

<table>
<thead>
<tr>
<th>n</th>
<th>In Vitro</th>
<th>Source</th>
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<tbody>
<tr>
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<tr>
<td>n</td>
<td>In Vitro</td>
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</tr>
<tr>
<td>7</td>
<td>Rat</td>
<td>Kita et al. (1983b)</td>
</tr>
<tr>
<td>26</td>
<td>Rat</td>
<td>Nakanishi et al. (1987)</td>
</tr>
<tr>
<td>88</td>
<td>Rat</td>
<td>Beurrier et al. (1999)</td>
</tr>
<tr>
<td>8</td>
<td>Rat</td>
<td>Do and Bean (2003)</td>
</tr>
<tr>
<td>7</td>
<td>Rat</td>
<td>Kita et al. (1983b)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ranges are in parentheses.

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### Table 2. Final calculated passive properties

<table>
<thead>
<tr>
<th>Passive Property</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Membrane time constant</td>
<td>12.8 ms</td>
</tr>
<tr>
<td>Capacitance</td>
<td>1.0 ( \mu F ) ( \text{cm}^{-2} )</td>
</tr>
<tr>
<td>Membrane resistance</td>
<td>12.753 ( \Omega ) ( \text{cm}^{-2} )</td>
</tr>
<tr>
<td>Input resistance</td>
<td>146.5 M( \Omega )</td>
</tr>
<tr>
<td>Cytoplasmic resistance</td>
<td>150.2 ( \Omega ) ( \text{cm} )</td>
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*Calculated using soma shunt estimated from the Nakanishi et al. (1987) data.
channels listed in Table 3. Consequently, we choose channel distributions that best fit observed STN behaviors (see the minimization method in the following text). Where the distribution is found to be critical to specific behaviors in the model, we are making a prediction of the expected arrangements of channels in the STN neuron. Where there is evidence for channel localization (such as a nonproximal CaT distribution), it is added as a constraint to the model.

We can reduce the number of parameters specifying the distribution by assuming linear distributions over the dendritic tree. This means that we can only capture linear proximal, distal, and uniform distributions rather than modeling possible nonuniformities. This assumption allows the dependence of observed physiological behaviors on channel co-localization to be exposed. An important side effect of the linearization is that it biases against central concentrations (biasing toward either distal or proximal distributions). With this assumption, the distribution and density of an individual channel may then be modeled using only four parameters: the channel density at the soma; the overall channel density across all the dendritic trees; the amount of density that is uniform across the trees; a single parameter specifying the linear distribution of the remaining density over the trees (ranging between 1, maximally proximal and –1, maximally distal; Fig. 2). In the case of the CaT channel, the parameters governing the distribution are permitted to vary within the nonproximal constraints (i.e., distributions ranging from near uniform excluding the soma to extremely distal are possible). The use of a multi-compartmental model over a single compartment allowed this constraint to be considered.

The final model has 46 free parameters and coefficients for a multi-compartmental model. In the following section, we describe the search procedure used in selecting values for these parameters.

Parameter selection

We begin by selecting a set of characteristic STN properties and use specific experimentally recorded instances of these to compare with the model neuron. The model is simulated under equivalent conditions for each experiment [including artificial cerebral spinal fluid (ACSF) composition, temperature, current injection protocols, etc.] and corresponding measurements are compared with those recorded in the experimental arrangement. An error value is derived from this comparison and model parameters are then adjusted so as to reduce this error.

The STN properties used in the definition of the error space are listed here with example simulations of the final model shown in Fig. 3. 1) Action potential properties characterized and recorded by Beurrer et al. (1999). These comprised six properties delineating action potential and afterhyperpolarization (AHP) form (Fig. 3A). 2) In vitro resting firing patterns recorded by Bevan and Wilson (1999) and Bevan et al. (2002) consisting of frequency and coefficient of variation measurements at different temperatures (Fig. 3B). 3) Hyperpolarization response characterized by Bevan et al. (2002) focusing on the shape of the “sag” during the hyperpolarization and the presence of a rebound response. The form of the poststimulus response (short or long) is not included in the error space, rather the presence of an increased posthyperpolarization firing sequence is simply desired (Fig. 3D). 4) Passive properties used in the derivation of the passive parameters are also included in the error space (although passive parameters are not modified during the minimization of active properties) (Fig. 3E). Finally (5) after the initial parameter search, an additional component is added to the definition of the error space characterizing the repetitive burst firing during a hyperpolarizing stimulus and simulated apamin protocol. This is compared with observations of Hallworth et al. (2003) and Beurrier et al. (1999).

In total there are a maximum of 30 error components. Each is a squared error difference of a specific measured characteristic in simulation and in experiment. For example, the squared difference of action potential half-width from recorded half-width is a single component.

These properties were chosen to be characteristic of rat STN projection neuron behavior, while omitting some of the distinguishing STN features, such as the “slow action potential” reported by Nakanishi et al. (1987) or the short and long posthyperpolarizing response classifications of Bevan et al. (2002). This allows us to assess the final model through its ability to replicate these features that were not used in the construction of the error space.

The selection of parameter values that minimize the model’s error proceeds using a form of the simulated annealing method (Press et al.
Each parameter is given an upper and lower bound. The starting point of the parameter search is the selection of random parameters within these set bounds. From the initial large parameter set of \( \leq 46 \) parameters, a random subset of 7 parameters is selected and the model error is minimized with respect to this subset. This is repeated many times with different randomly selected subsets all minimized from the same initial set of parameters. The subset of parameters that produces the lowest error is then used to modify the parameter values to produce a new initial set. This process is then repeated until minimization of all subsets no longer reduces the error.

Minimizing over small subsets of parameters has a twofold advantage. First, it allows convergence of the simulated annealing procedure within a reasonable time frame. Second, where coordinated parameter changes are required for effective error minimization, searching over multiple random subsets encourages these to be quickly found. It is difficult to assess the final parameters attained by the minimization procedure as there is little data with which to compare (particularly in the dendrites). Maximum conductance values are within general biologically realistic regions as a consequence of the upper and lower bounds placed on them in the search procedure. However, we could compare peak isolated currents in the model with equivalently recorded currents. For example, in the final model, the maximum proximal calcium current density is \(-85\ \mu A\ cm^{-2}\) using a voltage-clamp setup (calculated from the soma and dendritic trunks within 50 \( \mu m \)). This yields a peak current of \(-1.6\ nA\), which is smaller yet comparable to recordings of peak calcium currents in dissociated STN neurons using a similar protocol (approximately \(-2.4\ nA\)) (Song et al. 2000). However, this can only be considered as an illustration of the parameters being generally biologically plausible. Making such comparisons is difficult due to the limited availability and nature of the data.

All simulations were performed using the NEURON simulator (Hines and Carnevale 1997) with the CVODE numerical integration system.

**RESULTS**

The model reproduces the primary features of STN physiology that were used in the construction of the error space (Fig. 3, with final parameters given in the APPENDIX). With the same parameters, it also exhibits a number of key STN properties not included in the error set. These include the slow depolarizing (plateau) potential and the slow action potential (see Nakanishi et al. 1987). Using an error set that contains no rhythmic bursting properties, the model demonstrates robust rhythmic bursting in the presence of a hyperpolarizing current and simulated apamin. Apamin is simulated with a uniform 90% reduction over the neuron morphology of the sKCa conductance. When bursting properties are added to the error set, the final model is found to exhibit two bursting modes: a low-frequency mode with frequencies \(< 1\ Hz\) and a high-frequency mode with frequencies between 4 and 7 Hz. The model also reproduces the short and long posthyperpolarizing rebound responses observed in vitro (Bevan et al. 2002; Hallworth et al. 2003). We now characterize these and other key behaviors of the model and highlight the active channel interactions that underlie these behaviors.

**Action potential and spontaneous rest activity—key channels Na, KDR, NaP, Kv31**

Spontaneous resting activity exhibited in the model (5–15 Hz) is critically dependent on the persistent sodium channel (NaP). The persistent sodium current is a major component of the slow ramp depolarization preceding an action potential. This is consistent with the findings in rat subthalamic projection neurons in vitro (Bevan and Wilson 1999; Do and Bean 2003).

The characteristic action potential exhibited by the model (Fig. 3A) captures key features of the STN action potential. However, the half height width in the model is overly large [0.98 ms compared with 0.65 \( \pm \) 0.03 as recorded by Beurrier et al. (1999)]. This has the consequence of slowing the model down when firing fast. The Kv31 channel plays an important role in reducing the width of the action potential (Fig. 3A, dotted line), yet the width is not reduced sufficiently.

**Short and long posthyperpolarization response—key channels: CaT, CaL, sKCa**

As mentioned in the INTRODUCTION, some rat STN neurons exhibit a short posthyperpolarizing rebound response, whereas
others exhibit a long rebound burst (Hallworth et al. 2003). We can use the model to explore this diversity.

During the parameter search procedure, the reproduction of a rebound response was required to reduce the model error yet the extent of the response was not used as a constraint. The model produced a significant rebound that may be characterized as a long response (>100 ms, see Fig. 3D).

**SHORT REBOUND RESPONSES.** Three channel specific currents play a determining role in this rebound behavior: the Ca$_{\text{a1.2}}$–1.3 slow-voltage-activated calcium current (CaT), the Ca$_{\text{a3.2}}$ high-voltage-activated calcium current (CaL), and the small calcium-activated potassium current (sKCa). It is the balance of the channels’ spatial distributions and conductance levels that determines the nature of the rebound. For example, a reduction (20%) in the CaL-type channel conductance produces a short rebound response (Fig. 4, A and B). The primary current underlying this short rebound is mediated by the CaT channel (Fig. 5A). The shape and time course of the short response is defined by the time course of the CaT current. As the CaT channel is activated from hyperpolarized potentials and inactivates at depolarized potentials, this yields a short posthyperpolarization rebound current.

**LONG REBOUND RESPONSES.** It is possible to convert a short rebound burst (e.g., Fig. 4A) into a long burst by a reduction in sKCa channel conductance (Fig. 4, C and D) or by an increase in the CaL channel conductance (Fig. 4, D and B). In all cases, the CaT current is necessary for the generation of a rebound response (Fig. 5B, ■); this is consistent with the calcium-dependent nature of the burst. The generation of long bursts under reduced sKCa conductance conditions is comparable with the observation that apamin can extend burst duration in neurons that exhibit short bursts (Hallworth et al. 2003). In the model, there is an associated increase in resting firing rate with the simulated apamin condition. This is uncharacteristic of STN neurons where, in the presence of apamin, an increase in coefficient of variation is often observed.

The dendritic CaL current primarily underlies long bursts (Fig. 5B). At the soma, a transient L-type current occurs during the action potential (Fig. 5B, blue - - -). In the dendrites there is sufficient calcium entry at the initiation of the burst (via the combined CaT and CaL currents) to generate a depolarization that facilitates prolonged CaL channel activation and an associated depolarizing current. This leads to a positive feedback where, on average, CaL channels remain activated for long periods. The prolonged dendritic depolarization sustains the long rebound burst (Fig. 5B, blue - - -).

The spatial location of these channels over the model neuron is shown in Fig. 5C. Each channel has a linearly increasing density with distal location. This spatial relationship also plays a role in the nature of the rebound response. Potassium currents mediated via the sKCa channels limit the rebound burst duration by repolarizing the dendrites when internal calcium levels are elevated. This is particularly potent in distal locations where the CaL feedback system underlying extended dendritic depolarizations can significantly increase intracellular calcium levels near the membrane (intracellular calcium concentration and buffering is modeled within a volume immediately below the membrane, see the APPENDIX). Artificially lowering the sKCa conductance levels leads to a reduced potassium current and longer rebound bursts (Fig. 4B, ●). When the distribution of sKCa channel conductance is shifted to a less distal location, the repolarizing effect of the potassium current is again reduced. Although the total level of sKCa channel conductance is constant, there is less conductance concentrated in the distal areas where higher levels of intracellular calcium accumulate. The sKCa and CaL distributions move out of balance and, in this case, the rebound response becomes longer (Fig. 4B, ■).

The occurrence of a CaL-mediated dendritic depolarization underlying the long rebound burst is an all-or-none event. The

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feedback nature of the system generates robust initiation and termination of the dendritic CaL current (Fig. 5B). A trigger depolarization is required for the initiation of the response (mediated here by the CaT current). The termination of the sustained depolarization occurs when it drops below a critical level necessary for CaL activation (consequently breaking the feedback). As we have seen, different factors can influence when this occurs (such as the level or location of the sKCa potassium current).

Mechanisms of slow rhythmic bursting—key channels: CaT, CaL, sKCa

In the presence of a uniform reduction in the sKCa conductance (simulating the application of apamin) and constant hyperpolarizing current injection, the model generates slow rhythmic bursting (Fig. 6B). Two primary modes of rhythmic bursting are exhibited: a high-frequency mode (e.g., Fig. 6A) where the frequency lies between 4 and 7 Hz and a low-frequency mode (e.g., Fig. 6B) yielding a bursting frequency <1 Hz. A difference in the form of a single burst is also observed between the two modes. In the high-frequency mode, bursts are elevated above the inter-burst potential, whereas in the low-frequency mode, there is no elevation (Fig. 6, A and B).

The interaction of the CaT and CaL conductances determines the presence and nature of the rhythmic bursting. The sKCa conductance is less involved as it is significantly reduced due to the effects of simulated apamin. Similarly to the posthyperpolarization rebounds (Short and long posthyperpolarization response), the presence of a sufficient CaT conductance is necessary for the generation of individual bursts. Uniformly reducing the CaT conductance can eliminate rhythmic bursting. Increases in this conductance can lead to a jump from the low frequency to the high-frequency mode. This is illustrated in Fig. 6C, where bursting is prevented by decreasing CaT levels by 12% and a jump from low- to high-frequency modes occurs with a 16–20% increase. The role of the CaL current is similar to that in the short/long rebound burst behavior. In the low-frequency mode, increasing the CaL conductance increases the burst duration (Fig. 6D, —). There is also a decrease in the inter-burst interval (Fig. 6D, - - -) that leads to an overall increase in bursting frequency as the conductance density is increased.

FIG. 6. Rhythmic bursting. A: high-frequency rhythmic bursting. The model with a 12% reduction in dendritic linear CaL conductance and a hyperpolarizing current injection of −0.35 nA. In this example, burst frequency is 4.8 Hz. In all rhythmic bursting, the same simulated apamin conditions are maintained (90% reduction in sKCa conductances). B: low-frequency bursting exhibited by the model with a hyperpolarizing current injection of −0.25 nA. In this example the frequency is 0.53 Hz. C: influence of changes (−30–30%) in the low-threshold calcium CaT conductance on the rhythmic bursting frequency (note, the frequency is plotted on a logarithmic scale). Constant hyperpolarizing current used −0.25 nA. D: influence of dendritic CaL conductance changes on the burst lengths (—) and inter burst lengths (− −) during low-frequency rhythmic bursting. In C and D, the greyed region for each line shows the coefficient of variation of the rhythmic bursting at each point (with a scale bar inset).
HIGH FREQUENCY MODE. The high-frequency bursting mode arises from a dominant CaT current. During the inter-burst hyperpolarization the CaT channels become available for activation. Activation of a small fraction creates a weak current that begins the depolarization leading to burst initiation (Fig. 7B, inset). In a similar manner to long posthyperpolarization rebounds, on sufficient depolarization the CaL channels become active and generate a depolarizing plateau in the dendrites sustaining the burst (Fig. 7B). Burst termination occurs once the CaL-mediated depolarization drops below a critical threshold for sustaining the CaL activation feedback (see Short and long posthyperpolarization response). The membrane becomes hyperpolarized again as a result of the constant current injection. This allows the CaT channels to become deinactivated, eventually becoming available for activation and the burst cycle repeats. In this mode, the bursting frequency is highly influenced by the dominant role of the CaT channel. Channel characteristics, such as the deinactivation time course (here based in the kinetic description of Wang et al. 1991), influence the resulting frequency (4–7 Hz).

LOW-FREQUENCY MODE. The CaT current plays a different role in the low-frequency bursting mode. It is still necessary for rhythmic bursting to occur. However, it does not initiate bursts as in the high-frequency mode. The CaL current is responsible for burst initiation while retaining its role in sustaining the burst (and mediating burst duration) via a depolarizing plateau. At the end of a burst, the membrane potential begins to hyperpolarize due to the constant current injection (Fig. 7C). There remains a small but influential CaL current in the dendrites (Fig. 7D, inset) as the hyperpolarizing current injection is not large enough to completely reverse the dendritic depolarizing plateau. Together with a small CaT current (resulting from the fraction of CaT channels that deinactivate during the postburst hyperpolarization), this leads to a further depolarization of the distal dendritic membrane. This is not sufficient to initiate another burst. Instead, a very gradual increase in the CaL current occurs leading to a slowly increasing dendritic depolarization (Fig. 7D, inset). This continues until the majority of CaL currents activate and lead to the initiation of another burst.

MIXED MODE. From the low-frequency mode, it is possible to jump to a high-frequency mode by increasing the amount of CaT current via an overall increase in CaT conductance (as shown in Fig. 6C). It should also be possible to increase the post-burst CaT current by further hyperpolarizing the inter-burst potential. This would lead to a larger pool of deinactivated CaT channels after a burst and consequently a larger CaT rebound current. Increasing the constant hyperpolarizing current injection is one method of increasing the inter-burst hyperpolarization and thus indirectly increasing the CaT current. This can indeed lead to mode changes in the rhythmic bursting (Fig. 8A). For reduced CaL conductance levels, no rhythmic bursting is generated with medium current injections (−0.25 to −0.30 nA). For larger hyperpolarizing currents (e.g., −0.35 nA), a high-frequency bursting mode emerges. Default and larger values of CaL conductance generate robust low-frequency rhythmic bursting from medium current injection levels (Fig. 8A, ● and ▲). The frequency of bursting slows as the current injection is lowered (compare frequencies of −0.25 and −0.3 nA in Fig. 8A). This results from slowing the gradual increase in CaL-mediated depolarization (see Fig. 7D, inset). As the stimulus hyperpolarizes the membrane further, the model cell can jump between high- and low-frequency modes (Fig. 8B). The lowered bursting frequency (<4 Hz) for −0.35 nA current injection in Fig. 8A is an artifact of mixed modes of bursting. This is reflected in much larger coefficient of variation of burst frequency.

Channel types other than the CaT, CaL, or sKCa have less influence on the nature of rhythmic bursting or on posthyperpolarizing rebound responses. Large variations in the distributions and densities of other major channels introduce only relatively small changes in key rhythmic and rebound proper-

![FIG. 7. Mechanisms underlying the high- and low-frequency rhythmic bursting. A: 2 bursts in a high-frequency rhythmic bursting pattern generated as in Fig. 6A. B: currents underlying the high-frequency rhythmic bursting shown in A. Distal dendritic CaL currents are shown in blue and CaT currents in red. The dendritic location is the same as used in Fig. 5. Soma currents of each are shown with dotted lines using the same color code. Inset: currents rescaled at a single burst (the inset time bar is 50 ms). The shaded background highlights events during the burst. C: low-frequency rhythmic bursting. A current injection of −0.25 nA and simulated apamin are used in this example. D: currents underlying the low-frequency rhythmic bursting. Colors and line types as in B. Inset: currents rescaled during a burst (the time bar is 250 ms) with shaded background as in B.](http://jn.physiology.org/content/jn/75/5/2359/F7)

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ties (Fig. 9, A and B). Other model parameters, such as the time constant of the intracellular calcium-buffering model or the maximum calcium inactivation of the CaL channel also play limited roles in these properties (Fig. 9, A and B, ○ and ●).

**Slow action and depolarizing potentials—key channels: CaT, CaL, iSKCa**

Both the slow action potential (Fig. 10A) and the slow depolarizing potential (Fig. 10C, left) are caused by the same channel interactions underlying the short and long rebounds (Short and long posthyperpolarization response) and rhythmic bursting behaviors (Mechanisms of slow rhythmic bursting). The CaT current primarily underlies the slow action potential (Fig. 10B). CaT channels are made available for activation by the hyperpolarizing current injection and activated when there is a reduction in the current injection (see Nakanishi et al. 1987 for the protocol used in the generation of the slow action potential). The short time course of the potential follows the time course of inactivation of the CaT channel. A larger constant hyperpolarizing current injection and brief depolarizing stimulus is used for the slow depolarizing or plateau potential (Nakanishi et al. 1987). This generates a significantly larger CaT current, which is sufficient to trigger a CaL-mediated depolarizing plateau sustaining the longer depolarizing potential (Fig. 10D). Membrane hyperpolarization is important in the generation of these behaviors. Reducing the level of hyperpolarization eliminates the plateau (Fig. 10C, right). This reveals a hyperpolarization threshold for plateau generation that is consistent with in vitro observations (Otsuka et al. 2001).

**DISCUSSION**

Our model provides insight into the mechanisms underlying the physiology of rat subthalamic nerve cells. A large number of parameter values, such as morphology, passive properties, and some channel kinetic properties are obtained from measurements from the rat STN. Other channel kinetic parameter values are obtained from measurements from other brain regions. This produces a model with a restricted parameter set and generic channel behaviors. The remaining parameter values are selected using an error space defined over a range of rat STN recordings, from different laboratories and under different experimental conditions. Some of the channel interactions may reflect similar interactions underlying the dominant STN behaviors. The use of this type of model allows us to identify key channels and their cooperation in emergent behaviors to provide predictions of similar arrangements within STN projection neurons.

The parameter search procedure yields a model that captures a remarkable array of STN characteristics. The choice of parameters produces dendritic distributions of the high-voltage-activated Ca_{1.2–1.3} (L-type) channels and the small calcium-activated potassium channels. A dendritic distribution of the low-voltage-activated Ca_{3.2} (T-type) calcium channel is imposed on the model (following observations of Song et al. 2000). This spatial arrangement creates a dendrite-bound mechanism that plays a key role in the generation of a wide range of behaviors. In particular, it is responsible for the CaL-dependent depolarizing plateau. Long depolarizing plateaus are observed in STN neurons (Nakanishi et al. 1987; Otsuka et al. 2001). A sufficiently large and long trigger depolarization can initiate a CaL current that sustains the initial depolarization. This membrane depolarization in the dendrites in turn extends the activation of CaL channels by holding the voltage above their activation threshold, creating a positive feedback. As CaL channels are modeled with a slow calcium-mediated inactivation (Meuth et al. 2002), the resulting depolarizing plateau is able to sustain long bursts of action potentials at the soma. The model exhibits a similar mechanism...
underlying the plateau to that described by Otsuka et al. (2004). In our model, the primary mechanism is located in the dendrites as a consequence of imposing a dendritic constraint on the location of the CaT channels. In the model of Otsuka et al. (2004), a single compartment is used, enforcing co-localization of the key channel types (CaL, CaT, sKCa). We use a systematic parameter selection procedure within a multi-compartmental framework that creates a similar co-localization in the model presented. In addition, our model demonstrates the role that a depolarizing plateau may play in a wide range of characteristic STN behaviors, from rebound responses to rhythmic bursting.

**Interactions among the CaT, CaL, and sKCa channel types**

The balance in location and density between the three channel types CaL, CaT, and sKCa is critical in determining the presence and nature of this depolarizing plateau. For example, the variability in the observed nature of posthyperpolarization rebound bursts (short or long) in the rat STN could reflect differences in channel location and/or density. The CaT channel is required for the rebound burst to occur and provides the link between hyperpolarizing stimuli, which are necessary in many of the observed behaviors, and the range of emergent responses. The dendritic location of this channel type makes its influence on the dendrite-bound plateau particularly potent. In the model, it is extremely difficult to generate a plateau from localized depolarization alone (either in the soma or dendrites). However, under hyperpolarizing conditions, depolarization, or release from the hyperpolarization, can easily elicit a plateau. This is consistent with plateaus elicited by hyperpolarized conditions demonstrated by Otsuka et al. (2001). The dendritic and dispersed nature of the CaL-mediated mechanism makes plateau generation resistant to localized excitatory initiation.

The co-localization of these two channels facilitates robust plateau initiation under hyperpolarizing conditions. Sufficiently large CaT-mediated currents can provide a trigger depolarization to initiate a dendritic CaL-mediated plateau. If it is not sufficiently large, the CaT-mediated response may remain the dominant observation (as seen in the “slow action potential”). Increasing CaT or CaL channel densities, reducing sKCa density, and shifting the sKCa or CaL channel distributions can all facilitate the emergence of depolarizing plateaus. Large reductions in the density of CaT channels can abolish rebound responses completely. Together these three channels provide a sufficient (although not necessarily unique) parameter set to explain the diversity of rebound responses seen in the STN (Hallworth et al. 2003). Fig. 11 illustrates the key channel interactions.

The linear distribution of conductances that is assumed only allows a loose assessment of the coupling of different channel types. The linear simplification itself biases toward distal distributions. For the minimization procedure to generate peaks of channel concentration, it can only shift concentrations proximally or distally. The CaT constraint biases toward the distal shift. However, the parameter optimization procedure maintains a high level of coupling or co-localization of the sKCa, CaL, and CaT channels. For example, the co-localization of the sKCa and CaL channels is consistent with the observations that nifedipine (an L-type channel antagonist) has little effect on small rebound responses and significantly reduces long rebound responses (Hallworth et al. 2003). In the model, small rebound responses, nifedipine would be expected to seriously disrupt the CaL-mediated dendritic plateau by indirectly increasing the dominance of the co-localized sKCa channel and consequently reduce the response.
Rhythmic bursting

Rat STN neurons can rhythmically burst with very low frequency (Beurrier et al. 1999). This is observed in vitro under hyperpolarizing conditions and in the presence of apamin (Hallworth et al. 2003; Wilson et al. 2004). The model robustly exhibits slow rhythmic bursting in the presence of simulated apamin and hyperpolarizing current injection (Fig. 6B). It can also generate a high-frequency bursting mode with frequencies ranging from 4 to 7 Hz. Unlike the high-frequency mode, where the time constants of the CaT deactivation are a key determinant of burst frequency, there are no time constants in the equations of the model that are of the correct order to underlie the low-frequency bursting. There is a different dynamic in the interaction of these key channels in this low-frequency mode. The CaL channel not only sustains the depolarizing plateau but also is responsible for burst initiation. If the hyperpolarizing influence (e.g., from the current injection) is not sufficiently effective in the dendrites, a dendritic subthreshold depolarization can be maintained in the inter-burst interval. This creates a slow and creeping feedback system. The resulting dendritic depolarization is small and only able to activate a small proportion of CaL channels. However, their activation adds to the depolarization and the depolarizing process continues slowly. At a critical threshold, this dendritic depolarization initiates a somatic burst. This slow inter-burst feedback process is robust to parameter variability (e.g., see Figs. 6, C and D, and 9B) and can last for many seconds (with bursting frequencies <0.1 Hz). The dendritic nature of the CaL distribution consequently has a significant impact on low-frequency bursting. The separation of the dendritic depolarization from the soma facilitates the extended interval between somatic bursts by delaying engagement of the sodium mechanisms concentrated at the soma.

Deviations from experimental observations

Some behaviors exhibited by the model differ from experimental observations. For example, the width of a single action potential is notably larger than recorded experimentally (see Action potential and spontaneous rest activity). This may arise from a nonoptimal parameter selection (e.g., it may be possible to reduce the action potential width via changes in the Kv3.1 channel density or distribution), or, alternatively, the channel kinetic description may be inaccurate. Another deviation from experimental observation is a small subthreshold membrane oscillation observed during low-frequency inter-burst intervals (compare with Beurrier et al. 1999). This occurs immediately after a burst and is generated from a CaT current rebound arising from the postburst hyperpolarization. Similar to the action potential form in the preceding text, it may be possible to adjust parameters to reduce or eliminate this phenomenon. Such deviations are expected given the constraints imposed to reduce the number of free parameters (e.g., fixing kinetic descriptions).

As mentioned in the preceding text, the linear distribution of channel densities places a distal bias on the location of the mechanisms underlying the plateau potentials. Plateau potentials can be observed in dissociated STN cells (Do and Bean 2003). The linear constraint can only reveal clustering and co-localization of channel types and not the physical location due to this bias.

The demonstration of strong coupling between N-type calcium channels and sKCa channels (using the N-type antagonist ω-conotoxin GVIA) (see Hallworth et al. 2003) is not observed in the model. This is likely to be due to the error space used in the selection of parameters insufficiently constraining the N-type channel distribution.

Predictions

The model provides a number of decisive predictions for the nature of these cells. It has been experimentally demonstrated that modification of the sKCa or CaL channel potency can influence the length of posthyperpolarizing rebound responses. Increases in CaL or decreases in sKCa effective densities should extend short responses. Moreover, in the model the coupling of these two channel types is also related to the length of rebound response. If it is the distribution, rather than density, that governs the observed rebound variations in the rat STN neuron population, the model predicts that STN neurons that exhibit short responses should also exhibit a stronger coupling between sKCa and CaL channel types. Conversely, STN neurons exhibiting long rebound responses have a weaker coupling between these channels.

The CaT channel is necessary in the model as a trigger of many of the behaviors. This is compatible with the majority of behaviors examined emerging from hyperpolarizing stimuli. Blocking or disrupting the CaT current should mute the emergence of rebound responses and rhythmic bursting. Conversely, increasing the CaT potency should lead to the emergence of a high-frequency bursting mode (4-7 Hz). This range of rhythmic bursting frequency is not readily observed in vitro arrangements but can be observed in STN populations in animal models of Parkinson’s disease. It may be possible to generate such a rhythmic bursting mode in vitro with large hyperpolarizing stimuli and reduced (although not eliminated) CaL channel potency.

In summary, we have presented a model built on basic principles and assumptions that provides an explanation for...
some of the key behaviors exhibited in rat STN projection neurons. The behaviors emerge from only a small set of generic channel interactions that together can bring about a dendrite-bound depolarization capable of sustaining long bursts. Variations in these channel densities and distributions may underlie the variations in stimulus responses observed within the rat STN population. The nature and construction of the model framework is readily extensible and able to accommodate new data from the rat STN as it is available. The feedback from experimental data and testing of model predictions is a vital component of the model development process.

**APPENDIX**

**Model Specification**

The voltage of each compartment, $j$, with membrane surface area $A_j$, is given by Eq. 1. This includes the sum of all ionic currents passing through the membrane ($I_{ion}$) as specified in Eq. 3. Equations 1 and 3 are reproduced from the main text

$$ \frac{dv_j}{dt} = \frac{v_j - v_{n_j} - v_{f_j}}{\tau_{n,j}} - I_{ion} - I_j $$

$I_{ion} = I_{Na} + I_{KDR} + I_{KDNCa} + I_{KCa} + I_{NaP} + I_{CaT} + I_{HCN} + I_s$.

The kinetics of each ionic current component are defined from data of the associated channel type in specific cells. The origin of the data, equations, parameters, and $Q_{10}$ temperature adjustments are all listed here. $Q_{10}$ values are used to modify the rate of kinetic equations (see Hille 2001; for a good description of $Q_{10}$ and its origin).

**Na, NaP**: fast-acting sodium channel and persistent sodium

$$ I_{Na} = (g_{Na} m(v_j)^3 h(v_j) + g_{NaP}) (v_j - E_{Na}) \quad (A1) $$

Equations for the activation and inactivation functions [$m(v_j)$ and $h(v_j)$, respectively] are given in Traub et al. (1991) and reproduced below. They are modified for temperature alignment using a $Q_{10}$ of 1.98 and 1.5, respectively. The equations are based on electrophysiological data from Säh et al. (1988b). Persistent sodium is modeled in the preceding text, with voltage-dependent activation variants taken from data of Do and Bean (2003).

$$ m(v_j) = \alpha_m(v_j) [1 - m(v_j)] - \beta_m(v_j) m(v_j) \quad h(v_j) = \alpha_h(v_j) [1 - h(v_j)] - \beta_h(v_j) h(v_j) $$

$$ \alpha_m(v_j) = 0.32 \frac{(13.1 - v_j)}{\exp((13.1 - v_j)/4) - 1} \quad \alpha_h(v_j) = 0.128 \exp((17 - v_j)/18) $$

$$ \beta_m(v_j) = 0.28 \frac{(v_j - 40.1)}{\exp(v_j - 40.1) - 1} \quad \beta_h(v_j) = \frac{4}{\exp((40 - v_j)/5) + 1} $$

**KDR: potassium delayed rectifier**

$$ I_{KDR} = g_{KDR} n(v_j) (v_j - E_k) \quad (A2) $$

Equations for the activation function [$n(v_j)$] are given in Traub et al. (1991) and reproduced below. They are modified for temperature alignment using a $Q_{10}$ of 1.2

$$ n(v_j) = \alpha_n(v_j) [1 - n(v_j)] - \beta_n(v_j) n(v_j) $$

$$ \alpha_n(v_j) = 0.016 (35.1 - v_j) \quad \beta_n(v_j) = 0.25 \exp((20 - v_j)/40) $$

**Kv3.1: Kv3.1 fast rectifier**

$$ I_{Kv3.1} = g_{Kv3.1} p(v_j) (v_j - E_k) \quad (A3) $$

$$ p(v_j) = \frac{1}{1 + \exp(- (v_j + 5)/9)} $$

$$ \tau_p(v_j) = 18.71 \frac{\exp(- (v_j + 28)/6)}{\exp-(v_j + 4)/16} $$

**sKCa: small calcium-activated potassium channel**

$$ I_{sKCa} = g_{sKCa} w(v_j) (v_j - E_k) \quad (A4) $$

$$ w(v_j) = w_{sKCa}(v_j) - w(v_j) \quad \tau_w(v_j) = 40 $$

**Ih HCN channel**

$$ I_{Ih} = g_{Ih} f(v_j) (v_j - E_{IhCa}) \quad (A5) $$

Equations and data for the activation function [$f(v_j)$] are given in Huguenard and McCormick (1992) and reproduced in the following text. They are modified for temperature alignment using a $Q_{10}$ of 2.0

$$ \dot{f}(v_j) = \frac{f_{max}(v_j) - f(v_j)}{\tau_f(v_j)} \quad f_{max}(v_j) = \frac{1}{1 + \exp((v_j + 75)/5.5)} $$

$$ \tau_f(v_j) = \frac{1}{\exp(-14.59 - 0.086 v_j) + \exp(-1.87 + 0.0701 v_j)} $$

**CaT: low-voltage-activated calcium channel**

$$ I_{CaT} = g_{CaT} r(v_j) \xi(v_j) \quad (A6) $$

where $g_{CaT}$ is calculated as an effective conductance (from the uniform membrane permeability $\rho_{CaT}$ of compartment $j$) and $\xi(v_j)$ is derived from the Goldman-Hodgkin-Katz (GHK) equation

$$ \xi(v_j) = \frac{v_j}{[Ca^{2+}]_{o}} \frac{[Ca^{2+}]_{o} - [Ca^{2+}]_{i} \exp(-z \nu F R T/[Ca^{2+}]_{o})}{1 - \exp(-z \nu F R T/[Ca^{2+}]_{o})} \quad (A7) $$

$z$ is the ion valence (2 in this case), $F$ is Faraday’s constant, $T$ is temperature (in Kelvin), $R$ is the gas constant. The relationship between $\rho_{CaT}$ and $g_{CaT}$ is given by

$$ g_{CaT} = \rho_{CaT} \frac{F^2}{RT [Ca^{2+}]_{o}} \quad (A8) $$

This specification of $I_{CaT}$ reduces to the GHK current equation (modified by $r(v_j)^2 \xi(v_j)$ in the Hodgkin and Huxley manner), however is convenient for comparing conductance levels.
Equations for the activation \([r(v_j)]\) and inactivation \([s(v_j), d(v_j)]\) functions and electrophysiological data are given in Wang et al. (1991) and Coulter et al. (1989) and reproduced in the following text. Temperature alignment modifications using a \(Q_{10}\) of 1.52 were then made

\[
\begin{align*}
    r(v_j) &= \alpha_r(v_j)[1 - r(v_j)] - \beta_r(v_j)r(v_j) \\
    s(v_j) &= \alpha_s(v_j)[1 - s(v_j) - d(v_j)] - \beta_s(v_j)s(v_j) \\
    d(v_j) &= \beta_d(v_j)[1 - s(v_j) - d(v_j)] - \alpha_d(v_j)d(v_j) \\
    \alpha_r(v_j) &= \frac{1}{1 + \exp\left(\frac{(v_j + 28.2)}{13.5}\right)} \\
    \beta_r(v_j) &= \frac{\exp\left(-\frac{(v_j + 63.7)}{7.8}\right)}{1 + \exp\left(-\frac{(v_j + 28.8)}{13.5}\right)} \\
    \alpha_s(v_j) &= \exp\left[-\frac{(v_j + 160.3)}{17.8}\right] \\
    \beta_s(v_j) &= (\sqrt{0.25 + \exp\left(\frac{(v_j + 83.5)}{6.3}\right)} - 0.5) \exp\left(-\frac{(v_j + 160.3)}{17.8}\right) \\
    \alpha_d(v_j) &= \frac{1}{240.05 + \sqrt{0.25 + \exp\left(\frac{(v_j + 83.5)}{6.3}\right)}} \\
    \beta_d(v_j) &= (\sqrt{0.25 + \exp\left(\frac{(v_j + 83.5)}{6.3}\right)} - 0.5)\alpha_d(v_j)
\end{align*}
\]

**CaN, CaL**: high-voltage-activated calcium channels

\[
\begin{align*}
    I_{CaL} &= g_{CaL}\xi(v_j)h([Ca^{2+}\text{]}_i)\xi(v_j) \tag{A9} \\
    I_{CaN} &= g_{CaN}\xi(v_j)u(v_j)\xi(v_j) \tag{A10}
\end{align*}
\]

where \(\xi(v_j)\) is defined in Eq. A7, and \(g_{CaL}\) and \(g_{CaN}\) are interpreted in a similar manner to \(g_{CaT}\) in the preceding text. Common activation kinetics \(\xi(v_j)\) are given in Brown et al. (1993), CaN inactivation \([u(v_j)]\) is from Fox et al. (1987) (given in the following text). The calcium-mediated inactivation \([h([Ca^{2+}\text{]}_i)]\) of the CaL channel is based on data from Meuth et al. (2002) and given by

\[
    h([Ca^{2+}\text{]}_i) = h_c([Ca^{2+}\text{]}_i) - h_d([Ca^{2+}\text{]}_i) = \frac{0.47}{1 + \exp\left(\frac{([Ca^{2+}\text{]}_i - 0.7)}{0.15}\right)} \tau_{CaN}([Ca^{2+}\text{]}_i) = 1220
\]

A model \(Q_{10}\) of 1.95 was applied

\[
\begin{align*}
    q(v_j) &= \frac{q_c(v_j) - q_d(v_j)}{\tau_q(v_j)} \\
    u(v_j) &= \frac{u_c(v_j) - u_d(v_j)}{\tau_u(v_j)} \\
    q_c(v_j) &= \frac{1}{1 + \exp\left(-24.6 - v_j\right)/11.3} \tau_q(v_j) = \frac{1.25}{\cosh\left(-0.031(v_j + 37.1)\right)} \\
    u_c(v_j) &= \frac{1}{1 + \exp\left(v_j + 60.12.5\right)} \tau_u(v_j) = 98 + \cos\left[0.021(10.1 - v_j)\right]
\end{align*}
\]

\([Ca^{2+}\text{]}_i): intracellular calcium

Intracellular calcium levels were modeled in a sub-membrane shell with buffering and diffusion modeled as an exponential decay

\[
    [Ca^{2+}\text{]}_i = -(a_{CaL} + a_{CaN} + a_{CaT})[Ca^{2+}\text{]}_i - [Ca^{2+}\text{]}_i]_0 \frac{[Ca^{2+}\text{]}_i}{\tau_{Ca}} \tag{A11}
\]

where \(c\) is the conversion constant, \(\tau_{Ca}\) is the time constant of the decay, and \([Ca^{2+}\text{]}_i]_0\) is the basal intracellular calcium level.

A value of 185.7 ms for \(\tau_{Ca}\) was used in the simulations as determined from the parameter search procedure.

Conductance levels for each channel are specified in Table A1. Each channel is described by four parameters specifying the distribution over the cell morphology (see Fig. 2). Absent parameter values in the table indicate they were not modeled and excluded from the parameter search procedure. For example, constant rather than linear distributions were modeled for the sodium channels.

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