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Action Potential Initiation, Propagation, and Cortical Invasion in the Hyperdirect Pathway during Subthalamic Deep Brain Stimulation

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Abstract

BACKGROUND—High frequency (~130 Hz) deep brain stimulation (DBS) of the subthalamic region is an established clinical therapy for the treatment of late stage Parkinson's disease (PD). Direct modulation of the hyperdirect pathway, defined as cortical layer V pyramidal neurons that send an axon collateral to the subthalamic nucleus (STN), has emerged as a possible component of the therapeutic mechanisms. However, numerous questions remain to be addressed on the basic biophysics of hyperdirect pathway stimulation.

OBJECTIVE—Quantify action potential (AP) initiation, propagation, and cortical invasion in hyperdirect neurons during subthalamic stimulation.

METHODS—We developed an anatomically and electrically detailed computational model of hyperdirect neuron stimulation with explicit representation of the stimulating electric field, axonal response, AP propagation, and synaptic transmission.

RESULTS—We found robust AP propagation throughout the complex axonal arbor of the hyperdirect neuron. Even at therapeutic DBS frequencies, stimulation induced APs could reach all of the intracortical axon terminals with ~100% fidelity. The functional result of this high frequency axonal driving of the thousands of synaptic connections made by each directly stimulated hyperdirect neuron is a profound synaptic suppression that would effectively disconnect the neuron from the cortical circuitry.

CONCLUSIONS—The synaptic suppression hypothesis integrates the fundamental biophysics of electrical stimulation, axonal transmission, and synaptic physiology to explain a generic mechanism of DBS.

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Keywords

Corticofugal Axon; Pyramidal Neuron; Subthalamic Nucleus

Introduction

Subthalamic deep brain stimulation (DBS) is an established clinical therapy for advanced Parkinson's disease (PD). Direct modulation of the hyperdirect pathway, which consists of a special subset of cortical layer V pyramidal neurons whose corticofugal axons send a collateral to the subthalamic nucleus (STN), has emerged as a possible component of the therapeutic mechanisms of action for subthalamic DBS [1]. Axonal tracing studies show that the hyperdirect pathway arises from wide ranging cortical territories, with a strong representation from sensorimotor cortex [e.g. 2, 3, 4, 5]. Electrophysiological studies in rodents have found that subthalamic DBS generates antidromic activation of hyperdirect neurons [6]. These antidromic action potentials (APs) stochastically invade the soma [7], exhibit a resonant frequency at ~120 Hz [6], and suppress beta activity in the cortical local field potential [8]. Optogenetic studies have also demonstrated that selective stimulation of the hyperdirect pathway is directly associated with therapeutic benefit in rodent models of PD [9, 10].

Results from human studies coincide with the findings from animal experiments and highlight the hyperdirect pathway as a topic of special interest in clinical DBS research. EEG recordings have measured antidromic activation of cortex in patients during therapeutic subthalamic DBS [11, 12, 13, 14]. These cortical evoked potentials have been associated with normalization of the mu rhythm movement-related desynchronization in primary sensorimotor cortex [15, 16], as well as attenuation of cortical beta hypersynchrony [17] during subthalamic DBS. And more recently, the therapeutic effects of subthalamic DBS have been linked to disrupting the coupling between the phase of the beta rhythm and the amplitude of the gamma activity in motor cortex [18].

While experimental results have identified a key role for stimulation of the hyperdirect pathway in the therapeutic mechanisms of subthalamic DBS, numerous biophysical questions remain unaddressed. For example, subthalamic stimulation is known to generate action potentials (APs) in hyperdirect neurons, but at what fidelity with the stimulus train and how robustly do those APs propagate throughout the entire structure of the neuron. Hyperdirect neurons have complex axonal arbors and DBS stimuli are delivered at high frequencies (~130 Hz). Both of these factors suggest that the fidelity of DBS-induced AP initiation and propagation may be limited [19, 20, 21, 22]. Therefore, we developed an anatomically and electrically realistic computational model of hyperdirect neuron stimulation and used it to address three basic questions. First, how does subthalamic stimulation generate APs in hyperdirect neurons? Second, how do stimulation-induced APs propagate through the complex axonal arbor of hyperdirect neurons? Third, what effect do high frequency stimulation-induced APs have on hyperdirect synaptic connections?

Methods

The goal of this computational study was to extend the detailed experimental analyses of Li et al. [6] and Li et al. [7] who studied the direct activation of hyperdirect neurons during subthalamic stimulation. We developed a model system that attempted to mimic their experimental paradigm, while integrating anatomically and electrically accurate model components that broadened the scope of the analysis. Li et al. [6] showed that stimulation-induced APs do antidromically invade the cortex, and Li et al. [7] showed that they invade the soma of hyperdirect neurons in an irregular pattern when stimulated at therapeutic frequencies. We wanted to evaluate if that irregular pattern of APs recorded in the soma was most likely the result of stimulation-induced APs failing to initiate in the subthalamic axon collateral or failure of faithfully generated APs to invade the soma because of biophysical factors at the axon hillock. Then if somatic antidromic AP invasion is compromised during high frequency subthalamic stimulation, and the intracortical axonal arbor is still being barraged by high frequency APs, what is the likelihood of those APs faithfully propagating to their axon terminals. Understanding and quantifying these distinct phenomena have important implications for future attempts to evaluate the role of hyperdirect pathway modulation with DBS on pathological oscillations in the cortico-basal ganglia-thalamo-cortical network. Therefore, we concluded our analysis by quantifying the theoretical excitatory post-synaptic potentials that would be generated at the intracortical glutamatergic synapses of directly stimulated hyperdirect neurons.

Stimulation Model

A computational model of DBS was created in the Waxholm Space atlas of the Sprague Dawley rat [23] (Fig. 1). The voltage distribution generated by a microelectrode in the subthalamic nucleus (STN) was calculated using a finite element model (FEM) created in COMSOL. We constructed the FEM using volume representations of the brain, skull, and soft tissues that were segmented from a T2*-weighted magnetic resonance image with Seg3D [24]. Conductivities of 0.2 S/m, 0.02 S/m, and 0.33 S/m were defined for the brain, skull, and soft tissue, respectively. A monopolar point source was defined in the dorsolateral STN (Fig. 1E). The voltage distribution calculated from the FEM was used to stimulate a 3D multi-compartment cable model of a hyperdirect neuron model (Fig. 1F).

Neuron Model

The hyperdirect neuron model simulations were conducted with NEURON v7.3 [25] at 37 degrees Celsius and a time step of 5 μ s. A detailed list of the neuron model equations and parameters is provided in the Supplemental Material, and the NEURON code is available on ModelDB. The neuron model was assembled with an anatomical representation of the apical and basal dendrites, soma, axon hillock, axon initial segment, intracortical axonal arbor, corticofugal axon, and hyperdirect axon collateral to the STN (Fig. 1A–C). The individual model components were adapted from multiple sources. The anatomical structure, membrane dynamics, and model parameters for the cell body, apical, and basal dendrites were defined by Hu et al. [26], which were adapted from Mainen et al. [27]. This highly detailed, and experimentally validated, layer V pyramidal neuron model has been

extensively studied over the decades, representing a standard in the computational analysis of cortical action potentials.

We connected an axonal arbor to the somatodendritic neuron model via a single connection to the soma. The overall axonal arbor consisted of five key components: the axon hillock, axon initial segment, an unmyelinated intracortical axonal arbor, a myelinated corticofugal axon that terminated in the brain stem, and a myelinated axon collateral to the STN (Fig. 1A, B). The soma was connected to the axon hillock, which connected to the axon initial segment, which connected to the intracortical axonal arbor, which connected to the corticofugal axon, which had an axon collateral to the STN.

The three-dimensional reconstruction of the intracortical axonal arbor was defined by Binzegger et al. [29] (and assisted by personal communication) (Fig. 1C). The diameters of each branch in the arbor were defined with reference to the diameter of the axon initial segment (1.22 μm). A central axonal trajectory within the intracortical arbor was chosen to be extended into the corticofugal axon. The diameters for each daughter branch from this central corticofugal structure were drawn from Shu et al. [28] and set based on the order of the number of branches with the following ratios: 0th order 0.9 (the corticofugal axon), 1st order 0.5, 2nd order 0.4, and 3rd order 0.35. This corresponds to a corticofugal axon diameter of 1.098 μm , the 1st order branch set to a diameter of 0.61 μm , the 2nd order branch order set to a diameter of 0.488 μm and all remaining branches to 0.427 μm diameter.

The anatomical structure of the corticofugal axon from the point where it exits the cortical grey matter to a termination in the spinal cord was constructed to follow the internal capsule of the Waxholm Space atlas (Fig. 1A, B). This part of the axon was modeled as myelinated [26]. The corticofugal axon in internal capsule had a diameter of 3 μm with a mean internodal distance of 300 μm , and 1 μm long nodes of Ranvier each with a diameter of 1.5 μm .

The structure of the hyperdirect axon collateral into the STN was designed to mimic the anatomical reconstructions created by Kita and Kita [3] (Fig. 1D). The hyperdirect axon collateral was orientated such that the terminations were within the volume of the STN as defined from the Waxholm Space atlas [23] (Fig. 1D). The collateral was modeled using the same parameters as the main myelinated corticofugal axon except for having a reduced diameter of 1.098 μm (node of Ranvier diameter 0.55 μm) [30]. The endpoints of the hyperdirect axon collateral were modeled as passive nodes of Ranvier.

The membrane dynamics and diameters for the axon hillock and axon initial segment compartments were defined by Hu et al. [26]. The membrane dynamics of the unmyelinated axonal arbor were defined by Shu et al. [28]. The membrane dynamics of the myelinated axon compartments were defined by Hu et al. [26].

To simulate the generic effects of synaptic drive on the hyperdirect neuron model, we provided excitatory and inhibitory synaptic currents to the apical dendrites and soma, respectively [31]. The excitatory synaptic currents were applied to the apical dendrites with a timing drawn from a Poissonian distribution and an average firing frequency of 20 Hz. The excitatory synaptic input was suprathreshold for generation of an orthodromic propagating

AP, assuming no other influences on the neuron. The inhibitory synaptic currents were applied to the soma with a timing drawn from a Poissonian distribution and an average firing frequency of 40 Hz. This resulted in a hyperdirect neuron model that exhibited an average intrinsic firing rate of 10Hz.

Model Simulations

We coupled the extracellular electric field generated by subthalamic microstimulation with the neural membrane to simulate action potential initiation and propagation in the hyperdirect neuron model [32]. The stimulus was modeled as a 60 μ s monophasic cathodic pulse, delivered at a constant frequency ranging from 10 to 150 Hz (Fig. 2). The extracellular voltage distribution generated by the stimulus was applied to each compartment of the axon model (Fig. 1F). The second spatial derivative of that extracellular voltage distribution dictates the magnitude of the transmembrane currents induced by the stimulus pulse [32]. Those currents interact with the transmembrane sodium channel currents to generate an action potential if a strong enough stimulus is applied. We quantified the threshold stimulus necessary to initiate a propagating action potential in the neuron model as 18 μ A for our given electrode location. We then elected to use a suprathreshold stimulus of 36 μ A in our model analysis, corresponding with the $\sim$ 50 μ A stimuli used by Li et al. [7] in their experimental studies.

Post-Synaptic Currents

The final step in our analysis of subthalamic stimulation of the hyperdirect neuron model consisted of estimating the post-synaptic current that would be generated at an intracortical glutamatergic synapse connecting one of the hyperdirect axon terminals to a post-synaptic neuron. Neocortical synapses are known to display various forms of short-term dynamics [33]. To account for these dynamics, we implemented the Tsodyks-Markram phenomenological synapse model [31]. Pyramidal-to-pyramidal connections are typically depressing synapses [e.g. 34], as are pyramidal-to-interneuron synapses [e.g. 35]. Therefore, we parameterized the synapse model to follow the characteristics of an excitatory depressing synapse ($U = 0.5$; $D = 671$; $F = 17$) [33].

Results

Our simulations show that action potential (AP) initiation and propagation from subthalamic stimulation is a robust phenomenon in hyperdirect neurons. We found that high frequency stimulation-induced APs could faithfully propagate throughout the extensive intracortical axonal arbor and reach their axonal terminals with high fidelity. In turn, the thousands of intracortical synaptic connections made by each directly stimulated hyperdirect neuron are likely being driven to release neurotransmitters at an abnormally high rate during therapeutic DBS. Under such drive, cortical glutamatergic synapses rapidly depress, generating very little post-synaptic current as long as the stimulus train continues. Our model predicts that a key mechanism of high frequency DBS of the hyperdirect pathway is the generation of extensive synaptic suppression, in contrast to the stochastic signaling hypothesis proposed in earlier experimental studies [7].

Action Potential Initiation and Propagation

Electrical stimulation applied within the STN generates an extracellular voltage distribution that decays nonlinearly as a function of distance from the electrode (Fig. 1E). Application of that voltage distribution to the hyperdirect neuron model provides an extracellular driving force to the neural membrane that modulates the transmembrane potential (Fig. 1F). During the stimulus pulse, neural compartments close to the cathodic source become depolarized, while neural compartments further from the source become hyperpolarized [32]. The increase in the transmembrane potential, in the regions of depolarization, increases the conductance of the sodium currents (Fig. 2). When the stimulus is sufficiently strong, recruitment of the sodium currents is pushed beyond their threshold for action potential initiation. Action potential initiation takes place in the node of Ranvier closest to the cathodic source, which is in the hyperdirect axon collateral within the STN (Fig. 2B). The AP then propagates to the parent corticofugal axon in the internal capsule and bifurcates at the branch point. One AP propagates distally to the brain stem and/or spinal cord, while another AP propagates antidromically to cortex.

The response of the hyperdirect axon collateral to trains of extracellular stimuli was independent of stimulus frequency between 10–150 Hz (Fig. 2C). The axonal membrane recovers rapidly from the AP signaling and is ready to respond to a new stimulus after just a few milliseconds, especially for suprathreshold stimuli. Therefore, when considering stimulation frequencies relevant to clinical DBS (i.e. ~130 Hz) the model robustly predicts a 1:1 AP response to each suprathreshold stimulus pulse (Fig. 2).

Cortical Action Potential Invasion

The stimulation-induced antidromic AP propagating from the hyperdirect collateral to cortex, through the internal capsule, requires ~2 ms to reach the intracortical compartments of the neuron model traveling at ~3.8 m/s (Fig. 3A). The AP reaches the base of the intracortical axonal arbor first and then begins bifurcating at the various branch points, eventually invading the entire axonal arbor and reaching every terminal point (Fig. 3B). Antidromic invasion of the soma occurs at ~3.7 ms after the subthalamic stimulus pulse. The total span of time that APs reach intracortical terminal points in the neuron model range from 2–8.6 ms from a single stimulus (Fig. 3C). This results in a nearly continuous spread of intracortical axon terminal invasions over time if the stimulation frequency is greater than 100 Hz.

Somatic spiking activity represents an opportunity to directly compare the model simulations to experimental recordings. Figure 4 plots the somatic firing frequency as a function of the subthalamic stimulation frequency. The experimental results of Li et al. [7] show that somatic firing during high frequency subthalamic stimulation is substantially less than the stimulation frequency. The model predicts this phenomenon as well, but to a lesser extent. With no external influences or synaptic inputs on the somatodendritic compartments of the hyperdirect neuron model, antidromic invasion of the soma occurs in a 1:1 ratio with the stimulation frequency up to 50 Hz, and from 60–150 Hz it responds in a 1:2 ratio (Fig. 4A). The breakpoint from 1:1 to 1:2 firing in the model is related to the afterpotential of the

somatic AP, which puts the somatic membrane potential into a hyperpolarized state for tens of ms after each spike.

The in vivo Li et al. [7] experimental data showed that while somatic activity can sustain 1:1 antidromic firing at 10 Hz, it is unable to sustain 1:1 firing at 50 Hz or above. We hypothesized that this decreased somatic firing was likely influenced by both the biophysics of the somatic AP, as well as synaptic inputs that would have been present during their in vivo experimental recordings. Therefore, we simulated simplistic excitatory and inhibitory drive onto the layer V pyramidal neuron model (Fig. 4B). The excitatory drive generated orthodromic activity that increased the neuronal spiking under low frequency stimulation conditions, but the inhibitory drive reduced antidromic somatic invasion under high frequency stimulation conditions. Both of these synaptic input effects brought the model more into agreement with the experimental data. In addition, the Poissonian nature of the synaptic inputs helped to create an irregular pattern in the somatic firing (Fig. 4C). In situations where the antidromic AP failed to invade the soma, the failure occurred at the axon hillock (Fig. 4D).

Orthodromic APs generated by the excitatory synaptic input were robustly able to propagate out of the somatodendritic domains of the neuron and invade the axonal arbor [28]. However, once the subthalamic stimulation frequency exceeded ~40 Hz the stimulation-induced antidromic APs were plentiful enough to collision block the orthodromic APs from propagating past the axon initial segment (Fig. 4). This orthodromic collision block was accentuated at high stimulation frequencies where antidromic APs were arriving at the initial segment with 1:1 fidelity every 7–10 ms. Therefore, any synaptically driven orthodromic activity generated by the hyperdirect neuron may still be recordable in the soma, but the effect of that activity on the output of the axonal arbor was completely negated by the antidromic APs. As such, we found (through extensive model testing not shown) that the firing of the soma was effectively irrelevant to the firing of the intracortical axonal arbor under high frequency subthalamic stimulation.

Synaptic Driving

The basic purpose of electrical stimulation is to generate artificial APs and subsequently control the release of neurotransmitters in the stimulated neurons. Therefore, we focused our attention on characterizing the APs in the intracortical axonal arbor during subthalamic stimulation. The model predicted that every antidromic AP generated in the hyperdirect collateral in the STN propagated into the intracortical axonal arbor (Fig. 5). The intracortical axonal arbor had 182 terminations and 4166 sites identified as synaptic boutons in its original reconstruction [29] (Fig. 1C). The stimulation-induced APs propagated to every terminal with effectively perfect fidelity (Fig. 5B). This was true even when stimulation frequencies exceeded 100 Hz.

The high fidelity of subthalamic stimulation-induced APs in the hyperdirect neuron was robust to large changes in the geometrical or biophysical features of the unmyelinated intracortical axonal arbor (Fig. 6). Increasing or decreasing the sodium channel conductance by 50% had almost no effect on the frequency response of the arbor with the exception of one branch with 13 terminals in the reduced diameter state. Increasing or decreasing the

diameter of axonal compartments by 50% also had minimal effect. However, when the diameters were reduced by 50%, two-thirds of the branches experienced a 10–20% decrease in their response frequencies compared to the default model (Fig. 6E).

The simulated post-synaptic currents generated at putative intracortical connections of the hyperdirect axonal arbor showed a dramatic dependence on subthalamic stimulation frequency (Fig. 7). As the stimulation frequency increased, the steady-state excitatory post-synaptic currents decreased nonlinearly, leveling out to very small values at stimulation frequencies exceeding 100 Hz (Fig. 7C). This synaptic suppression with high frequency stimulation occurred quickly after the onset of the stimulus train and was not able to recover under the constant barrage of pre-synaptic APs (Fig. 7B).

Discussion

Direct stimulation of the hyperdirect pathway is thought to be an important component of the therapeutic mechanisms of subthalamic DBS [1]. Early rodent experiments addressing hyperdirect stimulation awakened the DBS research community to these special neurons of interest [6, 9]. Hyperdirect neurons have subsequently been a focus of numerous circuitry-based models attempting to quantify the network effects of subthalamic stimulation [e.g. 36, 37, 38]. However, dissecting the network effects of stimulating hyperdirect neurons requires first understanding the details of the stimulation-induced APs and their invasion of the thousands of synaptic boutons distributed throughout those neurons. We used an advanced computational model to evaluate stimulation-induced AP initiation, propagation, and synaptic effect over a wide range of subthalamic stimulation frequencies. Our results suggest that accounting for the intracortical axonal arbor is of paramount importance to dissecting the mechanisms of hyperdirect pathway modulation by DBS (Fig. 5). The model demonstrates that the hyperdirect intracortical axonal arbor robustly receives and transmits stimulation-induced APs at a very high fidelity during therapeutic DBS. This high frequency driving of the intracortical synapses subsequently suppresses the synaptic currents, which effectively disconnects the hyperdirect neuron from the brain circuitry (Fig. 7). Therefore, the results of this study suggest that directly stimulated hyperdirect neurons represent a barrier for either the generation or propagation of oscillatory activity within the network.

Hyperdirect neurons are uniquely positioned to influence intracortical activity, and transmit cortical information into the basal ganglia [39]. They have extensive synaptic connections throughout the brain [3], but do so via glutamatergic synapses that are susceptible to suppression under high frequency driving [33]. Therefore, we hypothesize that when enough hyperdirect neurons are directly stimulated (estimates suggest ~15% of the pathway [40]), the ability of the cortex to robustly generate and/or transmit pathological synchronized oscillations (e.g. long beta bursts [41]) becomes compromised and a therapeutic benefit can be observed. This effect does not require a complete elimination of signaling between cortex and basal ganglia via the hyperdirect pathway, but instead can occur by disconnecting a relatively small, but critical number of neurons from the circuit. Given the extensive intracortical axonal arbors of layer V pyramidal neurons [29] and their powerful synaptic influence [42], DBS-induced disconnection of even a small number of them would limit the oscillatory drive to the cortical circuitry and temper the overall system level synchrony [43,

44]. Such a phenomenon would also be consistent with recent clinical findings on the decreased sharpness of the beta oscillation waveform shape measured in cortex during therapeutic subthalamic DBS [45].

The basic concept of subcortical high frequency stimulation-induced intracortical synaptic suppression was actually one of the first experimentally supported hypotheses on the mechanisms of DBS. Urbano et al. [46] used voltage-sensitive dye imaging and electrophysiological recordings to demonstrate that subcortically stimulated axons could follow 120 Hz without marked reduction, but their intracortical synaptic transmission was substantially compromised. However, this work was largely ignored by the DBS research community, as most research efforts at the time were focused on understanding the interactions between stimulated basal ganglia neurons. One notable exception was the Kiss laboratory, which continued to evolve the synaptic suppression hypothesis using electrophysiological analyses [47, 48]. In addition, Rosenbaum et al. [49] recently applied computational models of short-term synaptic depression during high frequency stimulation to reconcile in vivo experimental finding from basal ganglia neurons. Together, these works motivated our effort to explicitly characterize hyperdirect neuron stimulation and evaluate a possible role for stimulation-induced synaptic suppression in cortex on the mechanisms of subthalamic DBS.

Our detailed model of hyperdirect neuron stimulation robustly predicts that APs are generated in a 1:1 ratio with the subthalamic stimulation frequency and then propagate antidromically up the corticofugal axon. Some experimental [50] and computational [21] studies have suggested that AP propagation failure can occur during high frequency stimulation. However, such failure events are not considered common or likely with large diameter myelinated axons [22, 51], as is the case for hyperdirect corticofugal axons [30, 52]. Of greater concern is the reliability of high frequency AP firing to propagate through the complex branching of the intracortical axonal arbor. Once again previous studies have suggested that failures are possible [20], and are dependent upon the sodium channel density and axon diameter [53, 54]. In addition, accumulation of inactivation in sodium channels can occur at very high frequencies, which can result in conduction failures [55]. Therefore, we performed extensive parameter sensitivity analyses to evaluate the robustness of our model predictions (Fig. 6). Those results showed very little effect on AP propagation and strongly support our conclusion that DBS generates a constant barrage of AP invasions into the axon terminals of hyperdirect neurons. Our theoretical findings are also consistent with the experimental results of Popovic et al. [56], who used voltage imaging of layer V pyramidal neuron axons to show that APs propagate without failure throughout the intracortical arbor for firing frequencies up to 400 Hz.

If APs invade a synaptic bouton at high frequencies for long periods of time, the available experimental evidence clearly shows a marked depression in post-synaptic currents [57]. The key question relevant to clinical DBS is how much synaptic suppression would be present at ~130 Hz stimulation for years on end. The magnitude of this effect is likely dependent upon many factors, including the type of synapse, neurotransmitter being released, and regulation of presynaptic calcium channels [58]. We employed a simple phenomenological model of synaptic dynamics [31], albeit explicitly parameterized to match the intracortical

glutamatergic synapses of layer V pyramidal neurons [33]. We have also evaluated the effects of high frequency driving on not only depressing variants of glutamatergic synapses, but also facilitating synapses, and in either case marked synaptic suppression is generated over long-term stimulation [59]. Nonetheless, one important limitation of the general Tsodyks-Markram synapse model is the failure to explicitly account for multiple pools of synaptic vesicles [60]. Detailed analyses of synaptic vesicles suggest there is a readily releasable pool, readily priming pool, premature pool, and resting pool [61]. Under high frequency stimulation conditions, the depletion and replenishment of these various pools can be difficult to estimate [62], and high frequency stimulation has been shown to enhance the rate of replenishment [63, 64]. Unfortunately, the details of replenishment during long-term stimulation are currently undocumented. This gap in knowledge represents an important opportunity for collaboration between the basic science of synaptic physiology and the clinical application of DBS technology.

The results of this study provide motivation for new electrophysiological analyses on long-term synapse function during high frequency driving, which could possibly be coupled with the impressive advances in genetically encoded calcium and voltage indicators [65]. Understanding the mechanistic details of synaptic suppression is important not only for traditional tonic DBS, but also new intermittent stimulation strategies [e.g. 66, 67]. Quantifying the time constants of synaptic suppression and recovery following the cessation and/or resumption of DBS will provide physiological guidance for the engineering design of novel stimulation paradigms that seek to minimize the number of stimuli necessary to maintain a sufficient level of synaptic suppression.

In conclusion, our modeling results show that subthalamic DBS-induced APs are generated in the subthalamic axon collateral of hyperdirect neurons. These APs propagate faithfully throughout the cortical axonal arbor, even at high stimulation frequencies. However, somatic antidromic AP invasion becomes intermittent during high frequency DBS and is not representative of the axonal activity. Any orthodromic activity that is generated by the hyperdirect neuron is collision blocked by the DBS-induced APs. And finally, the high frequency driving of cortical axons generates pronounced suppression of post-synaptic currents at hyperdirect synapses. Our findings support the synaptic suppression hypothesis as a general mechanism of DBS, and we propose that synaptic suppression represents the most basic concept currently available that can be reconciled with nearly all of the experimental and computational data on the effects of DBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cortical modulation is a key aspect of the mechanisms of deep brain stimulation (DBS).

DBS-induced action potentials in hyperdirect neurons faithfully propagate to cortex.

DBS-induced synaptic suppression of hyperdirect connections in cortex is a likely mechanism of subthalamic DBS.

Figure 1.

Subthalamic stimulation of a hyperdirect neuron. A) Sagittal and B) coronal view of the model system. The layer V pyramidal neuron (blue) is positioned in motor cortex and connected to the intracortical axonal arbor (pink). A corticofugal axon projects down internal capsule and provides a branching collateral to the subthalamic nucleus (STN) (green). C) Close-up view of the cortical region. Black dots represent synaptic bouton locations. D–F) Close-up view of the subthalamic region. Black dot represents the electrode location. Each panel shows the same field of view. D) Anatomical image of the STN and hyperdirect collateral. E) Electrical image of the voltage distribution generated by the stimulus. F) Extracellular voltage distribution applied to the neuron model. All scale bars = 500 μm .

Figure 2.

Action potential initiation. A) Anatomical schematic of the electrode location relative to the hyperdirect axon. B) Transmembrane voltage responses to a suprathreshold stimulus pulse. Resting membrane potential of -70 mV. C) Action potential response frequency as a function of the stimulation frequency. D) Transmembrane voltage response at the corticofugal branch point to the 130 Hz stimulus train.

Figure 3.

Cortical invasion. A) Action potential propagation along corticofugal axon. Colors denote the transmembrane voltage at the specified time points following the stimulus pulse. B) Antidromic invasion of the cortical model components. C) Times that action potentials reach the terminal ends of the intracortical axonal arbor for a single pulse or trains of pulses.

Figure 4.

Somatic firing. A, B) Antidromic action potential invasion of the soma as a function of the subthalamic stimulation frequency. A) Model results with no synaptic inputs to the dendrites. B) Model results with simulated excitatory and inhibitory synaptic inputs to the dendrites. In vivo experimental results of Li et al. [2012] plotted for reference. C) Transmembrane voltage of the soma from B with a stimulation frequency of 130 Hz. D) Transmembrane voltage of the soma, axon hillock, and initial segment for the time window marked with the black bar in C.

Figure 5. Intracortical axon firing. A) Numbering of the various axon terminations in cortex. B) Response frequency of the axon terminations and the soma as a function of the subthalamic stimulation frequency. C) Example transmembrane voltage traces at 130 Hz.

Figure 6.

Sensitivity analysis. A) Numbering of the various axon terminals. B) Response frequency of the axon terminals and the soma as a function of the subthalamic stimulation frequency for the default model. C) Response frequency after decreasing the sodium channel conductance of the intracortical axonal arbor by 50%. D) Response frequency after increasing the sodium channel conductance of the intracortical axonal arbor by 50%. E) Response frequency after decreasing the diameter of the intracortical axonal arbor by 50%. F) Response frequency after increasing the diameter of the intracortical axonal arbor by 50%.

Figure 7. Synaptic suppression. A) Neuron model. B) Subthalamic stimuli at 130 Hz generate action potentials that faithfully invade terminal #144. The simulated excitatory post-synaptic current (EPSC) generated by each pre-synaptic signal rapidly suppresses in response to the 130 Hz driving. C) The steady-state EPSC as a function of the stimulation frequency.