EFFECTS OF DENDRITIC SPIKING ON SYNAPTIC INTEGRATION IN GLOBUS PALLIDUS NEURONS

Jeremy R. Edgerton, Jesse E. Hanson and Dieter Jaeger
Department of Biology
Emory University
Atlanta, GA, USA

The globus pallidus (GP) occupies a central position in the basal ganglia circuitry. GP neurons receive excitatory inputs from the subthalamic nucleus (STN) and thalamus, inhibitory inputs from the striatum and from other GP neurons, and dopaminergic collaterals from the substantia nigra pars compacta (reviewed by Hauber, 1998). Although inhibitory synapses comprise approximately 90% of the total number of inputs (Shink & Smith, 1995), GP neurons fire at substantially higher average frequencies in vivo than in vitro, indicating that the excitatory inputs are able to effectively drive spiking despite the prevalence of inhibitory synapses (DeLong, 1971). This may be explained by the recent results of Hanson, Smith and Jaeger (2004), who demonstrated that rat GP neurons express dendritic sodium channels in sufficient numbers to generate propagating dendritic sodium spikes. The authors found that distal excitatory inputs, which were too far removed from the cell body to produce any somatic potential when dendritic spiking was suppressed by hyperpolarization, could nonetheless cause precisely-timed somatic spikes under normal conditions due to the active properties of the dendrites. These findings indicate that GP neurons possess an unusual mechanism of synaptic integration and are likely to process inputs in a unique way.

To investigate the effects of dendritic sodium spiking on synaptic integration, we have created a detailed compartmental model of a GP neuron. The morphological and passive properties of the modeled neuron were described in Hanson et al, 2004. The model contained 512 compartments and was based on a reconstructed rat GP neuron. The passive properties of the neuron were determined electrophysiologically by blocking active conductances with a cocktail of ion channel blockers.

Active intrinsic conductances in the model were based on published descriptions of GP current kinetics and on voltage clamp recordings from our lab. The model contained fast and persistant sodium channels, delayed-rectifier potassium channels, inactivating (A-type) potassium channels, calcium-activated potassium channels, voltage-dependent calcium channels, and hyperpolarization-activated cation channels. Conductance density parameters were optimized to replicate the spontaneous and current-evoked

activity of GP neurons in vitro. To determine the activity of the calcium-activated potassium channels, cytoplasmic calcium accumulation was simulated for a narrow sub-membrane shell with single-exponential clearance kinetics. In addition to the intrinsic channels, excitatory synaptic inputs from the STN and inhibitory inputs from the striatum were included. Versions of the model with and without spiking dendrites were compared in their properties of synaptic integration. We find that the capability to locally initiate dendritic sodium spikes had three effects on GP neurons: (1) their average output spike rate for a given level of excitation and inhibition was increased; (2) the variability of their output spike pattern, assessed by the coefficient of variation (CV), increased; and (3) the interaction between inhibitory inputs and excitatory inputs changed from an additive to a multiplicative interaction.

The increased output variability associated with spiking dendrites is illustrated in figure 1, below. When the model contained dendritic spike channels (left panels), it was more likely to fire in response to local random coincidences of excitation, resulting in an irregular output. By contrast, the model with passive dendrites (right panels) relied more on the global balance of excitation and inhibition as well as intrinsic spiking dynamics, resulting in a highly regular firing pattern.

Figure 2 shows the multiplicative integration mode of the spiking dendrite model (left panel) and the additive integration mode of the non-spiking dendrite model (right panel). With spiking dendrites, the model predicted that inhibition would primarily regulate the slope of the relationship between excitatory input and spiking output, with relatively little effect on the baseline (ie--no excitatory input) firing rate. By contrast, the model with non-spiking dendrites showed a rightward shift in the input-output relation as inhibition increased, with little influence over the slope of the relation.

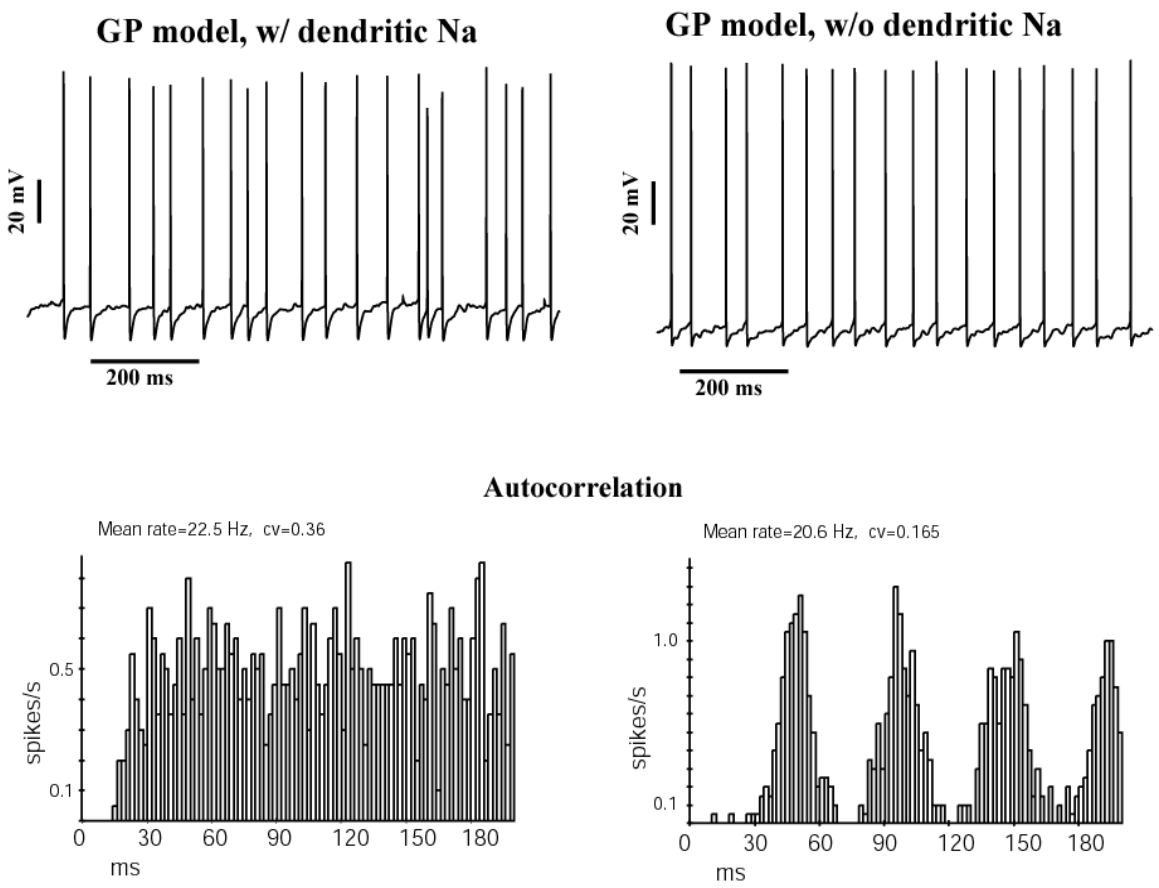

Figure 1. Spiking dendrites increase the variability of the model output compared to non-spiking dendrites.

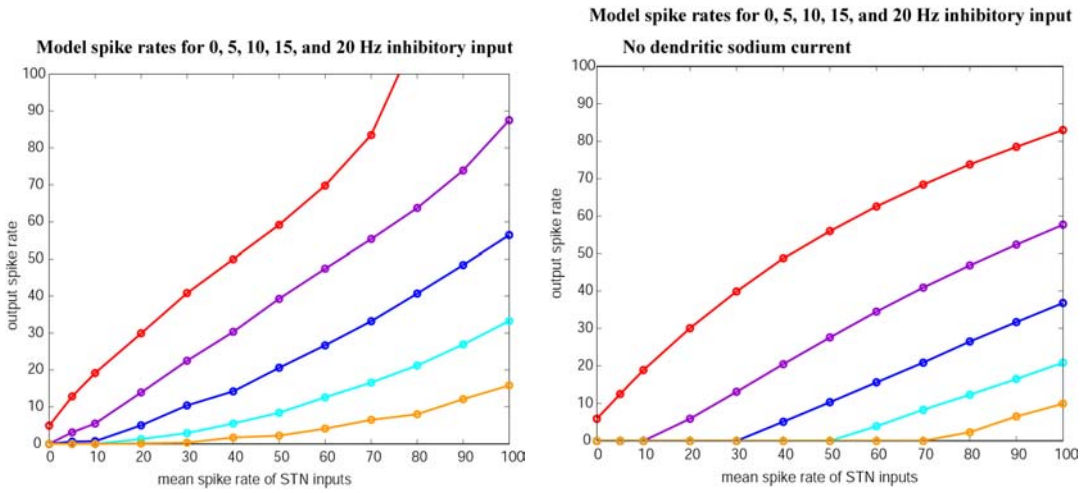

Figure 2. With spiking dendrites (left), inhibition primarily influenced the slope of the relationship between excitatory input and output spiking. With non-spiking dendrites (right), inhibition shifted the input-output curve rightward with little effect on the slope.

The findings of this study indicate that dendritic spikes have important effects on synaptic integration in globus pallidus neurons. In particular, the active properties of GP dendrites are expected to enhance the effectiveness of brief excitatory events in driving GP neurons to spike, resulting in increased firing rates and irregular spike patterns. It would be interesting to integrate this spiking dendrite model into a larger network model to more clearly define the role of GP neurons within the basal ganglia circuitry.

References

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