Modeling of the transient firing of the nigral dopamine neuron in vivo and in slices.

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The mechanisms for generating firing patterns of the dopamine neuron have been a subject of intensive study for several years. A highly periodic and irregular low-frequency single spiking and a burst firing are three distinct firing patterns that have been observed. In vivo, the neuron is seen to fire a burst at a high spiking frequency approximately equal $60Hz$ in response to a synaptic input and return to its normal low frequency single spiking. In slices, by contrast to other types of neurons, no electrical stimulation can evoke a similar burst. This is one of unexplained features of the dopaminergic neuron. A possible explanation may be that the synaptic input includes a component that can not be substituted by an electrical stimulus. This may employ some unknown messenger, which transmits from a postsynaptic terminal through the dendritic tree to the soma and evoke the burst, but the known mechanism of transmission of a synaptic excitation (propagation of an action-potential) is more natural to assume. In this paper, we address the bursting firing of the dopaminergic neuron. We are looking for the reason for in vivo vs. in slices difference in changing geometric characteristics of the neuron after slicing.

First we construct a model for isolated dendritic compartments and the soma. A previously built model [1] demonstrated a calcium subthreshold oscillation that underlies the single spiking pattern. It included two principal currents: noninactivating voltage-dependent calcium current with low threshold and calcium-dependent potassium current. The model also included calcium pump and took into account calcium buffering that was assumed instantaneous. This was the minimal system that demonstrated the periodic single spiking firing pattern only. To model other patterns and transitional behavior of the neuron, interaction between different parts of it has appeared to be important. Coupling of these models, written for each compartment of the neuron, gave better agreement with the experimental time-series. This has led to a widely accepted model that represents the neuron as an array of interacting oscillators. The oscillators have different natural frequencies, i.e., the smaller the radius of the dendritic compartment represented by a particular oscillator, the higher its natural frequency. The whole cell firing pattern is now determined by collective dynamics, in partic-

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ular synchronization, of the compartments. But occurrence of dendritically propagated sodium action-potentials is likely to pay a large role in synchronizing the neuron. Hence, we add spike-producing currents to the model for each compartment.

Then we investigate the simplest coupled oscillators model, i.e., a pair of electrically coupled compartments. We propose two physiologically different ways of obtaining the transitional burst. Both ways employs high natural frequency oscillations in the distal compartment, that forces the whole system to oscillate at this frequency during the transient. The difference in natural frequency can be achieved due to very different radii of the comartments, but the smaller the radius, the weaker the influence of the compartment. This means that the smaller compartment affects the larger one much less, and the coupling becomes unidirectional. Two following methods overcome this problem and mimic both the different natural frequency and the reciprocal character of the intercompartmental coupling.

The first method uses different timescales of the calcium dynamics to create the frequency difference. We suppose for this method that the buffering coefficients of the compartments are significantly different. The transitional frequency achieved by this method is approximately 5 times higher than the steady state frequency. The transitional fast spiking is forced by the second (fast) compartment. The higher the natural frequency of the second compartment, the higher the transitional frequency of the coupled system. Another necessary condition is that the first (slow) element must have a depolarized natural state during the transient. It is achieved by choosing the initial calcium concentration low. So, initially we need to start with a hyperpolarized state, for which the calcium channels are blocked, and, therefore, the calcium concentration is low. Then, the transient corresponds to the calcium build up, during which the voltage remains high.

The second method uses difference in delayed rectifier conductance to organize the frequency difference. The delayed rectifier conductance of the second element is taken to be higher, which mimics a gradient of this conductance along the dendrite. Then, in the first compartment, the delayed rectifier current is not strong enough to overcome inactivation of the sodium channel, and the trajectory goes into its slow calcium oscillations. But the second compartment has a much higher natural frequency because the delayed rectifier is strong enough for the sodium channel to become active right after a spike. The transitional frequency, achieved by this method, is approximately 10 times higher than the steady state frequency. Analogous to the

previous method, the fast transitional spiking is forced oscillations of the slow compartment, induced by the fast compartment. Having different reasons for fast spiking of the second compartment, the two methods are qualitatively the same. In particular, the second method also requires the depolarized state for the slow compartment during the transient.

Next, we discuss the role of the dendrite geometric features. We distinguish two main layouts for the neighboring compartments: tapering and branching. We consider first the simplest branching case, where two thinner compartments, attached to the thicker one, are identical. The simplicity of this case is that these two compartments can synchronize identically. As a result of the synchronization, the influence of small compartments sum. This implies that the conditions of the close radii and significant difference in the buffering coefficients (necessary to provide both reciprocal coupling and different frequency for two compartments), can be overridden in the case of branching. The more branches a large compartment has, the higher the difference in radii and the closer the buffering coefficients are allowed to be.

We show that a long part of the dendrite where the radius and other parameters remain about the same must be modeled as a linear array of identical compartments, as opposed to single compartment. The reason for this is that the boundary conditions of interaction with thicker or thinner part break symmetry of the compartments and do not allow identical synchronization. To show the importance of this, we consider the system of four compartments, two thick and two thin, connected in a series. A high-frequency transitional process was obtained for this system. We then uncouple the last, thin, compartment. The time-series for this case resembles the time-series of one of the thick elements in isolation, having very low frequency. Hence, we show that the interaction between identical compartments is very important and changes dynamics of the system substantially.

In conclusion, we summarize our results as follows. For the simplest coupled oscillators model, i.e., a pair of electrically coupled compartments, we have shown that is it possible to obtain a transient high-frequency spiking. This effect is based on forcing of the slow compartment by the fast one during the transient. The transient vs. steady state frequency difference depends primarily on the difference of natural frequencies of the compartments. We have investigated the possibility of the forcing for more realistic dendrite geometry, where the fast compartment has a smaller radius and, consequently, influences the slow compartment much weaker. We have shown that both

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branching and presence of long thin dendritic parts enforce the influence of fast compartments, contributing to the high-frequency transient. Thus, the firing pattern depends on the dendrite geometric features. Slicing cuts off distal dendrites, reducing the number of fast compartments, which may prevent the burst firing.

References

[1] C.J. Wilson and J.C. Callaway, Coupled oscillator model of the dopaminergic neuron of the substantia nigra. J. Neurophysiol. 83: 3084-3100, 2000.