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Neurocomputing 26–27 (1999) 107–115

NEUROCOMPUTING

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Effects of dopaminergic modulation of persistent sodium currents on the excitability of prefrontal cortical neurons: A computational study

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Abstract

Yang and Seamans (J. Neurosci. 16 (5) (1996) 1922–1935) have recently shown that pyramidal cells in rat prefrontal cortex respond to a brief current injection with a plateau potential that is mediated by slowly inactivating voltage-dependent sodium currents. They also report that dopamine receptor activation increases plateau duration and shifts its activation to more negative potentials. We model persistent sodium currents by including an additional slow inactivation parameter in the standard spike-generating sodium channel model. Our model reproduces the voltage plateau and the dopamine-induced increase in plateau duration. We extend the model by including a set of potassium currents and examine the effect of dopaminergic modulation of sodium current on neuronal excitability. We find that dopamine increases the gain of the current to firing frequency relationship. However, modulation of sodium current has minimal effects on the amplitude of subthreshold EPSPs.

Keywords: Dopamine; Prefrontal; Cortex; Sodium; Persistent

1. Introduction

The prefrontal cortex (PFC) is thought to play a major role in the planning and execution of complex behaviors. Dysfunction of PFC has been implicated in

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0925-2312/99/$ – see front matter
PII: S0925-2312(99)00005-3

schizophrenia [2] as well as other cognitive disorders. Dopamine plays a prominent neuromodulatory role in the PFC and many behavioral correlates of dopamine receptor activation have been identified [8]. While effects of dopamine at the macroscopic level are well characterized, the specific effects of dopamine on the pyramidal cells of the PFC are controversial. One particularly interesting suggestion put forth by Cohen and coworkers is that dopamine acts by increasing the gain of the cortical neurons, making these neurons more responsive to inputs [2]. In this work, we explore a particular biophysical mechanism that may underlie up regulation of the excitability, and thus the gain, of cortical neurons. We focus specifically on the modulation of sodium channels in layer V/VI pyramidal neurons.

Voltage-dependent sodium channels play many roles in neuronal function including axonal and dendritic action potential generation and boosting of subthreshold synaptic events [9,11]. Two types of voltage-dependent sodium channel behavior have been identified, a traditional transient current and a slowly inactivating or persistent sodium current. It is unknown if the two observed currents are generated by distinct populations of voltage-dependent sodium channels with independent kinetics or by a single population of sodium channels that possesses multiple gating modes. Recordings of single voltage-dependent sodium channels in sensorimotor cortical cells have provided support for the idea that persistent sodium currents are carried by the same population of channels that generate transient sodium currents [1]. A small proportion of channels express a gating mode in which the probability of a channel being open is high and relatively constant. This conceptual model was used by Fleidervish and colleagues to model sodium currents in layer V/VI pyramidal cells from slices of murine somatosensory cortex [4].

In a variety of cell types from several brain regions, dopamine has been shown to modulate voltage-dependent conductances e.g. [12–14]. Recently, Yang and Seamans have demonstrated that in layer V/VI pyramidal cells of rat PFC, dopamine modulates voltage-activated sodium channels while having no effect on passive membrane properties [14]. To study sodium currents in isolation, the authors abolished non-sodium currents by perfusing the cells extracellularly with cobalt, tetraethyl ammonium, and 4-aminopyridine. The cells responded to a 100 ms current injection with a fast sodium spike that was followed by a fast partial repolarization to a plateau potential. This plateau potential was tens of millivolts above rest and lasted several seconds, and was terminated by a spontaneous and rapid return to rest. The final, fast repolarization was often preceded by high-frequency voltage fluctuations. Application of agonists of the D1 dopamine receptor subtype prolonged the plateau potential elicited by a given current injection and shifted its activation threshold more negative potentials. Yang and Seamans suggest that D1 receptor stimulation causes a shift of the activation of slowly inactivating sodium currents to more negative voltages and also a decrease in the speed of inactivation.

This study was designed to address three questions: (1) Can a plateau potential be obtained using a minimal model that possesses a single population of Na channels with both slow and fast inactivation kinetics? (2) Do the proposed modifications in the biophysical properties of sodium channels account for the observed effects of dopamine receptor activation on the plateau potential? (3) What are the effects of

such dopaminergic modulation on super- and subthreshold behavior of a spiking neuronal model.

2. Methods

Computational modeling was performed to reproduce the experimental results from intracellular recordings in rat prefrontal cortex [14]. We constructed a single-compartment model of a layer V/VI pyramidal neuron that included leak, voltage-dependent sodium, delayed rectifier potassium, A-type potassium, a slow non-inactivating potassium (M-type), and synaptic conductances.

$$-C\frac{dV}{dt} = g_L(V-70) + g_{Na}m^3hs(V-V_{Na}) + g_A m_A^3 h_A(V-V_K) + g_M w(V-V_K) + g_{DR}n^4(V-V_K) + I_{syn}.$$

Currents were modeled in the following standard activation/inactivation schemes of Hodgkin and Huxley [5]. The parameters for A-type potassium conductances were taken from Hoffman and coworkers [6]. Parameters for all other currents were taken from McCormick and Huguenard [10] and Ermentrout [3].

Following Fleidervish and colleagues, slow inactivation was incorporated into the standard sodium channel model by including an additional slow inactivation parameter, s. The s dynamics satisfy

$$s' = \alpha_s(V)(1-s) - \beta_s(V)s,$$

where α and β have the following form:

$$\alpha = \phi_{\alpha s}0.1(V+40)/(1-\exp(-(V+V_{1/2\alpha s})/s_{in}))$$

and

$$\beta = \phi_{\beta s}4\exp(-(V+V_{1/2\beta s})/s_{out}).$$

The parameters for slow inactivation of sodium currents were taken from the experimental work of Fleidervish et al. [4]. Relative ratios of current densities were Na(100) : delayed rectifier(100) : A(50) : M(10) : leak(1.2). Synaptic currents were simulated by an alpha function

$$I_{syn} = t\exp(-t/\tau),$$

where $\tau = 10$ ms. The reversal of the synaptic current was 0 mV. Simulations were performed using the software XPPAUT written by G. Bard Ermentrout [3].

3. Results

Initial simulations were performed using a minimal model that contained only sodium and leak conductances. When the initial resting voltage was set to -70 mV,

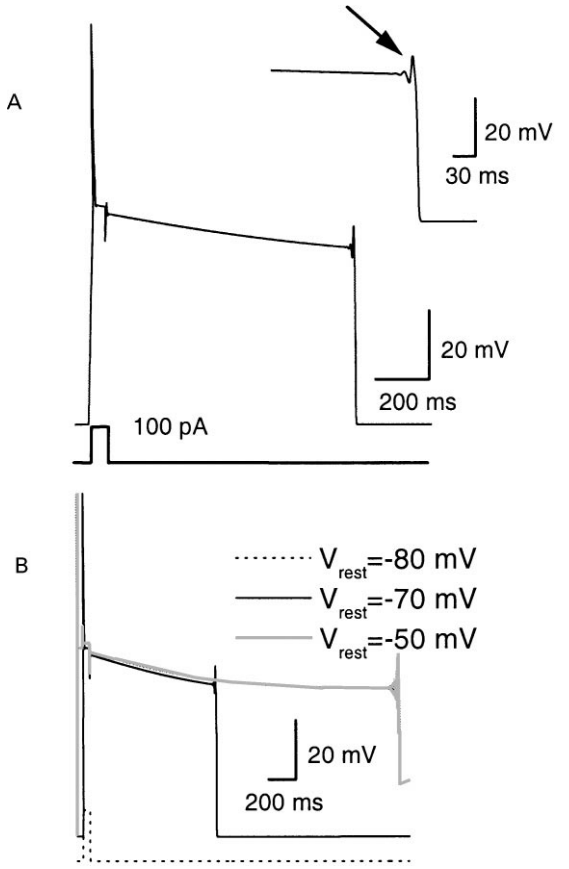

Fig. 1. Long duration plateau potentials are obtained with brief stimulation. (A) The voltage in a single-compartment model was measured. A 50 ms stimulus of 100 pA caused a fast sodium spike. The spike rapidly, but partially repolarized and maintained a voltage tens of millivolts above rest for several hundred milliseconds. Spontaneous oscillations occurred just prior to a rapid return to resting potential. The holding potential for this example is -70 mV. A 100 pA, 50 ms stimulus was used in all figures to obtain the plateau potentials. (B) The duration of the plateau potential is dependent on resting voltage. The plateau voltage is maintained for a longer period of time at -50 mV than at -70 mV. In addition the plateau occurs spontaneously at a holding potential -50 mV (Note earlier onset of fast spike). At -80 mV the plateau potential is not elicited by the stimulus.

a 50 ms, 100 pA current injection caused a rapid sodium spike that rapidly, but partially, repolarized to a voltage approximately 60 mV positive to rest, i.e. a plateau potential. The voltage continued to repolarize at a slow rate, and after approximately one second the membrane potential oscillated unstably, and then returned to the resting potential (Fig. 1A). The duration of the plateau was voltage dependent. At more depolarized resting potentials, the plateau lasted longer (Fig. 1B). These computational data demonstrate that a single population of sodium channels that

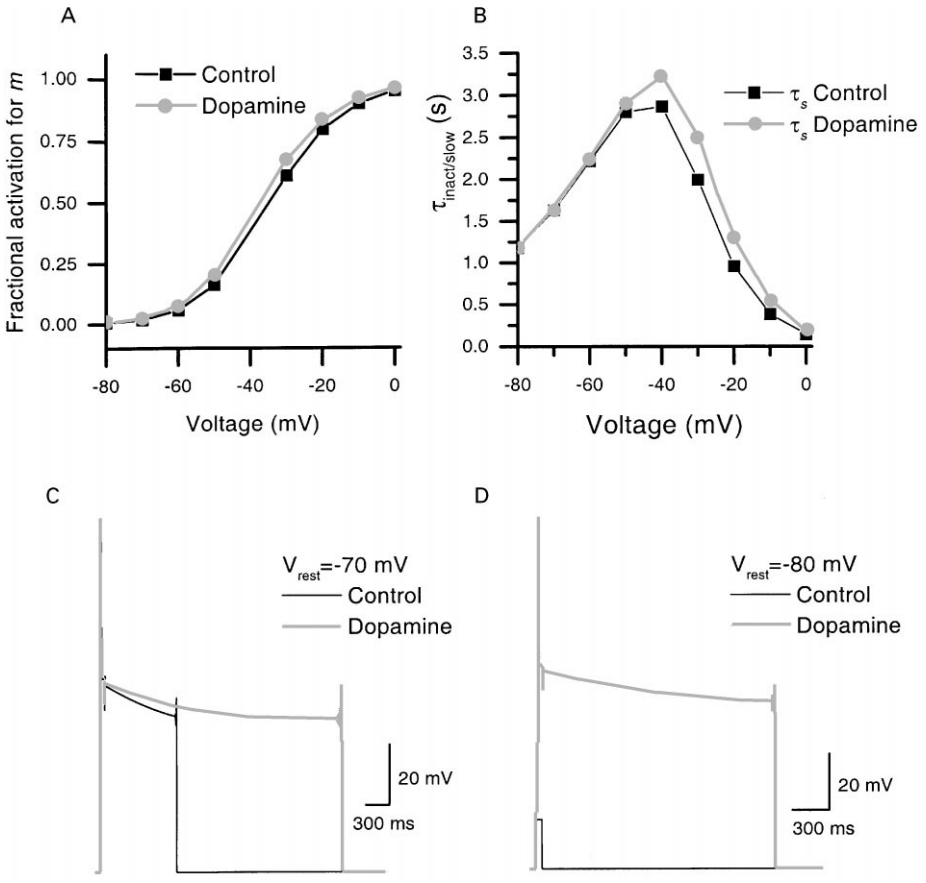

Fig. 2. Small changes in biophysical properties of sodium currents cause large changes in the properties of the plateau potential. (A) and (B) To mimic dopamine application, two biophysical parameters were altered. The threshold of activation for the activation variable, m, was shifted from -50 to -55 mV, and the amplitude of the rate constant for β for slow inactivation, $\phi_{\beta s}$, was decreased by 30%. These two changes resulted in the changes displayed and (A) and (B) in m_{inf} and $\tau_{inactivation/slow}$. (C) At any given voltage the plateau potentials lasted longer in the dopamine condition. (D) At more hyperpolarized potentials, dopamine allowed a plateau potential to be obtained where none was observed in control. The same stimulus that caused a plateau potential in the dopamine condition did not result in a plateau at -80 mV. The control data in (C) and (D) are redrawn from Fig. 1B.

possesses two modes of inactivation is sufficient to explain the experimentally observed plateau potentials, including the fine structure of the rapid return to rest at the end of the plateau.

Yang and Seamans reported that application of 40 μM of the specific D1 agonist SKF38393 increased the plateau duration and shifted its activation threshold to more negative potentials. They suggest that D1 receptor stimulation shifts of the activation of slowly inactivating sodium currents to more negative voltages and also decreases

the speed of the slow inactivation. These proposals were implemented in the model by small changes in the parameters of I_{Na}. The $V_{1/2}$ for the activation variable for sodium currents (m) was shifted 5 mV in the hyperpolarizing direction. The variable $\phi_{\beta s}$ was decreased by 30% from 0.0034 to 0.00238. We refer to this set of computational changes as the "dopamine" condition. These two alterations resulted in changes in voltage dependence of the activation variable m and in voltage dependence of the time constant of slow inactivation (τ_{slow}; Fig. 2A and B). Even though these changes were quite modest, their impact on the duration and voltage-dependence of the sodium plateau potential was dramatic (Fig. 2C and D). At a resting potential of -70 mV, the duration of the plateau potential was increased by 320% in the dopamine condition (Fig. 2C). Under control conditions, a 100 pA stimulus did not elicit a plateau potential at a resting potential of -80 mV. However, in the dopamine condition the same stimulus evoked a plateau of approximately 2 s (Fig. 2D). Thus, we conclude that the proposals of Yang and Seamans are sufficient to explain the dopaminergic modulation of sodium plateau potentials.

In order to study the effect of dopamine on superthreshold and subthreshold events, the model was extended to include several potassium conductances in addition to sodium and leak conductances. The model responded to an extended current injection with a series of action potentials. The same current injection resulted in twice as many action potentials in the dopamine condition (Fig. 3A). Notice that the single-channel population model for the persistent soduim current does not lead to membrane bistability. The relationship between the amount of current injected and the firing rate was measured. In the dopamine condition, rheobase was lowered, i.e. action potentials were obtained with smaller current injections. The model also responded with increased spike output over the entire physiological range of firing rates.

We next studied the influence of dopaminergic modulation of sodium currents on the shape of subthreshold events. A subthreshold excitatory postsynaptic potential (EPSP) was generated using an alpha function (see Methods). Modification of parameters to the dopamine condition resulted in minimal change in the amplitude and duration of the EPSP (Fig. 4).

4. Discussion

This study demonstrates that a plateau potential, the duration of which varies with resting membrane potential, may be generated by a single population of sodium channels having both fast and slow inactivation gates. We show that small dopamine-dependent changes in the kinetics of inactivation and in the voltage threshold for activation of sodium currents dramatically alters the duration and voltage dependence of the sodium plateau potential. This dopaminergic effect on the basic biophysical properties of sodium currents is so small as to be potentially quite difficult to measure experimentally. However, the resulting changes in the plateau potential are easily discernable.

When repolarizing potassium currents are included in the model, we find that the dopaminergic changes significantly lower the threshold for action potential genera-

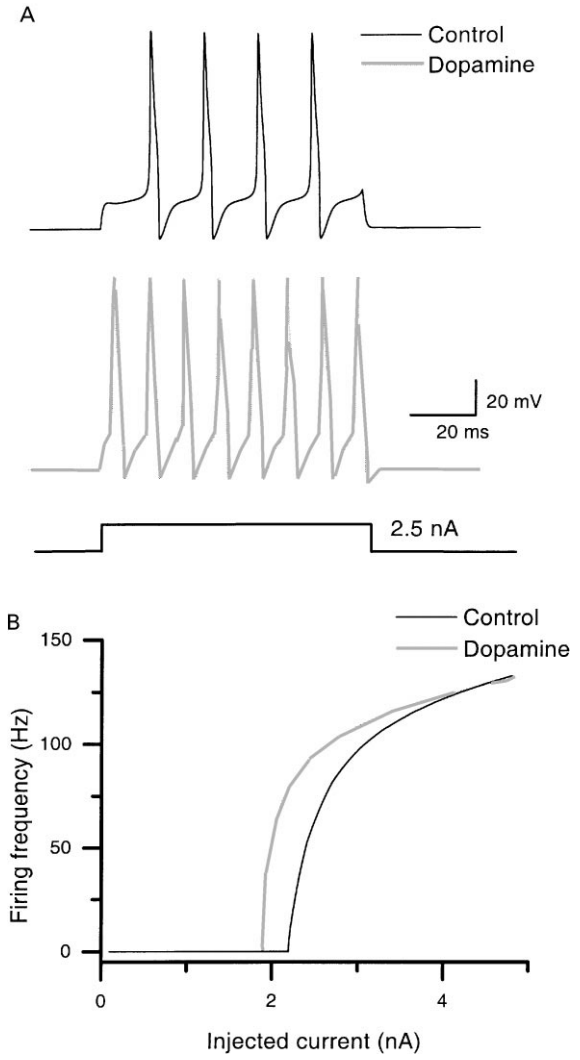

Fig. 3. The superthreshold properties of a spiking neural model are significantly affected in the dopamine condition. (A) Voltage-dependent conductances were added to obtaining a spiking model as described in the text. Incorporating the same biophysical changes as shown in Fig. 2A and B resulted in a larger number of spikes to a 2.5 nA stimulus. (B) The relationship between firing frequency and injected current establishes that in the dopamine condition the model is more excitable over a broad range of physiological firing rates.

tion and increase the neuron's input/output gain. At the same time, the effect on the subthreshold EPSP is minimal. However modulation of EPSPs by dopamine has been previously reported [7]. In our model, the shape of the EPSP is determined primarily by the A-type potassium conductance. The dopaminergic modulation of sodium currents at subthreshold voltage levels is masked by the dominant A-type

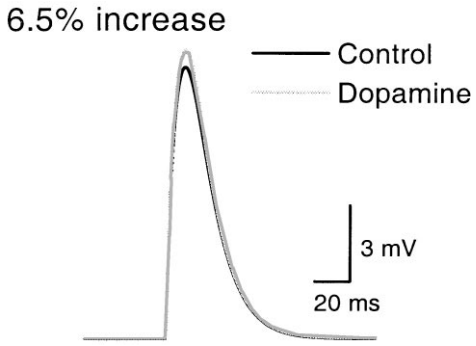

Fig. 4. Subthreshold events are affected slightly in the dopamine condition. The same model utilized to generate the data in Fig. 3 was used to study the modulation of subthreshold events. The peak amplitude of his subthreshold event was slightly influenced by incorporating the changes associated with dopamine application.

current. Dopamine has been reported to modulate a slow A-type potassium current in both cortical and neostriatal neurons [13,14], and this modulation may underlie the effects on EPSPs. A more complete model of dopaminergic modulation of various voltage-dependent currents would be required to explain the various actions of dopamine on prefrontal cortical cells. Nevertheless, the biphasic nature of the dopamine effect, with substantial superthreshold but minor subthreshold modulation, provides a concrete example of how heterogenous effects of neuromodulation may result from a single set of biophysical changes.

Acknowledgements

We would like to thank Drs. Jon Johnson and Nathan Urban for helpful discussions of this work.

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