



The Role of NMDA Currents in State Transitions of the Nucleus Accumbens Medium Spiny Neuron

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Abstract

The Nucleus Accumbens (NAcb) integrates information from a wide range of glutamatergic afferent inputs, including the prefrontal cortex, hippocampus and amygdala. One of the glutamatergic receptors, the NMDA channel, has been implicated in the non-linearity of the current-voltage relationship in these cells under certain input conditions. In order to examine the relationship of the different glutamatergic receptors to the membrane response, we modeled the AMPA, GABA_A and NMDA receptors in the Medium Spiny (MSP) cells and their afferent input. The model demonstrates that the NMDA current is capable of sustaining certain membrane states and contributes to the non-linearity of the membrane response to input.

Keywords: Nucleus Accumbens, Striatum, NMDA, Bistability, MSP

1. Introduction

The Nucleus Accumbens (NAcb) integrates afferent information from the prefrontal cortex, hippocampus, and amygdala, and its primary output is to the ventral pallidum. [1] Due to its privileged location receiving information from many of the cognitive areas of the brain, and the high level of dopaminergic innervation from the ventral tegmental area, the NAcb has been implicated in motivational behavior and addiction. [2] Dysfunction of information processing in this area has been hypothesized to underlie aspects of schizophrenia as well. [3] Due to the possible involvement of a dysfunction of glutamatergic signaling in schizophrenia, we chose to examine the role of the NMDA receptor in the behavior of the membrane in a multi-compartment model of the principal cell in the NAcb, the MSP cell. [4]

2. The Model

The medium spiny neuron was created in the NEURON simulation environment using a 29-compartment model. Appropriate channels were included from the available literature, including two sodium currents, four types of K⁺ currents, five Ca²⁺ currents, and two calcium-dependent potassium channels. The conductances of each channel were tuned to intracellular recordings. Synaptic inputs from the prefrontal cortex were simulated using Poisson-distributed trains of inputs applied to 84 synapses distributed throughout the cell's dendritic compartments. Feedforward inhibition was modeled in a similar fashion but with the inhibitory synapses concentrated in the soma and proximal dendrites. Excitatory synapses consisted of an AMPA/NMDA pair and inhibitory synapses consisted of one GABA_A current. Up- and down-state transitions were generated by changing the frequency of inputs to the cell, with the ratio of AMPA/NMDA inputs to GABA inputs constant at roughly 1:1.

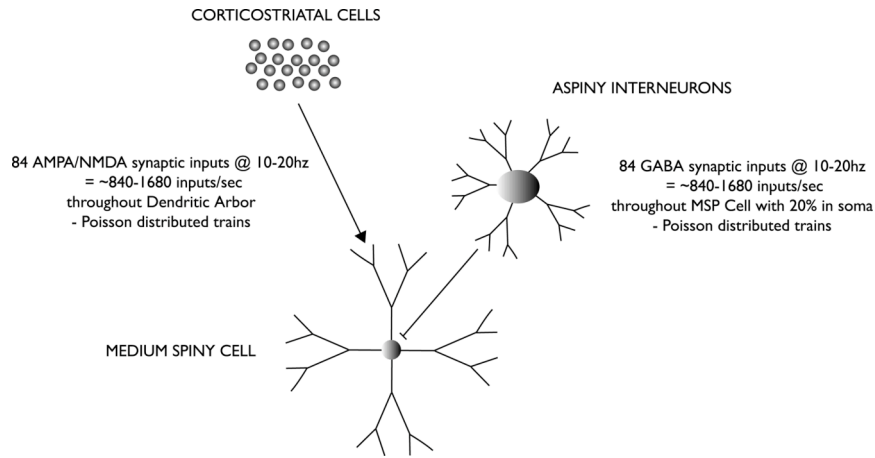


Fig.1. – Depiction of the architecture utilized for the simulation. Poisson-distributed trains were fed into a 29-compartment MSP cell with appropriate excitatory and inhibitory synaptic localizations throughout the cell.

Sodium and potassium currents were modeled according to Equation 1:

$$\overline{I_z} = \overline{g_z} m^x h^y (V_m - E_z). \quad (1)$$

Here, $\overline{g_z}$ and E_z represent maximum conductance and reversal potential of ion species z, respectively, and V_m is the membrane voltage of the cell. The parameters m and h are modeled according to the Hodgkin-Huxley formulation,

$$m' = \frac{m_\infty(V_m) - m}{\tau_m(V_m)}, \quad h' = \frac{h_\infty(V_m) - h}{\tau_h(V_m)}. \quad (2)$$

In this formulation, m represents the activation state of the channel, h represents the inactivation state of the channel, and m_∞ , h_∞ , τ_m , and τ_h are the steady state-activation curves and time constants for m and h .

Calcium channels were modeled using the Goldman-Hodgkin-Katz equation, which accounts for current rectification at elevated membrane potentials:

$$I_{Ca} = P_{Ca} z^2 \frac{V_m F^2}{RT} \frac{[Ca^{2+}]_i - [Ca^{2+}]_o \exp(-z F V_m / RT)}{1 - \exp(-z F V_m / RT)}. \quad (3)$$

Here, P_{Ca} is channel permeability to calcium ions, z is calcium valency, F is Faraday's constant, R is Boltzmann's constant, T is temperature, and $[Ca^{2+}]$ is intracellular or extracellular calcium concentration. Calcium concentration in a thin shell just inside the cellular membrane was tracked for each compartment and used to regulate both a large-conductance (BK, or I_C) and a small-conductance (SK, or I_{AHP}) calcium-dependent potassium current.

NMDA, AMPA, and GABA currents were modeled using a modified two-state synapse providing both summation and saturation. These currents obeyed the equation

$$I_z = \bar{g}_z (h - m)(V_m - E_z), \text{ where} \quad (4)$$

$$m' = \frac{-m}{\tau_m} \text{ and } h' = \frac{-h}{\tau_h}. \quad (5)$$

The NMDA current was modified to account for voltage-dependent magnesium blockade. These channels provide some detail (namely summation and saturation) while maintaining acceptable computational performance. Time constants were set according to published parameters and temperature corrected to 35 °C through division by a qfactor of 2. NMDA synaptic strength was set to match recent reports of single channel conductance multiplied by 5 – the estimated number of NMDA channels per synapse. [5] AMPA synaptic strength was set such that the NMDA:AMPA conductance ratio was 0.5:1 in magnesium free solution. [6] GABA synaptic strength was set to reported values for single-synapse conductance. [7]

Table 1. Synaptic current parameters for the MSP cell model.

Synaptic Currents	Location	$\bar{g}_z(pS)$	$E_z(mV)$	$\tau_{on}(ms)$	$\tau_{off}(ms)$	Source
AMPA	Dend	593	0	1.1	5.8	Myme 2003
GABA	Soma/Dend	435	-60	0.25	3.8	Nusser 1998
NMDA	Dend	290	0	2.82	125	Dalby 2003

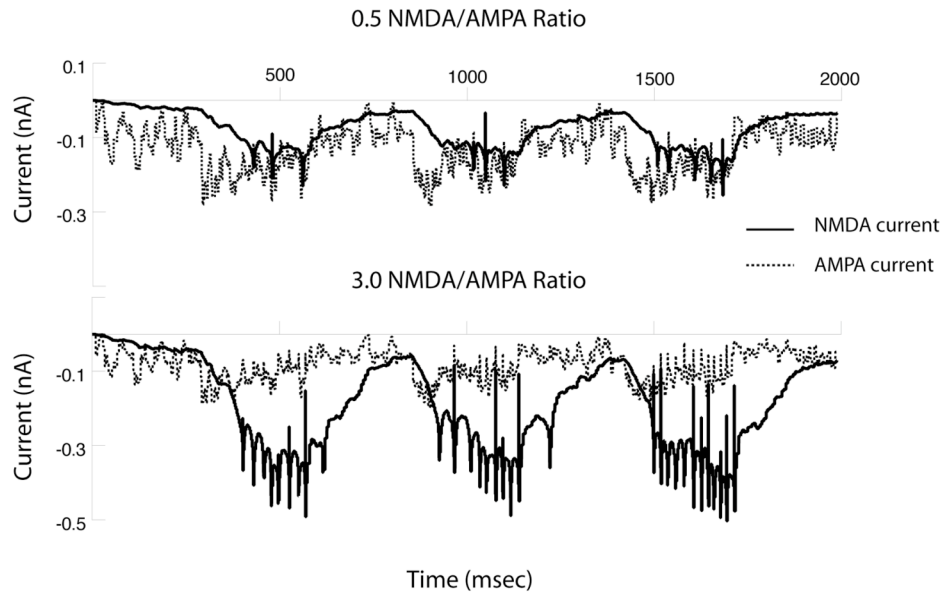


Fig.2. – Levels of whole cell AMPA and NMDA current throughout the 2 seconds of the simulation. Whole cell currents are shown for an NMDA/AMPA level of 0.5 and 3.0.

3. Results

The model reproduced up and down state transitions of the MSP cell. There were no spontaneous changes between states other than those driven by input changes. The NMDA to AMPA ratio was adjusted from 0.5 to 2 at 0.5 increments in order to evaluate what effect this has on state transitions of the membrane potential. There was a significant change in measurable whole cell current through the NMDA receptors when the current ratio was adjusted (Fig. 2). The increase in current through the NMDA channels led to a number of effects. There were significantly more spikes in the up state, and at higher NMDA/AMPA ratios there was a tendency for the membrane to stay in the “up” state and continue to fire action potentials. (Fig. 3) A comparison of the membrane potential to the NMDA current reveals that this current dominates the time course of the return to the “down” state of the membrane.

4. Conclusions

The model reproduces the changes in state brought about by shifts in the number of inputs. The influence of the NMDA currents on these transitions and its contribution to the up-state of the MSP cell has been discussed in the literature. [8] The model confirms that at realistic levels of NMDA current, this

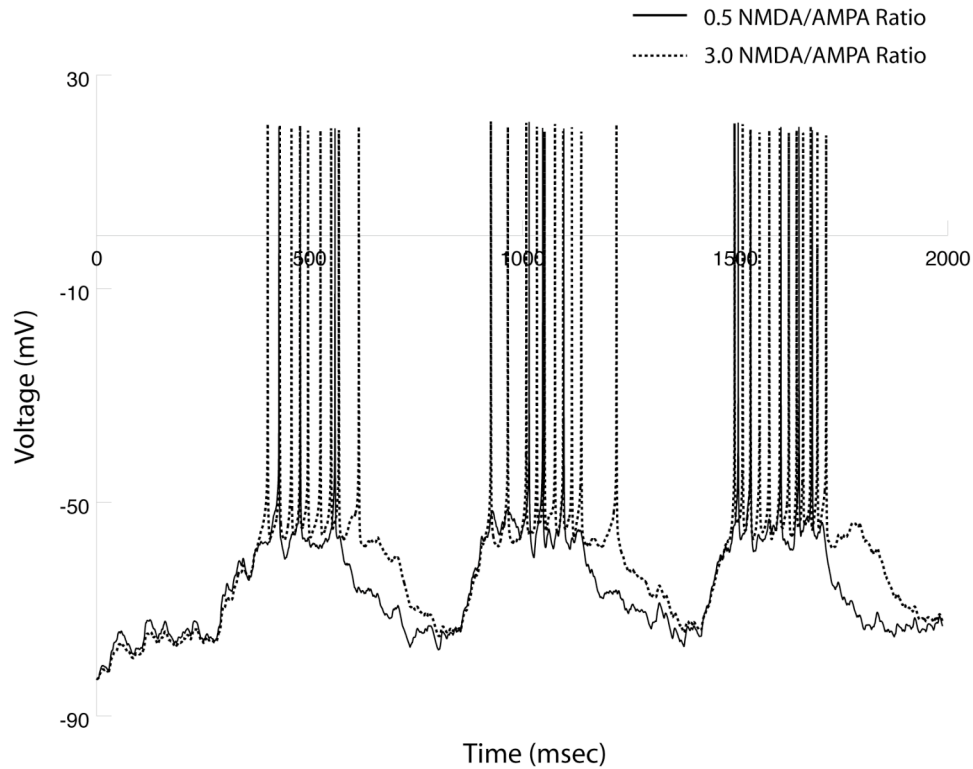


Fig. 3. Voltage traces from the MSP model showing representative traces from simulation runs with different NMDA/AMPA ratios. Note the increased time in the up state of the cell and the increased number of action potentials with the NMDA/AMPA ratio of 3.

current can indeed sustain the MSP cell in a higher voltage state, even after the number of inputs has decreased. The ratio of NMDA/AMPA in these cells is crucial to determining the effect of the NMDA current in the model, and has been demonstrated to change after cocaine treatment in rats. [9] Due to the longer time constant of the NMDA current, this current continues to flow after the period of firing that caused the up-state is over.

The NMDA receptor is involved in the induction of LTP, which has been discussed as a possible substrate for memory formation. The accumbens has also been implicated in reward-related learning and motivated behavior. [10] The NMDA receptor is a coincidence detector that will open only if glutamate is bound and the voltage levels relieve the Mg^{2+} block. It has been proposed that Ca^{2+} entering through these channels leads to an increase in AMPA receptor insertion and therefore strengthening the synapse. [11] If the NMDA/AMPA current ratio is involved in keeping the cell in the up state, learning could enhance the output of those MSP cells involved in the behavior. Since there is a large feedback loop in the cortico-accumbens circuit, this mechanism may be involved in the learning of motivated behavior.

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