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A reduced model of DA neuronal dynamics that displays quiescence, tonic firing and bursting

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ABSTRACT

Midbrain dopaminergic neurons send numerous projections to cortical and sub-cortical areas, and in a manner dependent upon their activities, diffusely release dopamine (DA) to their targets. Recent experimental studies have shown that DAergic neuronal bursting is associated with a significantly greater degree of DA release than an equivalent tonic activity pattern. Past computational models for DA cell activity relied upon somatodendritic mechanisms in order to generate DA neuronal bursting. However, recent experimental studies indicate that burst firing can be generated somatically with the dendrites silenced. These somatically induced bursts have characteristics consistent with normal bursting, suggesting that a single-compartmental model should be sufficient for generating the observed DA neuronal dynamics. In this work, we introduce such a model for DA neuronal dynamics and demonstrate that this model captures the qualitative behavior of DAergic neuronal dynamics: quiescence, tonic firing and bursting. In our conductance-based approach, the interplay between the L-type calcium and the calcium dependent SK potassium channel provides a scaffold for the underlying oscillation for the pacemaker-like firing patterns. The model includes terms which can selectively block the SK conductance, which would correspond to pharmacological manipulations using the drug apamin. Our modeling studies are in line with experimental evidence that a reduction of the SK conductance often induces DA neuronal bursting. Moreover, our model can reproduce findings that burst firing can be elicited via stimulus driven events, manifested by rises in the amount of NMDA. This model for DA cell activity could be further sculpted to include more detailed second messenger signaling processes in order to elucidate key differences between the two principal classes of midbrain DA neurons: those of the ventral tegmental area and the substantia nigra pars compacta.

1. Introduction

The neurotransmitter dopamine (DA) has been implicated in many neural and cognitive processes: motivation, sleep, mood, attention, working memory, learning, punishment and reward. DAergic neurons are predominantly located within the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) of the midbrain. These dopaminergic neurons send numerous projections to cortical and sub-cortical areas and diffusely release dopamine to their targets when the DA neuron fires.

The DA neurons of the VTA project to the amygdyla, prefrontal cortex, and the ventral striatum, and are thought to signal information related to motivational properties of stimuli and actions, e.g., the motivational salience of the stimulus or the error between the expected and received reward. Such a reward prediction error signal would be of critical importance in the action–selection process that ultimately fashions animal behavior. Numerous studies have focused on the tonic and phasic activity of the VTA DAergic neurons as encoding reward related signals. However, recent studies (e.g., Schultz, 2002) suggest that bursting behavior specifically conveys reward-related information. Moreover, dopamine release during burst firing events is substantially greater than during regular spiking (Gonon, 1988). Thus, understanding burst firing is essential when considering VTA neuronal dynamics. Here we introduce a single compartmental model of a VTA DAergic neuron (in the discussion we consider differences between VTA and SNc DA neurons). We demonstrate that this model captures the qualitative behavior of DAergic neuronal dynamics, yet is simple compared to existing, detailed, multi-compartmental models.

DAergic neurons display a wealth of dynamic behavior: pacemaker-like firing (seen in slice preparations), periods of burst activity, quiescence, and also sporadic activity in vivo (see e.g. Grace and Bunney, 1984a,b; Overton and Clark, 1997). Given this rich behavior and due to their biological importance, much

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work has been done on modeling DAergic neurons. Certain existing models only consider the subthreshold behavior of the DA cells (Amini et al., 1999; Canavier et al., 2007) and argue by analogy the expected behavior of the DA cells. Other models depend on the interaction between the activity at the soma and the dendrites (Wilson and Callaway, 2000; Kuznetsov et al., 2006; Canavier et al., 2007) in order to produce bursting dynamics (with this approach certain parameters may be unobservable). However, recent experimental findings (Blythe et al., 2009; Deister et al., 2009) indicate that burst firing can be generated somatically with the dendrites silenced. These somatically induced bursts had characteristics consistent with normal bursting, suggesting that somatic mechanisms for burst generation in a single-compartmental model should be sufficient for generating the observed DA neuronal dynamics. In this work, we introduce such a model for DA neuronal dynamics.

2. DA cell model

We introduce a single compartmental conductance based model for the dynamics of a DA neuron that combines conductance mechanisms previously included in Kuznetsov et al. (2006) and Amini et al. (1999). The dynamics of the membrane potential are taken to be

$$C_m \frac{dV}{dt} = I_{applied} - I^L_{\mathrm{Ca}}(V) - \chi_{APA} I^{SK}_K(V,u) - I_K(V) - I_{leak} - I_{GABA} - I^{dr}_K(V,n) - I_{NMDA}(V) - \chi_{TTX} I_{\mathrm{Na}}(V,h)$$

where $I_{applied}$ is a generic term met to incorporate effects due to intrinsic dynamics and either an applied current in vitro or the tonic input to the area in vivo. The DA neuron receives GABAergic inhibition, and, in this work, we do not explicitly track the dynamics for the GABA activity, but consider it to be given by $g_{GABA}\ (E_{GABA} - V)$ with g_{GABA} taken to be 0.01 ms/cm^2 and $E_{GABA} = -65$ mV. Additionally, we take the membrane capacitance to be $C_m = 1\ \mu$F/cm^2 and include a leak current, $I_{leak} = 0.02(E_{leak} - V)$ with $E_{leak} = -50$ mV. The generalized potassium current is given by

$$I_K(V) = \bar{g}_K \left(\frac{1}{1 + \exp\frac{-(V-k_1)}{k_2}} \right)(E_K - V) \tag{1}$$

with $E_K = -90$ mV (other parameters listed in Appendix A).

The L-type calcium current, I^L_{Ca}, is counterbalanced with the apamin sensitive SK-type potassium current, I^{SK}_K. Application of the drug apamin selectively blocks the SK current, which is principally dependent on both the voltage and calcium level, with the cytosolic calcium concentration denoted by u.

The L-type calcium current is of the form as in Kuznetsov et al. (2006) with

$$I^L_{\mathrm{Ca}}(V) = G^L_{\mathrm{Ca}}(V)(E_{\mathrm{Ca}} - V) \tag{2}$$

with $E_{\mathrm{Ca}} = 100$ mV and the voltage dependent conductance G^L_{Ca} given by

$$G^L_{\mathrm{Ca}}(V) = \bar{g}^L_{\mathrm{Ca}} \left(\frac{\alpha_C(V)}{\alpha_C(V) + \beta_C(V)} \right)^4$$

with

$$\alpha_C(V) = -0.0032 \frac{(V+50)}{\exp(-(V+50)/5) - 1}$$

and

$$\beta_C(V) = \exp\left(\frac{-(V+55)}{40} \right)$$

Whereas the SK potassium current is given by

$$I^{SK}_K(V,u) = G_{SK}(u)(E_K - V) \tag{3}$$

where $G_{SK}(u) = \bar{g}_{SK}\left(\frac{u^4}{u^4 + K_1^4}\right)$.

Calcium enters the cell predominantly via the L-type calcium channel. The Ca^{2+} is then ejected via a pump. Thus, calcium, u, varies as

$$\frac{du}{dt} = \frac{2 f_{\mathrm{Ca}}}{r} \left(\frac{I^L_{\mathrm{Ca}}}{H} - I_{pump} \right) \tag{4}$$

where the cytosolic buffering constant is given by $f_{\mathrm{Ca}} = 0.01$; H is a lumped term involving the valence of calcium and Faraday's number ($H \approx 0.0193$); the radius, r, of the neuron is taken to be $r = 20\ \mu$m. The pump dynamics are taken to be (akin to Canavier et al., 2007):

$$I_{pump}(u) = \frac{M_{pump} u}{(u + K_{pump})} \tag{5}$$

with $M_{pump} = 450$ (nM μm)/ms and $K_{pump} = 700$ nM.

2.1. Subthreshold behavior: modeling pharmacology

Tetrodotoxin (TTX) blocks the sodium current, and, without the sodium dynamics, no spikes occur. There are several other processes that become activated during spikes (these are referred to as active processes) and are rendered mostly redundant under TTX application: the delayed rectifying current (I^{dr}_K) and NMDA (I_{NMDA}) currents. Under TTX application ($\chi_{TTX} = 0$), our model captures the qualitative underlying, 'subthreshold' activity. As seen in Fig. 1a under TTX application and $I_{applied} = 0.4\ \mu$A/cm^2, the system exhibits a slowly oscillating potential (SOP) (Kang and Kitai, 1993) that is hypothesized to play a role in providing the underlying structure for regular firing (e.g., Amini et al., 1999). As the membrane potential rises above −40 mV, had TTX not been applied, the DA neuron would fire in this regime.

With the further addition of the drug apamin, the SK-channels are silenced and the L-type calcium signal would then dominate the subthreshold behavior (Ping and Shepard, 1996). The parameter χ_{APA} is associated with the strength of the SK channels, setting $\chi_{APA} = 1$ signifies no apamin applied whereas $\chi_{APA} = 0$ would signify the complete blockage of SK channels due to a high concentration of apamin. In Fig. 1b, the produced voltage trace exhibits a square-wave-like behavior with long plateaus of depolarization (similar to experimental findings, e.g., Ping and Shepard, 1996). It is hypothesized that upon these plateaus of depolarization burst firing is initiated, suggesting that burst generation critically depends upon the calcium dynamics (Grace and Bunney, 1984a).

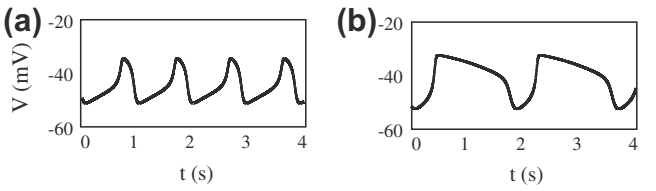

Fig. 1. The subthreshold behavior of a DA neuron. In (a), note the slowly oscillating potential (SOP), whereas, in (b) there are plateaus of depolarization where burst events are hypothesized to occur. The values for χ_{APA} are 1 and 0.025 in (a) and (b), respectively. Note that as M_{pump} is reduced, the underlying frequency would then oscillate at a slower frequency or possibly fall into a stable fixed point.