In the visual pathway, the first processing center of visual information is located in the retina, and spike output of the retinal ganglion cells (RGCs) codes the processed information that is transmitted to the lateral geniculate nucleus (LGN) and then to the visual cortex. Thus, it is of great importance to investigate the characteristics of the intrinsic firing that RGCs exhibit, particularly, how the firing is generated and how it can be modulated under different physiological and pharmacological conditions.

Several previous studies suggested that the discharges of RGCs are largely dependent on the kinds of synaptic inputs, while some other studies reported that the firing activities of RGCs are mainly determined by the intrinsic ionic channel dynamics. For instance, electrophysiological recordings on mouse RGCs have revealed that a persistent sodium current has a crucial effect on the generation of spontaneous activity. Another experimental study on rat RGCs has demonstrated that the emergence of rebound excitation is probably triggered by the hyperpolarization-activated mixed-cation current. It was also found that adaptation in the firing activity of RGCs can be generated and modulated by a slowly inactivating sodium current and a delayed-rectifier potassium current. Investigations also found that synaptic currents can regulate the firing activities of RGCs, e.g., N-methyl-D-aspartate (NMDA) synaptic current has been shown to regulate resting activity, spontaneous burst activity, and the delay of spike onset in RGCs.

Tonic and phasic activities are two typical firing behaviors observed in many types of neurons, e.g., LGN relay neurons, midbrain dopaminergic neurons, pallidal neurons, locus coeruleus neurons, olfactory receptor neurons, and RGCs. Generally speaking, tonic firing refers to a sustained response, which activates during the course of the stimulus; while phasic firing refers to a transient response with one or few action potentials at the onset of stimulus followed by accommodation. It was reported that tonic and phasic activities observed in guinea pig RGCs could be significantly regulated by the activation of cGMP-gated currents. However, the mechanisms underlying the generation of these 2 firing patterns are still unclear. Thus, in this study, our primary objective is to investigate the possible ionic mechanisms that generate tonic and phasic firing behaviors using computational approaches.

Over the past 2 decades, several computational models have been successfully constructed to model the diverse firing behaviors of RGCs. Based on data from salamander RGCs obtained with whole cell recordings, Fohlmeister, Coleman, and Miller constructed an excitability model, consisting of 5 voltage-gated ion channels, specifically, sodium, delayed-rectifier potassium,
calcium, A-type potassium, and calcium-activated potassium channels (FCM model). The model has excellent performance in reproducing the repetitive activities of RGCs. Subsequently, in order to analyze the adapting firing behavior of RGCs, Kim and Rieke revised the conventional sodium current by introducing 2 slow variables, aiming to mimic the inactivation of sodium current. Thus, the revised sodium current, together with a leakage current, constituted a new model (KR model). Numerical results indicated that the KR model can the adapting behavior seen in experimental observations.

To investigate the generation of tonic and phasic activities, we combined and modified these 2 models (FCM and KR). Our results demonstrate that the new model cannot only maintain the capacity in reproducing the repetitive firing and adapting activities seen in the 2 previous models, but it can also exhibit the tonic and phasic activities. Results from our modified model may help identify the ionic mechanisms for these 2 firing patterns. In the last part of this study, potential modulatory effects of NMDA-mediated synaptic input on the tonic and phasic activities were studied, and some interesting phenomena were observed.

Results

Reproducing the repetitive firing and adapting activity of RGCs

Simulation results shown in Figure 1 illustrate that the modified model can reproduce the general repetitive spiking activity similar to that observed in previous experiments and

![Figure 1](image1)

**Figure 1.** Repetitive firing activity of retinal ganglion cell without adaptation under constant stimulus intensity, $\lambda = 0$. (A-C) The value of $I$ is 0.5, 1.5, 2.5 $\mu$A/cm$^2$ respectively.

![Figure 2](image2)

**Figure 2.** Adapting firing behavior of retinal ganglion cell when subjected to constant current injection. (A) Simulated adapting behavior using the modified model ($I = 1.5$ $\mu$A/cm$^2$, $\lambda = 2.0$). (B) Variation of sodium current. (C and D) Variations of the 2 slow variables, $s_1$ and $s_2$. 
model results\textsuperscript{5,24-26} when the 2 slow variables $s_1$ and $s_2$ are not included. The larger the stimulus intensity, more spikes the neuron would elicit.

As illustrated in Figure 2A, under a constant stimulus, the model exhibits the adapting firing behavior which is similar to that observed in previous experiments.\textsuperscript{27-29} Diagrams illustrated in Figure 2B–D are the variations of the sodium current and the 2 slow variables, the changes of which are analogous to previous reports.\textsuperscript{8}

**Functional effects of different ion channels on the adapting activity**

A recent pharmacological experiment on guinea pig RGCs indicated that in addition to sodium channel inactivation, the generation of adapting behavior may depend on delayed-rectifier potassium channels, but has little relation to calcium channels and calcium-dependent potassium channels.\textsuperscript{6} As our model contains these channels, each of them was removed to explore whether the variation of these ion channels can lead to similar conclusions as reported.\textsuperscript{6}

It was shown that depolarized and hyperpolarized prepulse exhibit different suppressive effects on the subsequent adapting activities in RGCs,\textsuperscript{6} i.e., spikes in the adaptation period following depolarized prepulse is fewer than that following hyperpolarized prepulse. Results demonstrated in Figure 3A–B can confirm this phenomenon. Results in Figure 3C–F demonstrate that compared with the data in Figure 3B (all channels are included), removal of the calcium channel (Fig. 3C) and the calcium-dependent potassium channel (Fig. 3D) have little influence on the firing rate of the original adapting activity. The delayed-rectifier potassium channel in our model mainly contributes to the repolarization of the action potentials and removal of it makes the membrane potential stay in a high-depolarized state (data not shown). When decreasing $g_{K}$ to a low level, the corresponding result presented in Figure 3E shows that it changes the adapting firing behavior observably, consistent with experimental results.\textsuperscript{6}

Blocking the A-type potassium channel leads to an obvious change in the firing behavior of RGCs (Fig. 3F). However, Wieck and Demb\textsuperscript{6} suggested that adding the 4-aminopyridine (4-AP) to specifically block the A-type potassium channels would not change the adapting firing behavior significantly. Thus, there is some inconsistency between model results and the experimental observations.

**Tonic and phasic activity are mainly controlled by the collective actions of $I_{Na}$ and $I_{K}$**

A recent experimental study together with computer modeling of CA1 pyramidal cells suggested that transient sodium current and delayed-rectifier potassium current activate collectively in determining the response properties of CA1 pyramidal cells, especially the tonic firing activity.\textsuperscript{30} Since our model contains a sodium current (the inactivating type) and the delayed-rectifier potassium current, whether they contribute to produce the tonic and phasic activities of RGCs was investigated.

Model results in Figure 4A–C show that the neuron exhibits typical tonic activity in response to small stimulus steps, while larger stimuli make the action potentials disappear in the late period of stimulus, consistent with a phenomenon called
depolarization block (and comparable with the firing in CA1 pyramidal cells). This result induced by increased stimulus intensity, is quite similar to what was observed in previous experiments.

Results in Figure 4D–F show that the neuron generates phasic activity with only one spike during a small stimulus step (Fig. 4D), and that increased stimulus amplitude makes the neuron elicit more spikes (Fig. 4E–F). This trend of phasic activity induced by increased stimulus amplitude is also quite similar to previous experimental observations.

A more intuitive result is demonstrated in Figure 5A, which shows how the spike counts of tonic and phasic activities vary with increases of injected current. One can also observe from Figure 5A that the spike counts of phasic activities are significantly lower than those of tonic activities. Results in Figure 5B also show that phasic RGC always fire its first spike in a short latency, while tonic RGC has a long latency under weak stimulus, and a short latency under strong stimulus.

To further illustrate the roles of $g_{Na}$ and $g_K$ in shaping the tonic and phasic activity in depth, a dynamic map of the two firing patterns under different combinations of $g_{Na}$ and $g_K$ is shown in Figure 6. It is clear that for a constant stimulus ($I = 2.8 \mu A/cm^2$), phasic activity is preferred when the values of $g_{Na}$ and $g_K$ are approximate, indicating that rapid accommodation in phasic activity is probably caused by the balanced activation of sodium current and potassium current. Tonic activity is more likely to emerge when $g_{Na}$ is much bigger than $g_K$, suggesting that sustained firing is likely to be induced by the larger amplitude of sodium current (which is well recognized to be responsible for the generation of action potentials). It should be noted that the proportion of $g_K$ relative to $g_{Na}$ in mimicking the phasic activity is large, which may beyond the physiological range. As spike block needs a large proportion of outward potassium channels, and in our study, we only adjusted the conductance of one potassium channel (Delayed-rectifier type), thus, the $g_K$ is much higher than its true value in balancing the effect of $g_{Na}$. This is a limitation of our model.

Differential roles of magnesium concentration in the modulation of tonic and phasic activities

In the above sections, we discussed tonic and phasic activities elicited in response to constant current steps, without any simulated synaptic inputs. However, previous studies have suggested that firing behaviors of RGCs could be influenced by synaptic inputs, especially the NMDA-type. Thus, in this section, the tonic and phasic activities of RGCs are analyzed under simulated NMDA-type input instead of square current steps, to investigate whether these 2 kinds of input lead to distinct firing activities.

Since previous evidence has indicated that NMDA currents can be modulated by extracellular magnesium concentrations, variations of synaptic conductance ($\overline{g}_{NMDA}$) with respect to membrane voltage under 3 different magnesium concentrations are illustrated in Figure 7A. It is clear that when no magnesium is present, the value of $\overline{g}_{NMDA}$ is constant (according to the expression demonstrated in Box 1). However, when magnesium is present, the value of $\overline{g}_{NMDA}$ changes in a sigmoidal manner with respect...
to voltage, similar to reported results. The variation of NMDA current with respect to voltage is also provided in Figure 7B. The manner in which variation of synaptic strength induced by magnesium influences the tonic and phasic activities of RGCs were further studied.

In the case of tonic activity, when the magnesium concentration is zero (Figure 8A), it is apparent that the increase of synaptic conductance (when large enough) induces the disappearance of action potentials in the late period of stimulus, which is similar to the results in Figure 4. Under a moderate level of magnesium (0.5 mM in Figure 8C–D1), the tonic spike count decreases in response to a small synaptic conductance, but it increases under a large synaptic conductance. And when the level of magnesium is relatively high (1.0 mM in Fig. 8E1–F1), spike count in response to small synaptic conductance stimuli continues to decrease, while the spike count during large simulated synaptic conductances tend to decrease.

However, in the case of phasic activity, the presence of magnesium ions suppresses the firing of the neuron (Fig. 8A2–F2), regardless of the amplitude of simulated synaptic conductance. The variations of spike counts with the increase of maximal synaptic conductance under 3 different levels of magnesium concentration for the tonic and phasic activities is shown in Figure 9. From this, one can clearly see that the NMDA synaptic current, which is modulated by magnesium concentration, exhibits differential roles in modulating the dynamics of tonic and phasic activities.

**Discussion**

In the present study, we performed a computational investigation of the generation of tonic and phasic firing behaviors of RGCs using an ionic model, and analyzed the modulation of tonic and phasic activities by Mg2+ regulated NMDA synaptic currents. Our results show that the modified model provides insights regarding the possible ionic mechanisms underlying the initiation of these 2 firing activities. Our results also demonstrate that the magnesium dependence embedded in the NMDA-mediated synaptic current differentially influences the spike counts of tonic and phasic activities.
Figure 7. Variations of \( \tilde{g}_{\text{NMDA}} \) and \( I_{\text{Na}} \) with respect to membrane potential under different concentrations of magnesium ions, the maximal conductance is 0.5 mS/cm². (A) \( \tilde{g}_{\text{NMDA}} \) vs voltage. (B) \( I_{\text{Na}} \) vs voltage.

Box 1. Specific expressions of currents and the corresponding gating variables

| Currents | Gating variables |
|----------|------------------|
| \( I_{\text{Na}} = g_{\text{Na}} m^3 h s_1 s_2 (V - V_{\text{Na}}) \) | \( \alpha_n = \frac{-0.1(V + 30)}{\exp(-(V + 30)/10) - 1} \) \( \beta_n = 4 \exp(-(V + 55)/18) \) |
| | \( \alpha_h = 0.07 \exp(-(V + 50)/20) \) \( \beta_h = \frac{1}{1 + \exp(-(V + 20)/10)} \) |
| | \( \alpha_s = 0.00034 \exp(-V/63) \) \( \beta_s = 0.0014 \frac{1}{1 + \exp(-V + 47)/4.7} \) |
| \( I_K = g_K n^4 (V - V_K) \) | \( \alpha_n = 0.02(V + 40)/10 \) \( \beta_n = 0.4 \exp(-(V + 50)/80) \) |
| \( I_{\text{Ca}} = g_{\text{Ca}} C^3 (V - V_{\text{Ca}}) \) | \( \alpha_s = 0.3(V + 13)/10 \) \( \beta_s = 10 \exp(-(V + 38)/18) \) |
| \( I_A = g_A a^3 b(V - V_K) \) | \( \alpha_s = 0.006(V + 90)/10 \) \( \beta_s = 0.1 \exp(-(V + 30)/10) \) |
| | \( \alpha_h = 0.04 \exp(-(V + 70)/20) \) \( \beta_h = \frac{0.6}{1 + \exp(-(V + 40)/10)} \) |
| \( I_{\text{KCa}} = g_{\text{KCa}} \left[ \frac{[Ca^{2+}]}{[Ca^{2+}]_{\text{dist}}} \right] \left( V - V_K \right) \) | \( I_L = g_L (V - V_L) \) |
| \( I_{\text{NMDA}} = \tilde{g}_{\text{NMDA}} (V - V_{\text{NMDA}}) \) | \( \tilde{g}_{\text{NMDA}} = \frac{g_{\text{NMDA}}}{1 + e^{-0.062 \left[ Mg^{2+} \right]/3.57}} \) |
Figure 8. Modulation of tonic and phasic activities by magnesium concentration (mM) under different maximal synaptic conductances (mS/cm²), $\lambda = 0$. (A1-F1) Tonic activity. (A2-F2) Phasic activity. Variations of $I_{NMDA}$ are shown in the bottom of each subgraphs, and the zero value of $I_{NMDA}$ was adjusted to ~80.
As 2 widely observed firing behaviors in neuronal systems, tonic and phasic firing activities have been found in neurons from different brain regions. The functional roles for these 2 behaviors have also been subject to intensive investigations during the past decades. For instance, they possess prominent effects in the encoding of reward and punishment signals, modulation of conditioned fear behaviors, occupation of dopamine receptors, mediation of behavioral conditioning, and synaptic plasticity. Since tonic and phasic firings encode important neural information, the underlying mechanisms should be clarified. Based on our model results, we infer that in RGCs, 2 currents, i.e., the inactivating sodium current and the delayed-rectifier potassium current, contribute collectively to the occurrence of tonic and phasic activities. Similar conclusions have been drawn in CA1 pyramidal cells, in which it was shown that tonic activity is triggered by the concerted actions of transient sodium currents and delayed-rectifier potassium currents. However, an important distinction is that the sodium current we used in the RGC model is responsible for adapting activities of ganglion cells, whereas the sodium current in the CA1 pyramidal cell model does not induce adapting behaviors of pyramidal cells. Nevertheless, Bianchi et al. also reported that adaptation currents in the pyramidal cell model exhibit some regulatory roles in the tonic activity, consequently, the inference we draw that two adaptation currents (inactivating sodium current and delayed-rectifier potassium current) contribute collectively to the generation of tonic and phasic activities in the RGCs, is reasonable.

Although our modified model has many good features, there is still a disadvantage that the model fails to reproduce the effect of $I_{\text{A}}$ on influencing the adapting activity of RGCs. Weick and Demb applied 4-AP to specifically block $I_{\text{A}}$, however, other studies have shown that 4-AP cannot only block $I_{\text{A}}$ but can also affect calcium channels, calcium-dependent potassium channels, and sodium channels. Thus, the effect of 4-AP may be more general and diffuse. In our model, we only altered the activation of $I_{\text{A}}$, and this might be the reason that our model result is inconsistent with the experimental observation.

NMDA receptors are a major receptor participating in the synaptic transmission of neural signals, and many neurons in the brain have already been found to express this receptor, e.g., midbrain dopaminergic cells, hippocampal pyramidal neurons, and RGCs. The roles of magnesium ions in the activation of NMDA current have also been widely reported. Thus, changes of magnesium concentration would lead to corresponding variations of NMDA synaptic current with subsequent influences on the firing behavior of postsynaptic neurons. In our model study, we find that magnesium concentration effects embedded in the NMDA synaptic current are vital in regulating the tonic and phasic activities of RGCs, and that the regulation is rather different for the 2 firing patterns.

As the sole output neurons in the retina, the activities of ganglion cells have attracted much attention for their significant roles in the encoding and transmission of visual signals, which may be manifested in a variety of firing patterns. The modified model we proposed in this study has successfully reproduced several firing behaviors, thus, it can be used as a good basis for simulating some other firing patterns, and to further uncover the possible mechanisms that may mediate those firing patterns.

**Models and Methods**

The model we proposed in this study was integrated from the FCM model and the KR model. Similar to the FCM model, our model mainly contains 5 voltage-gated ion channels, i.e., inactivating sodium ($I_{\text{Na}}$), delayed-rectifier potassium ($I_{\text{K}}$), calcium ($I_{\text{Ca}}$), A-type potassium ($I_{\text{A}}$), and calcium-activated potassium ($I_{\text{CaK}}$) channels. The expressions and parameters for the ion channels were adopted from reference 23. In the last part of our study, the effects of synaptic input, particularly the NMDA-type was considered, and the expression of $I_{\text{NMDA}}$ was adopted from reference 23.

Detailed description of the modified model is as following:

![Figure 9](image.png)

**Figure 9.** Variations of spike counts with respect to $g_{\text{NMDA}}$ under different magnesium concentrations. (A) Tonic activity. (B) Phasic activity.
\[
C_m \frac{dV}{dt} = -I_Na - I_K - I_{Ca} - I_A - I_{KCa} - I_{NMDA} - I_L + I + \lambda \xi(t)
\]

(1)

where, \( C_m = 1 \ \mu F/cm^2 \) is the specific membrane capacitance, \( I \) is the stimulus current applied to the neuron, \( \xi(t) \) is the Gaussian white noise, with zero mean, and

\[
\langle \xi(t) \xi(t - \tau) \rangle = \delta(\tau)
\]

(2)

\( \delta(\tau) \) is the delta function, \( \lambda \) is the noise intensity.

Specific expressions and gating variables for each currents are illustrated in Box 1, where \( g_{Na}, g_K, g_{Ca}, g_A, g_{KCa}, g_i \) are the maximal conductances for the corresponding ion channels, and their values are: 80, 12, 2.2, 36, 0.05, and 0.05 respectively; \( V_{Na}, V_K, V_Ca \) are the equilibrium potentials, and the values for \( V_{Na}, V_K \) are 35, -75 mV respectively, while the value of \( V_Ca \) is time-dependent (Eq. 2).

\[
V_{Ca} = \frac{RT}{ZF} \ln \left( \frac{[Ca^{2+}]_e}{[Ca^{2+}]_i(t)} \right)
\]

(2)

where \( R = 8.314 \ J/(M\cdotK) \) is the gas constant, \( T = 295 \ K \) is the temperature in Kelvin, \( Z \) is the ionic valency, \( F = 96485 \ C/M \) is the Faraday constant, \( Ca^{2+} \) is the extracellular calcium ions, and the variation of intracellular calcium ion concentration \( [Ca^{2+}] \), obeys the Equation 3.1

\[
\frac{d[Ca^{2+}]_i}{dt} = \frac{-SI_{Ca}}{Fr} - \frac{[Ca^{2+}]_i - [Ca^{2+}]_{res}}{\tau_{Ca}}
\]

(3)

where \( r = 22 \ \mu m \) means the depth of the shell beneath the membrane for the calcium pump, and \( \tau_{Ca} \) is the time constant for calcium current, which value is 1.5 ms. The residual level of the free intracellular calcium ions is \([Ca^{2+}]_{res} = 0.001 \ mM\), and the calcium dissociation constant is \([Ca^{2+}]_{diss} = 0.001 \ mM/dm^3\).

In the expression of \( I_{Na}, I_K, \) and \( I_{KCa} \) are 2 slow variables which can mimic the inactivation of \( I_{Na} \). As reported by Kim and Rieke, \( I_K \) is voltage-dependent, while \( I_{KCa} \) is spike-dependent.8

The voltage-dependent gating variables are described below:

\[
\frac{dx}{dt} = \alpha_x (1-x) - \beta_x x \ (x = m, h, n, c_a, b, s_i)
\]

(4)

And the spike-dependent slow variable \( s_i \) is described by the following equation:

\[
\frac{ds_i}{dt} = \alpha_s (1-s_i)
\]

(5)

Except when the neuron fires a spike, the variable \( s_i \) should be decreased by a factor of 0.77.8

In the expression of \( I_{NMDA}, g_{NMDA} \) is the synaptic conductance, \( V_{NMDA} \), is the synaptic reversal potential, which is 0 \( mV \), \( g_{NMDA} \) is the maximal conductance, and \([Mg^{2+}] \) is the extracellular magnesium concentration.

Simulations of the RGCs activities were performed in the MATLAB environment (R2010a), and the fourth-order Runge-Kutta algorithm was employed to calculate the voltage values of RGCs with time step of 0.01 ms.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
1. Kandel ER, Schwartz JH, Jessell TM. Principles of neural science. New York, NY: McGraw-Hill, 2000.
2. Arai I, Yamada Y, Asaka T, Tachibana M. Light-evoked oscillatory discharges in retinal ganglion cells are generated by rhythmic synaptic inputs. J Neurophysiol 2004; 92:715-25; PMID:15277593; http://dx.doi.org/10.1152/jn.00159.2004
3. Brown SP, Masland RH. Spatial scale and contrast substrate of contrast adaptation by retinal ganglion cells. Nat Neurosci 2001; 4:44-51; PMID:11135644; http://dx.doi.org/10.1038/882888
4. Margolis DJ, Derwiler PB. Different mechanisms generate maintained activity in ON and OFF retinal ganglion cells. J Neurosci 2007; 27:5994-6005; PMID:17537971; http://dx.doi.org/10.1523/JNEUROSCI.1030-07.2007
5. Fohlemiter JF, Miller RF. Impulse encoding mechanisms of ganglion cells in the tiger salamander retina. J Neurophysiol 1997; 78:1935-47; PMID:9325362
6. Weick M, Demb JB. Delayed-rectifier K channels contribute to contrast adaptation in mammalian retinal ganglion cells. Neuron 2011; 71:166-79; http://dx.doi.org/10.1016/j.neuron.2011.04.033
7. Lee SC, Ishida AT. Ih without Kir in adult rat retinal ganglion cells. J Neurophysiol 2007; 97:3790-9; PMID:17488978; http://dx.doi.org/10.1152/jn.00241.2006
8. Kim JK, Rieke F. Slow Na+ inactivation and variance adaptation in salamander retinal ganglion cells. J Neurophysiol 2003; 90:1506-16; PMID:12598639
9. Gortessem J, Miller RF. N-methyl-D-aspartate receptors contribute to the baseline noise of retinal ganglion cells. J Neurosci 2003; 23:10506-16; PMID:12598639
10. Sernagor E, Grzywacz NM. Spontaneous activity in developing turtle retinal ganglion cells. J Neurophysiol 1999; 81:1069-87; PMID:10355608
11. Diamond JS, Copenhagen DR. The contribution of NMDA and non-NMDA receptors to the light-evoked input-output characteristics of retinal ganglion cells. Neuron 1993; 11:725-38; PMID:8104431; http://dx.doi.org/10.1016/0896-6273(93)90082-3
12. Augustinat S, Rukseas. Analysis of bursting activity in phasic and tonic components of dLGN relay cell responses. Biophysica (Vilnius) 2004; 4:19-25
13. Aggarwal M, Wickens JR. A role for phasic dopamine neuron firing in habit learning. Neuron 2011; 72:892-4; PMID:22196325; http://dx.doi.org/10.1016/j.neuron.2011.12.006
14. Favre J, Tah J, Baumann T, Burchiel K. Computer analysis of the tonic, phasic, and kinesthetic activity of palidial discharges in Parkinson patients. Surg Neurol 1999; 51:665-72; discussion 672-3; PMID:10562397; http://dx.doi.org/10.1016/S0090-9954(99)00630-0
15. Devilbliss DM, Waterhouse BD. Phasic and tonic patterns of locus coeruleus output differentially modulate sensory network function in the awake rat. J Neurophysiol 2011; 105:60-87; PMID:20980542; http://dx.doi.org/10.1152/jn.00445.2010
16. Madrid R, Sanchez M, Alvarez O, Bacigalupo J. Tonic and phasic receptor neurons in the vertebrate olfactory epithelium. Biophys J 2003; 84:4167-81; PMID:12770919; http://dx.doi.org/10.1016/S0006-3495(03)75141-8
17. Tabata T, Kano M. Heterogeneous intrinsic firing properties of vertebrate retinal ganglion cells. J Neurophysiol 2002; 87:30-41; PMID:11784727
18. Mitra P, Miller RF. Normal and rebound impulse firing in retinal ganglion cells. Vis Neurosci 2007; 24:79-90; PMID:17430611

19. Rothe T, Bähring R, Carroll P, Granyn R. Repetitive firing deficits and reduced sodium current density in retinal ganglion cells developing in the absence of BDNF. J Neurobiol 1999; 40:407-19; PMID:10440740; http://dx.doi.org/10.1002/(SICI)1097-4695(19990905)40:3<407::AID-NEU12>3.0.CO;2-T

20. Kuznetsov KI, Maclow VY, Fedulova SA, Veselovsky NS. Calcium signals induced by tonic firing in rat retinal ganglion cells. Int J Physiol Pathophysiol 2012; 3:53-9; http://dx.doi.org/10.1615/IntJPhysPathophys.v3.i1.60

21. Kawa F, Sterling P. cGMP modulates spike responses in the dendritic morphologies of retinal ganglion cells. J Physiol 2002; 538:787-90; PMID:11826165; http://dx.doi.org/10.1113/jphysiol.2001.013009

22. Fohlmeister JF, Coleman PA, Miller RF. Modeling sodium current modulates retinal ganglion cell response rate to electrical stimulation. J Neural Eng 2011; 8:066007; PMID:22077996; http://dx.doi.org/10.1088/1741-2550/8/6/066007

23. Sikora MA, Gottesman J, Miller RF. A computational model of the ribbon synapse. J Neurosci Methods 2005; 145:47-61; PMID:15922025; http://dx.doi.org/10.1016/j.jneurner.2004.11.023

24. Fohlmeister JF, Miller RF. Mechanisms by which cell geometry controls repetitive impulse firing in retinal ganglion cells. J Neurophysiol 1997; 78:1948-64; PMID:9325363

25. Sheasby BW, Fohlmeister JF. Impulse encoding across the dendritic morphologies of retinal ganglion cells. J Neurophysiol 1999; 81:1685-98; PMID:10290294

26. Fohlmeister JF, Cohen ED, Newman EA. Mechanisms and distribution of ion channels in retinal ganglion cells: using temperature as an independent variable. J Neurophysiol 2010; 103:1357-74; PMID:20053849; http://dx.doi.org/10.1152/jn.00123.2009

27. Wong RC, Cloherry SL, Ibbotson MR, O’Brien BJ. Intrinsic physiological properties of rat retinal ganglion cells with a comparative analysis. J Neurophysiol 2012; 108:2008-23; PMID:22786958; http://dx.doi.org/10.1152/jn.00190.2011

28. O’Brien BJ, Isayama T, Richardson R, Berson DM. Intrinsic physiological properties of cat retinal ganglion cells. J Physiol 2002; 538:787-802; PMID:11826165; http://dx.doi.org/10.1113/jphysiol.2001.030009

29. Tsai D, Morley JW, Suanning GJ, Lovell NH. Frequency-dependent reduction of voltage-gated sodium current modulates retinal ganglion cell response rate to electrical stimulation. J Neural Eng 2011; 8:066007; PMID:22077996; http://dx.doi.org/10.1088/1741-2550/8/6/066007

30. Bianchi D, Marasco A, Limongiello A, Marchetti C, Marie H, Tirozzi B, Miglione M. On the mechanisms underlying the depolarization block in the spiking dynamics of CA1 pyramidal neurons. J Comput Neurosci 2012; 35:207-25; PMID:22310969; http://dx.doi.org/10.1007/s10877-012-0383-y

31. Yang YC, Lee CH, Kuo CC. Ionic flow enhances low-affinity binding: a revised mechanistic view into Mg2+ block of NMDA receptors. J Physiol 2010; 588:633-50; PMID:20026615; http://dx.doi.org/10.1113/jphysiol.2009.178913

32. Wu YN, Johnson SW. Rotenone reduces Mg2+-dependent block of NMDA currents in substantia nigra dopamine neurons. Neurotoxicology 2009; 30:320-5; PMID:19428506; http://dx.doi.org/10.1016/j.neuro.2009.01.002

33. Vargas-Caballero M, Robinson HP. Fast and slow voltage-dependent dynamics of magnesium block in the NMDA receptor: the asymmetric trapping block model. J Neurosci 2004; 24:6171-80; PMID:15240809; http://dx.doi.org/10.1523/JNEUROSCI.1380-04.2004

34. Ha J, Kuznetsov A. Interaction of NMDA receptor and pacemaking mechanisms in the midbrain dopaminergic neuron. PLoS One 2013; 8:e69984; http://dx.doi.org/10.1371/journal.pone.0069984

35. Schultz W. Getting formal with dopamine and reward. Neuron 2002; 36:241-63; PMID:12383780; http://dx.doi.org/10.1016/S0896-6273(02)00967-4

36. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Distinct tonic and phasic anticipatory activity in lateral habenula and dopamine neurons. Neuron 2010; 67:144-55; PMID:20624598; http://dx.doi.org/10.1016/j.neuron.2010.06.016

37. Ciocchi S, Herry C, Grenier F, Wolf SB, Leritzus JJ, Vlachos I, Ehrlich I, Sprengel R, Deisseroth K, Stadler MB, et al. Encoding of conditioned fear in central amygdala inhibitory circuits. Nature 2010; 468:277-82; PMID:21068837; http://dx.doi.org/10.1038/nature09559

38. Dreyer JK, Herrick KF, Berg RW, Houtsma GD. Influence of phasic and tonic dopamine release on receptor activation. J Neurosci 2010; 30:14273-83; PMID:20962248; http://dx.doi.org/10.1523/JNEUROSCI.1894-10.2010

39. Tsai HC, Zhang F, Adamantidis A, Stuber GD, Bonci A, de Leece L, Deisseroth K. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. Science 2009; 324:1080-4; PMID:19389999; http://dx.doi.org/10.1126/science.1168878

40. Kim U, McCormick DA. The functional influence of burst and tonic firing mode on synaptic interactions in the thalamus. J Neurosci 1998; 18:9500-16; PMID:9801387

41. Hopper RA, Garthwaite J. Tonic and phasic nitric oxide signals in hippocampal long-term potentiation. J Neurosci 2006; 26:1513-21; PMID:17093072; http://dx.doi.org/10.1523/JNEUROSCI.2259-06.2006

42. Rogawski MA, Barker JL. Effects of 4-aminopyridine on calcium action potentials and calcium current under voltage clamp in spinal neurons. Brain Res 1983; 280:180-5; PMID:6652477; http://dx.doi.org/10.1016/0006-8993(83)91190-3

43. Perkova-Kirova P, Gagov H, Krien U, Duridanova D, Nasek T, Schubert R. 4-aminopyridine affects rat arterial smooth muscle BK(Ca) currents by changing intracellular pH. Br J Pharmacol 2000; 131:1643-50; PMID:11139442; http://dx.doi.org/10.1038/sj.bjp.0703742

44. Mei Y, Wu MM, Huan CL, Sun JT, Zhou HQ, Zhang ZH. 4-aminopyridine, a specific blocker of K(+) channels, inhibited inward Na(+)-current in rat cerebellar granule cells. Brain Res 2000; 873:46-53; PMID:10915809; http://dx.doi.org/10.1016/S0006-8993(00)02469-0

45. Shah MM, Haylett DGK. K+ currents generated by NMDA receptor activation in rat hippocampal pyramidal neurons. J Neurophysiol 2002; 87:2983-9; PMID:12037201