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Reduced Cooperativity of Voltage-Gated Sodium Channels in the Hippocampal Interneurons of Aged Mouse Model of Alzheimer's Disease

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Abstract

Beta amyloid ($A\beta$) associated with Alzheimer's disease (AD) leads to abnormal behavior in inhibitory neurons, resulting in hyperactive neuronal networks, epileptiform behavior, disrupted gamma rhythms, and aberrant synaptic plasticity. Previously, we used a dual modeling-experimental approach to explain several observations, including failure to reliably produce action potentials (APs), smaller AP amplitudes, higher resting membrane potential, and higher membrane depolarization in response to a range of stimuli in hippocampal inhibitory neurons from 12–16 month old female APPswe/PSEN1DeltaE9 (APdE9) AD mice as compared to age-matched non-transgenic (NTG) mice. Our experimental results also showed that AP initiation in interneurons from APdE9 mice are significantly different from that of NTG mice. APs in interneurons from NTG mice are characterized by abrupt onset and an upstroke that is much steeper and occurs with larger variability as compared to cells from APdE9 mice. The phase plot (the rate of change of membrane potential versus the instantaneous membrane potential) of APs produced by interneurons from APdE9 mice shows a biphasic behavior whereas that from NTG mice shows a monophasic behavior. Here we show that using the classic Hodgkin-Huxley (HH) formalism for the gating of voltage-gated sodium channels (VGSCs) in a single-compartment neuron, we cannot reproduce these features and a model that takes into account a cooperative activation of VGSCs is needed. We also argue that considering a realistic multi-compartment neuron where the kinetics of VGSC is modeled by HH formalism as done in the past, wouldn't explain our observations when APs from both NTG and APdE9 mice are considered simultaneously. We further show that VGSCs in interneurons from APdE9 mice exhibit significantly lower cooperativity in their activation as compared to those from NTG mice.

Keywords

Beta Amyloid; Alzheimer's disease; Interneurons; Cooperative gating of Na^+ channels; channelopathy

1 Introduction

The accumulation of beta amyloid ($A\beta$) oligomers and plaques due to the imbalance between synthesis and clearance is believed to be the driving force behind Alzheimer's disease (AD) pathogenesis (Hardy and Selkoe, 2002; Hébert et al, 2008; Sperling et al,

2011). Pathological levels of $A\beta$ have been linked to the disruption of several neuronal functions where a fine balance between the activity of excitatory and inhibitory neurons is key to the execution of the function. For example, excitatory neurons located near $A\beta$ plaques are shown to have enhanced activity that may result from decreased synaptic inhibition (Busche et al, 2008). $A\beta$ has also been shown to disrupt the natural brain rhythms associated with the sleep/wake cycle, decreasing the slow oscillation responsible for non-rapid eye movement sleep rhythms (Roh et al, 2012; Berridge, 2014). Gamma (Verret et al, 2012a) as well as beta rhythms (Pena et al, 2010) are also altered in neurons exposed to pathological levels of $A\beta$. Transgenic animal lines and AD patients both contain pathological levels of $A\beta$ and exhibit spontaneous epileptiform activity, indicating a correlation between the excessive $A\beta$ and imbalance between excitation and inhibition (Minkeviciene et al, 2009; Palop and Mucke, 2009; Amatniek et al, 2006). Furthermore, the acute application of $A\beta$ oligomers has been correlated with a decline in long term potentiation (Oddo et al, 2003; Townsend et al, 2006; Walsh et al, 2002), enhanced synaptic depression (Hsieh et al, 2006; Kamenetz et al, 2003; Hazra et al, 2013), and cognitive impairments (Roberson et al, 2011; Verret et al, 2012a). Despite strong evidence in favor of impaired neuronal network activity, the mechanism leading to such network behavior is incompletely understood (Palop and Mucke, 2010).

Several studies have attributed the altered neuronal network activity to the dysfunction of inhibitory neurons. The application of γ -aminobutyric acid type A ($GABA_A$) agonist diazepam markedly reduced the activity of hyperactive neurons near $A\beta$ plaques suggesting that an impaired synaptic inhibition rather than intrinsic firing of excitatory neurons underlies the hyperactivity (Busche et al, 2008). Due to their key role in gamma rhythm, Verret et al (Verret et al, 2012a) investigated parvalbumin inhibitory neurons (PV) in detail and found that the impairment of these cells leads to the observed spontaneous epileptiform activity, hypersynchrony, and reduced gamma oscillatory activity in human amyloid precursor protein (APP) (hAPP) transgenic mice and AD patients. In line with these observations, Hazra et al. reported the failure of inhibitory neurons to reliably fire action potentials (APs) leading to hippocampal dysfunction and profound disruptions in dentate gyrus (DG) circuit activity in APP^{sw}/PSEN1^{DeltaE9} (APdE9) aged mouse model of AD (Hazra et al, 2013). All these observations highlight the importance of the aberrant inhibitory neurons' activity in the early stages of AD and raises the key question: how do the pathological levels of $A\beta$ oligomers mediate the impairment of inhibitory neurons?

Previously, we used dual theoretical-experimental approach to identify the pathways leading to the impaired activity of inhibitory interneurons in the molecular layer of DG of aged mice model of AD. These cells are responsible for the feed-forward inhibition, exerting a powerful control on the excitability of the hippocampus by projecting into the perforant pathway fibers or into the perisomatic regions of granule cells (Armstrong et al, 2011). Our model explained many features, including failure to reliably produce APs, smaller AP amplitudes, higher resting membrane potential, and higher membrane depolarization in response to a range of stimuli in these inhibitory neurons from 12–16 month old female APdE9 mice as compared to age-matched non-transgenic (NTG) mice (Perez et al, 2016).

We also observed alterations in the initiation of APs produced by inhibitory neurons from APdE9 mice (Perez et al, 2016). Interneurons from NTG mice produce APs with rapid onset, steeper initiation upstroke, and a phase plot (the rate of change of membrane potential versus the instantaneous membrane potential) that is monophasic. Moreover, APs in NTG mice have larger onset variability (the membrane potential threshold at which AP initiates). In the presence of pathological amounts of A β oligomers, these characteristics change drastically. Under similar stimuli, APs produced by interneurons from APdE9 mice have less rapid and less variable onset. Furthermore, the onset potential is shifted to more negative values as compared to cells from NTG mice. In addition, we observed a transition from mono to biphasic behavior of the AP phase plot in interneurons from APdE9 mice.

Our previous single-compartment neuronal model that used the classic Hodgkin-Huxley (HH) formalism of voltage-gated sodium channels (VGSCs) fails to reproduce all these features of APs produced by interneurons from both NTG and APdE9 mice. We also argue that considering a realistic multi-compartment neuron where the kinetics of VGSC is modeled by HH formalism as done in the past (Yu et al, 2008a; McCormick et al, 2007), wouldn't explain our observations when APs from both NTG and APdE9 mice are considered simultaneously. To reproduce our observations, a model incorporating the cooperative activation of VGSCs is needed. Comparing the model results with experimental observations, we further show that the cooperativity in activation of VGSCs in interneurons from APdE9 mice is significantly reduced by A β as compared to cells from NTG mice.

2 Computational methods

Our formalism of single-compartment neuron is based on Wang-Buzsaki model (Wang and Buzsáki, 1996). The equations are modified to better represent the previously observed properties of APs produced by inhibitory interneurons in the molecular layer of DG, responsible for the feed-forward inhibition (Perez et al, 2016). For the purpose of this study, we incorporate the cooperative gating of VGSCs in the model following the protocol in (Huang et al, 2012). We remark that using the exact equations of Wang-Buzsaki model (Wang and Buzsáki, 1996) or those used by (Saraga et al, 2003) does not change our main conclusions. Similarly, our conclusions remain the same when dynamic ion concentrations and/or other membrane currents mentioned below are included in the model (conclusion based on simulation that are not included in the paper).

The change in the membrane potential (V_m) with respect to time is given by contributions from active and passive membrane currents (I_m), applied stimulus (I_{stim}), and random synaptic inputs (I_{noise}). That is,

$$C \frac{dV_m}{dt} = I_m + I_{stim} + I_{noise}. \quad (1)$$

I_m is given by contributions from total Na⁺ current (I_{Na}) and total K⁺ current (I_K).

$$I_m = -(I_{Na} + I_K), \quad (2)$$

where

$$I_K = I_K^{DR} + I_K^L \quad (3)$$

$$I_{Na} = I_{Na}^T + I_{Na}^L.$$

K^+ currents include delayed rectified (I_K^{DR}) and leak (I_K^L) currents. Na^+ currents include voltage-gated transient (I_{Na}^T) and leak (I_{Na}^L) currents. The two K^+ currents are given as:

$$I_K^{DR} = G_K^{DR} n^4 (V_m - V_K) \quad (4)$$

$$I_K^L = G_K^L (V_m - V_K).$$

In eq. 4 (and eq. 5), G_x represents the maximum conductance of a given channel x and n represents the activation variable of K^+ channel. The M, A, and Ca^{2+} -gated K^+ currents used in our previous work (Perez et al, 2016) are ignored as they do not change our conclusions. We also removed h current, chloride leak, and Ca^{2+} current because their presence has no noticeable effect on our results. In addition, we eliminated ion concentration dynamics as their presence do not change our conclusions.

The two Na^+ currents used in the model are

$$I_{Na}^T = G_{Na}^T (m_1^3 h_1 p + m_2^3 h_2 (1 - p)) (V_m - V_{Na}) \quad (5)$$

$$I_{Na}^L = G_{Na}^L (V_m - V_{Na}).$$

V_K and V_{Na} in eqs. 4 and 5 are the reversal potentials for K^+ and Na^+ currents respectively. The values for these parameters were obtained previously (Perez et al, 2016) by using extracellular K^+ concentration of 3 mM in the tissue (bath solution) and allowing both intracellular and extracellular K^+ and Na^+ concentrations to evolve dynamically. Steady state intracellular concentrations of K^+ and Na^+ were 3 mM and 20 mM, while extracellular concentrations were 140 mM and 135 mM respectively. We remark that changing the values of V_K and V_{Na} slightly do not change our results significantly. For example, using smaller

intracellular Na^+ concentration (we tested values as low as 10 mM) does not change the main conclusions in this paper.

The model for cooperative gating of VGSCs was originally developed by Naundorf *et al* (Naundorf et al, 2006). However, our equations are more closely related to the work published by Huang *et al* (Huang et al, 2012). The model in (Huang et al, 2012) has two populations of VGSCs. The channels gate cooperatively in the first population, while in the second population, channels gate independently. p in eq. 5 is the fraction of cooperative VGSCs. h_1 and m_1 are the gating variables for cooperative VGSCs, and h_2 and m_2 are the gating variables for non-cooperative VGSCs. In line with (Huang et al, 2012), we use the same inactivation variable h for both cooperative and non-cooperative population of VGSCs. We also assume that the activation of non-cooperative VGSCs is rapid enough so that the steady state value of m_2 ($m_{2,\infty}$) can be used.

The change in the gating variables is modeled by the rate equations

$$\frac{dq}{dt} = \frac{(q_\infty - q)}{\tau_q}, q = m_1, n, h. \quad (6)$$

Where q_∞ represents the steady state value of the gating variable q . The steady state of variable h is given as

$$h_\infty = \frac{1}{1 + e^{(V_m + 53.0)/7.0}}. \quad (7)$$

The steady state value of the gating variables m_1 , m_2 , and n are given by

$$q_\infty = \frac{\alpha_q}{\alpha_q + \beta_q}. \quad (8)$$

τ_q represents the time constant of a given gating variable q and is given by

$$\tau_h = 0.37 + 2.78 \frac{1}{1 + e^{(V_m + 40.5)/6.0}}, \quad (9)$$

for h variable, and

$$\tau_q = \frac{1}{\alpha_q + \beta_q}, \quad (10)$$

for m_1 and n gating variables. α_q and β_q are given by

$$\alpha_{m_1} = \frac{0.1(V_m^+ + 30)}{1 - e^{-0.1(V_m^+ + 30)}}$$

$$\beta_{m_1} = 4e^{-(V_m^+ + 55)/18}$$

$$\alpha_{m_2} = \frac{0.05(V_m + 30)}{1 - e^{-0.1(V_m + 30)}} \quad (11)$$

$$\beta_{m_2} = 4e^{-(V_m + 55)/18}$$

$$\alpha_n = \frac{0.01(V_m + 34)}{1 - e^{-0.1(V_m + 34)}}$$

$$\beta_n = 0.125e^{-(V_m + 44)/80}$$

V_m^+ in the above equations is the mean field approximation of a coupled population of Markov models for individual Na^+ channels (Huang et al, 2012), and is given as

$$V_m^+ = V_m + m_{1,\infty} hKJp\omega, \quad (12)$$

$$\omega = 1 - p\sigma,$$

Where K is the coupling strength between VGSCs, J is the number of surrounding VGSCs (with $KJ=700\text{mV}$), σ is a pseudo-random number drawn from a uniform distribution between 0 and 1, and ω is the level of cooperativity, whose value can range between 0.15 and 1.0. In this formalism, ω varies after each AP. All other constants not explicitly stated in this section may be found in Table 1.

The synaptic input (I_{noise}) is modeled as random noise with uniform distribution over the range $[-1 \mu\text{A}/\text{cm}^2, 1 \mu\text{A}/\text{cm}^2]$. After reaching the steady state in the absence of external stimulus, we apply a DC stimulus (I_{stim}) that lasts for 500ms. In line with the experimental

protocol (Perez et al, 2016; Hazra et al, 2013), we repeat the simulation with varying stimulus strength, ranging from 160pA–300pA in 20 pA increments. For each stimulus and a given fraction of cooperative channels, we take the second and third action potentials, gathering the phase plot information for the two action potentials.

2.1 Numerical Methods

The rate equations are solved in Fortran 90 using 4th order Runge-Kutta method, with a time step of 0.01 ms. The analysis of the data is performed in Matlab. Codes reproducing key results are available upon request from authors.

3 Results

Previously, we found that in addition to several other differences, AP initiation in interneurons responsible for the feed-forward inhibition in the molecular layer of DG, from NTG and APdE9 mice are significantly different (see Fig. (3c) and (3d) in (Perez et al, 2016)). Using the phase plot that graphs the rate of change of membrane potential (dV_m/dt) versus the instantaneous membrane potential, we found that AP initiation in interneurons from NTG mice are characterized by abrupt onset and an upstroke which is much steeper as compared to interneurons from APdE9 mice. This behavior is manifested as almost vertical take-off at AP initiation (Fig. 3d in (Perez et al, 2016)). While, the initial kink in the phase plot is similar in the two cases, the rise in dV_m/dt in the case of interneurons from APdE9 mice is biphasic. Furthermore, the AP onset threshold (the membrane potential at which dV_m/dt crosses 15 mV/ms) (Naundorf et al, 2006) in interneurons from NTG mice varies significantly more as compared to interneurons from APdE9 mice. Interneurons from APdE9 mice display a 5 mV range in onset variability, less than half when compared to interneurons from NTG mice (12 mV) in response to the same range of external stimuli. Furthermore, AP onset in interneurons from APdE9 mice is shifted to more negative membrane potential values as compared to interneurons from NTG mice (Fig. (3c) and (3d) in (Perez et al, 2016)). In the following, we use computational modeling to explain this behavior as AP initiation provides useful information about the function of VGSCs.

We begin by using the classical HH formalism for the Na^+ current which is given as (Perez et al, 2016)

$$I_{NA}^T = G_{Na}^T m_{\infty}^3 h (V_m - V_{Na}),$$

where,

$$m_{\infty} = \frac{1}{1 + e^{-(V_m + 30)/9.5}},$$

$$\frac{dh}{dt} = \frac{h_{\infty} - h}{\tau_h},$$

$$h_{\infty} = \frac{1}{1 + e^{(V_m + 53)/7}}.$$

$$\tau_h = 0.37 + \frac{2.78}{1 + e^{(V_m + 40.5)/6}}.$$

Everything else in the model remains the same as described in the Methods section. Using this formalism, we generate phase plots similar to Fig. (3c) and (3d) in (Perez et al, 2016) (Fig. 1A and B). The noteworthy characteristics of phase plots without cooperative VGSCs is a slow onset, monophasic rise, and AP onset that occurs in a narrow range of membrane potential values. The slow rise and low variability in AP onset threshold are contrary to what we see in the observed phase plots of interneurons from both NTG and APdE9 mice. In fact, this behavior of the HH formalism of a single-compartmental neuron is inconsistent with the observed features of AP initiation in other neurons as well (Naundorf et al, 2006).

Based on extensive experimental work, Verret et al (Verret et al, 2012a) found that the impairment of parvalbumin inhibitory neurons leads to the observed spontaneous epileptiform activity, hypersynchrony, and reduced gamma oscillatory activity in hAPP transgenic mice and AD patients. They also found reduced levels of VGSC subunit Nav1.1 in the inhibitory neurons, and that restoring Nav1.1 levels in hAPP mice increased gamma oscillations, and reduced hypersynchrony, memory deficits, and premature mortality. To test the effect of the reduced VGSCs expression on AP initiation characteristics including the transition from monophasic behavior of phase plot in NTG mice to biphasic behavior in APdE9 mice, we decreased G_{Na}^T significantly and found no comparable effect on AP initiation (Fig. 1C and D). Increasing G_{Na}^T or changing other currents do not change the phase plot significantly either (not shown).

Next we use the model that incorporates the cooperative activation of VGSCs to reproduce the phase plots similar to those observed experimentally. We vary the level of cooperativity amongst VGSCs between 15% and 80% and compare our results to those observed in NTG and APdE9 mice models. Specifically, we are interested in how the variation in the fraction of cooperative VGSCs, p , affects the phase plots of APs from simulated neurons taken at varying stimulus strength with added synaptic noise. As shown in Fig. 2, at low cooperativity, the phase plots from the model exhibit a slow biphasic onset that occurs in a narrow range of membrane potential values, similar to the behavior observed in APdE9 mice models. This biphasic onset persists until the fraction of cooperative VGSCs is increased to approximately 50%, where it then becomes monophasic, similar to what is seen in NTG mice and healthy human neurons. This is more clear from the expanded view of Fig. 2 as shown in Fig. 3.

In addition to changing from being biphasic for low fraction of cooperative VGSCs to being monophasic at high fraction of cooperative VGSCs, we also notice a gradual increase in the

average initial slope of the phase plot, indicating the rapidness of action potential onset (Fig. 3). To show this more quantitatively, we take the average of the initial slope of the phase plot for the second action potential using different stimuli as a function of the fraction of cooperative VGSCs (Fig. 4A). The larger the fraction of cooperative VGSCs, the more rapid the change in the membrane potential. At higher cooperativity of VGSCs, AP exhibits an almost vertical take off similar to what is observed in healthy neurons. This rapid onset also occurs at more variable membrane potential threshold as we increase p (Fig. 4B). At lower fraction of VGSCs with cooperative activation, we observe AP onset occurring in much smaller range (3–5 mV) when compared to the case when the fraction of VGSCs with cooperative activation is larger (7–12 mV). This behavior is consistent with the observed onset variability of action potential in interneurons from APdE9 and NTG mice respectively. We also see that on average the threshold for action potential onset shifts to negative values as we decrease cooperativity in the activation of VGSCs.

4 Discussion

Substantial evidence points towards the dysfunction of inhibitory neurons in the hippocampus of different mice models of AD and AD patients (Hazra et al, 2013; Verret et al, 2012b; Perez et al, 2016). We previously showed that interneurons in DG of APdE9 mice failed to reliably produce APs in response to external stimulus (Perez et al, 2016), resulting in profound disruptions in DG circuit activations, abnormally large field potentials corresponding to the wider neuronal activation maps, and impaired synaptic plasticity (Hazra et al, 2013). This dysfunction of inhibitory neurons also results in epileptiform activity and the disruption of natural brain rhythms (Pena et al, 2010; Verret et al, 2012b; Palop and Mucke, 2010). Using data-driven computational modeling, we explained many features of the inhibitory neurons in the molecular layer of DG from APdE9 mice and age-matched NTG mice (Perez et al, 2016). However, our model failed to explain several key observation about AP initiation in interneurons from NTG mice. Neither did our model explain the differences between various features of AP initiation in interneurons from NTG and APdE9 mice. AP initiation carries key information about the function of VGSCs as they are responsible for the rapid onset seen in both time trace and phase plot of APs. In this paper, we exploit this information and show that the reduced cooperativity in the activation of VGSCs could explain the observed changes in the characteristics of AP produced by inhibitory neurons in the hippocampus of APdE9 mice when compared to NTG mice.

In addition to many adverse effects on neuronal function, $A\beta$ peptides cause an increase in the levels of beta-secretase 1 (BACE1) – the enzyme also responsible for the cleavage of VGSC subunit Nav1.1. Due to the correlation between APP and BACE1, impaired APP processing often leads to higher levels of VGSC subunit Nav1.1. However, it is largely retained inside the cell (Kim et al, 2011, 2007; Corbett et al, 2013; Luo et al, 2001), resulting in a significant decrease in the expression of VGSCs on the cell surface (Kim et al, 2007). While the reduction in the expression of VGSCs does not explain the different features of AP initiation observed in NTG and APdE9 mice, it is possible that the loss of VGSCs at random places affects the cooperativity in the activation of these channels. Testing this hypothesis requires carefully designed future experiments, investigating the spatial loss of VGSCs in AD.

We remark that the multi-compartmental nature of the cell could also lead to biphasic behavior of AP where the sharp kink results from the axon's initial segment (AIS) and the subsequent slower phase is caused by somadendritic compartments (Yu et al, 2008b; McCormick et al, 2007). Thus, the switching of AP onset from being monophasic in NTG mice to being biphasic in APdE9 mice could be due to the changes in the morphology or spatial distributions of ion channels in interneurons in the brain with AD. However, a close examination of the observation made by McCormick and colleagues while modeling the detailed morphology of the neuron with HH formalism (Yu et al, 2008b; McCormick et al, 2007) indicates that our data cannot be explained by simply considering the multi-compartment nature of interneurons. Their modeling results show that at the point of AP initiation in AIS, APs are monophasic, have slow rise and relative low variability in their membrane potential threshold. APs in soma or down the axon on the other hand, are biphasic, exhibit rapid rise, and have greater variability in their membrane potential threshold (note the different combinations of the three properties of APs in AIS and Soma). APs produced by inhibitory neurons from NTG mice in our experiments, on the other hand, are monophasic, exhibit rapid rise and larger variability in membrane potential threshold. While APs produced by inhibitory neurons from APdE9 mice are biphasic, exhibit slow rise and smaller variability in membrane potential threshold. So even if one was to assume that all APs in case of APdE9 mice were recorded from the soma or down the axon of interneurons and those in NTG mice were recorded from AIS, or vice versa, the combination of the three properties still wouldn't be consistent with the multi-compartment theory. Furthermore, we are certain that all AIPs in our experiments were recorded from the soma. Nevertheless, we cannot completely rule out the possibility of some complex changes in the anatomy of the cell that could lead to the observed AP characteristics that are hallmarks of interneurons from APdE9 mice. Investigating such structural and anatomical changes requires an exhaustive search of different cell morphologies, which is beyond the scope of this study.

To summarize, changes in the slope, onset variability, and the shape of phase plot of AP yield key information about the function of VGSCs in neuronal membrane, and how they are affected by the deposition of $A\beta$ plaques as well as the presence of increased BACE1 activity often observed in AD models (Naundorf et al, 2006; Corbett et al, 2013; Kim et al, 2007). Here we show that at low cooperativity between VGSCs, our model reproduces several features of AP initiation such as a less rapid onset, a smaller variability in threshold in response to a fluctuating input, and a biphasic behavior seen in inhibitory neurons from AD mice model. When cooperativity between VGSCs is restored, so is the normal AP initiation seen in interneurons from age-matched NTG mice.

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Fig. 1.

Phase plot of simulated neuron at control (a) and reduced (b) G_{NA}^T , in response to a stimulus of the same magnitude. The membrane potential shows a slow rise during AP initiation when HH type formalism for VGSCs with no cooperativity is used. Rate of change of membrane potential as a function of instantaneous membrane potential of simulated neuron at $G_{NA}^T = 24.0 \text{ mS/cm}^2$ (A). An expanded view of (A) shows that the onset lacks the rapid rise observed experimentally (B). Reducing the expression of VGSCs ($G_{NA}^T = 16.0 \text{ mS/cm}^2$) (C) does not significantly affect the pace of the onset. (D) shows an extended view of (C).

Fig. 2.

Phase plots of simulated neurons at varying fraction of VGSCs with cooperative activation. Each individual plot contains contributions from the second and third AP of a spike train in response to a range of stimulus values from 160pA and 300pA, increased in 20pA increments. Incorporating cooperativity in the gating of VGSCs leads to AP initiation consistent with experimental results. Furthermore, the cooperativity in the gating of VGSCs decreases in interneurons from APdE9 mice. Rate of change of membrane potential as a function of instantaneous membrane potential of the neuron during APs as we increase the fraction of VGSCs with cooperative opening: (A) $p = 0.2$, (B) $p = 0.3$, (C) $p = 0.4$, (D) $p = 0.5$, (E) $p = 0.6$, (F) $p = 0.7$, (G) $p = 0.8$, and (H) $p = 0.9$.

Fig. 3.

Expanded view of the phase plots from Fig. (2). (A) $p = 0.2$, (B) $p = 0.3$, (C) $p = 0.4$, (D) $p = 0.5$, (E) $p = 0.6$, (F) $p = 0.7$, (G) $p = 0.8$, and (H) $p = 0.9$.

Fig. 4.

Lack of cooperativity in the activation of VGSCs also explains the reduced rapidness of AP onset and the smaller variability in the AP threshold membrane potential in interneurons from APdE9 mice. Average slope of the initial onset in the phase plot (A) and variability in onset threshold membrane potential (B) of AP as we vary the fraction of VGSCs with cooperative activation.

Table 1

Units and description of the parameters used in the model.

Parameter	Units	Description
C	$1.0 \mu\text{F}/\text{cm}^2$	Membrane capacitance
G_{Na}^T	$24.0 \text{ mS}/\text{cm}^2$	Maximum conductance of VGSCs
G_K^{DR}	$3.0 \text{ mS}/\text{cm}^2$	Maximum conductance of K^+ current
G_K^L	$0.02 \text{ mS}/\text{cm}^2$	Conductance of leak K^+ current
G_{Na}^L	$0.07 \text{ mS}/\text{cm}^2$	Conductance of leak Na^+ current
V_{Na}	50 mV	Reversal potential for Na^+
V_K	-102 mV	Reversal potential for K^+