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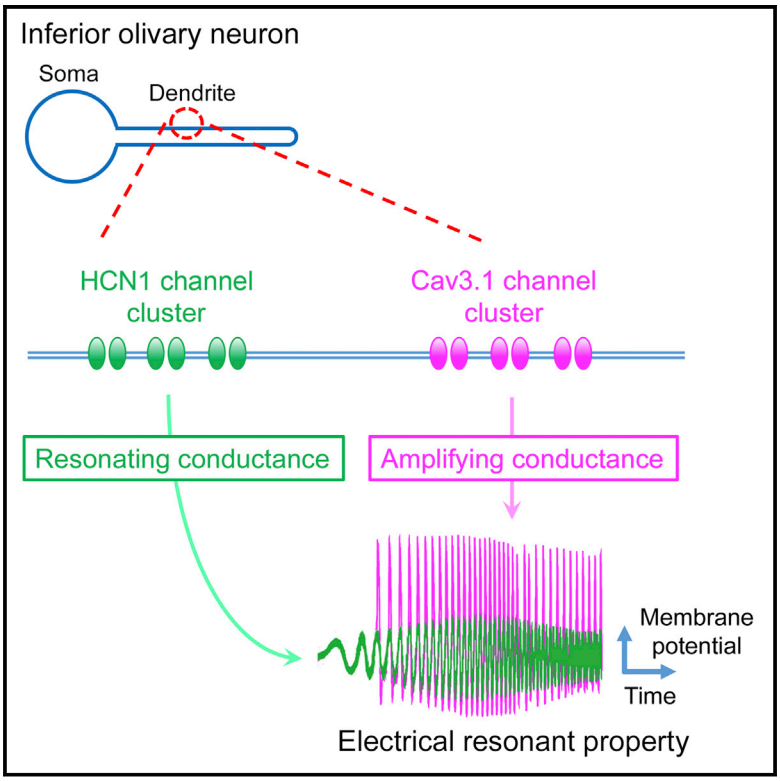
Ionic Basis for Membrane Potential Resonance in Neurons of the Inferior Olive

Graphical Abstract



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In Brief

Matsumoto-Makidono et al. find that electrical resonance in inferior olivary neurons is mainly mediated by the activation of HCN1 and Cav3.1 channels, which act as frequency-dependent resonating conductance and depolarization-dependent amplifying conductance, respectively.

Highlights

- Activation of Cav3.1 in resonance is membrane potential dependent
- Activation of HCN1 in resonance is dependent on frequency of input currents
- HCN1 and Cav3.1 puncta are clustered on dendrites of inferior olivary neurons
- HCN1 and Cav3.1 act as resonating and amplifying conductances, respectively

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Ionic Basis for Membrane Potential Resonance in Neurons of the Inferior Olive

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SUMMARY

Some neurons have the ability to enhance output voltage to input current with a preferred frequency, which is called resonance. Resonance is thought to be a basis for membrane potential oscillation. Although ion channels responsible for resonance have been reported, the precise mechanisms by which these channels work remain poorly understood. We have found that resonance is reduced but clearly present in the inferior olivary neurons of Cav3.1 T-type voltage-dependent Ca^{2+} channel knockout (KO) mice. The activation of Cav3.1 channels is strongly membrane potential dependent, but less frequency dependent. Residual resonance in Cav3.1 KO mice is abolished by a hyper-polarization-activated cyclic nucleotide-gated (HCN) channel blocker, ZD7288, and is partially suppressed by voltage-dependent K^+ channel blockers. Resonance is inhibited by ZD7288 in wild-type mice and impaired in HCN1 KO mice, suggesting that the HCN1 channel is essential for resonance. The ZD7288-sensitive current is nearly sinusoidal and strongly frequency dependent. These results suggest that Cav3.1 and HCN1 channels act as amplifying and resonating conductances, respectively.

INTRODUCTION

Membrane potential oscillation is thought to play crucial roles in the generation of the neural rhythms that underlie various brain functions (Buzsaki, 2006; Hutcheon and Yarom, 2000; Llinás, 1988; Wang, 2010). It has been proposed that the ability to generate subthreshold membrane potential oscillations (STOs) is attributable to the electrical resonant properties of the neuronal membrane (Hutcheon and Yarom, 2000; Llinás, 1988). The magnitude of membrane voltage in response to sinusoidal current injection is strongly enhanced when the frequency of the injected current is close to a specific frequency (the resonant frequency) (Erchova et al., 2004; Hutcheon and Yarom, 2000; Lampl and Yarom, 1997; Puil et al., 1986), which is the result of a frequency-dependent enhancement of membrane impedance. Enhanced impedance is caused by electrical resonance that occurs in circuits electrically equivalent to the parallel resonant circuit inherent to the plasma membrane (Erchova et al., 2004; Hutcheon and Yarom, 2000; Narayanan and Johnston, 2008; Puil et al., 1986). The resistor and capacitor depend on the passive membrane property, and the phenomenological inductor is thought to be mediated by voltage-dependent ion channels (Hutcheon and Yarom, 2000).

There are several ion channel candidates for resonance, such as T-type voltage-dependent Ca^{2+} channels (T-type VDCCs), hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, persistent Na^+ channels, and M-type voltage-dependent K^+ (Kv) channels (Hutcheon and Yarom, 2000; Wang, 2010). It has been proposed that these channels can be classified into two groups (Hutcheon et al., 1996a; Hutcheon and Yarom, 2000). One group acts as resonating conductances that operate as phenomenological inductors, and the other acts as amplifying conductances that potentiate resonating conductance activity. The classification of these channels is mostly based on whether a channel blocker can significantly shift the resonant frequency (Hutcheon et al., 1996a; Hutcheon and Yarom, 2000). However, the precise roles of candidate ion channels in resonance remain unclear. For example, theoretical analyses suggest that T-type VDCCs have the potential to act as a resonating conductance (Hutcheon et al., 1994; Hutcheon and Yarom, 2000). However, the resonant frequency is not affected by the appropriate blockers in some studies (Gutfreund et al., 1995; Ströhmann et al., 1994; Ulrich, 2014), suggesting that T-type VDCCs act as an amplifying conductance. To clarify the roles of ion channels in resonance, not only the resonant frequency but also the kinetics of conductances should be carefully examined. However, to date, few studies have focused on the kinetics of candidate conductances responsible for resonance generation.