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Double trouble? Potential for hyperexcitability following both channelopathic up- and downregulation of I_h in epilepsy

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Studies of pathological ion channel regulation as an underlying mechanism of epilepsy have revealed alterations in the h-current in several animal models. While earlier reports indicate that downregulation of the h-current is pro-excitatory on the single neuron level, we found an upregulation of I_h in hyperexcitable CA1 pyramidal neuron dendrites following experimental febrile seizures. In addition, in several CA1 pyramidal neuron computational models of different complexity, h-current upregulation has been shown to lead to pro-excitable effects. This focused review examines the complex impact of altered h-current on neuronal resting membrane potential (RMP) and input resistance (R_{in}), as well as reported interactions with other ionic conductances.

Keywords: h-current, excitability, acquired channelopathy, epilepsy

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INTRODUCTION

The study of channelopathies, pathological changes in the expression and function of ion channels, has gained momentum in recent years in epilepsy research – several idiopathic epilepsies (inherited) have been linked to underlying mutations in channel encoding genes (for reviews see, Catterall et al., 2008; Hirose et al., 2005; Lerche et al., 2005; Mulley et al., 2003). For the study of the inherited, genetically determined pathologies, a number of experimental models reproducing human mutations and symptoms have been generated (for review see, Avanzini et al., 2007). Similarly, the study of symptomatic **epilepsy** (developed after a brain insult) in animal models has identified several acquired **channelopathies** – so named because the channelopathies develop in response to the brain insult or subsequent status epilepticus (for review see, Pitkanen and Lukasiuk, 2009). The channel types affected by the acquired channelopathies include $GABA_A$-receptor-channels (Brooks-Kayal et al., 1998; Sanchez et al., 2005), voltage-dependent Na^+ channels (Ellerkmann et al., 2003; Howard et al., 2007), Ca^{2+} channels (Becker et al., 2008; Su et al., 2002), and K^+ channels (Bernard et al., 2004; Howard et al., 2007; Shin et al., 2008; Shruti et al., 2008). However, the most frequently acquired channelopathy concerns the mixed cation **h-current** in a number of different epilepsy models: perinatal seizure-inducing hypoxia (Zhang et al., 2006), the kainate model of temporal lobe epilepsy (Shah et al., 2004), the pilocarpine model of temporal lobe epilepsy (Jung et al., 2007; Marcelin et al., 2009; Shin et al., 2008), the fluid percussion injury (FPI) model of post-traumatic epilepsy (Howard et al., 2007), and prolonged experimental **febrile seizures** (Chen et al., 2001a; Dyhrfjeld-Johnsen et al., 2008).

In most experimental paradigms for investigation of the acquired h-channelopathies, a seizure-induced reduction in I_h was reported (Jung et al., 2007; Marcelin et al., 2009; Shah et al., 2004; Shin et al., 2008; Zhang et al., 2006). The downregulated h-current was linked to hyperexcitability and

Epilepsy
A family of neurological seizure disorders characterized by abnormal electrical discharges in the brain, resulting in behavioral symptoms ranging from staring spells to intense convulsions and loss of consciousness. Idiopathic epilepsies do not result from an identifiable external cause and are presumed to be genetic, while symptomatic epilepsies have an identifiable cause such as severe head trauma.

Channelopathy
Pathological expression or function of ion channels, either inherited (genetically encoded) or acquired (developed in response to an injury or insult).

h-Current
An inward (depolarizing) non-inactivating ionic current tonically active at the resting membrane potential. The h-channels are assembled from the channel subunits HCN1-4. The h-current (I_h) is activated by hyperpolarization of the cell membrane and modulated by cAMP and pH.

Febrile seizure
A type of seizure caused by high fever in 3–5% of infants and young children. Prolonged febrile seizures increase the risk of developing epilepsy later in life.

seizures through the resulting increase in neuronal input resistance. However, our recent paper on dendritic h-channelopathy in the experimental febrile seizure model reported a ~70% increase in the h-current density along with depolarized half-activation potential ($V_{1/2}$) and slower kinetics in hyperexcitable CA1 pyramidal neuron dendrites (**Figure 1**). The depolarized $V_{1/2}$, along with the overall increase in h-current density, means that smaller stimuli are required to strongly activate I_h from the resting membrane potential (RMP) in CA1 pyramidal neurons following febrile seizures.

This focused review concentrates on recent data on mechanisms of h-current regulation and re-examines the long-standing dichotomy (Poolos, 2004) of potential for both channelopathic upregulation and downregulation of I_h resulting in hyperexcitability.

MECHANISMS OF ACTIVITY-DEPENDENT I_h REGULATION

In the studies of acquired h-current channelopathies mentioned above, alterations of maximal current levels as well as altered activation properties and kinetics have been reported. Below, we summarize a number of processes that are known to affect hyperpolarization-activated cation (HCN) channel properties, expression levels, and trafficking with an emphasis on activity-dependent mechanisms.

In addition to the relatively well-established modulation of HCN channel activation by intracellular pH (Munsch and Pape, 1999) and cAMP (DiFrancesco, 1993; Wainger et al., 2001), recent years have seen a number of additional mechanisms impacting the half-activation voltage of I_h. This includes allosteric gating by the membrane phospholipid phosphatidylinositol-4,5 biphosphate (PIP_2) (Zolles et al., 2006) as well as activation of the p38 mitogen-activated protein kinase (p38 MAPK) (Poolos et al., 2006) and diacylglycerol (DAG) (Fogle et al., 2007) signaling pathways who strongly modulate the half-activation voltage of I_h.

In plasticity studies, protocols commonly used to induce long-term potentiation (LTP) and long-term depression (LTD) were shown to modulate intrinsic neuronal excitability. Specifically, increased HCN channel protein synthesis resulted in decreased neuronal excitability following the LTP induction (Fan et al., 2005; see also van Welie et al., 2004). This process was shown to depend on calcium influx through NMDA-receptors following action potential (AP) back-propagation and a subsequent, calcium/calmodulin-dependent protein kinase II (CamKII) activation (Fan et al., 2005). Conversely, a downregulation of the h-current leads to increased neuronal excitability following the LTD induction, through the activation of group 1 metabotropic glutamate receptors and the protein kinase C (PKC) pathway (Brager and Johnston, 2007).

Recent investigations of h-current regulation following kainate-induced seizures *in vivo* and in organotypic slice cultures have shown a profound downregulation of HCN1 channel expression (McClelland et al., 2008). The reduced expression was linked to a seizure-induced upregulation of neuron-restrictive silencing factor (NRSF), which binds strongly to the HCN1 encoding gene and restricts transcription. Blocking NRSF function prevents seizure-induced reduction of HCN1 expression.

In the experimental febrile seizure model, a lasting increase in the maximal h-current is accompanied by a depolarized half-activation potential and slower time-constants (Chen et al., 2001a; Dyhrfjeld-Johnsen et al., 2008), while the HCN1 subunit expression is decreased (Brewster et al., 2002). These complex alterations could potentially be explained by a seizure-induced increase in the formation of HCN1/HCN2 heteromeric channels with different properties than homomeric channels (Brewster et al., 2005; Chen et al., 2001b), through increased glycosylation of HCN1 subunits (Zha et al., 2008).

Not only the density and properties of I_h, but also the specific subcellular distribution of HCN-channels are subject to activity-dependent regulation: in CA1 pyramidal cells, the characteristic increasing h-current density along the apical dendrites of CA1 pyramidal neurons (Dyhrfjeld-Johnsen et al., 2008; George et al., 2008; Lorincz et al., 2002; Magee, 1998) is established and maintained by excitatory input from the enthorinal cortex (Shin and Chetkovich, 2007). Blockade of excitatory neurotransmission results in an even distribution of HCN-channels throughout the neuronal compartments. In recent years, live-imaging of CA1 pyramidal neurons transfected with GFP-tagged HCN1 channels has revealed an immediate and a strong decrease in HCN channel mobility following bath application of glutamate. The decreased mobility resulted from a >2-fold increase in the fraction of surface expressed HCN-channel proteins (Noam et al., 2008). These results indicate the potential for rapid activity-dependent regulation of I_h by fast removal or insertion of existing HCN channel proteins. A candidate for such regulation, the chaperone protein TRIP8b, co-localizes with HCN1 subunits in pyramidal neurons (Santoro et al., 2004). Interestingly, a disruption of the interaction between the HCN1 subunits and TRIP8b has been reported as a mechanism underlying the channelopathic mislocation of h-channels in the kainate model of temporal

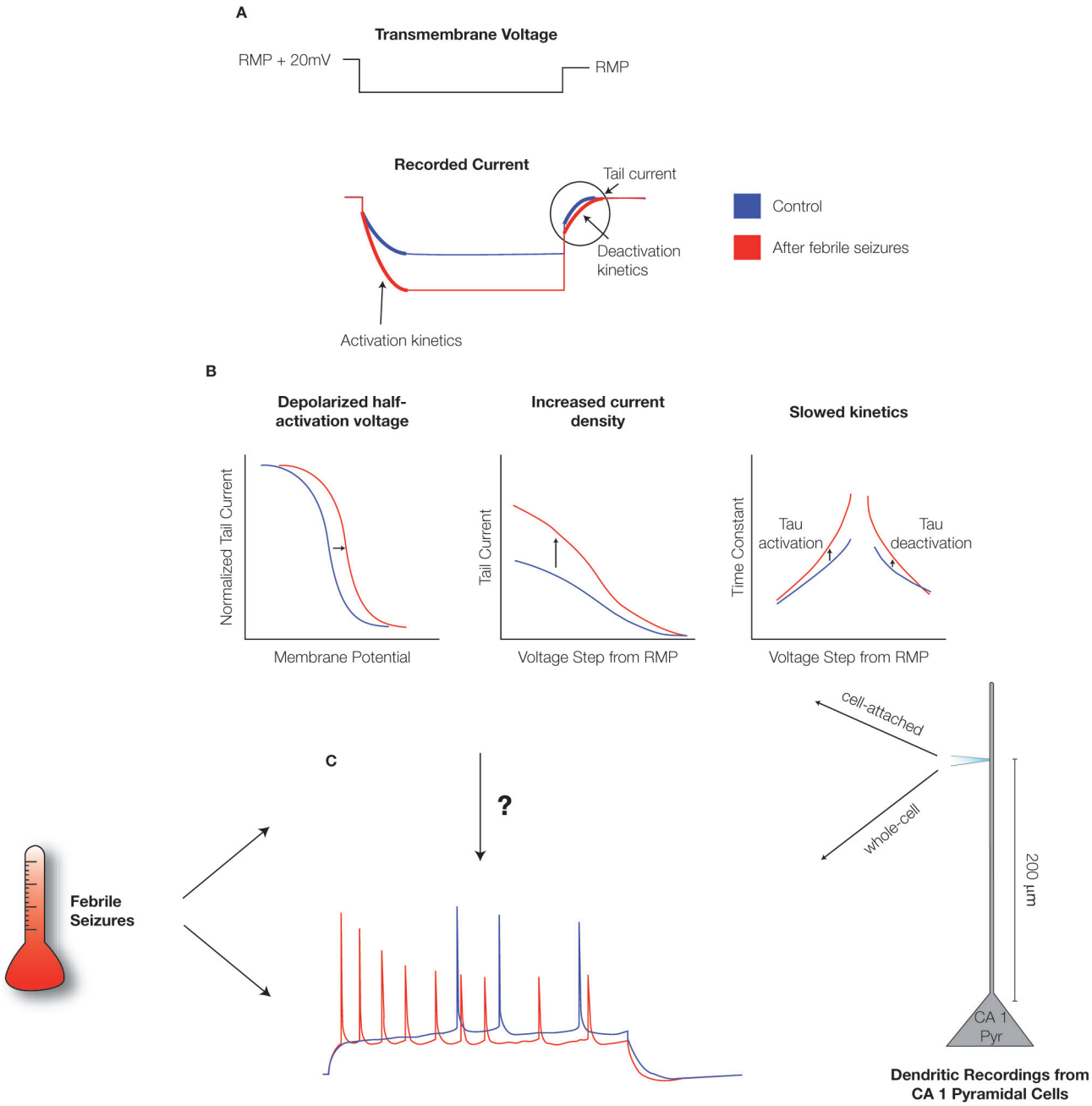

Figure 1 | Febrile seizures alter I_h in CA1 pyramidal neurons. (**A**) Schematic of the cell-attached, dendritic recordings of I_h from CA1 pyramidal cells from control animals and from animals that were exposed to hyperthermia-induced, experimental prolonged febrile (fever-induced) seizures. The dendritic patch was held in voltage-clamp mode, a voltage command was applied, and the resulting currents were recorded. The activation and de-activation kinetics, along with the maximal currents, were derived from the recordings as indicated. (**B**) Analysis of current recordings showed that febrile seizures result in altered properties of I_h in the dendrites of CA1 pyramidal neurons: a depolarized half-activation potential, slower time-constants of activation and de-activation, and ~70% increased current density (Dyhrfjeld-Johnsen et al., 2008). (**C**) Whole-cell dendritic current injection experiments in the current-clamp mode showed that CA1 pyramidal dendrites are hyperexcitable following febrile seizures. However (as illustrated by the arrow with the question mark), this raised the question of how the changes in I_h parameters relate to the observed increases in excitability.

lobe epilepsy (Shin et al., 2008). This suggests that altered h-current densities in epilepsy may not only be due to altered levels of channel proteins, but also depend on altered trafficking and localization of neuronal structures.

UP OR DOWN? AN EXCITING DICHOTOMY

In the study of voltage-gated channel alterations in neurological disorders, a key question is how the plasticity of intrinsic properties affects single neuron excitability (Beck and Yaari, 2008). With

the multitude of potential mechanisms for regulating I_h expression and characteristics described above, it is perhaps not surprising that different acquired h-channelopathies have been discovered in different animal models of epilepsy. However, an apparent contradiction exists between the studies suggesting that single neuron hyperexcitability results from a downregulation (Jung et al., 2007; Shah et al., 2004) or an upregulation (Chen et al., 2001a; Dyhrfjeld-Johnsen et al., 2008) of the h-current.

UNIQUE PROPERTIES OF THE h-CURRENT

To explore the dichotomy, it is necessary to bear in mind some unique properties of I_h: the h-current is hyperpolarization-activated and non-inactivating with a reversal potential between −25 and −40 mV (Robinson and Siegelbaum, 2003), making the current an inward or depolarizing (hence, per definition, an "excitatory") current with respect to the resting potential. I_h is tonically active at the RMP of most neurons (Kaupp and Seifert, 2002), resulting in a contribution to both the neuronal RMP and input resistance (R_{in}) as demonstrated, e.g., by the hyperpolarization accompanied by increased R_{in} following h-current blockade (Magee, 1998) or h-channel deletion (Nolan et al., 2007). By contributing to both the neuronal RMP and R_{in}, the h-current plays a dual role in determining neuronal excitability by influencing the resting distance from the firing threshold of the cell as well as the amount of depolarization caused by excitatory currents.

HANGING IN THE BALANCE: I_h EFFECTS ON RMP AND R_{in}

When assessing the effect of altered I_h, a common practice dictates that recordings are made from a common holding potential. This ensures that other voltage-gated conductances and the membrane voltage relative to firing threshold remain the same in control and altered h-current condition. However, as emphasized in combined computational and experimental studies (Dyhrfjeld-Johnsen et al., 2008; George et al., 2008), this practice masks the excitatory effects of I_h by negating the impact on the RMP, and also on the amount of depolarization required to reach firing threshold.

An increased h-current density leads to a depolarized RMP closer to the firing threshold, but also a decreased R_{in} due to the increased number of HCN-channels open at rest (**Figure 2A**). Conversely, a decreased h-current density results in a hyperpolarized RMP further away from the firing threshold, but an increased input resistance due to a decreased number of HCN-channels open at rest (**Figure 2A**). Injecting a constant current to hold a neuron with altered I_h at the control RMP (**Figure 2B**) creates a situation in which increased h-current density only leads to decreased R_{in}, while decreased I_h only leads to increased R_{in}. The effects are further pronounced (**Figure 2**) when the altered h-current density is accompanied by changes in the half-activation potential: a depolarized $V_{1/2}$, along with upregulated I_h density, further increases the h-current at more depolarized membrane potentials (Chen et al., 2001a; Dyhrfjeld-Johnsen

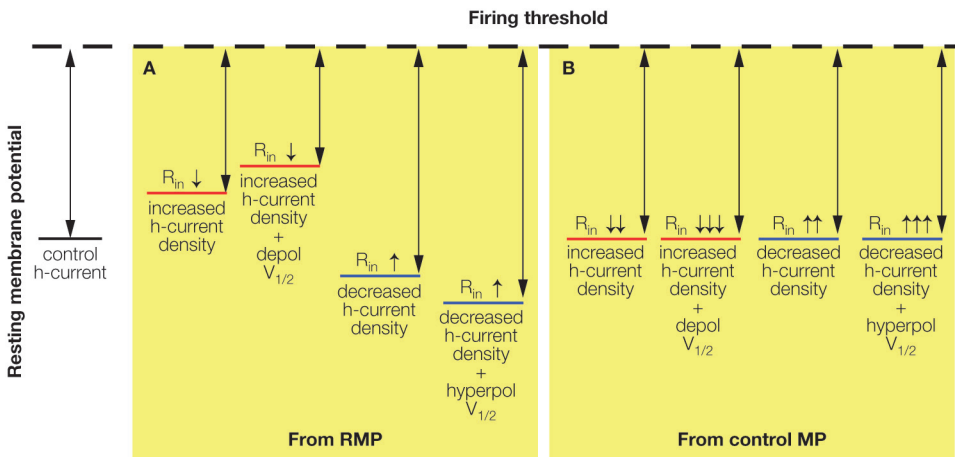

Figure 2 | Effects of altered I_h on RMP and R_{in}. (A) Increased h-current density depolarizes the neuronal RMP (bringing it closer to firing threshold) but decreases the R_{in} (reducing the effect of inputs). Decreased h-current density hyperpolarizes the neuronal RMP (bringing it further away from firing threshold) but increases the R_{in} (increasing the effect of inputs). The effects on the RMP are further increased when the h-current $V_{1/2}$ is depolarized or hyperpolarized in addition to density changes. **(B)** Holding neurons with altered I_h at the control resting membrane potential (control MP) abolishes the depolarizing or hyperpolarizing effects on the RMP, but further accentuates the respective decrease or increase of R_{in} by increased or decreased h-current density.

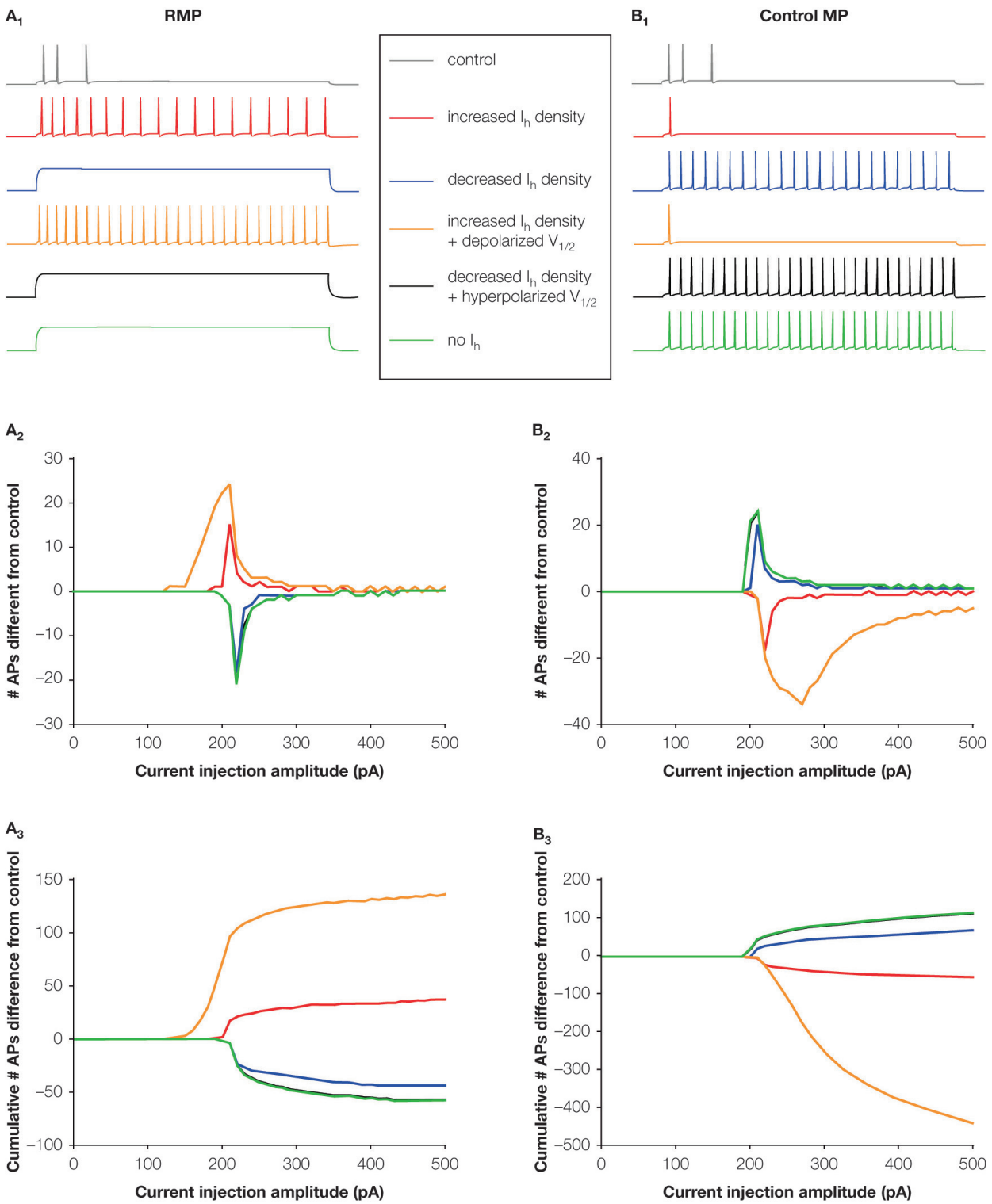

Figure 3 | Altered h-current changes neuronal excitability. The response of the modified control CA1 pyramidal neuron model (Dyhrfjeld-Johnsen et al., 2008; Golding et al., 2001) and models with altered I_h to a 1000 ms depolarizing current injection from RMP (left column) and held at the common holding potential equal to the control RMP (right column). **(A1, B1)** Example traces from current injections with 210 pA amplitude. **(A2, B2)** The number of APs fired in models with altered I_h that differs from the control model for each current injection amplitude. Positive numbers indicate *hyper*excitability, while negative numbers indicate *hypo*excitability. **(A3, B3)** The cumulative number of APs fired in models with altered I_h that differs from the control model illustrates the impact of different combinations of h-current alterations.

et al., 2008), while a hyperpolarized $V_{1/2}$ accompanying downregulated I_h density further decreases the h-current even at hyperpolarized membrane potentials (Jung et al., 2007).

Using a modified version of a previously published CA1 pyramidal neuron compartmental model (Dyhrfjeld-Johnsen et al., 2008; Golding et al., 2001), the direct effect of altered I_h on AP firing in response to the steady-state dendritic current injection can be assessed (**Figure 3**).

When current injections are performed at the "free-floating" RMP with control or altered h-current levels, an increase in the number of APs fired is seen in the models with increased h-current density, but not in the decreased I_h (**Figures 3A1–A3**). Conversely, when the models are held at a common membrane potential before the current injection, only the models with decreased I_h fire more APs than the control model (**Figures 3B1–B3**). Interestingly, even complete removal of the h-current from the model does not result in hyperexcitability from the RMP.

Similarly, excitability-enhancing effects of increased I_h were also obtained using dendritic EPSP summation as outcome measure, in both a relatively simple (**Figures 4A1, A2**) and a more complex (**Figures 4B1, B2**) model of CA1 pyramidal cells (Dyhrfjeld-Johnsen et al., 2008). In both the models, increased I_h accompanied by a depolarized $V_{1/2}$ leads to decreased temporal summa-

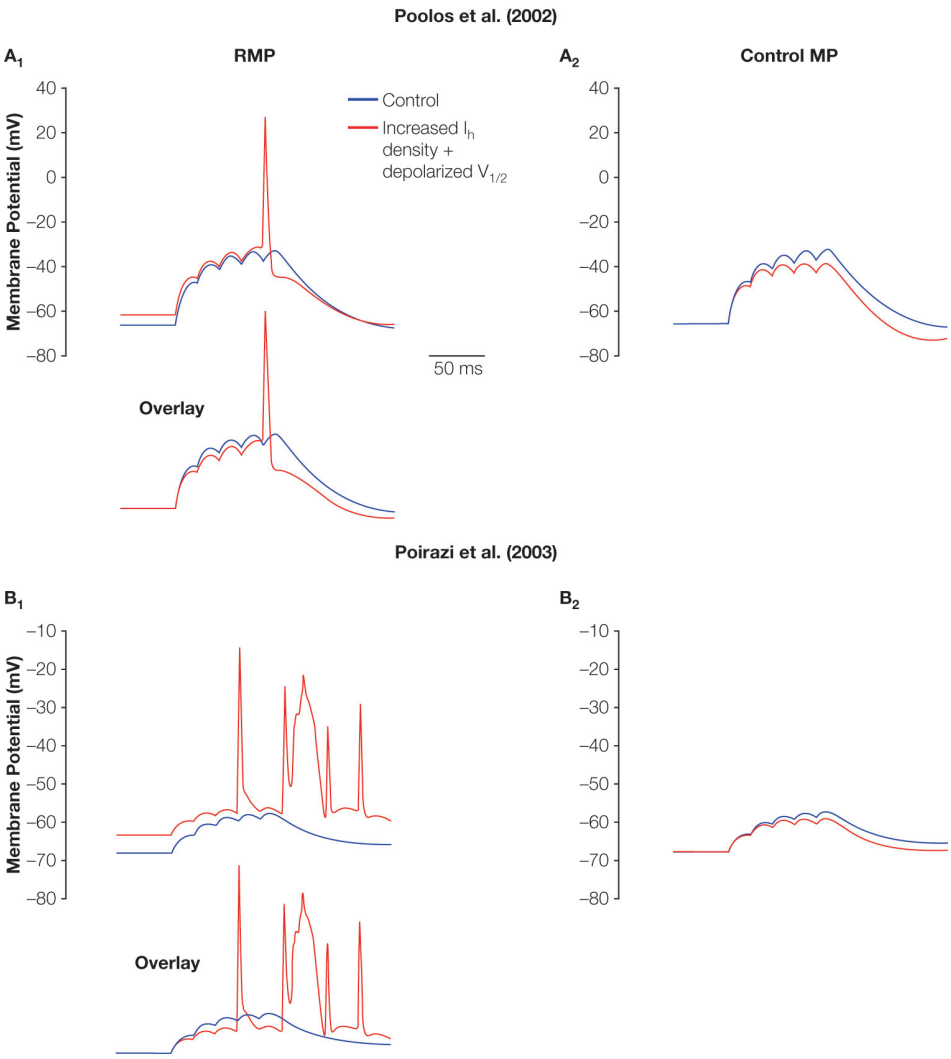

Figure 4 | Effect of increased I_h on summation and AP firing. The effect of five small EPSPs from the RMP **(A1, B1)** and the common holding potential at control RMP **(A2, B2)** in two CA1 pyramidal neuron models (**A1, A2**, Poolos et al., 2002; **B1, B2**, Poirazi et al., 2003) with control I_h (blue) and increased I_h density with depolarized $V_{1/2}$ (red). Note that the increased I_h leads to less summation, but firing of APs is abolished when the depolarization of the RMP is eliminated by holding the cells at a common control RMP.

tion of EPSP inputs due to the decreased R_{in} (see overlays in **Figures 4A1,B1**). However, models with increased I_h are closer to threshold and fire APs in response to the simulated synaptic input due to the depolarized RMP. From a common control RMP, only the decreased temporal summation due to the decreased R_{in} remains in the models with increased I_h (**Figures 4A2,B2**). Therefore, it is important to allow the effects of the altered h-current on both RMP and R_{in} to come into play when assessing the direct impact on neuronal excitability.

INTERACTIONS WITH OTHER CONDUCTANCES

The h-current does exert effects on neuronal excitability not only by influencing the RMP and R_{in}, but also through interactions with other voltage-gated channels. Recent data show that the shunting effect of I_h is achieved through the activation of non-inactivating, voltage-gated potassium conductances (George et al., 2008). These results showed that RMP depolarization by I_h leads to a steady-state activation of a K^+ channel, which may produce dual excitatory and inhibitory effects of I_h depending on the input strength. Computational and experimental data suggested that a physiological candidate for the K^+ current was the M-current, whose regulation through neuromodulation may switch the role of I_h in signal integration from inhibitory to excitatory (George et al., 2008). In the febrile seizure model, we reported a downregulation of a presumed persistent potassium current (Dyhrfjeld-Johnsen et al., 2008), suggesting a reduction of such an interaction as an additional mechanism for increased excitability following the h-current upregulation.

Increased I_h may also interact with inhibitory synaptic inputs resulting in post-inhibitory rebound firing in CA1 pyramidal cells after febrile seizures (Chen et al., 2001a), and a similar effect is well-known to occur in thalamo-cortical projection neurons (Crunelli and Leresche, 1991; Soltesz et al., 1991). Additionally, depolarized dendritic membrane potentials could facilitate the propagation of distal dendritic Ca^{2+}-spikes to the soma (Jarsky et al., 2005). Conversely, the membrane hyperpolarization following the reduction of I_h has been shown to release constraints on distal dendritic Ca^{2+} spikes (Tsay et al., 2007), suggesting a potential pro-excitatory role for downregulation of the h-current in epilepsy.

Finally, in the post-traumatic, hyperexcitable dentate gyrus, mossy cells exhibit extensive modifications in Na^+, K^+, and h-currents, without altered I–F and I–V curves (Howard et al., 2007). The importance of the opposing, apparently coordinated and homeostatic-like changes in several conductances of single neurons was elucidated computationally in a realistic large-scale model of the dentate gyrus (Dyhrfjeld-Johnsen et al., 2007; Howard et al., 2007), demonstrating that individually the ion channel perturbations could significantly affect network activity.

SUMMARY AND CONCLUSION

In CA1 pyramidal cell models, only an increased functional I_h appears to be underlying direct pro-excitatory effects on single neuron firing, as previously demonstrated in three different CA1 neuron computational models of widely differing complexity (Dyhrfjeld-Johnsen et al., 2008). However, as the result depends on the balance between the effects on RMP and R_{in}, the conclusion could be affected by other intrinsic properties determined by neuron type, developmental stage, and neuromodulation. Furthermore, through interaction with other voltage-gated and ligand-gated conductances (Dyhrfjeld-Johnsen et al., 2008; George et al., 2008; Howard et al., 2007; Tsay et al., 2007), normal and altered h-current may modify neuronal excitability in a complex fashion.

Additionally, the h-current is involved in determining resonance frequencies of neurons (Hu et al., 2002; Wang et al., 2006) and likely to play a significant role in pathological network oscillatory behavior in epilepsy. In recent years, the response of CA1 pyramidal neurons to the hippocampal theta rhythm has been shown to be impaired due to the downregulated h-current in the pilocarpine model of temporal lobe epilepsy (Marcelin et al., 2009). This finding suggests additional roles for h-channelopathies in impaired learning and memory (Nolan et al., 2003, 2004). Finally, neurons with high I_h have recently been implicated in the initiation of highly excitable, network-wide UP states (Kang et al., 2008).

While this focused review concentrates on channelopathic alteration of the h-current in pyramidal neuron dendrites, I_h is also expressed in axonal terminals (Bender et al., 2007; Lujan et al., 2005) and inhibitory interneurons (Aponte et al., 2006; Lupica et al., 2001; Maccaferri and McBain, 1996). Along with the complex effects on pyramidal neuron excitability discussed above, it is emphasized that factors ranging from direct effects on RMP and R_{in} to interactions with other ion channels, h-channel localization, and neuronal subtype must be taken into account when judging whether upregulation or downregulation of I_h leads to hyperexcitability in a given animal model.

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