HHS Public Access

Author manuscript

Prog Biophys Mol Biol. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Prog Biophys Mol Biol. 2021 November ; 166: 119–132. doi:10.1016/j.pbiomolbio.2021.06.002.

I_h from synapses to networks: HCN channel functions and modulation in neurons

Crescent L. Combe[#], **Sonia Gasparini**[#]

Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA

[#] These authors contributed equally to this work.

Abstract

Hyperpolarization activated cyclic nucleotide gated (HCN) channels and the current they carry, I_h, are widely and diversely distributed in the central nervous system (CNS). The distribution of the four subunits of HCN channels is variable within the CNS, within brain regions, and often within subcellular compartments. The precise function of I_h can depend heavily on what other channels are co-expressed. In this review, we give an overview of HCN channel structure, distribution, and modulation by cyclic adenosine monophosphate (cAMP). We then discuss HCN channel and I_h functions, where we have parsed the roles into two main effects: a steady effect on maintaining the resting membrane potential at relatively depolarized values, and slow channel dynamics. Within this framework, we discuss I_h involvement in resonance, synaptic integration, transmitter release, plasticity, and point out a special case, where the effects of I_h on the membrane potential and its slow channel dynamics have dual roles in thalamic neurons.

Keywords

membrane potential; resonance; dendritic integration; subcellular distribution; neurotransmitter release; plasticity

1. INTRODUCTION

After the initial description of a current activated by hyperpolarization in the heart (named funny current, or I_f, Brown et al., 1979), a hyperpolarization-activated current, permeable to Na^+ and K^+, was discovered almost ubiquitously in the brain. Among the first brain regions where I_h was identified were the hippocampus (Halliwell and Adams, 1982), the dorsal root ganglion (Mayer and Westbrook, 1983), the midbrain red nucleus (Kubota et al., 1985), the

Corresponding author: Sonia Gasparini, Neuroscience Center of Excellence, Louisiana State University Health Sciences Center – New Orleans, Room 905 Lions, 2020 Gravier St., New Orleans, LA 70112, sgaspa1@lsuhsc.edu.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

sensorimotor cortex (Spain et al., 1987) and the nucleus prepositus hypoglossi (Bobker and Williams, 1989).

Fast forward to the late 1990s: the molecular identity of I_h was revealed, almost at the same time, by a number of research teams (Santoro et al., 1997, 1998; Gauss et al., 1998; Ludwig et al., 1998). Consensus on the nomenclature was achieved and the protein subunits mediating I_h were named hyperpolarization activated cyclic nucleotide gated (HCN) channels. In particular, four subunits were identified in mammals, with differential dependencies on voltage and cAMP, as discussed in section 2. I_h functions have been studied with blockers and, from the early 2000s, genetic knockout models that have allowed the study of the effects of I_h in more complex behaviors in live animals. In addition, I_h has been found to underlie a series of brain diseases. The majority of the changes in this case fall in the category of transcriptional channelopathies, due to the disruption of the regulation of I_h expression (Waxman, 2001; Biel et al., 2009), or, in some cases a disrupted regulation of cAMP modulation, such as seems to be the case in neuropathic pain (Emery et al., 2012). Inherited genomic mutations have been described in epilepsy (Rivolta et al., 2020; Hung et al., 2021; Porro et al., 2021). Excellent reviews have been published recently on the involvement of I_h in pathologies, and pharmacological approaches to targeting HCN channels (Sartiani et al., 2017; Chang et al., 2019; Santoro and Shah, 2020; Balducci et al., 2021).

Since their initial descriptions, the functions of I_h and HCN channels in neurons have been somewhat of a conundrum because these channels mediate both excitatory and inhibitory effects, sometimes even in the same neurons under different conditions. These effects have their basis in the influence of I_h on the resting membrane potential and on input resistance. Because their reversal potential is between −50 and −20 mV (Pape, 1996), when HCN channels are active near a neuron's resting membrane potential, the influx of inward current depolarizes the membrane potential and therefore maintains it closer to the threshold for an action potential (excitatory effect). This is exemplified in Fig. 1A, where the application of ZD7288, an I_h blocker (Harris and Constanti, 1995; Gasparini and DiFrancesco, 1997), hyperpolarizes the membrane potential, such that the same depolarizing stimulus that was generating an action potential in control conditions (Fig. 1A1) remains sub-threshold when I_h is blocked (Fig. 1A2). On the other hand, by contributing an increase in membrane conductance, HCN channels significantly dampen changes in the membrane potential, therefore requiring larger inputs to initiate an action potential (inhibitory effect). This aspect is exemplified in Fig. 1A3, where, upon compensation of the ZD7288-induced depolarization with tonic current, the neuron fires more action potentials in response to the same depolarizing current, due to the larger input resistance when I_h is blocked (as visible from the change in potential highlighted by the orange arrows). This dichotomy between functions is particularly evident in the single-neuron hyperexcitability seen in epilepsy, where either up- or down-regulation of I_h have been observed, in different animal models (Noam et al., 2011). The relative contribution of the excitatory and inhibitory roles of I_h in this context can be dissected using computational simulations (Dyhrfjeld-Johnsen et al., 2009). We discuss the various functions I_h exerts by regulating the membrane potential in section 3.2 below. Moreover, HCN channels have relatively slow activation and deactivation kinetics, which confer slow time-dependent changes in response to changes in the membrane

potential. These slow channel dynamics are essential for some of the effects of I_h in neurons, which we discuss in section 3.1; interestingly, in some cases it is the slow deactivation upon depolarization that determines the effects of I_h, as in the case of excitatory synaptic potentials and their summation (Magee, 1999, 2000), as discussed in section 3.1.3. In other cases, the slow activation and deactivation act synergistically to confer resonance and/or oscillatory behavior to certain neurons, as discussed in section 3.1.2.

2. OVERVIEW OF HCN CHANNELS

HCN channels are part of the superfamily of six-transmembrane channels, most structurally related to two known voltage-gated potassium channels, K_v10 and K_v11, and to cyclic nucleotide-gated channels. There is more than one oddity about the HCN channel: the selectivity pore has a structure that should confer K^+ selectivity, yet it is also permeable to Na^+. Also, the polarity of its voltage gate is reversed, such that hyperpolarization opens the pore, and depolarization causes the pore to close. Finally, although the structure of HCN channels is related to the broader class of cyclic nucleotide-gated channels because of the presence of the cyclic nucleotide-binding domain, cyclic nucleotides are not required for HCN channel opening, although cAMP binding directly to the channel does increase the open probability.

2.1 STRUCTURE

Using cryo-EM (single-particle electron cryo-microscopy), Lee and MacKinnon (2017, 2019) elucidated the full-length three-dimensional structure of a human HCN channel at 3.5 Å resolution, confirming some previously proposed structural elements and answering some of the questions regarding HCN's special characteristics. The overall structure is comprised of four identical subunits, each with a pore region, voltage sensor, HCN domain, cyclic nucleotide binding domain (CNBD) and C-linker. The HCN domain, CNBD and C-linker are in the cytosol. The HCN domain seems to contact both the voltage sensor and the cytoplasmic domains via the C-linker and has been found to both ensure correct insertion of channels at the membrane and to functionally associate cAMP binding and voltage sensitivity (Porro et al., 2019; Wang et al., 2020). The C-linker connects the S6 transmembrane helix to the CNBD. In the cytosol, a portion of each C-linker sits on the C-linker of the adjacent subunit, contributing to tetramerization (Zagotta et al., 2003). When cAMP binds the CNBD, the C-linkers transmit movement to the transmembrane domains of the channel, discussed further in section 2.3.

Each pore-forming portion of a subunit is formed from helices designated S5 and S6, which are linked to the voltage-sensing domain S1-S4. Between S5 and S6 are amino acids forming the selectivity filter region that match that of potassium-selective channels, yet it acts more like a non-selective channel. This may be due to a twist in the geometry of the HCN filter, such that the amino acid sequences that line the pore in a K^+ channel, creating four binding sites, are only partially available in HCN channels (Lee and MacKinnon, 2017). For this reason, if K^+ is not in the pore at the time, Na^+ is not prevented from flowing through (Lee and MacKinnon, 2017). As a consequence, the relative permeabilities to K^+ and Na^+ for HCN channels (from 3:1 to 5:1, reviewed in Pape, 1996 and Biel et al., 2009)

are not as biased towards K^+ as in potassium channels (from 14:1 to more than 250:1, Hille, 2001), and because its reversal potential, between −50 and −20 mV (Pape, 1996), is more depolarized than a typical resting membrane potential, I_h is a net inward current throughout its activation range for physiological Na^+ and K^+ concentrations.

In the three-dimensional structure of most voltage-gated potassium channels, S1-S4 would interact with S5 and S6 in an adjacent subunit, rather than S5 and S6 of the same polypeptide chain that they are in. This arrangement is referred to as “domain-swapped”. This necessitates that the linker between S4 and S5 is a long alpha-helix running horizontally between subunits, which is thought to act like a belt around the subunits, allowing the pore to open or close upon movement of S4 (Long et al., 2005). HCN channels are not domain-swapped; S1-S4 are linked to S5 and S6 in the same polypeptide chain. The cryo-EM maps show that the S4 helix is longer compared to that of K_v channels and was initially proposed to act in the same fashion as an S4-S5 linker, albeit with inverted gating (Lee and MacKinnon, 2017). However, the deletion of this S4-S5-linker-like region does not interfere with gating via hyperpolarization (Flynn and Zagotta, 2018).

Like other voltage sensors, S4 of HCN channels moves toward the cytosol with hyperpolarization (Männikkö et al., 2002), however there are additional steps that may explain the inverted gating. In HCN’s open state, S4 has moved 10 Å toward the cytosol, broken into two helices, and bent away from the HCN domain, such that the bottom portion of S4 is almost parallel to the cytoplasmic membrane (Dai et al., 2019; Kasimova et al., 2019; Lee and MacKinnon, 2019). One interpretation has been that by doing this, S4 moves S5 enough that there is room for the pore domain to relax to an open position. Another feature revealed by crystal structure is that S4 and S5 are closely aligned, with several points of contact (Lee and MacKinnon 2017). Based on this, a slightly different interpretation has been that the channel is held closed by interactions between residues in S4 and S5 that are broken when S4 moves down in response to hyperpolarization, and then the open conformation is stabilized by interactions between the C-linker and CNBD with the HCN domain of adjacent subunits (Lee and MacKinnon, 2017; Cowgill et al., 2019; Ramentol et al., 2020). Overall, it appears that the closed state of HCN is energetically a little expensive, and that hyperpolarization-induced movement and bending of S4 releases constraints on the conformation, allowing the channel pore region to relax into an open configuration. Channel opening, then, is mostly a matter of releasing the constraints that hold the channel in a closed conformation “at rest”.

2.2 SUBUNITS AND DISTRIBUTION

Four different subunit types have been discovered (HCN1–4), differing in the speed of activation and deactivation, and sensitivity to voltage and to modulation via cAMP. HCN1 has the most depolarized $V_{1/2}$ and fastest activation speed (within hundreds of ms, Santoro et al, 2000), while full activation of HCN2 and HCN4 can take seconds (Ishii et al., 1999; Seifert et al., 1999; Santoro et al., 2000). As such, HCN activation is about 10 times slower in thalamic relay cells where HCN2 and HCN4 predominate than in hippocampal CA1 where HCN1 is elevated (Santoro et al 2000). There is evidence that different subunit types form heteromers which have intermediate characteristics (Chen et al., 2001).

The extent to which cAMP modifies voltage dependence is highest for HCN4, followed by HCN2, and lowest for HCN1 (reviewed in Robinson and Siegelbaum, 2003; Biel et al., 2009; Sartiani et al., 2017). HCN3 is generally considered to be insensitive to cAMP (Mistrík et al., 2005; Stieber et al., 2005). It is interesting that the subunit-specific built-in voltage regulation and cAMP affinity can work in opposite directions. A homomeric channel of HCN4 would have the slowest activation kinetics and intermediate voltage dependent gating, but would be most likely to bind cAMP, thus increasing its activation speed. Hypothetically, this could confer multi-level control of I_h, e.g. in the presence of neuromodulators upstream of cAMP.

In situ hybridization (Moosmang et al., 1999; Monteggia et al., 2000; Santoro et al., 2000) and immunohistochemistry (Notomi and Shigemoto, 2004) demonstrated that all four subunits are expressed in the adult rodent brain, each with their own distinct patterns, overlapping in some cases. Distribution depends on brain area, developmental stage, and subcellular compartment. Notomi and Shigemoto (2004) published a detailed region-by-region immunohistochemistry study of HCN subunit expression in rat and in their recent review, Santoro and Shah (2020) have compiled extensive RNA data from both human and mouse databases. Briefly, in the adult rodent, HCN1 expression is most prominent in the olfactory bulb, neocortex, hippocampus, cerebellum, and superior colliculus, a visual processing area in the midbrain. HCN2 expression is widespread and diffuse. HCN3 expression is low overall but shows local intense protein expression in the olfactory bulb and piriform cortex, hypothalamus, tegmental nuclei and habenular nucleus (Notomi and Shigemoto, 2004; Mistrík et al., 2005). HCN4 is most abundant in the olfactory bulb and thalamus (Notomi and Shigemoto, 2004; Moosmang et al., 1999; Santoro et al., 2000).

Highly heterogeneous expression of I_h within a single cell type in the olfactory bulb prompted Angelo et al. to suggest a role for I_h in allowing for more parameters and higher dimensional representation of information in odor circuits (Angelo and Margrie, 2011; Angelo et al., 2012). A similar phenomenon has been found in different classes of interneurons in the accessory olfactory bulb (Maksimova et al., 2019). In layer I of the medial agranular cortex, some interneurons (regular spiking and burst-accommodating) have a developmental-associated increase in I_h over time while other interneurons (non-accommodating) seem to have a decrease in I_h over the same time period (Bohannon and Hablitz, 2018). Cell-type specific expression in the hippocampus (Zemankovics et al., 2010) and olfactory bulb (Holderith et al., 2003) may serve to promote cell-specific participation in oscillatory activity.

In many neurons, HCN channel distribution is not widespread, but rather restricted to somatic, dendritic, and/or axonal compartments. Trafficking and subcellular distribution of HCN channels is regulated by TRIP8b (Santoro et al., 2004; Shin et al., 2008; Lewis et al., 2009; Han et al., 2011). Such heterogeneity in ion channel distribution has been suggested to be a way by which the computational power of neurons is multiplied (Gasparini and Magee, 2006; Nusser, 2009; Gidon et al., 2020). In dopaminergic neurons of the substantia nigra pars compacta (SNc), a development-associated redistribution of HCN channels shifts HCN2 and HCN4 subunits from a purely somatic expression to both somatic and dendritic compartments (Dufour et al., 2014). Differences in the compartmentalization of I_h would

presumably reshape these cells' ability to integrate GABA-mediated signaling (Neuhoff et al., 2002) by determining their response to hyperpolarization as they mature. For these neurons, hyperpolarization, and the following rebound firing may be critical signals for reward prediction error (Neuhoff et al., 2002; Otomo et al., 2020). SNc dopaminergic neurons also have the unusual feature of an axon emanating from a dendrite. Engel and Seutin (2015) determined that there is a relatively high expression of I_h in the area of dendrite near the axon in SNc dopaminergic neurons that were characterized by the presence of a prominent sag. The high density of HCN channels lowers the input resistance near the axon, which may then narrow the window for coincidence detection (Engel and Seutin, 2015).

In layer V neocortical pyramidal neurons, Atkinson and Williams (2009) found a 10-fold increase in HCN1 and I_h in the apical dendrites during the first postnatal month of development, while somatic expression comprised HCN2 and remained steady. The adult expression pattern in these cells is a gradient of I_h along the apical dendrite that increases with distance from soma. This pattern is duplicated in pyramidal neurons of hippocampus, subiculum, and neocortex (Magee, 1998; Williams and Stuart, 2000; Lörincz et al., 2002). The functional relevance of these expression patterns and their developmental maturation is discussed in the dendritic synaptic integration section (3.1.3).

At variance with the pattern described above, there is a uniform distribution of I_h in the apical dendrites of layer V pyramidal neurons in the medial entorhinal cortex (Medinilla et al., 2013), somata and dendrites of juxtaglomerular olfactory neurons (Holderith et al., 2003), and dendrites of Purkinje neurons (Angelo et al., 2007). Bullis et al. (2007) characterized principal neurons in stratum radiatum of area CA1 in the hippocampus that have pyramidal cell morphologies with a reverse gradient of I_h in the apical dendrite (higher at soma). The gradient is shallow, and the total apical arbor is shorter, but the net effect seems to be essentially the same as that found in CA1 pyramidal neurons; inputs along apical dendrite are normalized when measured at the soma (Bullis et al., 2007), as discussed in section 3.1.3.

In thalamic reticular neurons, HCN2 is expressed in spines along with GluR4 receptors, possibly providing a brake on excitatory input to these cells and shaping their output (Abbas et al., 2006; Ying et al., 2007). In monkey prefrontal cortex pyramidal neurons, HCN1 and HCN1/2 channels were found in spines, co-localized with α_{2A}-adrenoreceptors (Wang et al., 2007). This arrangement was hypothesized to provide the smallest functional compartment within which HCN channels (presumably the HCN1/2 heteromers) could be negatively modulated by norepinephrine during a working memory task. However, in other pyramidal neurons, HCN1 and HCN2 expression is lower in spines than on dendritic shafts (Lörincz et al., 2002; Notomi and Shigemoto, 2004; Dougherty et al., 2013). While the restriction of HCN channels to small compartments in close proximity to other interacting currents or modulators in some neurons makes some sense intuitively, the functional impact of exclusion of HCN from spines in other neurons is unclear.

In basket cells of the hippocampus, HCN channels are mostly found in the axon (Notomi and Shigemoto, 2004; Roth and Hu, 2020; but see Aponte et al., 2006 for somatic expression

as well), where they facilitate fast spiking by opposing hyperpolarization that would otherwise accumulate via Na^+/K^+ ATPases during high-frequency trains of action potentials (discussed also in section 3.2.1; Roth and Hu 2020). Cerebellar basket cells also express HCN in the axon and at low levels in the soma (Southan et al., 2000; Luján et al., 2005). In these cells there is a gradual concentration, during postnatal development, of HCN1 in the axon and axon terminals that make inhibitory synapses on Purkinje cells. As the basket cells are the main inhibitory drive on the Purkinje neurons, and the Purkinje neurons are the only output of the cerebellum, this postnatal accumulation of HCN1 may play a major role in shaping the output of the cerebellum. Southan et al. (2000) found that the presence of I_h in cerebellar basket cell axon terminals enhanced GABAergic neurotransmission, so a gradual increase during development may serve to sharpen Purkinje cell output.

2.3 MODULATION

As opposed to most voltage-gated channels, the HCN channel can be modulated directly by the second messenger cAMP, bypassing the involvement of PKA and phosphorylation of the channel, as was first discovered in cardiac sino-atrial node cells (DiFrancesco and Tortora, 1991) and subsequently demonstrated in hippocampal neurons (Pedarzani and Storm, 1995). cAMP binding directly to the CNBD increases the open probability of HCN channels but is not a prerequisite for channel opening. When the CNBD is deleted from the cytoplasmic domain, a partial autoinhibition of HCN that this domain confers in the absence of cAMP is eliminated, such that channels behave as if they have cAMP bound (Wainger et al., 2001). In the absence of cAMP, salt bridges between the HCN domain and C-linkers of opposite and adjacent subunits also help keep the channel closed (Porro et al., 2019). The cryo-EM structure of HCN1 bound to cAMP shows that binding of cAMP in a pocket in the CNBD of each subunit induces relatively small conformational changes that twist the C-linkers and consequently the transmembrane domains of the channel in the direction of opening, therefore widening but not opening the channel pore (Lee and MacKinnon, 2017; Gross et al., 2018). Subunits that demonstrate a larger response to cAMP (such as HCN2 and HCN4) may undergo larger conformational changes in response to cAMP binding (Zagotta et al., 2003; Porro et al., 2019).

Binding of cAMP also increases voltage sensitivity of the HCN channel by inducing conformational changes that ultimately affect the position of the voltage sensor (Porro et al., 2019). The overall effect of cAMP binding is to allow HCN channels to open at more depolarized membrane potentials, as evidenced by a depolarized shift in $V_{1/2}$, the membrane potential at which there is 50% of the maximal conductance. This effect is subunit-specific; the $V_{1/2}$ of HCN1 is only marginally shifted by cAMP (~2 mV; Santoro et al., 1998), the $V_{1/2}$ of HCN3 is shifted slightly in the hyperpolarized direction (Mistrik et al., 2005; Stieber et al., 2005), and the $V_{1/2}$ of HCN2 and HCN4 can be shifted in the depolarized direction by 10 to 20 mV (Wainger et al., 2001; Iishii et al., 1999; Seifert et al., 1999). As a consequence of the depolarized shift in $V_{1/2}$, the activation kinetics, that are themselves voltage-dependent, become faster in the presence of cAMP (Wainger et al., 2001).

Because of its sensitivity to cAMP, I_h is subject to regulation by neuromodulators that increase or decrease cAMP. Serotonin induces depolarization and decreases input resistance

via a current with kinetics and pharmacology matching I_h in brainstem neurons (Bobker and Williams, 1989), thalamocortical neurons (Pape and McCormick, 1989) and CA1 pyramidal neurons (Gasparini and DiFrancesco, 1999). In addition to serotonin, it was shown that norepinephrine induces small depolarizations from V_{rest} and both serotonin and norepinephrine dampen the voltage response to hyperpolarizing pulses by increasing I_h (Pape and McCormick 1989). In the above studies, upon identifying an I_h-dependent effect, researchers reproduced the effect with a cAMP analog and/or an adenylate cyclase activator. Histamine has similar effects on I_h in thalamocortical neurons (McCormick and Williamson, 1991) as does dopamine in retinal ganglion cells (Chen and Yang, 2007). Adenosine, on the other hand, was shown to decrease I_h amplitude and shift its activation curve in the hyperpolarized direction, removing the constraint on burst firing in thalamocortical neurons. This effect was reproduced by inhibiting adenylyl cyclase (Pape, 1992). Excellent reviews (Pape, 1996; He et al., 2014; Sartiani et al., 2017) go into detail about neuromodulators and I_h.

cAMP modulation of HCN channels is disrupted by TRIP8b (Lewis et al., 2009; Santoro et al., 2009; Zolles et al., 2009). This soluble auxiliary subunit might directly compete with cAMP for a binding site on the CNBD (Han et al., 2011; DeBerg et al., 2015; Bankston et al., 2017) or prevent cAMP from inducing the conformational change described above, interfering with modulation in an allosteric manner (Hu et al., 2013; Saponaro et al., 2014, 2018; Porro et al., 2020). TRIP8b also controls subcellular trafficking (Santoro et al., 2004), but this process seems to be controlled by different binding sites on TRIP8b and on the HCN channel (Lewis et al., 2009).

As for other cyclic nucleotides, nitric oxide stimulates soluble guanylate cyclase, elevating cGMP levels which then have an effect on I_h in thalamocortical neurons that is similar to cAMP (Pape and Mager, 1992). In superior olivary complex neurons, however, nitric oxide has differential effects on HCN1 and HCN2, hyperpolarizing and depolarizing the $V_{1/2}$, respectively (Kopp-Scheinpflug et al., 2015). The effect on HCN2, but not HCN1, was found to be dependent on cGMP.

HCN channels are subject to modulation by several additional factors (reviewed in detail by Lewis et al., 2010; He et al., 2014; Sartiani et al., 2017): other cyclic nucleotides and their upstream effectors; protons; temperature; PIP_2; posttranslational modifications, including phosphorylation by PKA; scaffolding proteins; and at least one additional auxiliary subunit besides TRIP8b.

Finally, as are all biophysical processes, I_h is sensitive to temperature. How much a biological process is affected by temperature is quantified by Q_{10}, the ratio of the rates of a process at two different temperatures separated by 10°C (Sterratt, 2014). Q_{10} will have a value for any process that is affected by temperature, such as activation and deactivation kinetics. It is helpful to keep this in mind when reading literature where experiments may be performed at different temperatures. Q_{10} values for I_h have been reported for activation, deactivation, and current amplitude (Magee, 1998).

3. GENERAL FUNCTIONS

As discussed in section 2.2, HCN channels are among those with the most varied subcellular distribution; rarely are they distributed uniformly along the axo-somato-dendritic axis. Most commonly, they show gradients or concentration in specific subcellular compartments. As a consequence, their contributions to neuronal function will be diversified according to their distribution. Additionally, the contribution of HCN channels to neuronal function will depend on the complement of other channels that are co-expressed in those specific neurons or compartments. In some cases, especially in the case of $Ca_V3.2$ (T-type) Ca^{2+} channels, the interactions of these two channels can have effects that are distinctly different from those of I_h alone.

In the next sections, we present some examples of the many functions that have been revealed for HCN channels. We propose that these functions can be categorized depending on whether it is predominantly the slow channel dynamics or the steady effect on the membrane potential that determine each of them. Figure 2 shows a summary of these functions based on location (dendritic or axonal) in a schematic neuron; the color of the ellipses around the traces represent whether the effect of I_h on a particular function is mostly due to the slow channel dynamics (red) or the membrane potential (blue). In one example the contribution of I_h involves both (purple).

3.1 SLOW CHANNEL DYNAMICS

3.1.1 Slow activation and deactivation kinetics of I_h result in sag and rebound—

Due to its peculiar voltage-dependence, depolarized reversal potential and slow channel dynamics, I_h tends to oppose voltage changes in a self-limiting manner (Fig. 1). In order to illustrate the time- and voltage-dependence of HCN conductance (and current) activation, and its effect on the membrane potential, we used a computer simulation with a multicompartmental model of a CA1 pyramidal neuron, where I_h is active at rest (Maccaferri et al., 1993). Given a hyperpolarizing step from the resting membrane potential (V_{rest}), neurons with appreciable I_h will demonstrate a sag potential (Fig. 1B1, highlighted in green); I_h is activated by the step and opposes it with a net, slow inward current, pulling the membrane potential back up towards rest, until the h-conductance and current reach a steady state (Fig. 1B2, B3). Upon cessation of the hyperpolarizing current injection, the membrane potential relaxes to V_{rest} following the membrane time constant; at the same time, I_h starts to turn off, but because it is slow to do so (Fig. 1B2, B3), inward current via I_h still briefly depolarizes the cell above V_{rest}, resulting in a depolarizing overshoot of the membrane potential which then slowly returns to rest (Fig. 1B1, highlighted in red). This transient overshoot in the depolarized direction is commonly referred to as (post-inhibitory) rebound. Depending on the complement of other voltage-dependent channels expressed in neurons, this rebound may result in one or more action potentials (Cooper and Stanford, 2000; Ferrante et al., 2017). In CA1 pyramidal neurons, I_h-dependent rebound spiking is ordinarily masked by the A-type potassium current. If I_A is removed, an I_h-dependent rebound spiking is uncovered (Ascoli et al., 2010).

An analogous, opposite phenomenon to the depolarizing sag happens with a depolarizing step if I_h is partially active at V_{rest}. I_h turns off in response to depolarization and

deactivation of the inward I_h current pulls the membrane potential back down toward V_{rest}. Once the depolarizing step ends, the membrane potential undergoes a hyperpolarizing overshoot before I_h has time to activate, finally coming back to rest as I_h returns the membrane potential to its resting state. This self-limiting effect of I_h can be related to oscillatory activity (discussed in section 3.1.2). Sag and rebound are referred to as "damped oscillations" by Hutcheon and Yarom in their review of the mechanisms underlying resonance (Hutcheon and Yarom, 2000).

Although the presence of a sag has been used in the past as evidence of I_h expression and a way to characterize particular neuronal subtypes (for example, dopaminergic neurons in the substantia nigra pars compacta, see Lacey et al., 1989; Yung et al., 1991), there may be examples where the sag is negated by additional factors. Layer V neurons in the medial entorhinal cortex have appreciable I_h as demonstrated by ZD7288-induced increases in input resistance and EPSP summation, without visible sag (Medinilla et al., 2013). Likewise, fast spiking basket cells of the dentate gyrus were shown to have HCN channels by pharmacology, single-cell PCR, and several electrophysiological parameters, without showing a visible sag (Aponte et al., 2006). According to these authors, I_h in these neurons could have a shallow activation curve that makes it less sensitive to changes in the membrane potential and/or a time-course of activation that overlaps with the membrane time constant, resulting in an imperceptible sag and rebound. It is therefore probable that different combinations of the kinetics of HCN channels and the passive membrane properties (in particular the activation time constant τ_h and the membrane time constant τ_m, as explained below in section 3.1.2) will make the sag more visible in some cells than others.

3.1.2 Slow channel dynamics mediate resonance—Some neurons have an intrinsic property, called resonance, that allows them to be more responsive to certain frequency input (Hutcheon and Yarom, 2000; Hashimoto, 2020) at what is called a cell's peak resonant frequency. In different neuronal types, this characteristic can manifest either in spontaneous voltage oscillations that can be sub- or supra-threshold, or in the tendency to respond best to inputs arriving within a certain frequency window. This may be a neuron's way of discriminating between different frequency inputs and/or facilitate participation in oscillatory activity at that preferred frequency (Richardson et al., 2003; Tohidi and Nadim, 2009).

One way to probe for a peak resonant frequency is by injecting a ZAP (impedance (Z) amplitude profile, also called chirp) input current, a sinusoidal input current with constant amplitude and a frequency that changes linearly from 0 to up to 20 Hz (Fig. 3A). The frequency at which the impedance amplitude reaches its maximum is the resonance frequency. In a system with constant impedance, the amplitude of the voltage response will remain constant across all frequency input. A peak in the voltage response arises when there are attenuated voltage responses on either side of a given frequency, allowing neurons to behave as band-pass filters due to a combination of neuronal passive and active properties, as described below.

A neuron's passive properties, membrane capacitance (C_m) and membrane resistance (R_m), provide neurons with a low-pass filter with a cutoff frequency of $1/(2*\pi*\tau_m)$ determined

by the membrane time constant ($\tau_m = R_m * C_m$). As the frequency of the oscillating current input increases, the voltage across the membrane has less and less time to change, resulting in attenuated voltage responses at frequencies higher than the cutoff determined by τ_m (Fig. 3B).

A neuron's active properties, and in particular, voltage-gated currents such as I_h, that actively oppose changes in the membrane potential, provide neurons with a high-pass filter, i.e. a mechanism for dampening low-frequency oscillations. For currents to be able to fill this role, they need to exhibit 1) a reversal potential at the base of their activation curve, and 2) slow activation kinetics (Hutcheon and Yarom, 2000). I_h preferentially attenuates low frequency oscillations (Fig. 3C), since its activation by hyperpolarization opposes further hyperpolarization, satisfying requirement 1. Requirement 2 is met because I_h has an activation time constant (τ_h) of tens or hundreds of ms, depending on the membrane potential and subunit composition. Because of these two features, I_h effectively opposes slow membrane potential changes, therefore attenuating the voltage response at lower frequencies, up to a cutoff frequency of $1/(2*\pi*\tau_h)$ (Hutcheon and Yarom, 2000). More rapid changes to the membrane potential outpace I_h activation, allowing sinusoidal current at those frequencies to maximally change the membrane potential (Fig. 3C), up to the cutoff frequency determined by τ_m (Fig. 3D). As mentioned in section 3.1.1 for the generation of sag, if τ_h and τ_m are comparable and therefore overlap, this phenomenon is not apparent.

Some neurons exhibit intrinsically oscillating rhythmic activity that can be either sub- or supra-threshold, when an amplifying current, such as persistent Na^+ current (I_{NaP}), is also present (Hutcheon and Yarom, 2000). Spontaneous subthreshold oscillations can result from this interaction because the two currents activate with voltage changes in opposite directions, and because I_h activation and deactivation are slow with respect to changes in I_{NaP} (Dickson et al., 2000). Stellate cells in layer II of the entorhinal cortex, which provide the input to the dentate gyrus through the perforant pathway, have spiking and subthreshold oscillations due to interaction between I_h and I_{NaP} (Alonso and Llinás, 1989; Dickson et al., 2000). In these neurons, subthreshold oscillations are abolished when I_h is blocked (Fig. 2C, Giocomo and Hasselmo, 2008).

These layer II stellate cells show a dorso-ventral gradient in the frequency of subthreshold oscillations (Giocomo et al., 2007). Along the dorso-ventral axis, an increase in τ_h is correlated with a smaller peak resonant frequency (Giocomo and Hasselmo, 2008), which may be the result of the decrease in the amplitude of I_h along the axis (Garden et al., 2008), or may be related to a gradient in subunit differences as well. Such a dorso-ventral gradient in the ratio of HCN1 and HCN2 has been demonstrated in the hippocampus (Dougherty et al., 2013). The resonance gradient in the entorhinal cortex disappears in HCN1 knockout mice, suggesting that HCN1 channels are responsible for the gradient, although resonance is not completely abolished. In these mice, there is a remaining uniform resonant frequency that is lower (roughly 2 Hz), consistent with a slower τ_h left by other HCN subunits (Giocomo and Hasselmo, 2009). One interpretation is that HCN1 channels would usually suppress the lower resonant frequency because they are expressed at higher densities (Nolan et al., 2007). It has been suggested that this gradient in I_h amplitude and τ_h may determine

grid cell size and spacing along the dorso-ventral axis, via differences in subthreshold oscillations (Giocomo et al., 2011) and/or integration properties (Garden et al., 2008).

In some lateral geniculate nucleus thalamocortical relay cells, high frequency bursts with inter-burst frequency 1–2 Hz, were found to depend on an interaction between I_h and low-threshold T-type Ca^{2+} current (McCormick and Pape, 1990a, 1990b). This phenomenon is discussed further, in section 3.3. Inferior olive neurons, which project from the brainstem to the cerebellum, and provide excitatory input to Purkinje neurons, demonstrate spontaneous oscillations, both subthreshold and spiking, that have a refractory period in between calcium spikes that is dependent on I_h (Bal and McCormick, 1997). Resonance in these neurons is abolished in HCN1 knockout mice (Matsumoto-Makidono et al., 2016). Hippocampal oriens-lacunosum moleculare interneurons, which provide inhibition to the most distal apical dendrite of CA1 pyramidal neurons, exhibit intrinsic spontaneous firing which is not blocked by glutamate receptor agonists. The frequency of spontaneous firing is I_h-dependent and slows down in ZD7288 (Maccaferri and McBain, 1996).

Other examples can be found in which oscillations are not spontaneous, but are driven, with a peak resonant frequency set up by I_h. Cells falling into this category may still participate in oscillatory activity if they are driven by afferent input. For example, in the hippocampus, I_h-dependent resonance is in the theta range (Hu et al., 2002). Input from medial septum interneurons, as well as excitatory input from the entorhinal cortex and CA3, entrains CA1 in theta oscillations, which is thought to be tied to particular behaviors or events and may facilitate communication within or between regions of the CNS (reviewed in Colgin, 2013). Non-spontaneously active cells with I_h-dependent resonance include some pyramidal neurons in the neocortex (Hutcheon et al., 1996), some, but not all, cell types in the hippocampus (Zemankovics et al., 2010), pyramidal neurons in the subiculum (Wang et al., 2006), neurons in the olfactory amygdala (Vera et al., 2014), and some, but not all, interneurons in the olfactory bulb (Hu et al., 2016).

Resonance due to I_h can co-exist with other resonant mechanisms. Such appears to be the case in CA1 pyramidal neurons where it has been shown that at more hyperpolarized membrane potentials, I_h has a greater impact on resonance that gives way to an I_M effect at more depolarized potentials (Hu et al., 2002). In these cells, theta oscillations driven by the medial septum appear to comprise two distinct phenomena, rather than a continuous modulation of resonance (Hu et al., 2002). Peak resonant frequency specifically in the apical dendrites of these CA1 pyramidal neurons can be attributed to I_h (Narayanan and Johnston, 2007; Hu et al., 2009). Hu et al. (2009) suggested that this resonance has a particular role in filtering input from the medial entorhinal cortex, which provides the major excitatory input to distal apical dendrites in CA1, where I_h expression is high.

3.1.3 The slow channel dynamics of HCN channels in dendritic synaptic integration—

HCN channels control the time course of excitatory synaptic potentials (EPSPs). In neurons where I_h is active at rest, its slow voltage-dependent deactivation during depolarizing input effectively produces a time-dependent hyperpolarization that shortens the duration of the EPSPs (Magee, 1999). When I_h is blocked, EPSPs are wider and show more temporal summation (Fig. 2E, Medinilla et al., 2013). As a consequence, the differential

expression of HCN channels in neurons, and in particular the steep gradient in density along the dendrites of pyramidal neurons, endows dendritic EPSPs recorded locally with progressively faster decays along the dendritic apical tree, as more and more I_h shortens the EPSP duration. This reduction in the half-width of the EPSPs ends up compensating for the dendritic filtering the EPSPs experience in their propagation to the soma, due to the passive properties of dendrites, which becomes progressively larger with the distance from the soma (Rall et al., 1967). The end result is that most inputs will show the same degree of temporal summation for frequencies up to 100 Hz when recorded at the soma (Magee, 1999; Williams and Stuart, 2000); this compensation is removed when I_h is blocked, such that distal inputs will show a larger degree of temporal summation than proximal ones. In CA1 pyramidal neurons, the gradient in I_h, along with the increase in EPSP amplitude along the apical dendrites (Magee and Cook, 2000), is considered responsible for normalizing the impact of synaptic inputs, making it independent of their location (Magee, 2000). Using an elegant computational approach, Angelo et al. (2007) have shown that HCN channels affect EPSP time course and summation both by acting as a static shunt conductance and because of their slow voltage-dependent deactivation kinetics. The shunt conductance decreases EPSP amplitudes, and the slow deactivation kinetics of I_h curtails the EPSP width in a cumulative fashion during a train. These authors concluded that normalization of EPSP summation can be achieved with uniformly larger HCN channel densities in the dendrites of most neurons, as they found in cerebellar Purkinje neurons, as well as non-uniform distributions. On the other hand, the HCN channel gradient creates a gradient of inductance in CA1 apical dendrites, which produces temporal synchrony of rhythmic inputs arriving at different locations of the dendritic tree (Vaidya and Johnston, 2013). Because I_h turns off (decreasing inward current) and on (increasing inward current) in response to depolarizing and hyperpolarizing phases of oscillatory input, respectively, the peaks and troughs of the membrane potential in response to the oscillatory current input occur earlier than they would for passive dendrites (Narayanan and Johnston, 2008). This phenomenological inductance supplied by I_h provides a mechanism for phase advance of voltage in relation to the oscillatory inputs; as a result, the peak voltage occurs progressively earlier in the phase for higher I_h densities in the distal dendrites. This effect counters the passive dendritic filtering that would cause a phase delay for distal dendritic inputs with respect to proximal ones. Thus, the responses to these inputs are synchronous when recorded at the soma but shifted in time in the presence of ZD7288. Because of its slow channel dynamics, as explained in section 3.1.2, I_h only affects low frequency oscillations; therefore, this synchrony is prominent at frequencies that are relevant for active states of the hippocampal network, such as rhythmic gamma frequency bursts arriving in the theta frequency range, a pattern that is also optimal for plasticity induction (Larson et al., 1986).

We discuss effects of I_h on membrane potential in section 3.2, but it is worth noting here that another interesting role of I_h in synaptic integration is that it maintains the resting membrane potential depolarized with respect to the reversal potential for GABA receptors in CA1 pyramidal neurons (Pavlov et al., 2011). In the absence of I_h, the integration time window for action potential generation is widened, showing that hyperpolarizing inhibition is necessary for input integration to be temporally precise. In neurons of the subthalamic nucleus, which express mostly HCN2 and HCN3 subunits with a more hyperpolarized

activation threshold, I_h is not active at rest; its main effect is to counteract GABAergic inhibition from the globus pallidus and generate a single rebound spike rather than a burst by preventing the de-inactivation of $Ca_V3.2$ channels, therefore helping prevent akinesia and bradykinesia (Atherton et al., 2010).

In some cases, the impact of HCN channels on dendritic integration can be observed in neurons where the density of the channels increases during development or decreases following pathological states. In principal cells of the medial superior olive, a 30 mV-depolarizing shift in the activation curve of HCN channels, due to intracellular diffusible factors, as well as >10-fold increase in the maximal conductance, gives rise to a large h-conductance active at rest in mature neurons (Khurana et al., 2012). By reducing the membrane time constant, this change sharpens the window of coincidence detection for these neurons at the onset of hearing, contributing to the developmental changes that confer the sub-millisecond temporal precision required for the transmission of sound localization cues. With I_h intact, only coincident (within ≤ 200 μs) stimulation of ipsilateral and contralateral inputs will reliably generate action potentials (Fig. 2D; Khurana et al., 2012). When I_h is blocked, inputs separated by as much as 600 μs will still sometimes generate action potentials. In another developmental event, layer V (thick/tufted 5B) neocortical pyramidal neurons experience a >10-fold age-dependent increase in the density of apical dendritic HCN channels (mostly HCN1) in the first postnatal month (Atkinson and Williams, 2009). This increase is related to a functional development where the cell is initially one continuous electrical compartment, followed by the emergence of distinct somatic and dendritic compartments that handle synaptic integration differently as the network matures (Atkinson and Williams, 2009). The increase in HCN1 gives rise to an effective time-dependent hyperpolarization upon deactivation, as described above, shortening EPSP duration. As a consequence, the cells switch from somatic integrators where action potentials are generated by efficient summation at the axonal site of integration, to compartmentalized integrators with the generation of dendritic spikes that forward propagate to trigger axonal action potential firing (Larkum and Zhu, 2002). In the mature 5B neurons, because of the density gradient, HCN channels have dual functional roles, depending on whether the increase in conductance or the depolarization aspect is more pronounced (Harnett et al., 2015). At the soma and proximal dendrites, a lower density of HCN channels primarily serve to depolarize the membrane potential, with a limited effect on the membrane conductance. In the tuft, the high membrane conductance imparted by HCN activity decreases excitability by decreasing summation, in a manner consistent with the studies described above, shortening the decay of EPSPs, and dampening the regenerative recruitment of the channels (Na^+, Ca^{2+} and NMDA) required for the initiation of supra-linear processes. These effects combined could allow for synaptic inputs arriving at basal and apical dendrites that carry different streams of information to be integrated independently (Williams, 2004). As for pathology-related changes, sciatic nerve injury causes a decrease in HCN channel function in layer V neurons of the anterior cingulate cortex, that results in enhanced EPSP integration, due to slower EPSPs, and more neuronal firing, which results in mechanical pain hypersensitivity (Santello and Nevian, 2015). All the normal attributes could be restored in injured animals when I_h function was increased by selective modulation of $5\text{-}HT_7$ receptors.

3.2 STEADY DEPOLARIZING EFFECT ON MEMBRANE POTENTIAL

3.2.1 Role of I_h in axonal function and transmitter release via steady effect on V_m—

HCN channels can be found in some presynaptic terminals, where they play a role in transmitter release via control of V_{rest}. The first report of HCN channels contributing to neurotransmitter release came from the neuromuscular junction of crayfish muscle cells innervated by glutamatergic axons (Beaumont and Zucker, 2000). The activation of serotonin receptors in the presynaptic terminals leads to increased synaptic strength that was shown to depend on depolarization caused by cAMP modulation, and subsequent Cs^+ and ZD7288-sensitive inward current. Similarly, HCN1 channels are preferentially localized in the axons and terminals of cerebellar basket cells (Luján et al., 2005), where they depolarize the membrane potential; their blockade by ZD7288 significantly decreases the amplitude and frequency of spontaneous IPSCs recorded in the soma of Purkinje cells, many of which originate from neighboring basket cells (Fig. 2H, Southan et al., 2000). However, involvement of HCN channel-mediated depolarization in presynaptic LTP at the mossy fiber-CA3 synapses in the rat hippocampus (Mellor et al., 2002) was later ascribed to a non-specific effect of the blocker ZD7288 at high concentrations (Chevaleyre and Castillo, 2002), possibly due to the block of T-type Ca^{2+} channels (Sánchez-Alonso et al., 2008). Nonetheless, in the hippocampus, HCN channels were found at perforant path terminals making synapses onto dentate gyrus granule cells (Bender et al., 2007). HCN channels could have a role in the stabilization and maturation of those synapses, by providing a steady presynaptic depolarization, since their expression in terminals reached a peak in the second postnatal week and waned subsequently, due to decreased transport into the axon.

In mouse cerebellar mossy fibers, HCN2 channels are uniformly distributed in boutons and axons, where they modulate conduction velocity, which is increased by noradrenaline and decreased by serotonin and adenosine, which up- and down-regulate $[cAMP]_i$, respectively (Byczkowicz et al., 2019). In addition, I_h blockade by ZD7288 significantly decreases the maximal failure-free firing frequency in these neurons, that are able to fire at > 1 kHz (Fig. 2F, Byczkowicz et al., 2019). In these neurons the increase in conduction velocity may be due to faster voltage-gated Na^+ channel activation, as provided by maintenance of membrane depolarization via HCN2 channels. On the other hand, in another neuronal type known for high frequency firing, the principal cells of the medial superior olive, HCN channels expressed in the axon initial segment depolarize the resting membrane potential and decrease spike probability by raising the action potential threshold, either by increasing Na^+ channel inactivation and/or by activating K_v1 channels (Ko et al., 2016). In these neurons, 5-HT released from the raphe decreases I_h activation, and hyperpolarizes selectively the axonal, but not somatic or dendritic, resting potential, therefore increasing the distance from the action potential threshold without degrading the temporal resolution needed for the integration of location-dependent stimuli (see Khurana et al., 2012 in section 3.1.3).

Parvalbumin-expressing perisoma-inhibiting interneurons of the dentate gyrus, express heteromers composed of HCN1 and HCN2 subunits in axons and perisomatic terminals (Aponte et al., 2006). In these neurons, block of HCN channels in the remote axon prevents the induction of persistent firing at gamma (~50 Hz) frequencies that efficiently inhibit

large populations of granule cells (Elgueta et al., 2015); this effect is not due just to the hyperpolarization of the membrane potential, since it is not reversed by depolarizing the resting potential with 5 mM KCl. Recent data suggest that the role of HCN channels in this case is to dynamically counter the strong hyperpolarizing current during repetitive firing mediated by Na^+/K^+ ATPases that are densely expressed at this location (Roth and Hu, 2020).

Most of the examples in this section point to a facilitatory role of I_h in action potential generation and conduction, and neurotransmitter release. Opposite evidence comes from the glutamatergic terminals onto entorhinal layer III cortical neurons, where pharmacological or genetic ablation of HCN1 channels reduces the tonic depolarization that this current provides, and the resulting hyperpolarization relieves $Ca_V3.2$ T-type Ca^{2+} channels of inactivation. This increased Ca^{2+} influx results in an increase in terminal excitability and transmitter release, as measured by an increase in frequency of miniature EPSCs recorded in the target neuron (Fig. 2G, Huang et al., 2011). This counterintuitive finding points out again the relevance of the environment where I_h is expressed, as well as the interactions with other voltage-dependent channels.

3.2.2 Role of I_h in plasticity and memory functions through regulation of V_m

—Similar to what described for Huang et al., 2011 in 3.2.1, a somewhat counterintuitive consequence of the effect of the interaction between HCN and $Ca_V3.2$ channels has been found for the synapses onto distal dendrites of hippocampal CA1 neurons from neurons in layer III of the entorhinal cortex. These axons form the temporo-ammonic pathway, terminating in the stratum lacunosum-moleculare. Nolan et al. (2004) demonstrated an increased long-term potentiation (LTP) at these synapses, but not at the Schaffer collateral synapses, in HCN1 knockout mice where the deletion was restricted to the forebrain. In addition, these mice showed an enhanced performance in spatial learning tasks. The initial interpretation was that HCN1 channels, that are expressed in high density in these distal dendrites, exert an inhibitory constraint on hippocampal-dependent memory by regulating dendritic integration and plasticity at these synapses, with a mechanism, due to the slow channel dynamics of I_h, similar to what is described in 3.1.3 (Magee, 1999). However, subsequently, it was found that the genetic deletion or pharmacological block of HCN channels resulted in larger, regenerative, dendritic Ca^{2+} spikes following brief tetanic stimulation (Tsay et al., 2007). I_h tonically depolarizes the resting membrane potential in the distal dendrites of CA1 pyramidal neurons and thereby increases inactivation of T- and N-type Ca^{2+} channels, shortening dendritic calcium spikes. In HCN1 knockout mice, the membrane potential hyperpolarizes, and activation of the now available calcium channels by the EPSP causes the plateaus to last longer (Fig. 2B; Tsay et al., 2007); these non-linear events are thought to be more significant for induction of long-term potentiation at these synapses (Golding et al., 2002). Removing HCN channels in this case has dual, interacting, excitatory effects by 1) increasing the input resistance and therefore the amplitude of the EPSPs and 2) hyperpolarizing the V_m to a level where T- and N-type Ca^{2+} channels were de-inactivated and therefore could be activated by those EPSPs. Conversely, in layer V pyramidal neurons of the medial prefrontal cortex, the activation of HCN1 channels promotes persistent firing directly through tonic membrane depolarization (Thuault et

al., 2013). This conclusion was reached because persistent firing, that was abolished in HCN1 knockout mice or in the presence of ZD7288, could be rescued by DC current injection to reestablish a more depolarized resting potential. However, genetic deletion of HCN1 channels restricted to these neurons was sufficient to impair certain working memory performances, that are thought to be supported by persistent firing (Zylberberg and Strowbridge, 2017), therefore highlighting the permissive role of I_h on some learning paradigms. Taken together, these two examples of opposing effects of I_h on neuronal excitability, and ultimately memory functions, highlight how I_h impact strongly depends on the complement of other ion channels expressed in each specific neuronal subtype.

Purkinje neurons in the cerebellum are spontaneously active, and their firing frequency is modulated by the timing of excitatory (through climbing and parallel fibers) and inhibitory inputs (from basket and stellate cells). The high density of HCN1 channels in their dendrites dynamically oppose hyperpolarization to keep the V_m close to the action potential threshold, whether the most recent input was excitatory or inhibitory, enabling integration that is independent of the previous history of the neurons, and providing at the same time a more effective dynamic range (Nolan et al., 2003). As a consequence, in wild-type mice, spontaneous firing terminates only at a trough of an hyperpolarizing ramp, and quickly resumes upon depolarization, such that the firing frequency is similar upon hyperpolarization and depolarization (Fig. 2A; Nolan et al., 2003). In HCN1 knockout mice, however, the membrane potential is strongly hyperpolarized by the same ramp, due to lack of I_h, and neurons take much longer to resume spiking upon depolarization. This effect has profound repercussions on plasticity in these neurons, that are involved in learning motor tasks that require accurate repetition of a series of similar movements, generated by fluctuating inhibitory and excitatory inputs. As a consequence, HCN1 knockout mice have profound deficits when learning to balance on a rotating rod (Nolan et al., 2003).

3.3 An example of I_h controlling neuronal activity via both slow dynamics and V_m in the same neuron

The two effects we dissected in the examples above, on the membrane potential and slow dynamics, coexist in thalamocortical neurons. The thalamus contains multiple nuclei that act as relay stations and as a gateway between the various subcortical areas and the cortex (Steriade and Llinás, 1988). The membrane potential in thalamocortical relay neurons is controlled by the interplay of I_h and various leak K^+ channels (Meuth et al., 2003; Bista et al., 2015), which are differentially modulated by neuromodulators via ascending systems from the brainstem. Interestingly, in these neurons, I_h is mostly composed of HCN2 and HCN4 subunits (Kanyshkova et al., 2009; Zobeiri et al., 2019), whose activation can be strongly modulated by cAMP (Wainger et al,. 2001; Iishii et al., 1999; Seifert et al., 1999). For this reason, changes in the intracellular concentration of cAMP, due to neuromodulators, can dramatically shift the activation curve of I_h, and therefore its contribution to the membrane potential. Due to the complement of other channels in these neurons, the level of resting membrane potential can switch the neuronal firing between two completely different modes. When devoid of external innervation, thalamocortical relay neurons are characterized by rhythmic bursts of action potentials at a frequency of 0.5–4 Hz (McCormick and Prince, 1988; Pape, 1996). These bursts are originated by a slow, I_h-dependent, depolarizing

ramp from hyperpolarized potentials, reaching the activation threshold of T-type Ca^{2+} channels, which, with their activation and inactivation dynamics, mediate the short Ca^{2+} plateaus triggering a series of fast Na^+/K^+ action potentials (Fig. 2I, left; McCormick and Pape, 1990a). Upon repolarization, the hyperpolarized overshoot activates I_h, which slowly depolarizes V_m to the point where T-type Ca^{2+} channels are activated, and so on. On the other hand, noradrenaline or serotonin cause a depolarization of the membrane potential by increasing the intracellular concentration of cAMP, therefore shifting the activation curve of I_h to the right, as well closing leak K^+ channels (McCormick, 1992), and these same neurons fire sequences of single action potentials (Pape and McCormick, 1989). This can be simulated by a depolarizing current injection (Fig. 2I, right; McCormick and Pape, 1990a). A recent study with knock-in mice that express a mutant HCN2 channel retaining normal voltage-dependent gating but disrupted cAMP-binding, suggests that the cAMP regulation of these channels is essential for regulating the transition between the burst and tonic firing modes (Hammelmann et al., 2019). These two different firing modes, modulated by complex synaptic interactions with inhibitory and excitatory afferents from other thalamic nuclei or extra-thalamic areas, are thought to be the basis of the activity of these neurons during sleep and wake states, respectively (Steriade and Llinás, 1988).

4. CONCLUSIONS

Because of their dual effects on excitability, arising from a stabilizing effect on the membrane potential (excitatory) and a decrease in input resistance (inhibitory), as well as their slow channel dynamics that give rise to resonance and the tuning of the window for synaptic integration, the functions of I_h and HCN channels in neurons are multifaceted. Here we have framed the widespread and diverse contribution of this current to neuronal function as being largely attributable to one or the other of these effects. We hope that our treatment of the literature provides a useful reference for readers seeking a general knowledge of I_h and HCN channels in the CNS, as well as a unique perspective for readers already familiar with the field, in the context of this special issue dedicated to the 40 years from the discovery of the “funny” current.

Acknowledgements

We thank Dr. Val Rousseau for the simulations in Figure 1B, and Dr. Chris Knowlton for helpful discussion. SG thanks Dr. Dario DiFrancesco for instilling the knowledge of electrophysiology and I_h biophysics and functions during her PhD training, and the Instructors at the Course in Ion Channels in Synaptic and Neural Circuit Physiology at Cold Spring Harbor Laboratory for hosting the lecture on HCN channels and I_h that inspired this review.

Funding:

This work was supported by the National Institutes of Health (grant number NIH R01 MH115832 under the CRCNS program to co-PIs SG and Carmen C. Canavier).

Abbreviations

5-HT	5-hydroxytryptamine (or serotonin)
cAMP	cyclic adenosine monophosphate

cGMP	cyclic guanosine monophosphate
CNBD	cyclic nucleotide binding domain
CNS	central nervous system
cryo-EM	cryogenic electron microscopy
EPSP	excitatory postsynaptic potential
EPSC	excitatory postsynaptic current
GABA	gamma aminobutyric acid
HCN	hyperpolarization activated cyclic nucleotide gated channel
IPSC	inhibitory postsynaptic current
KO	knockout
LTP	long term potentiation
NMDA	N-methyl-D-aspartate
PIP_2	phosphatidylinositol 4,5-bisphosphate
PKA	protein kinase A
SNc	substantia nigra pars compacta
TRIP8b	tetratricopeptide-repeat containing Rab8b-interacting protein
wt	wild-type
ZAP	impedance (Z) amplitude profile

REFERENCES

Abbas SY, Ying S-W, Goldstein PA (2006) Compartmental distribution of hyperpolarization-activated cyclic-nucleotide-gated channel 2 and hyperpolarization-activated cyclic-nucleotide-gated channel 4 in thalamic reticular and thalamocortical relay neurons. Neuroscience 141:1811–1825. [PubMed: 16806719]

Alonso A, Llinás RR (1989) Subthreshold Na+ -dependent theta-like rhythmicity in stellate cells of entorhinal cortex layer II. Nature 342:175–177. [PubMed: 2812013]

Angelo K, London M, Christensen SR, Häusser M (2007) Local and Global Effects of Ih Distribution in Dendrites of Mammalian Neurons. J Neurosci 27:8643–8653. [PubMed: 17687042]

Angelo K, Margrie TW (2011) Population diversity and function of hyperpolarization-activated current in olfactory bulb mitral cells. Sci Rep 1:50. [PubMed: 22355569]

Angelo K, Rancz EA, Pimentel D, Hundahl C, Hannibal J, Fleischmann A, Pichler B, Margrie TW (2012) A biophysical signature of network affiliation and sensory processing in mitral cells. Nature 488:375–378. [PubMed: 22820253]

Aponte Y, Lien C-C, Reisinger E, Jonas P (2006) Hyperpolarization-activated cation channels in fast-spiking interneurons of rat hippocampus. J Physiol 574:229–243. [PubMed: 16690716]

Ascoli GA, Gasparini S, Medinilla V, Migliore M (2010) Local Control of Postinhibitory Rebound Spiking in CA1 Pyramidal Neuron Dendrites. J Neurosci 30:6434–6442. [PubMed: 20445069]

Atherton JF, Kitano K, Baufreton J, Fan K, Wokosin D, Tkatch T, Shigemoto R, Surmeier DJ, Bevan MD (2010) Selective Participation of Somatodendritic HCN Channels in Inhibitory But Not Excitatory Synaptic Integration in Neurons of the Subthalamic Nucleus. J Neurosci 30:16025–16040. [PubMed: 21106841]

Atkinson SE, Williams SR (2009) Postnatal development of dendritic synaptic integration in rat neocortical pyramidal neurons. J Neurophysiol 102:735–751. [PubMed: 19458150]

Bal T, McCormick DA (1997) Synchronized Oscillations in the Inferior Olive Are Controlled by the Hyperpolarization-Activated Cation Current I h. J Neurophysiol 77:3145–3156. [PubMed: 9212264]

Balducci V, Credi C, Sacconi L, Romanelli MN, Sartiani L, Cerbai E (2021). The HCN channel as a pharmacological target: why, where, and how to block it. Prog Biophys Mol Biol. 2021 Jul 22:S0079-6107(21)00092-4

Bankston JR, DeBerg HA, Stoll S, Zagotta WN (2017) Mechanism for the inhibition of the cAMP dependence of HCN ion channels by the auxiliary subunit TRIP8b. J Biol Chem 292:17794–17803. [PubMed: 28864772]

Beaumont V, Zucker RS (2000) Enhancement of synaptic transmission by cyclic AMP modulation of presynaptic I h channels. Nat Neurosci 3:133–141. [PubMed: 10649568]

Bender RA, Kirschstein T, Kretz O, Brewster AL, Richichi C, Rüschenschmidt C, Shigemoto R, Beck H, Frotscher M, Baram TZ (2007) Localization of HCN1 Channels to Presynaptic Compartments: Novel Plasticity That May Contribute to Hippocampal Maturation. J Neurosci 27:4697–4706. [PubMed: 17460082]

Biel M, Wahl-Schott C, Michalakis S, Zong X (2009) Hyperpolarization-activated cation channels: from genes to function. Physiol Rev 89:847–885. [PubMed: 19584315]

Bista P, Cerina M, Ehling P, Leist M, Pape H-C, Meuth SG, Budde T (2015) The role of two-pore-domain background K+ (K2P) channels in the thalamus. Pflüg Arch - Eur J Physiol 467:895–905.

Bobker DH, Williams JT (1989) Serotonin augments the cationic current Ih in central neurons. Neuron 2:1535–1540. [PubMed: 2483327]

Bohannon AS, Hablitz JJ (2018) Developmental Changes in HCN Channel Modulation of Neocortical Layer 1 Interneurons. Front Cell Neurosci 12:20. [PubMed: 29440994]

Brown HF, DiFrancesco D, Noble SJ (1979) How does adrenaline accelerate the heart? Nature 280:235–236. [PubMed: 450140]

Bullis JB, Jones TD, Poolos NP (2007) Reversed somatodendritic I_h gradient in a class of rat hippocampal neurons with pyramidal morphology: I_h in PLP neurons. J Physiol 579:431–443. [PubMed: 17185334]

Byczkowicz N, Eshra A, Montanaro J, Trevisiol A, Hirrlinger J, Kole MH, Shigemoto R, Hallermann S (2019) HCN channel-mediated neuromodulation can control action potential velocity and fidelity in central axons. eLife 8:e42766. [PubMed: 31496517]

Chang X, Wang J, Jiang H, Shi L, Xie J (2019) Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels: An Emerging Role in Neurodegenerative Diseases. Front Mol Neurosci 12:141. [PubMed: 31231190]

Chen L, Yang X-L (2007) Hyperpolarization-activated cation current is involved in modulation of the excitability of rat retinal ganglion cells by dopamine. Neuroscience 150:299–308. [PubMed: 17942239]

Chen S, Wang J, Siegelbaum SA (2001) Properties of hyperpolarization-activated pacemaker current defined by coassembly of HCN1 and HCN2 subunits and basal modulation by cyclic nucleotide. J Gen Physiol 117:491–504. [PubMed: 11331358]

Chevaleyre V, Castillo PE (2002) Assessing the role of Ih channels in synaptic transmission and mossy fiber LTP. Proc Natl Acad Sci 99:9538–9543. [PubMed: 12093909]

Colgin LL (2013) Mechanisms and Functions of Theta Rhythms. Annu Rev Neurosci 36:295–312. [PubMed: 23724998]

Cooper AJ, Stanford IM (2000) Electrophysiological and morphological characteristics of three subtypes of rat globus pallidus neurone in vitro. J Physiol 527:291–304. [PubMed: 10970430]

Cowgill J, Klenchin VA, Alvarez-Baron C, Tewari D, Blair A, Chanda B (2019) Bipolar switching by HCN voltage sensor underlies hyperpolarization activation. Proc Natl Acad Sci 116:670–678. [PubMed: 30587580]

Dai G, Aman TK, DiMaio F, Zagotta WN (2019) The HCN channel voltage sensor undergoes a large downward motion during hyperpolarization. Nat Struct Mol Biol 26:686–694. [PubMed: 31285608]

DeBerg HA, Bankston JR, Rosenbaum JC, Brzovic PS, Zagotta WN, Stoll S (2015) Structural Mechanism for the Regulation of HCN Ion Channels by the Accessory Protein TRIP8b. Structure 23:734–744. [PubMed: 25800552]

Dickson CT, Magistretti J, Shalinsky MH, Fransén E, Hasselmo ME, Alonso A (2000) Properties and Role of I h in the Pacing of Subthreshold Oscillations in Entorhinal Cortex Layer II Neurons. J Neurophysiol 83:2562–2579. [PubMed: 10805658]

DiFrancesco D, Tortora P (1991) Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. Nature 351:145–147. [PubMed: 1709448]

Dougherty KA, Nicholson DA, Diaz L, Buss EW, Neuman KM, Chetkovich DM, Johnston D (2013) Differential expression of HCN subunits alters voltage-dependent gating of h-channels in CA1 pyramidal neurons from dorsal and ventral hippocampus. J Neurophysiol 109:1940–1953. [PubMed: 23324324]

Dufour MA, Woodhouse A, Goaillard J-M (2014) Somatodendritic ion channel expression in substantia nigra pars compacta dopaminergic neurons across postnatal development. J Neurosci Res 92:981–999. [PubMed: 24723263]

Dyhrfjeld-Johnsen J, Morgan RJ, Soltesz I (2009) Double trouble? Potential for hyperexcitability following both channelopathic up- and downregulation of Ih in epilepsy. Front Neurosci 3:1. [PubMed: 19753087]

Elgueta C, Köhler J, Bartos M (2015) Persistent Discharges in Dentate Gyrus PerisomaInhibiting Interneurons Require Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel Activation. J Neurosci 35:4131–4139. [PubMed: 25762660]

Emery EC, Young GT, McNaughton PA (2012) HCN2 ion channels: an emerging role as the pacemakers of pain. Trends Pharmacol Sci 33:456–463. [PubMed: 22613784]

Engel D, Seutin V (2015) High dendritic expression of Ih in the proximity of the axon origin controls the integrative properties of nigral dopamine neurons. J Physiol 593:4905–4922. [PubMed: 26350173]

Ferrante M, Shay CF, Tsuno Y, William Chapman G, Hasselmo ME (2017) Post-Inhibitory Rebound Spikes in Rat Medial Entorhinal Layer II/III Principal Cells: In Vivo, In Vitro, and Computational Modeling Characterization. Cereb Cortex 27:2111–2125. [PubMed: 26965902]

Flynn GE, Zagotta WN (2018) Insights into the molecular mechanism for hyperpolarization-dependent activation of HCN channels. Proc Natl Acad Sci 115:E8086–E8095. [PubMed: 30076228]

Garden DLF, Dodson PD, O'Donnell C, White MD, Nolan MF (2008) Tuning of synaptic integration in the medial entorhinal cortex to the organization of grid cell firing fields. Neuron 60:875–889. [PubMed: 19081381]

Gasparini S, DiFrancesco D (1997) Action of the hyperpolarization-activated current (I-h) blocker ZD 7288 in hippocampal CA1 neurons. Pflugers Arch-Eur J Physiol 435:99–106. [PubMed: 9359908]

Gasparini S, DiFrancesco D (1999) Action of serotonin on the hyperpolarization-activated cation current (I-h) in rat CA1 hippocampal neurons. Eur J Neurosci 11:3093–3100. [PubMed: 10510173]

Gasparini S, Magee JC (2006) State-dependent dendritic computation in hippocampal CA1 pyramidal neurons. J Neurosci 26:2088–2100. [PubMed: 16481442]

Gauss R, Seifert R, Kaupp UB (1998) Molecular identification of a hyperpolarization-activated channel in sea urchin sperm. Nature 393:583–587. [PubMed: 9634235]

Gidon A, Zolnik TA, Fidzinski P, Bolduan F, Papoutsi A, Poirazi P, Holtkamp M, Vida I, Larkum ME (2020) Dendritic action potentials and computation in human layer 2/3 cortical neurons. Science 367:83–87. [PubMed: 31896716]

Giocomo LM, Hasselmo ME (2008) Time Constants of h Current in Layer II Stellate Cells Differ along the Dorsal to Ventral Axis of Medial Entorhinal Cortex. J Neurosci 28:9414–9425. [PubMed: 18799674]

Giocomo LM, Hasselmo ME (2009) Knock-Out of HCN1 Subunit Flattens Dorsal–Ventral Frequency Gradient of Medial Entorhinal Neurons in Adult Mice. J Neurosci 29:7625–7630. [PubMed: 19515931]

Giocomo LM, Hussaini SA, Zheng F, Kandel ER, Moser M-B, Moser EI (2011) Grid Cells Use HCN1 Channels for Spatial Scaling. Cell 147:1159–1170. [PubMed: 22100643]

Giocomo LM, Zilli EA, Fransén E, Hasselmo ME (2007) Temporal Frequency of Subthreshold Oscillations Scales with Entorhinal Grid Cell Field Spacing. Science 315:1719–1722. [PubMed: 17379810]

Golding NL, Staff NP, Spruston N (2002) Dendritic spikes as a mechanism for cooperative long-term potentiation. Nature 418:326–331. [PubMed: 12124625]

Gross C, Saponaro A, Santoro B, Moroni A, Thiel G, Hamacher K (2018) Mechanical transduction of cytoplasmic-to-transmembrane-domain movements in a hyperpolarization-activated cyclic nucleotide–gated cation channel. J Biol Chem 293:12908–12918. [PubMed: 29936413]

Halliwell JV, Adams PR (1982) Voltage-clamp analysis of muscarinic excitation in hippocampal neurons. Brain Res 250:71–92. [PubMed: 6128061]

Hammelmann V, Stieglitz MS, Hülle H, Meur KL, Kass J, Brümmer M, Gruner C, Rötzer RD, Fenske S, Hartmann J, Zott B, Lüthi A, Spahn S, Moser M, Isbrandt D, Ludwig A, Konnerth A, Wahl-Schott C, Biel M (2019) Abolishing cAMP sensitivity in HCN2 pacemaker channels induces generalized seizures. JCI Insight 4:e126418.

Han Y, Noam Y, Lewis AS, Gallagher JJ, Wadman WJ, Baram TZ, Chetkovich DM (2011) Trafficking and Gating of Hyperpolarization-activated Cyclic Nucleotide-gated Channels Are Regulated by Interaction with Tetratricopeptide Repeat-containing Rab8b-interacting Protein (TRIP8b) and Cyclic AMP at Distinct Sites. J Biol Chem 286:20823–20834. [PubMed: 21504900]

Harnett MT, Magee JC, Williams SR (2015) Distribution and Function of HCN Channels in the Apical Dendritic Tuft of Neocortical Pyramidal Neurons. J Neurosci 35:1024–1037. [PubMed: 25609619]

Harris NC, Constanti A (1995) Mechanism of block by ZD 7288 of the hyperpolarization-activated inward rectifying current in guinea pig substantia nigra neurons in vitro. J Neurophysiol 74:2366–2378. [PubMed: 8747199]

Hashimoto K (2020) Mechanisms for the resonant property in rodent neurons. Neurosci Res 156:5–13. [PubMed: 31870695]

He C, Chen F, Li B, Hu Z (2014) Neurophysiology of HCN channels: From cellular functions to multiple regulations. Prog Neurobiol 112:1–23. [PubMed: 24184323]

Hille B (2001) Ion Channels of Excitable Membranes, Third Edition. Sinauer Associates.

Holderith NB, Shigemoto R, Nusser Z (2003) Cell type-dependent expression of HCN1 in the main olfactory bulb. Eur J Neurosci 18:344–354. [PubMed: 12887416]

Hu H, Vervaeke K, Graham LJ, Storm JF (2009) Complementary theta resonance filtering by two spatially segregated mechanisms in CA1 hippocampal pyramidal neurons. J Neurosci Off J Soc Neurosci 29:14472–14483.

Hu H, Vervaeke K, Storm JF (2002) Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na+ current in rat hippocampal pyramidal cells. J Physiol 545:783–805. [PubMed: 12482886]

Hu L, Santoro B, Saponaro A, Liu H, Moroni A, Siegelbaum S (2013) Binding of the auxiliary subunit TRIP8b to HCN channels shifts the mode of action of cAMP. J Gen Physiol 142:599–612. [PubMed: 24277603]

Hu R, Ferguson KA, Whiteus CB, Meijer DH, Araneda RC (2016) Hyperpolarization-Activated Currents and Subthreshold Resonance in Granule Cells of the Olfactory Bulb. eNeuro 3:ENEURO.0197–16.2016.

Huang Z, Lujan R, Kadurin I, Uebele VN, Renger JJ, Dolphin AC, Shah MM (2011) Presynaptic HCN1 channels regulate Ca V 3.2 activity and neurotransmission at select cortical synapses. Nat Neurosci 14:478–486. [PubMed: 21358644]

Hung A, Forster IC, Mckenzie CE, Berecki G, Petrou S, Kathirvel A, Soh MS, Reid CA (2021) Biophysical analysis of an HCN1 epilepsy variant suggests a critical role for S5 helix Met-305 in voltage sensor to pore domain coupling. Prog Biophys Mol Biol. 2021 Jul 21:S0079-6107(21)00086-9

Hutcheon B, Miura RM, Puil E (1996) Subthreshold membrane resonance in neocortical neurons. J Neurophysiol 76:683–697. [PubMed: 8871191]

Hutcheon B, Yarom Y (2000) Resonance, oscillation and the intrinsic frequency preferences of neurons. Trends Neurosci 23:216–222. [PubMed: 10782127]

Ishii TM, Takano M, Xie L-H, Noma A, Ohmori H (1999) Molecular Characterization of the Hyperpolarization-activated Cation Channel in Rabbit Heart Sinoatrial Node*. J Biol Chem 274:12835–12839. [PubMed: 10212270]

Kanyshkova T, Pawlowski M, Meuth P, Dubé C, Bender RA, Brewster AL, Baumann A, Baram TZ, Pape H-C, Budde T (2009) Postnatal expression pattern of HCN channel isoforms in thalamic neurons: relationship to maturation of thalamocortical oscillations. J Neurosci Off J Soc Neurosci 29:8847–8857.

Kasimova MA, Tewari D, Cowgill JB, Ursuleaz WC, Lin JL, Delemotte L, Chanda B (2019) Helix breaking transition in the S4 of HCN channel is critical for hyperpolarization-dependent gating. eLife 8:e53400. [PubMed: 31774399]

Khurana S, Liu Z, Lewis AS, Rosa K, Chetkovich D, Golding NL (2012) An essential role for modulation of hyperpolarization-activated current in the development of binaural temporal precision. J Neurosci 32:2814–2823. [PubMed: 22357864]

Ko KW, Rasband MN, Meseguer V, Kramer RH, Golding NL (2016) Serotonin modulates spike probability in the axon initial segment through HCN channels. Nat Neurosci 19:826–834. [PubMed: 27110919]

Kopp-Scheinpflug C, Pigott BM, Forsythe ID (2015) Nitric oxide selectively suppresses IH currents mediated by HCN1-containing channels. J Physiol 593:1685–1700. [PubMed: 25605440]

Kubota M, Nakamura M, Tsukahara N (1985) Ionic conductance associated with electrical activity of guinea-pig red nucleus neurones in vitro. J Physiol 362:161–171. [PubMed: 2410599]

Lacey MG, Mercuri NB, North RA (1989) Two cell types in rat substantia nigra zona compacta distinguished by membrane properties and the actions of dopamine and opioids. J Neurosci Off J Soc Neurosci 9:1233–1241.

Larkum ME, Zhu JJ (2002) Signaling of Layer 1 and Whisker-Evoked Ca2+ and Na+ Action Potentials in Distal and Terminal Dendrites of Rat Neocortical Pyramidal Neurons In Vitro and In Vivo. J Neurosci 22:6991–7005. [PubMed: 12177197]

Larson J, Wong D, Lynch G (1986) Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res 368:347–350. [PubMed: 3697730]

Lee C-H, MacKinnon R (2017) Structures of the Human HCN1 Hyperpolarization-Activated Channel. Cell 168:111–120. [PubMed: 28086084]

Lee C-H, MacKinnon R (2019) Voltage Sensor Movements during Hyperpolarization in the HCN Channel. Cell 179:1582–1589. [PubMed: 31787376]

Lewis AS, Estep C, Chetkovich DM (2010) The fast and slow ups and downs of HCN channel regulation. Channels 4:215–231. [PubMed: 20305382]

Lewis AS, Schwartz E, Chan CS, Noam Y, Shin M, Wadman WJ, Surmeier DJ, Baram TZ, Macdonald RL, Chetkovich DM (2009) Alternatively spliced isoforms of TRIP8b differentially control h channel trafficking and function. J Neurosci Off J Soc Neurosci 29:6250–6265.

Long SB, Campbell EB, MacKinnon R (2005) Voltage Sensor of Kv1.2: Structural Basis of Electromechanical Coupling. Science 309:903–908. [PubMed: 16002579]

Lörincz A, Notomi T, Tamás G, Shigemoto R, Nusser Z (2002) Polarized and compartment-dependent distribution of HCN1 in pyramidal cell dendrites. Nat Neurosci 5:1185–1193. [PubMed: 12389030]

Ludwig A, Zong X, Jeglitsch M, Hofmann F, Biel M (1998) A family of hyperpolarization-activated mammalian cation channels. Nature 393:587–591. [PubMed: 9634236]

Luján R, Albasanz JL, Shigemoto R, Juiz JM (2005) Preferential localization of the hyperpolarization-activated cyclic nucleotide-gated cation channel subunit HCN1 in basket cell terminals of the rat cerebellum. Eur J Neurosci 21:2073–2082. [PubMed: 15869503]

Maccaferri G, Mangoni M, Lazzari A, DiFrancesco D (1993) Properties of the hyperpolarization-activated current in rat hippocampal CA1 pyramidal cells. J Neurophysiol 69:2129–2136. [PubMed: 7688802]

Maccaferri G, McBain CJ (1996) The hyperpolarization-activated current (Ih) and its contribution to pacemaker activity in rat CA1 hippocampal stratum oriens-alveus interneurones. J Physiol 497:119–130. [PubMed: 8951716]

Magee JC (1998) Dendritic Hyperpolarization-Activated Currents Modify the Integrative Properties of Hippocampal CA1 Pyramidal Neurons. J Neurosci 18:7613–7624. [PubMed: 9742133]

Magee JC (1999) Dendritic I h normalizes temporal summation in hippocampal CA1 neurons. Nat Neurosci 2:508–514. [PubMed: 10448214]

Magee JC (2000) Dendritic integration of excitatory synaptic input. Nat Rev Neurosci 1:181–190. [PubMed: 11257906]

Magee JC, Cook EP (2000) Somatic EPSP amplitude is independent of synapse location in hippocampal pyramidal neurons. Nat Neurosci 3:895–903. [PubMed: 10966620]

Maksimova MA, Cansler HL, Zuk KE, Torres JM, Roberts DJ, Meeks JP (2019) Interneuron Functional Diversity in the Mouse Accessory Olfactory Bulb. eNeuro 6:ENEURO.0058–19.2019.

Männikkö R, Elinder F, Larsson HP (2002) Voltage-sensing mechanism is conserved among ion channels gated by opposite voltages. Nature 419:837–841. [PubMed: 12397358]

Matsumoto-Makidono Y, Nakayama H, Yamasaki M, Miyazaki T, Kobayashi K, Watanabe M, Kano M, Sakimura K, Hashimoto K (2016) Ionic Basis for Membrane Potential Resonance in Neurons of the Inferior Olive. Cell Rep 16:994–1004. [PubMed: 27425615]

Mayer ML, Westbrook GL (1983) A voltage-clamp analysis of inward (anomalous) rectification in mouse spinal sensory ganglion neurones. J Physiol 340:19–45. [PubMed: 6887047]

McCormick DA (1992) Cellular mechanisms underlying cholinergic and noradrenergic modulation of neuronal firing mode in the cat and guinea pig dorsal lateral geniculate nucleus. J Neurosci 12:278–289. [PubMed: 1309574]

McCormick DA, Pape HC (1990a) Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. J Physiol 431:291–318. [PubMed: 1712843]

McCormick DA, Pape HC (1990b) Noradrenergic and serotonergic modulation of a hyperpolarization-activated cation current in thalamic relay neurones. J Physiol 431:319–342. [PubMed: 1712844]

McCormick DA, Prince DA (1988) Noradrenergic modulation of firing pattern in guinea pig and cat thalamic neurons, in vitro. J Neurophysiol 59:978–996. [PubMed: 3367206]

McCormick DA, Williamson A (1991) Modulation of neuronal firing mode in cat and guinea pig LGNd by histamine: possible cellular mechanisms of histaminergic control of arousal. J Neurosci 11:3188–3199. [PubMed: 1658246]

Medinilla V, Johnson O, Gasparini S (2013) Features of proximal and distal excitatory synaptic inputs to layer V neurons of the rat medial entorhinal cortex. J Physiol-Lond 591:169–183. [PubMed: 23006478]

Mellor J, Nicoll RA, Schmitz D (2002) Mediation of Hippocampal Mossy Fiber Long-Term Potentiation by Presynaptic Ih Channels. Science 295:143–147. [PubMed: 11778053]

Meuth SG, Budde T, Kanyshkova T, Broicher T, Munsch T, Pape H-C (2003) Contribution of TWIK-Related Acid-Sensitive K+ Channel 1 (TASK1) and TASK3 Channels to the Control of Activity Modes in Thalamocortical Neurons. J Neurosci 23:6460–6469. [PubMed: 12878686]

Mistrík P, Mader R, Michalakis S, Weidinger M, Pfeifer A, Biel M (2005) The Murine HCN3 Gene Encodes a Hyperpolarization-activated Cation Channel with Slow Kinetics and Unique Response to Cyclic Nucleotides. J Biol Chem 280:27056–27061. [PubMed: 15923185]

Monteggia LM, Eisch AJ, Tang MD, Kaczmarek LK, Nestler EJ (2000) Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. Mol Brain Res 81:129–139. [PubMed: 11000485]

Moosmang S, Biel M, Hofmann F, Ludwig A (1999) Differential distribution of four hyperpolarization-activated cation channels in mouse brain. Biol Chem 380:975–980. [PubMed: 10494850]

Narayanan R, Johnston D (2007) Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability. Neuron 56:1061–1075. [PubMed: 18093527]

Narayanan R, Johnston D (2008) The h Channel Mediates Location Dependence and Plasticity of Intrinsic Phase Response in Rat Hippocampal Neurons. J Neurosci 28:5846–5860. [PubMed: 18509046]

Neuhoff H, Neu A, Liss B, Roeper J (2002) I(h) channels contribute to the different functional properties of identified dopaminergic subpopulations in the midbrain. J Neurosci 22:1290–1302. [PubMed: 11850457]

Noam Y, Bernard C, Baram TZ (2011) Towards an integrated view of HCN channel role in epilepsy. Curr Opin Neurobiol 21:873–879. [PubMed: 21782415]

Nolan MF, Dudman JT, Dodson PD, Santoro B (2007) HCN1 Channels Control Resting and Active Integrative Properties of Stellate Cells from Layer II of the Entorhinal Cortex. J Neurosci 27:12440–12451. [PubMed: 18003822]

Nolan MF, Malleret G, Dudman JT, Buhl DL, Santoro B, Gibbs E, Vronskaya S, Buzsáki G, Siegelbaum SA, Kandel ER, Morozov A (2004) A Behavioral Role for Dendritic Integration: HCN1 Channels Constrain Spatial Memory and Plasticity at Inputs to Distal Dendrites of CA1 Pyramidal Neurons. Cell 119:719–732. [PubMed: 15550252]

Nolan MF, Malleret G, Lee KH, Gibbs E, Dudman JT, Santoro B, Yin D, Thompson RF, Siegelbaum SA, Kandel ER, Morozov A (2003) The Hyperpolarization-Activated HCN1 Channel Is Important for Motor Learning and Neuronal Integration by Cerebellar Purkinje Cells. Cell 115:551–564. [PubMed: 14651847]

Notomi T, Shigemoto R (2004) Immunohistochemical localization of Ih channel subunits, HCN1–4, in the rat brain. J Comp Neurol 471:241–276. [PubMed: 14991560]

Nusser Z (2009) Variability in the subcellular distribution of ion channels increases neuronal diversity. Trends Neurosci 32:267–274. [PubMed: 19299025]

Otomo K, Perkins J, Kulkarni A, Stojanovic S, Roeper J, Paladini CA (2020) In vivo patch-clamp recordings reveal distinct subthreshold signatures and threshold dynamics of midbrain dopamine neurons. Nat Commun 11:6286. [PubMed: 33293613]

Pape HC (1992) Adenosine promotes burst activity in guinea-pig geniculocortical neurones through two different ionic mechanisms. J Physiol 447:729–753. [PubMed: 1593463]

Pape HC (1996) Queer current and pacemaker: the hyperpolarization-activated cation current in neurons. Annu Rev Physiol 58:299–327. [PubMed: 8815797]

Pape H-C, Mager R (1992) Nitric oxide controls oscillatory activity in thalamocortical neurons. Neuron 9:441–448. [PubMed: 1326294]

Pape H-C, McCormick DA (1989) Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature 340:715–718. [PubMed: 2475782]

Pavlov I, Scimemi A, Savtchenko L, Kullmann DM, Walker MC (2011) I h -mediated depolarization enhances the temporal precision of neuronal integration. Nat Commun 2:199. [PubMed: 21326231]

Pedarzani P, Storm JF (1995) Protein kinase A-independent modulation of ion channels in the brain by cyclic AMP. Proc Natl Acad Sci 92:11716–11720. [PubMed: 8524835]

Porro A, Saponaro A, Gasparri F, Bauer D, Gross C, Pisoni M, Abbandonato G, Hamacher K, Santoro B, Thiel G, Moroni A (2019) The HCN domain couples voltage gating and cAMP response in hyperpolarization-activated cyclic nucleotide-gated channels. eLife 8:e49672. [PubMed: 31769408]

Porro A, Thiel G, Moroni A, Saponaro A (2020) cyclic AMP Regulation and Its Command in the Pacemaker Channel HCN4. Front Physiol 11:771. [PubMed: 32733276]

Porro A, Abbandonato G, Veronesi V, Russo A, Binda A, Antolini A, Granata T, Castellotti B, Marini C, Moroni A, DiFrancesco JC, Rivolta I (2021). Do the functional properties of HCN1

mutants correlate with the clinical features in epileptic patients? Prog Biophys Mol Biol. 2021 Jul 23:S0079-6107(21)00089-4

Rall W, Burke RE, Smith TG, Nelson PG, Frank K (1967) Dendritic location of synapses and possible mechanisms for the monosynaptic EPSP in motoneurons. J Neurophysiol 30:1169–1193. [PubMed: 4293410]

Ramentol R, Perez ME, Larsson HP (2020) Gating mechanism of hyperpolarization-activated HCN pacemaker channels. Nat Commun 11:1419. [PubMed: 32184399]

Richardson MJE, Brunel N, Hakim V (2003) From Subthreshold to Firing-Rate Resonance. J Neurophysiol 89:2538–2554. [PubMed: 12611957]

Rivolta I, Binda A, Masi A, DiFrancesco JC (2020) Cardiac and neuronal HCN channelopathies. Pflüg Arch - Eur J Physiol 472:931–951.

Robinson RB, Siegelbaum SA (2003) Hyperpolarization-Activated Cation Currents: From Molecules to Physiological Function. Annu Rev Physiol 65:453–480. [PubMed: 12471170]

Roth FC, Hu H (2020) An axon-specific expression of HCN channels catalyzes fast action potential signaling in GABAergic interneurons. Nat Commun 11:2248. [PubMed: 32382046]

Sánchez-Alonso JL, Halliwell JV, Colino A (2008) ZD 7288 inhibits T-type calcium current in rat hippocampal pyramidal cells. Neurosci Lett 439:275–280. [PubMed: 18534748]

Santello M, Nevian T (2015) Dysfunction of Cortical Dendritic Integration in Neuropathic Pain Reversed by Serotoninergic Neuromodulation. Neuron 86:233–246. [PubMed: 25819610]

Santoro B, Chen S, Luthi A, Pavlidis P, Shumyatsky GP, Tibbs GR, Siegelbaum SA (2000) Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS. J Neurosci 20:5264–5275. [PubMed: 10884310]

Santoro B, Grant SGN, Bartsch D, Kandel ER (1997) Interactive cloning with the SH3 domain of N-src identifies a new brain specific ion channel protein, with homology to Eag and cyclic nucleotide-gated channels. Proc Natl Acad Sci 94:14815–14820. [PubMed: 9405696]

Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER, Siegelbaum SA, Tibbs GR (1998) Identification of a gene encoding a hyperpolarization-activated pacemaker channel of brain. Cell 93:717–729. [PubMed: 9630217]

Santoro B, Piskorowski RA, Pian P, Hu L, Liu H, Siegelbaum SA (2009) TRIP8b Splice Variants Form a Family of Auxiliary Subunits that Regulate Gating and Trafficking of HCN Channels in the Brain. Neuron 62:802–813. [PubMed: 19555649]

Santoro B, Shah MM (2020) Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels as Drug Targets for Neurological Disorders. Annu Rev Pharmacol Toxicol 60:109–131. [PubMed: 31914897]

Santoro B, Wainger BJ, Siegelbaum SA (2004) Regulation of HCN Channel Surface Expression by a Novel C-Terminal Protein-Protein Interaction. J Neurosci 24:10750–10762. [PubMed: 15564593]

Saponaro A, Cantini F, Porro A, Bucchi A, DiFrancesco D, Maione V, Donadoni C, Introini B, Mesirca P, Mangoni ME, Thiel G, Banci L, Santoro B, Moroni A (2018) A synthetic peptide that prevents cAMP regulation in mammalian hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. eLife 7:e35753. [PubMed: 29923826]

Saponaro A, Pauleta SR, Cantini F, Matzapetakis M, Hammann C, Donadoni C, Hu L, Thiel G, Banci L, Santoro B, Moroni A (2014) Structural basis for the mutual antagonism of cAMP and TRIP8b in regulating HCN channel function. Proc Natl Acad Sci 111:14577–14582. [PubMed: 25197093]

Sartiani L, Mannaioni G, Masi A, Novella Romanelli M, Cerbai E (2017) The Hyperpolarization-Activated Cyclic Nucleotide–Gated Channels: from Biophysics to Pharmacology of a Unique Family of Ion Channels Garland CJ, ed. Pharmacol Rev 69:354–395. [PubMed: 28878030]

Seifert R, Scholten A, Gauss R, Mincheva A, Lichter P, Kaupp UB (1999) Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis. Proc Natl Acad Sci 96:9391–9396. [PubMed: 10430953]

Shin M, Brager D, Jaramillo TC, Johnston D, Chetkovich DM (2008) Mislocalization of h channel subunits underlies h channelopathy in temporal lobe epilepsy. Neurobiol Dis 32:26–36. [PubMed: 18657617]

Southan AP, Morris NP, Stephens GJ, Robertson B (2000) Hyperpolarization-activated currents in presynaptic terminals of mouse cerebellar basket cells. J Physiol 526:91–97. [PubMed: 10878102]

Spain WJ, Schwindt PC, Crill WE (1987) Anomalous rectification in neurons from cat sensorimotor cortex in vitro. J Neurophysiol 57:1555–1576. [PubMed: 3585479]

Steriade M, Llinás RR (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649–742. [PubMed: 2839857]

Sterratt DC (2014) Q10: The Effect of Temperature on Ion Channel Kinetics. In: Jaeger D, Jung R (eds) Encyclopedia of Computational Neuroscience. Springer, New York, NY. 10.1007/978-1-4614-7320-6_236-1.

Stieber J, Stöckl G, Herrmann S, Hassfurth B, Hofmann F (2005) Functional Expression of the Human HCN3 Channel. J Biol Chem 280:34635–34643. [PubMed: 16043489]

Thuault SJ, Malleret G, Constantinople CM, Nicholls R, Chen I, Zhu J, Panteleyev A, Vronskaya S, Nolan MF, Bruno R, Siegelbaum SA, Kandel ER (2013) Prefrontal Cortex HCN1 Channels Enable Intrinsic Persistent Neural Firing and Executive Memory Function. J Neurosci 33:13583–13599. [PubMed: 23966682]

Tohidi V, Nadim F (2009) Membrane Resonance in Bursting Pacemaker Neurons of an Oscillatory Network Is Correlated with Network Frequency. J Neurosci 29:6427–6435. [PubMed: 19458214]

Tsay D, Dudman JT, Siegelbaum SA (2007) HCN1 Channels Constrain Synaptically Evoked Ca2+ Spikes in Distal Dendrites of CA1 Pyramidal Neurons. Neuron 56:1076–1089. [PubMed: 18093528]

Vaidya SP, Johnston D (2013) Temporal synchrony and gamma-to-theta power conversion in the dendrites of CA1 pyramidal neurons. Nat Neurosci 16:1812–1820. [PubMed: 24185428]

Vera J, Pezzoli M, Pereira U, Bacigalupo J, Sanhueza M (2014) Electrical resonance in the θ frequency range in olfactory amygdala neurons. PloS One 9:e85826. [PubMed: 24465729]

Wainger BJ, DeGennaro M, Santoro B, Siegelbaum SA, Tibbs GR (2001) Molecular mechanism of cAMP modulation of HCN pacemaker channels. Nature 411:805–810. [PubMed: 11459060]

Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, Vijayraghavan S, Brennan A, Dudley A, Nou E, Mazer JA, McCormick DA, Arnsten AFT (2007) Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell 129:397–410. [PubMed: 17448997]

Wang W-T, Wan Y-H, Zhu J-L, Lei G-S, Wang Y-Y, Zhang P, Hu S-J (2006) Theta-frequency membrane resonance and its ionic mechanisms in rat subicular pyramidal neurons. Neuroscience 140:45–55. [PubMed: 16527421]

Wang Z-J, Blanco I, Hayoz S, Brelidze TI (2020) The HCN domain is required for HCN channel cell-surface expression and couples voltage- and cAMP-dependent gating mechanisms. J Biol Chem 295:8164–8173. [PubMed: 32341127]

Waxman SG (2001) Transcriptional channelopathies: An emerging class of disorders. Nat Rev Neurosci 2:652–659. [PubMed: 11533733]

Williams SR (2004) Spatial compartmentalization and functional impact of conductance in pyramidal neurons. Nat Neurosci 7:961–967. [PubMed: 15322550]

Williams SR, Stuart GJ (2000) Site Independence of EPSP Time Course Is Mediated by DendriticI h in Neocortical Pyramidal Neurons. J Neurophysiol 83:3177–3182. [PubMed: 10805715]

Ying S-W, Jia F, Abbas SY, Hofmann F, Ludwig A, Goldstein PA (2007) Dendritic HCN2 Channels Constrain Glutamate-Driven Excitability in Reticular Thalamic Neurons. J Neurosci 27:8719–8732. [PubMed: 17687049]

Yung WH, Häusser MA, Jack JJ (1991) Electrophysiology of dopaminergic and non-dopaminergic neurones of the guinea-pig substantia nigra pars compacta in vitro. J Physiol 436:643–667. [PubMed: 2061849]

Zagotta WN, Olivier NB, Black KD, Young EC, Olson R, Gouaux E (2003) Structural basis for modulation and agonist specificity of HCN pacemaker channels. Nature 425:200–205. [PubMed: 12968185]

Zemankovics R, Káli S, Paulsen O, Freund TF, Hájos N (2010) Differences in subthreshold resonance of hippocampal pyramidal cells and interneurons: the role of h-current and passive membrane characteristics. J Physiol 588:2109–2132. [PubMed: 20421280]

Zobeiri M, Chaudhary R, Blaich A, Rottmann M, Herrmann S, Meuth P, Bista P, Kanyshkova T, Lüttjohann A, Narayanan V, Hundehege P, Meuth SG, Romanelli MN, Urbano FJ, Pape H-C, Budde T, Ludwig A (2019) The Hyperpolarization-Activated HCN4 Channel is Important for Proper Maintenance of Oscillatory Activity in the Thalamocortical System. Cereb Cortex 29:2291–2304. [PubMed: 30877792]

Zolles G, Wenzel D, Bildl W, Schulte U, Hofmann A, Müller CS, Thumfart J-O, Vlachos A, Deller T, Pfeifer A, Fleischmann BK, Roeper J, Fakler B, Klöcker N (2009) Association with the Auxiliary Subunit PEX5R/Trip8b Controls Responsiveness of HCN Channels to cAMP and Adrenergic Stimulation. Neuron 62:814–825. [PubMed: 19555650]

Zylberberg J, Strowbridge BW (2017) Mechanisms of Persistent Activity in Cortical Circuits: Possible Neural Substrates for Working Memory. Annu Rev Neurosci 40:603–627. [PubMed: 28772102]

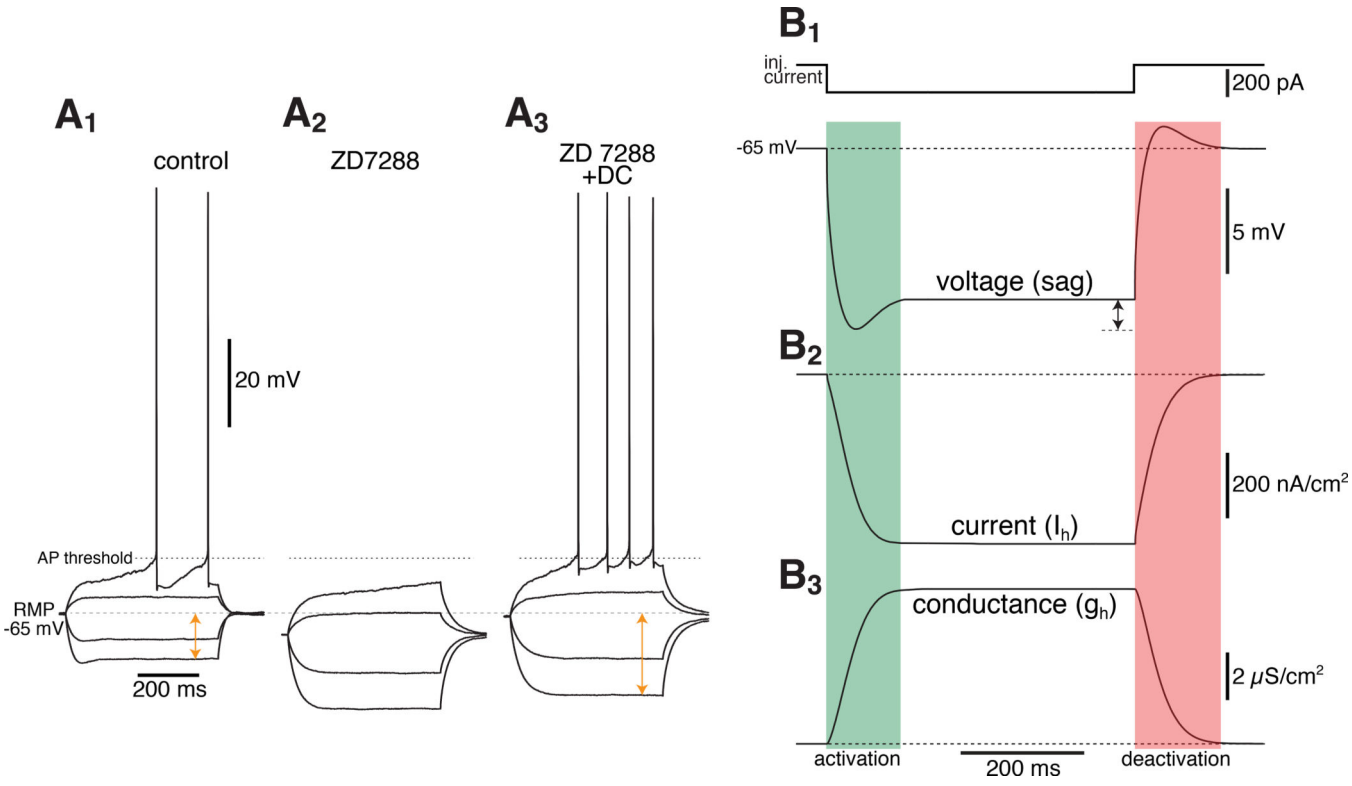

Figure 1.

Effects of HCN channel activation on neuronal excitability. A1) current clamp recordings from a CA1 pyramidal neuron in response to 500 ms current hyperpolarizing and depolarizing steps (−200 to 100 pA). Notice the characteristic sag during the 200 pA-hyperpolarizing step, as well as the fact that the neuron reaches the threshold for action potential initiation for the 100 pA-depolarizing current injection. A2) the perfusion of ZD7288 (20 μM) causes a hyperpolarization of the membrane potential, as well the removal of the sag during hyperpolarization. As a consequence of an increase in the input resistance, the voltage change is larger, particularly at steady state because of the sag removal. A3) when ZD7288 hyperpolarization is compensated by the injection of tonic current to overcome loss of I_h's contribution of the resting membrane potential, the larger depolarizing step generates more action potentials than in control conditions, due to the larger input resistance. The difference in voltage displacement between control conditions and ZD7288 is made clearer by comparing the orange arrows in the two conditions. B) Model simulation to show the time course of the changes in the voltage (B1), h-current (I_h, B2), and h-conductance (g_h, B3), in a multicompartmental model of a CA1 pyramidal neuron a during a 500-ms long hyperpolarizing current injection (−200 pA). Units in B2 and B3 are expressed as current and conductance densities, respectively. Details are in the text.

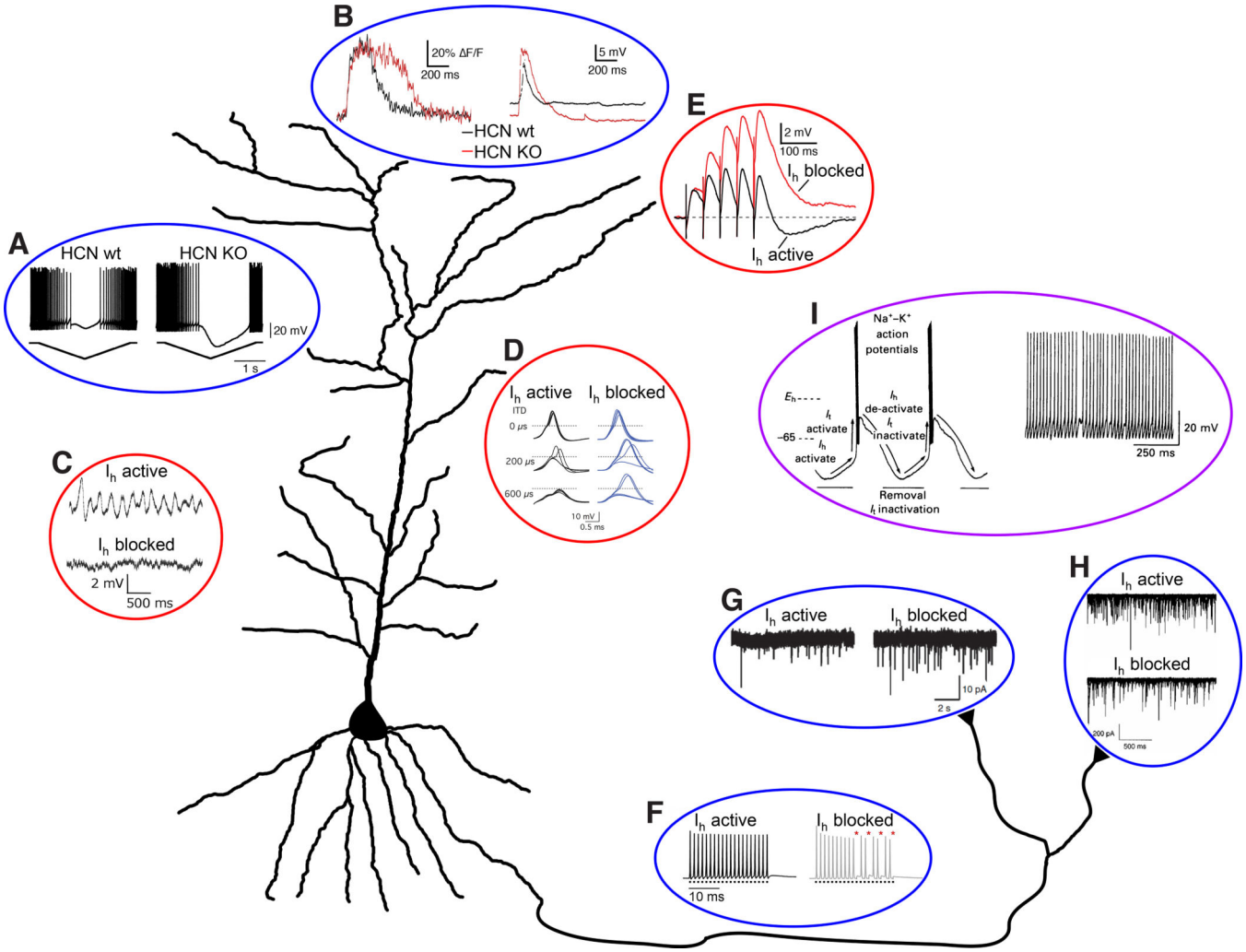

Figure 2.

The contribution of HCN to neuronal functions can be divided into contribution of I_h to the steady effect on the membrane potential (blue circles), slow dynamics (red circles), or a combination of both (purple circle). Detailed descriptions of each phenomenon can be found in the text. A) I_h stabilizes the membrane potential after inhibitory input in Purkinje neurons; this effect is eliminated in HCN1 knockout mice (modified, with permission, from Nolan et al., 2003). B) I_h depolarizes the resting membrane potential in distal dendrites of CA1 pyramidal neurons indirectly shortening dendritic calcium spikes; in HCN1 knockout mice the plateaus are longer (modified, with permission, from Tsay et al., 2007). C) the slow kinetics of I_h allow for subthreshold oscillations in entorhinal cortex layer III stellate cells; oscillations are abolished when I_h is blocked (modified, with permission, from Giocomo and Hasselmo, 2008). D) in principal neurons of the medial superior olive, the window for coincidence detection is sharpened by I_h; the window widens when I_h is blocked (modified, with permission, from Khurana et al., 2011). E) the slow deactivation of I_h curtails EPSPs in distal dendrites of pyramidal CA1 neurons, such that temporal summation is much larger when I_h is blocked (modified, with permission, from Medinilla et al., 2013). F) in cerebellar mossy fibers, I_h opposes hyperpolarization in the axon, allowing for high

frequency firing that fails when I_h is blocked (modified, with permission, from Byczkowicz et al., 2019). G) I_h depolarizes the presynaptic terminal of certain synapses in entorhinal cortex layer III, indirectly inhibiting glutamate release; release increases when I_h is blocked (modified, with permission, from Huang et al., 2011). H) I_h in the axons and terminals of cerebellar basket cells depolarizes the membrane potential and increases GABA release; release decreases when I_h is blocked (modified, with permission, from Southan et al., 2000). I) a slow I_h-dependent depolarization in thalamocortical relay neurons (left) allows T-type Ca^{2+} activation and a burst of Na^+/K^+ action potentials. Tonic firing (right) ensues when the membrane potential is depolarized to simulate larger I_h activation (modified, with permission, from McCormick and Pape, 1990a).

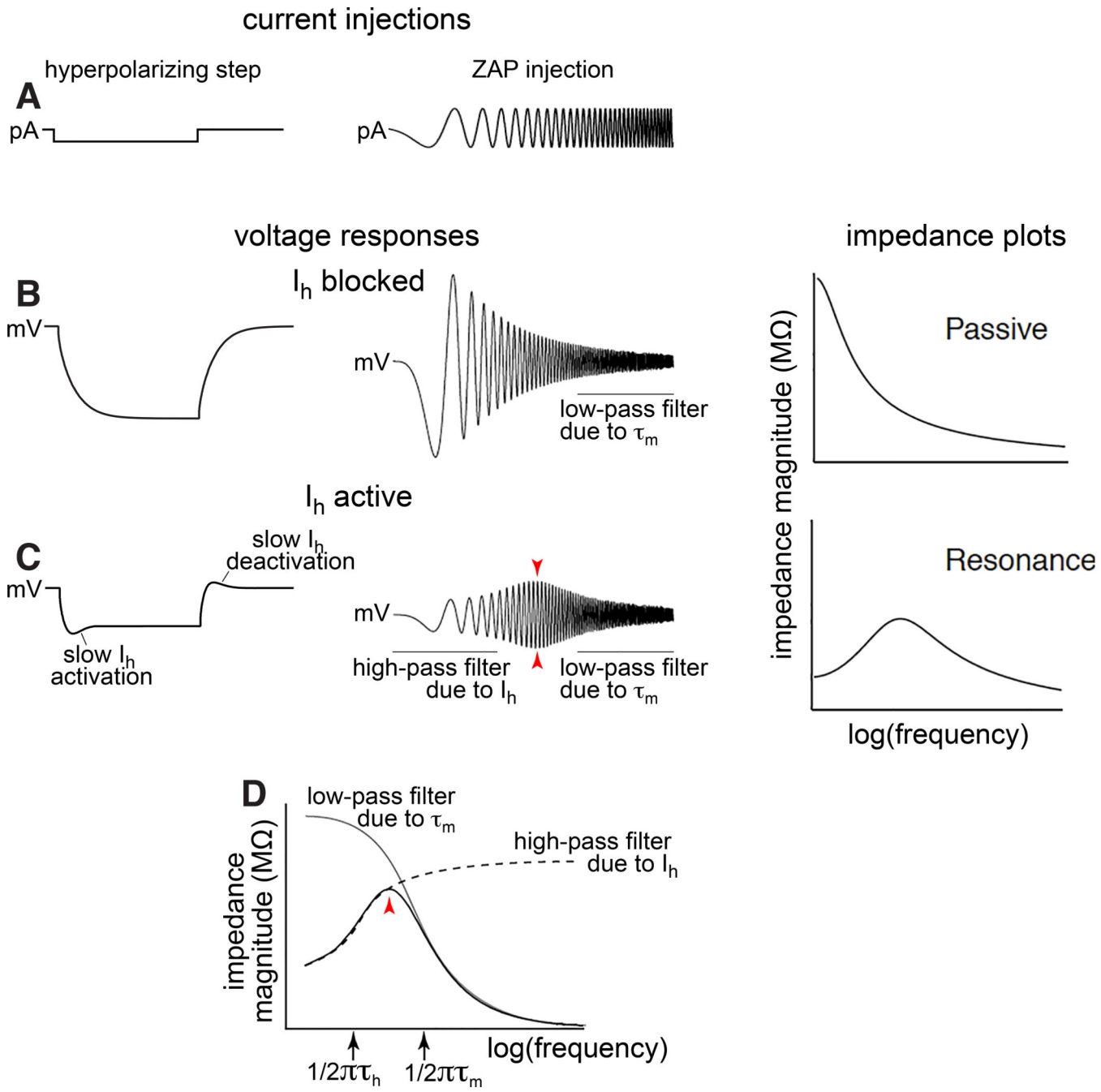

Figure 3.

Contribution of I_h to the resonance properties of neurons. A) current injection protocols for a hyperpolarizing step (left) and a ZAP or chirp current (right, details in the text). B and C, corresponding voltage profiles with I_h blocked, leaving mostly the passive properties of neurons (B) and with I_h active (C). The plots on the right show the impedance amplitude as a function of the frequency (logarithmic scale), obtained from the traces in the middle, for the two conditions. D) The combination of the low-pass filter due to the passive properties of the membrane (grey line) and the high-pass filter imposed by the slow activation of I_h (dotted line) creates a resonance profile, with a peak denoted by the red arrowhead. Note the

arrowheads in C) with the same meaning. Modified, with permission, from Hutcheon and Yarom (2000).