HCN currents in neurons

Short title: Neuronal I_h

Mala M. Shah,
Department of Pharmacology,
UCL School of Pharmacy,
University College London,
WC1N 1AX,
UK.

Tel: +44 (0)20 7753 5897
e-mail: mala.shah@ucl.ac.uk

Abstract

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are voltage-gated ion channels that activate at potentials negative to -50 mV and are predominantly permeable to Na^+ and K^+ ions. Four HCN subunits (HCN1-4) have been cloned. These subunits have distinct expression patterns and biophysical properties. In addition, cyclic nucleotides as well as multiple intracellular substances including various kinases and phosphatases modulate the expression and function of the subunits. Hence, the characteristics of the current, I_h, are likely to vary amongst neuronal subtypes.

In many neuronal subtypes, I_h is present post-synaptically, where it plays a critical role in setting the resting membrane potential and the membrane resistance. By influencing these intrinsic properties, I_h will affect synaptic potential shapes and summation and thereby, neuronal excitability. Additionally, I_h can have an effect on resonance properties and intrinsic neuronal oscillations. In some neurons, I_h may also be present pre-synaptically in axons and synaptic terminals where it modulates neuronal transmitter release. Hence the effects of I_h on neuronal excitability are complex. It is necessary to fully understand these as I_h has a significant impact on physiological conditions such as learning as well as patho-physiological states such as epilepsy.

Introduction

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are voltage-gated ion channels (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014). Each channel is composed of four alpha subunits, with each subunit having six transmembrane segments. The voltage sensor is located in the fourth transmembrane segment (S4 segment) of each subunit (Mannikko et al. 2002). HCN channels open at potentials more negative to -50 mV (i.e. with hyperpolarization) and are thus active at rest in many neurons (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014). They are permeable to both Na^+ and K^+ (Ludwig et al. 1998; Santoro et al. 1998). At the normal resting membrane potential (RMP) of neurons (-60 mV - -70 mV), though, the HCN channel current (I_h) is predominantly formed by a net inward Na^+ current. Hence, I_h is depolarizing at rest (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014).

Four HCN channel subunits, HCN1 – 4, have been cloned so far (Ludwig et al. 1998; Santoro et al. 1998). These subunits can assemble in homomers or heteromers. The biophysical properties of the HCN1-4 homomeric channels differ significantly (Wainger et al. 2001). Thus, HCN1 homomeric channels activate relatively rapidly compared with HCN2, HCN3 and HCN4 homomeric channels. This variation in the subunit biophysical properties together with the distinct expression profile of the subunits is likely to impart diverse biophysical characteristics of I_h in particular neurons. To determine the biophysical properties, it is essential to record the current.

Multiple proteins affect the expression and biophysical properties of HCN subunits. The activation curves of HCN1-4 current are shifted to the right by cyclic nucleotides, though the extent of the shift varies depending on the subunit composition (Ludwig et al. 1998; Santoro et al. 1998; Wainger et al. 2001; Robinson and Siegelbaum 2003; Biel et al. 2009). HCN subunit expression and channel function are also regulated by kinases, phosphatases and auxiliary subunits such as TPR-containing Rab8b interacting protein (TRIP8b) (Biel et al. 2009; Shah 2014). This dynamic modulation of HCN channels differs within neurons as well as within individual neuronal subcellular compartments (axons, dendrites and somata). Consequently, the current density and kinetics will vary considerably within neurons and amongst neuronal subtypes.

The differential I_h characteristics will have a significant impact on neuronal function. I_h acts as a high-pass filter, opposing any slow changes in membrane potential. Membrane hyperpolarization slowly activates I_h, The resulting inward current then causes the membrane potential to depolarize, producing a 'sag' (Fig 1). In contrast, membrane depolarization triggers slow deactivation of the HCN channels that are open at rest. Consequently, the membrane potential hyperpolarizes (Fig 1). Hence, I_h significantly affects the neuronal input resistance (defined as the change in voltage induced by a given current injection). If I_h is open at rest, it will affect the membrane resistance too. By affecting the cell impedance, I_h regulates neuronal excitability in multiple ways including affecting subthreshold resonance properties, intrinsic oscillations and synaptic integration (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014).

How I_h modulates neuronal excitability will depend on the subcellular and neuronal expression level of HCN subunits. For example, some hippocampal and cortical projection neurons (including pyramidal cells) express relatively low levels of HCN1 and HCN2 subunits at the soma (Lorincz et al. 2002; Notomi and Shigemoto 2004).

Inhibition of these somatic HCN channels results in RMP hyperpolarization but no significant change in neuronal firing (Magee 1998; Shah et al. 2004; Shah 2014). In contrast, HCN subunits are located at a much higher density in pyramidal cell dendrites (Lorincz et al. 2002; Notomi and Shigemoto 2004). Interestingly, inhibiting dendritic I_h in pyramidal neurons causes a significant increase in the number of action potentials elicited by depolarization, despite the RMP being significantly hyperpolarized (Shah et al. 2004). This is at least in part because the decrease in I_h results in a greater enhancement of dendritic than somatic input resistance (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014). In addition, the RMP hyperpolarization caused by reduced I_h alters the activity of other dendritic ion channels such as T-type Ca^{2+} channels (Tsay et al. 2007), which may contribute to the augmented dendritic input resistance and excitability in the absence of I_h. The amplified dendritic input resistance together with the possible alterations in other dendritic ion channel properties is likely to boost synaptic potential amplitudes and slow the decay of synaptic potentials, leading to greater synaptic potential summation in pyramidal cell dendrites compared with somata (Magee 2000; Shah 2014). This is at least one of the reasons for the increased long-term potentiation at distal hippocampal CA1 pyramidal dendrites in HCN1 null mice compared with wildtypes (Nolan et al. 2004).

I_h also exists in subsets of inhibitory and excitatory synaptic terminals, where it regulates neurotransmitter release (Shah 2014). Given that I_h is subject to activity-dependent regulation (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014), the contribution of I_h towards neuronal network excitability is likely to be complex. I_h has been suggested to affect theta rhythm power in the hippocampus (Nolan et al. 2004) and contribute to learning and memory (Nolan et al. 2004) as well as spatial navigation (Giocomo et al. 2011; Hussaini et al. 2011), though the cellular mechanisms for this phenomenon remain to be fully evaluated. Moreover, alterations in I_h have been suggested to occur during many disorders such as epilepsy and neuropathic pain (Robinson and Siegelbaum 2003; Biel et al. 2009; Shah 2014). Hence, fully understanding how I_h affects cellular function is likely to be critical for determining how it contributes to physiological states such as learning as well as pathophysiological conditions.

Acknoweledgements: Work in the laboratory is supported by the European Research Council and the Biotechnology and Biological Sciences Research Council UK.

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Figure Legend

Fig 1: Example 'sag' recorded from an entorhinal cortical layer III pyramidal cell dendrite when short current pulses are injected. The sag in the hyperpolarizing direction is due to activation of I_h whereas that in the depolarizing direction is due to deactivation of I_h.

Fig 1, Introduction