Neuron, Vol. 21, 9–12, July, 1998, Copyright ©1998 by Cell Press

H-Current: Properties of a Neuronal and Network Pacemaker

Minireview

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The recent cloning of the genes encoding the channel subunits underlying the h-current (I_h) by three different groups has renewed interest in the functional role of this unusual conductance (Gauss et al., 1998; Ludwig et al., 1998; Santoro et al., 1998). This often maligned current (termed I_f for "funny" in cardiac tissue and I_Q for "queer" in the hippocampus) is activated by hyperpolarization beyond approximately −50 to −70 mV, does not inactivate, is carried by Na^+ and K^+ ions, and slowly depolarizes the cell toward its equilibrium potential of approximately −30 mV (reviewed by Pape, 1996). Although relatively small in maximal conductance, this current can form a significant portion of the total membrane conductance at subthreshold membrane potentials, precisely the region of membrane voltage in which synaptic and nonsynaptic computations occur, and therefore it may contribute to the responsiveness and pattern of activity generated by neurons. The ability of neurotransmitters to modulate the voltage dependence of I_h through the production of cyclic nucleotides imparts an additional level of flexibility.

As one may gather from the terms "funny" and "queer," the question as to the precise role of I_h in cellular activity has left many investigators scratching their heads. However, part of this dilemma arises from an incomplete knowledge of the properties of the network in which the cells are imbedded. Here, we will review the role of I_h in those multicellular networks whose properties have been examined in detail. For a review of the molecular biology of h-channels and their role in cardiac pacemaking, the reader is referred to the accompanying Minireview by Clapham (1998).

Role of I_h in the Neuronal Activity of Single Neurons

I_h is an evolutionarily ancient current present not only in many different neuronal cell types in both vertebrate and invertebrate nervous systems but also in a wide variety of nonneuronal tissues such as heart and smooth muscle, glands, and, as one of the recent cloning papers demonstrated, sperm flagella (Gauss et al., 1998). The voltage dependence and kinetics of activation of I_h in these different cell types vary considerably. This variability is to be expected, given that (1) the current is generated from a family of channels (Ludwig et al., 1998; Santoro et al., 1998), (2) it is differentially sensitive to cyclic nucleotides through its cyclic nucleotide binding domain, and (3) at least some channel subunits are potentially modifiable through protein phosphorylation (Pape, 1996; Gauss et al., 1998; Ludwig et al., 1998; Santoro et al., 1998). It is assumed that the properties of I_h are adjusted to fit its particular function in the neuron and neuronal circuits in which it resides.

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Three interrelated roles for I_h have been demonstrated in the control of neuronal activity of single cells that are fundamental to understanding its role in network function: (1) determination of the resting membrane potential and membrane conductance; (2) regulation of the response of the neuron to hyperpolarization, such as during the arrival of inhibitory postsynaptic potentials (IPSPs); and finally (3) the generation of, or contribution to, "pacemaker" potentials that control the rate of rhythmic oscillations.

In neurons, the determination of the resting membrane potential plays an important role in the control of neuronal processing and sensitivity to synaptic inputs. First, tonic depolarization of neurons results in an increase in the number of excitatory postsynaptic potentials that are successful in generating action potentials. Secondly, depolarization may completely change the firing mode of the cell (and consequently the network), such as from a state of slow rhythmic burst firing to tonic single spike activity, as in the relay neurons of the thalamus (McCormick and Bal, 1997). Often, a small percentage of I_h is tonically activated at rest, and therefore this conductance contributes to the determination of the resting membrane potential: block of I_h with the application of extracellular Cs^+ in many cell types results in a hyperpolarization of a few millivolts. In addition to this tonic influence, the arrival of IPSPs or the activation of K^+ currents (e.g., I_{KCa}) will also increase I_h. Through its depolarizing effect, this increased activation of I_h can shape the amplitude and time course of these hyperpolarizations (e.g., see Figure 1C), and in so doing may contribute strongly to the control of cellular responsiveness.

Perhaps the most interesting aspect of I_h is its widespread contribution to the generation of "pacemaker" potentials (diFrancesco, 1993). In sinoatrial node cells and Purkinje fibers of the heart, the hyperpolarization that follows each action potential activates a slow form of I_h (termed I_f). The activation of I_f contributes to the slow depolarization (pacemaker potential) that brings the membrane voltage to action potential threshold. Obviously, the larger and faster I_f becomes, such as during the stimulation of β-adrenergic receptors and the generation of cAMP, the faster the membrane potential will be depolarized in between action potentials, resulting in an increase in heart rate. Interestingly, a related phenomenon occurs in many different cell types.

In mammalian neurons, I_h is responsible for the generation of pacemaker potentials in the relay cells of the thalamus. When all external synaptic influences are reduced or removed, these neurons hyperpolarize into a membrane potential range where rhythmic bursts of action potentials are discharged at 0.5–4 Hz (Figure 1A). These rhythmic bursts are produced through the interaction of a low threshold Ca^{2+} current, I_T, and I_h (reviewed by Pape, 1996; McCormick and Bal, 1997). The activation of I_T results in a low threshold Ca^{2+} spike and often in a high frequency burst of action potentials (Figure 1A). The inactivation of I_T terminates the Ca^{2+} spike and is followed by hyperpolarization of the neuron, resulting in the activation of I_h. The activation of I_h then slowly

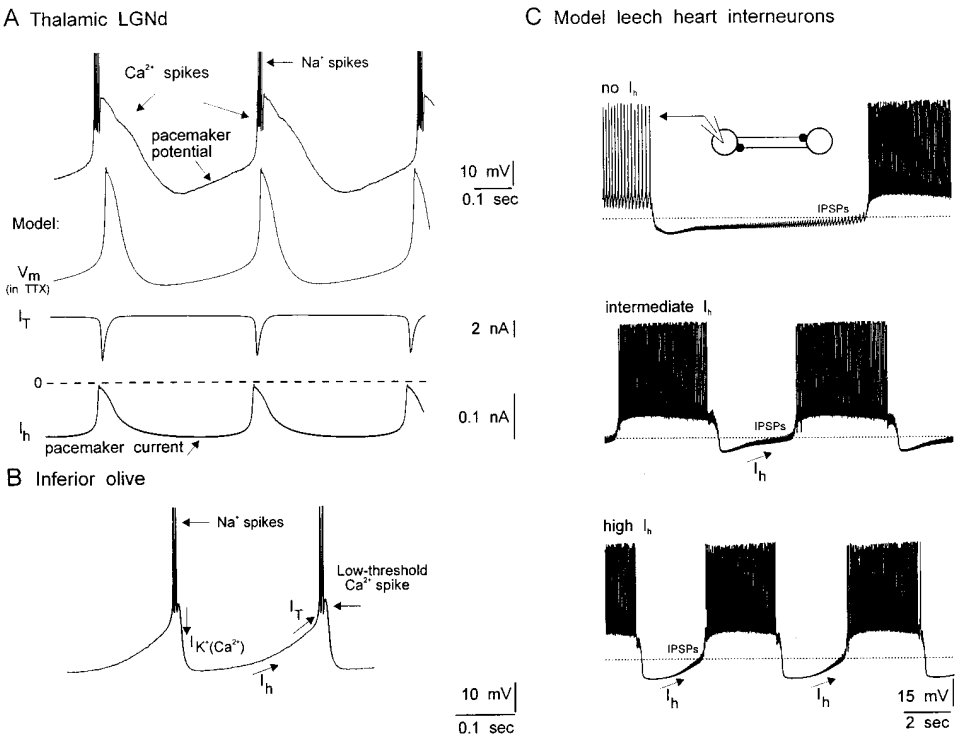

Figure 1. The H-Current Is Involved in the Generation of Rhythmic Activities in Neurons

(A) The generation of rhythmic burst firing in thalamic relay neurons occurs through the interaction of the low threshold Ca^{2+} current I_T and I_h. From McCormick and Huguenard (1992).

(B) Inferior olivary neurons generate rhythmic Ca^{2+} spikes through the interaction of a low threshold Ca^{2+} current and a Ca^{2+}-activated K^+ current. I_h strongly influences the rate of oscillation. From Bal and McCormick (1997).

(C) I_h controls the rate of rhythmic oscillations in models of inhibitory networks in leech ganglionic interneurons. Increasing the maximal conductance of I_h increases the rhythmic discharge rate in this neuronal network. From Olsen et al. (1995).

depolarizes the neuron to threshold for generation of another Ca^{2+} spike, and therefore continuous rhythmic burst firing may be sustained (Figure 1A). Computer simulations reveal that cAMP-mediated modulation of I_h may tightly regulate the prevalence and rate of rhythmic burst firing (McCormick and Huguenard, 1992; reviewed by McCormick and Bal, 1997).

A similar role for I_h has also recently been demonstrated in inferior olivary neurons. Inferior olivary (IO) cells, which are the sole source for climbing fibers to the cerebellum, can generate rhythmic Ca^{2+} spikes through the interaction of the low threshold Ca^{2+} current and Ca^{2+}-activated K^+ channels (Llinás and Yarom, 1986). The hyperpolarization of IO neurons by the activation of Ca^{2+}-activated K^+ currents also results in the activation of I_h, which then controls the rate of repolarization of the membrane potential and, subsequently, the rate of rhythmic oscillation in these neurons (Figure 1B; Bal and McCormick, 1997). Although less well investigated, results suggest a similar role for I_h in the generation of oscillations in hippocampal neurons (Maccaferri and McBain, 1996; Strata et al., 1997) and respiratory neurons in the preBötzinger complex of the ventrolateral medulla (Rekling and Feldman, 1998).

Role of I_h in the Generation of Network Activity

The h-current, through its control of the response of neurons to hyperpolarization, is involved in the generation of a number of network behaviors, particularly when these are rhythmogenic. Circulation of blood in the leech is achieved through the rhythmic contraction of heart tubes, which themselves are controlled by the slow rhythmic discharge of a small network of neurons in a nearby ganglion. This rhythmic discharge is generated through reciprocal inhibition between pairs of neurons. Action potential discharge in one of these neurons results in the inhibition and hyperpolarization of the other. However, this hyperpolarization also results in the activation of I_h, which slowly depolarizes the cells back toward firing threshold (Figure 1C). Once firing threshold is reached, then the other neuron may be inhibited, and so on (Figure 1C). Computational models of such interactions indicate that enhancement of I_h may sensitively control the rate of rhythmic oscillations in these networks (Figure 1C; Olsen et al., 1995). Similar examples of the role of I_h in rhythmic activity have been demonstrated in other invertebrate preparations, including the generation of rhythmic chewing and digestive movements by the pyloric ganglia in the lobster and crab (reviewed by Marder and Calabrese, 1996).

In the mammalian brain, a particularly instructive example of the involvement of I_h in network behavior is found in the generation of synchronized oscillations in the thalamus (Figure 2). During nonrapid eye movement (non-REM) sleep, the electroencephalogram (EEG) is characterized by the generation of two prominent rhythms termed delta and spindle waves (Figure 2A). Delta waves are characterized by 0.5–4 Hz frequencies, while spindle waves appear as epochs of 6–14 Hz oscillatory activity

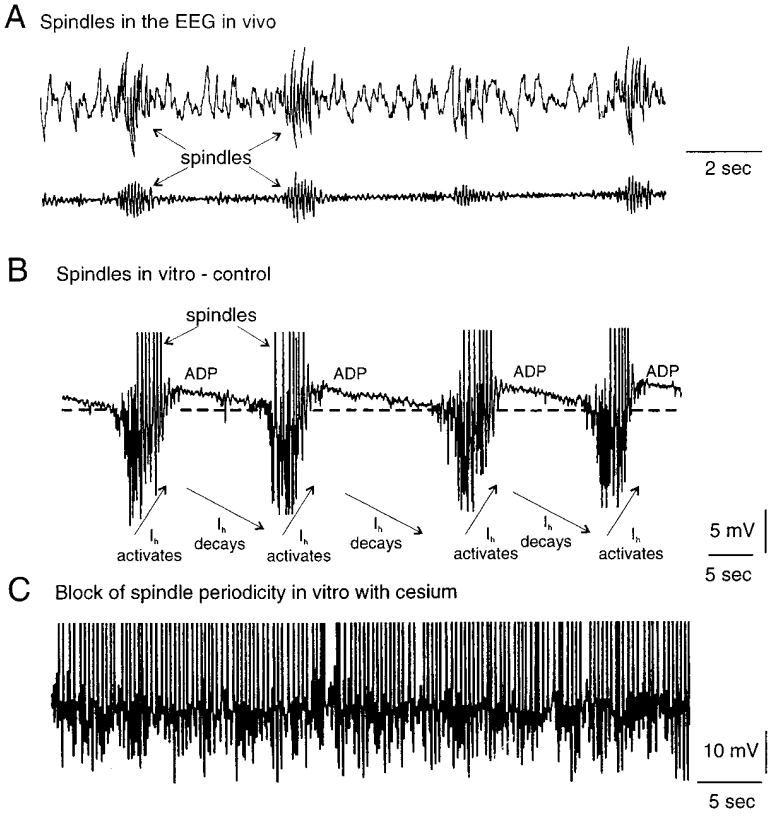

Figure 2. The Slow Activation and Deactivation of I_h Controls Slow Periodicities in Thalamocortical Rhythms

(A) The EEG exhibits two prominent rhythms during non-REM sleep, delta waves and spindle waves. Filtering the EEG for spindle waves illustrates these well (bottom trace). From Steriade and Llinás (1988).

(B) Intracellular recording from thalamocortical neurons in vitro during the generation of spindle waves reveals that the refractory period in between these network oscillations is associated with an afterdepolarization (ADP), which is generated by the activation of I_h. From Bal and McCormick (1996).

(C) Following the block of I_h with the extracellular application of Cs^+, the slow periodicity of spindle waves is abolished. From Bal and McCormick (1996).

that wax and wane over a 1–3 s period and recur on a regular basis of once every few seconds (Figure 2A). Although the physiological significance of these oscillations is unclear (they may play a role in the gating of information through the thalamus), the cellular mechanisms of their generation has recently been revealed. Spindle waves are generated in the thalamus through an interaction between the GABAergic neurons of the thalamic reticular nucleus and the excitatory thalamic relay cells (reviewed by McCormick and Bal, 1997). During this interaction, reticular cells evoke barrages of IPSPs in relay neurons. These barrages of IPSPs activate I_h, which in turn activates low threshold Ca^{2+} spikes, which then, through the generation of bursts of action potentials, reexcite the reticular cells. The activation of I_h contributes to the generation of this rhythmic activity in two ways. First, the interaction of I_T and I_h imparts on thalamic relay cells an endogenous "harmonic" of 0.5–4 Hz (see Figure 1A). The interaction of this 0.5–4 Hz rhythm with the arrival of IPSPs at 6–14 Hz results in the generation of rebound Ca^{2+} spikes at a rate of approximately one every two to four IPSPs, meaning that, although the synchronized network rhythm is carried by a local complex of neurons, individual cells discharge only during a subset of these cycles. Second, the slow activation and deactivation of I_h generates the slow periodicity of spindle waves—the reoccurrence of these events once every few seconds (Figures 2B and 2C; Bal and McCormick, 1996). Interestingly, this slow periodicity may not only result from the slow kinetics of I_h but also from the modification of this current through changes in the intracellular concentration of Ca^{2+} (Lüthi and McCormick, 1998), which is likely to be mediated by an indirect mechanism such as the Ca^{2+}-dependent modification of another second messenger system (Zaza et al., 1991; see, however, Hagiwara and Irisawa, 1989). Recently, we have demonstrated that increases in $[Ca^{2+}]_i$ in thalamic relay cells can result in modifications of I_h that are similar to those observed following increases in $[cAMP]_i$. Together, the voltage-dependent activation of I_h through the arrival of repetitive IPSPs, as well as the Ca^{2+}-dependent shift in the voltage dependence and kinetics of this current owing to the generation of rebound Ca^{2+} spikes, induces a gradual depolarization of thalamic cells during the generation of spindle waves. This gradual depolarization results in the abolition of this rhythm through the inactivation of I_T and the generation of the 3–20 s refractory period (Figure 2B). One intriguing possibility is that the cessation of generalized absence seizures in children may involve a similar mechanism (i.e., depolarization due to activation of I_h).

Network oscillations can also occur in the inferior olive (Llinás and Yarom, 1986; Bal and McCormick, 1997). In contrast to the thalamus, synchronized oscillations in the inferior olive are generated largely through electrotonic coupling of cellular oscillators mediated through gap junctions between these neurons. I_h is involved in these network oscillations by controlling the propensity of each cell to oscillate and the periodicity of this oscillation (Bal and McCormick, 1997).

Concluding Remarks

The contribution of I_h to the generation of rhythmic oscillations in other networks is suspected but yet to be examined in detail. For example, many cortical and hippocampal pyramidal cells as well as interneurons also exhibit significant levels of I_h (Pape, 1996; Maccaferri

and McBain, 1996; Strata et al., 1997). Does this current contribute to the generation of network oscillations such as slow rhythms in the cortical EEG or theta waves in the hippocampus? Or perhaps does it have a different role—the control of membrane potential and neuronal responsiveness during nonoscillatory activity? Subtle modulations of I_h as a result of cellular activity or neurotransmitter action, as small as they may appear on the single cell level, have to be considered as a way to dramatically alter the macroscopic behavior of a network. The identification of the molecular identity of these channels will no doubt be of immense help in achieving a thorough biophysical understanding of these processes.

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