

PERSPECTIVES

Queer channels in hippocampal basket cells: h-current without sag

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Hyperpolarization-activated cationic currents (I_h) observed in the heart and the brain, have puzzled physiologists since their initial discovery 25 years ago. Unlike most voltage-gated channels, I_h channels (or h-channels) are activated by hyperpolarizing voltage steps to potentials more negative than -60 mV but are not inactivating. Their reversal potential near -30 mV imposes a depolarizing current near the resting membrane potential. Thus, h-channels control the resting membrane potential and the input resistance. Their presence is typically signalled in current clamp records by a depolarizing deflection (also termed 'sag') in response to hyperpolarizing pulses of current. These channels oppose not only hyperpolarizations but also depolarizations via their slow deactivation. As a result the h-current has also been designated I_f for 'funny' or I_Q for 'queer'. A family of four mammalian genes encoding the Hyperpolarization-activated and Cyclic Nucleotide-gated cationic subunits (HCN1–4), which in the form of tetramers build h-channels, has been identified, making it now possible to address the physiological role of I_h at the molecular level. The targeting of HCN channels is controlled by Trip8b, a Rab-interacting brain-specific protein (Santoro *et al.* 2004). h-Channels are encountered at high density in the apical dendrites of CA1 hippocampal pyramidal neurons. They largely determine the integration of

incoming synaptic signals and accelerate the kinetics of dendritic EPSPs (Magee, 2000). h-Channels contribute to several forms of activity-dependent regulation of intrinsic excitability in the context of learning, memory and epilepsy. Their number and/or properties have been shown to be regulated by synaptic or network activity. They are not only present in principal cortical neurons, but have also been reported in a subset of GABAergic interneurons (Maccaferri & McBain, 1996; Lupica *et al.* 2001). However, h-current was thought to be absent in many neuronal types since in these neurons, the depolarizing sag (the hallmark of neurons expressing I_h) was not observed upon injection of hyperpolarizing current pulses.

In this issue of *The Journal of Physiology*, Aponte *et al.* (2006) show that the absence of depolarizing sag is not a sufficient criterion to conclude that h-channels are lacking. Another recent study came to the same conclusion in thalamic GABAergic interneurons where h-channel activity was masked by a prominent leak K^+ conductance (Rateau & Ropert, 2006). Thus, these studies invite us to re-examine the presence and the function of I_h in neurons in which the electrophysiological signature of I_h has not been identified. The study of Aponte and coworkers shows that heteromeric HCN1/2 channels shape the integrative properties and the synaptic output of hippocampal basket cells (BCs), a subtype of fast-spiking GABAergic interneurons that inhibit the perisomatic region of principal cells and control the number of active cells and the timing of their discharge. This study shows that h-channels contribute to the low input resistance and the fast apparent membrane time constant of BCs. In fact, the remarkably fast kinetics of EPSPs in BCs may not only result from the opening of rapidly gated AMPA-type glutamate receptors and the K^+ channel-mediated shaping of the potential, but could also be due to h-channels. Moreover, h-channels clamp the interneurons at a subthreshold potential, setting them in a ready-to-fire state. BCs are not only very fast integrative neurons but are also fast and precise signalling devices (Jonas *et al.* 2004). At their

output side, the fast-kinetics of Na^+ and K^+ channels allow them to generate action potentials at frequencies of several hundred hertz under physiological conditions. Very high rates of axonal firing may lead to the hyperpolarization of the axon as a result of intra-axonal accumulation of Na^+ ions. Aponte *et al.* (2006) showed that h-channels are present in the axon and indeed set axonal excitability. Thus, h-channels may stabilize the axonal membrane potential and may preserve the presynaptic action potential waveform. Similarly, h-channels may also clamp the potential of the presynaptic terminal in a ready-to-release mode via the potential-dependent modulation of background calcium levels (Awatramani *et al.* 2005). Although non-specific effects cannot be ruled out, this mechanism might account for the observed presynaptic inhibitory effect of the h-channel blocker ZD7288.

Aponte *et al.*'s paper adds new fuel to the burning question of the role of h-channels in the axon and the presynaptic terminal, but several key issues remain to be addressed with direct recording from the axon and the terminal (Southan *et al.* 2000). It will be important to determine whether the biophysical properties of I_h are identical in the different neuronal compartments (i.e. somato-dendritic regions, axons and presynaptic terminals) and to understand how neurotransmitter release might be controlled by h-channels in the presynaptic terminal.

References

- Aponte Y, Lien C-C, Reisinger E & Jonas P (2006). *J Physiol* **574**, 229–243.
- Awatramani GB, Price GD & Trussell LO (2005). *Neuron* **48**, 109–121.
- Jonas P, Bischofberger J, Fricker D & Miles R (2004). *Trends Neurosci* **27**, 30–40.
- Lupica CR, Bell JA, Hoffman AF & Watson PL (2001). *J Neurophysiol* **86**, 261–268.
- Maccaferri G & McBain CJ (1996). *J Physiol* **497**, 119–130.
- Magee JC (2000). *Nat Rev Neurosci* **1**, 181–190.
- Rateau & Ropert N (2006). *J Neurophysiol* **95**, 3073–3085.
- Santoro B, Wainger BJ & Siegelbaum SA (2004). *J Neurosci* **24**, 10750–10762.
- Southan AP, Morris NP, Stephens GJ & Robertson B (2000). *J Physiol* **526**, 91–97.