works, and the preparation developed in this study will provide a valuable new approach for studying active cochlear mechanisms *in vitro*. A number of important questions remain, however. Chan and Hudspeth proposed a supplemental role for hair cell somatic motility in the cochlear amplifier, but this is not entirely consistent with data showing that disrupting prestin completely eliminates nonlinear cochlear amplification[7]. Also, as the cochlear amplifier is a whole-organ phenomenon, and as it depends upon a normal traveling wave[15], the exciting findings from this study must be tested in sensitive living cochlea. Chan and Hudspeth's study will surely inspire such *in vivo* studies.

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Channeling a 'funny' side of memory

Daniel Johnston

Voltage-gated ion channels shape the integration of synaptic input in dendrites. Forebrain-restricted deletion of the hyperpolarization-activated channel HCN1 enhances spatial learning, demonstrating a behavioral role for an active dendritic conductance.

The role of synaptic potentiation and depression in various forms of learning and memory is well established. However, attention has recently been focused on other potential mechanisms, with the idea that synaptic plasticity may not be the whole story in the neurobiology of learning and memory[1,2]. In a paper published in *Cell*[3], Nolan *et al.* take a major step forward in linking synaptic plasticity, dendritic integration and memory. In an impressive collaboration among different laboratories, this study reports a role for a particular ionic current (once called the 'funny' current) in certain forms of memory. The results strongly suggest that postsynaptic mechanisms beyond the synapse are a critical component of learning and memory in the behaving animal.

A cation current active at hyperpolarized membrane potentials was first described in heart cells and was called the 'funny' current for its unusual properties[4]. A similar current was later described in neurons and more descriptively, but less concisely, called the hyperpolarization-activated, cyclic nucleotide–gated, nonselective cation current (I_h). Four genes, *HCN1–4*, encode the channels underlying I_h, with *HCN1* and *HCN2* forming I_h channels in many neurons[4]. In their new paper[3], Nolan *et al.* deleted the *HCN1* gene from the forebrain of mice and analyzed the behavioral and physiological consequences of the loss of I_h from neurons in this region. Surprisingly, they find that a significant decrease in I_h actually enhances learning in a hippocampus-dependent spatial memory task and increases long-term potentiation (LTP) specifically at direct perforant path (temporoammonic) inputs from layer III of entorhinal cortex to CA1 neurons in the hippocampus.

In a previous paper[5], Nolan *et al.* found that deletion of the *HCN1* gene from the entire mouse led to profound deficits in motor learning. For example, mice could not learn to navigate to a submerged platform in a water maze experiment, even if given visible cues such as a flag on the platform, but instead tended to swim in circles. Nolan *et al.* now show that, in contrast, mice with a forebrain-only deletion of *HCN1* ($HCN1^{f/f,cre}$) have no such deficits in motor learning and perform similarly to control mice on the visible platform version of the water maze experiment. Moreover, when required to find a hidden platform based on the location of spatial cues, these mice learn faster than control mice and also have reduced path lengths when swimming to the platform. An intriguing finding is that both contextual and cued fear conditioning were unaltered in the $HCN^{f/f,cre}$ mice. Because contextual fear conditioning is also thought to be a hippocampus-dependent spatial memory task, these results clearly show that the role of I_h in animal behavior is complex, with different contributions to different types of learning.

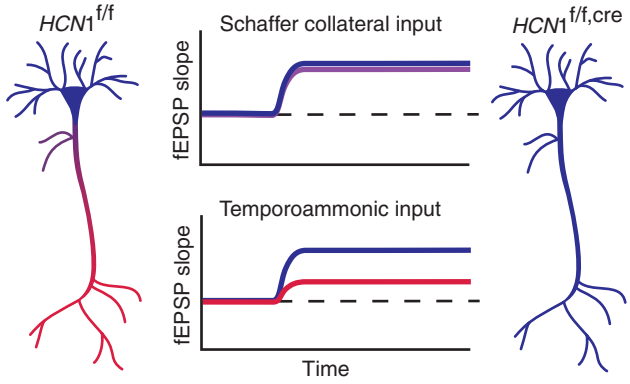

Figure 1 The loss of I_h enhances LTP specifically at distal inputs to CA1 pyramidal neurons. The density of I_h channels in CA1 dendrites increases with distance from the soma, as indicated by the blue (lower channel density) to red (higher channel density) gradient. When these channels are absent, LTP is unaffected at Schaffer collateral inputs to CA1 (top graph), which synapse onto proximal dendrites, but is enhanced at temporoammonic inputs (bottom graph), which synapse onto distal apical dendrites where I_h expression is normally high. Upper line on graphs refers to neuron at right, and lower line refers to neuron at left.

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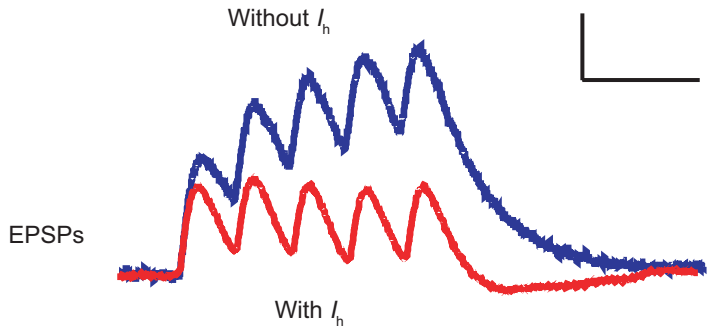

Figure 2 The loss of I_h enhances temporal summation of excitatory synaptic input. The summation of synaptic input depolarizes the neuron, deactivates I_h and reduces the summation of the input by hyperpolarizing the cell (red). When I_h is blocked or removed genetically, the amount of temporal summation is increased significantly (blue). Modified from ref. 7. (Scale bars: 5 mV, upper trace; 4 mV, lower trace; 100 ms)

I_h has many unique and difficult-to-intuit properties. It is partially active at rest, further activated by hyperpolarization and deactivated by depolarization. As a nonselective cation current, however, it has a reversal potential of around –30 mV, so turning on the current with hyperpolarization tends to depolarize the cell, whereas turning it off with depolarization leads to a hyperpolarization. In CA1 pyramidal neurons, the density of I_h channels increases with distance from the soma and is about sevenfold higher in the distal apical dendrites[6]. Summated excitatory synaptic input, which depolarizes the neuron, deactivates I_h and thus suppresses temporal summation[7]. Because of the density gradient of I_h along the dendrites, however, temporal summation is more dampened for distal than for proximal inputs, with the net result that the temporal summation of all inputs reaching the soma is about equal (that is, normalized[7]). The effect of I_h in reducing temporal summation is also somewhat dependent on the frequency of synaptic input, being greatest at intermediate frequencies and lesser at low and high frequencies[8].

With this background on the properties of I_h and its effect on synaptic integration, how does the loss of I_h in the forebrain lead to enhanced spatial memory? Focusing on the neuronal mechanisms that might underlie the behavioral phenotype of $HCN^{f/f,cre}$ mice, Nolan *et al.* found changes in hippocampal-dependent network oscillations. Both low- and high-frequency oscillations appeared unchanged in the knockout mice, but power in the intermediate range, or theta frequency band (4–9 Hz), was enhanced. This is particularly interesting in light of the frequency-dependent effects of I_h on temporal summation mentioned above. In whole-cell recordings, CA1 pyramidal neurons had more negative resting potentials, higher input resistances and longer membrane time constants, all characteristic features of a loss of I_h (ref. 9). Furthermore, Nolan *et al.* found enhanced LTP only at the temporoammonic input from layer III of entorhinal cortex to these neurons (**Fig. 1**). Because the synapses from this pathway terminate at the most distal regions of the apical dendrites of CA1 neurons, where the density of I_h is normally the highest, the authors argue that the enhanced LTP is due to a greater temporal summation at those synapses. In other words, I_h can be thought of as a partial brake that reduces dendritic depolarization. Take away the brake in the knockout animals, and greater depolarization can occur with a given synaptic input, leading to greater spread of synaptic input to the soma and possibly to more LTP (**Fig. 2**). The more distal the input, the greater this effect would be.

Undoubtedly, this work raises many interesting questions and highlights areas for further study. For example, why does the loss of I_h specifically affect only certain forebrain memory tasks[10], and why does it affect motor learning and spatial memory in opposite ways? Given that there are many other voltage-gated ion channels expressed in dendrites that affect synaptic integration[11–13], do any of these interact with I_h and also affect learning and memory?

Despite these and other lingering questions, the results of Nolan *et al.* are a watershed of sorts in the field for several reasons. First, they clearly ascribe a role for I_h in hippocampal-dependent learning and memory. Second, because I_h is so heavily expressed in dendrites and has substantial effects on dendritic integration of synaptic input, a new emphasis on the role of dendritic mechanisms and intrinsic excitability in learning and memory emerges from this study. Tens of thousands of synaptic inputs impinge on the dendritic tree, and this study and others[1] suggest that the ways in which the dendrites and the intrinsic properties of the neuron modify these inputs are important in the memory storage process itself. I_h has also been shown recently to be 'plastic'[14,15], or subject to activity-dependent changes, suggesting that changes in I_h during learning might be a substrate for memory. Thus, the results of this study are not 'funny' at all, but instead serious and intriguing.

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