

bined. The best way to investigate how neural responses are combined would be to record all of the inputs to an ensemble of neurons and all of its outputs. This can be done in some invertebrate systems (such as the wind-sensing system of the cricket<sup>6</sup>), but it is generally beyond reach for vertebrates. The best we can do for now is to pretend that the neurons we do record come from a single ensemble (as may in fact be the case for these median nerve fibers) and examine how effectively their activity could be used to distinguish among conditions under different ensemble coding schemes. On a coarse time scale, Georgopoulos and colleagues<sup>7</sup> showed that responses from multiple motor cortex neurons can be combined to provide an accurate representation of movement direction by averaging the neurons' preferred directions weighted by the intensity of each neuron's response as a fraction of its maximum firing rate.

Although averaging over many neurons has been successful for some problems, it is likely to be too slow to explain the speed with which forces can be discriminated. This speed means that at most the first few spikes, and perhaps only the first spike, from any neuron can contribute. Thorpe and colleagues<sup>8</sup>, trying to explain rapid visual discriminations, proposed that recruitment order from an ensemble of neurons, which uses information about which spike came from which neuron, would allow rapid read-

out of basic information about a stimulus. Simulation studies have shown that this is feasible<sup>9</sup>, but until this new study, no direct experimental evidence had appeared. Johansson and Birznieks demonstrate that decoding the order of first spike times measured from somatosensory nerve fibers provides a robust and rapid method for identifying the direction of a stimulus. They point out, as has Thorpe, that recruitment order is relatively robust with respect to small variations in spike timing.

Johansson and Birniecks's data give one hint about how this recruitment order code might arise in these somatosensory fibers. The data show that response latency in individual fibers is related to the direction of stimulation and the distance between the stimulation site and the afferents' termination site in the finger. We can speculate that fiber diameter might also be involved in recruitment order, as it is known to be in muscle fibers<sup>10</sup>.

We can distinguish two different kinds of timing in spike trains. Response latency (first spike time, in quiet neurons such as most of those considered here) is locked to stimulus onset or an abrupt change in stimulus, and is often very precise. If, after an abrupt change, the stimulus remains relatively stable for some period, then spike times are controlled by network properties, observed as rate variation. If spike timing is related only to rate variation on a time scale

of tens of milliseconds, then statistical considerations predict that second spike times will be substantially more variable<sup>11</sup>, and therefore less informative, than first spike times, just as Johansson and Birznieks observe.

Determining the precision with which spike times are generated and how and with what precision they are interpreted by downstream neurons is likely to remain a central problem in systems neuroscience for some time. Johansson and Birznieks show that rapid reactions can be understood in light of recruitment order. It remains to be seen how generally applicable recruitment order is as an ensemble neural code.

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## Storing memories in dendritic channels

Michael Häusser

**An elegant study in this issue shows that induction of synaptic plasticity can also trigger long-lasting increases in dendritic excitability near the potentiated synapses. This may represent a new locus for memory storage and a substrate for metaplasticity.**

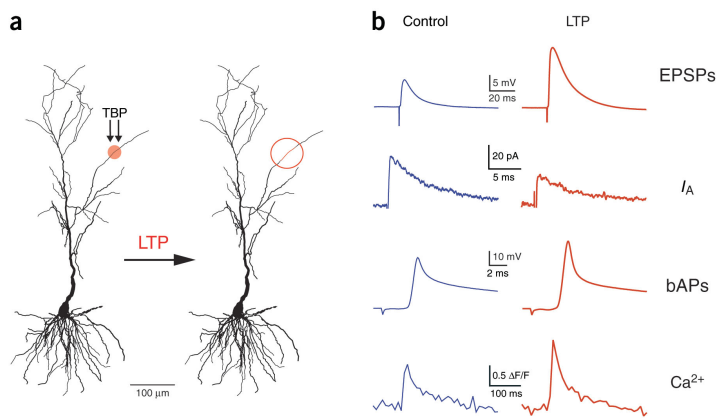
Storage of memories must involve some long-term physical changes in the brain. But where should we look for these changes? Most neuroscience textbooks will tell you that memory storage involves modification of the strength of synaptic connections between neurons. This view, proposed over 50 years ago by the psychologist Donald Hebb, has been enormously influential and forms the basis of learning in many neural network models. Much experimental work

has also supported this idea, particularly in simpler systems such as *Aplysia*, as well as in mammalian systems where Hebbian long-term potentiation and depression (LTP and LTD) have been demonstrated at many synaptic connections and shown to be correlated with learning. Nevertheless, there remains some controversy about whether these synaptic changes alone are both necessary and sufficient to fully account for memory storage in the brain<sup>1</sup>.

In this issue, Frick and colleagues<sup>2</sup> demonstrate a new locus for activity-dependent changes in neural circuits: long-term changes in dendritic excitability. The past decade has seen a revolution in our understanding of how dendrites help neurons process the thousands

of synaptic inputs they receive. Direct dendritic recordings, combined with imaging experiments, have shown that dendrites express just about every known type of voltage-gated channel, often at different densities from the soma. These channels endow dendrites with the power to support active back-propagation of action potentials (APs) and even to generate local spikes, both of which can trigger increases in dendritic calcium by activating dendritic voltage-gated calcium channels<sup>3</sup>. These forms of excitability can also be important in the induction of synaptic plasticity, with dendritic spikes and back-propagating APs being involved in gating LTP induction at distal and more proximal synapses, respectively<sup>4,5</sup>. Dendritic voltage-gated channels are

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**Figure 1** Plastic dendrites. **(a)** Schematic illustration of the induction of long-term potentiation (LTP) at distal synapses in a CA1 pyramidal neuron using a theta-burst protocol (TBP). After LTP induction, a zone of enhanced dendritic excitability (red) exists near the potentiated synapses. **(b)** Mechanisms and consequences of enhanced dendritic excitability<sup>2</sup>. Top, somatic EPSPs recorded before and after LTP induction. Second row, cell-attached dendritic recording showing that activation of dendritic A-type potassium channels near the potentiated synapses (using a voltage step from  $-72$  mV to  $+57$  mV) is inhibited after LTP induction. This is associated with an enhancement of AP back-propagation into this dendritic region (third row) and an increase in the local dendritic calcium signal triggered by the back-propagating AP (fourth row).

also subject to modulation by several neurotransmitters and second-messenger systems, thus allowing the integrative properties of dendrites to be varied over a wide range<sup>6</sup>. Given that LTP induction activates many of the same second-messenger systems, can the same induction protocol also trigger long-term changes in dendritic excitability?

Frick and colleagues<sup>2</sup> addressed this question by directly monitoring dendritic excitability before and after LTP induction in CA1 pyramidal cells using a powerful combination of techniques: dendritic patch-clamp recording and calcium imaging. This is an impressive feat, as it represents the first time that (usually ephemeral) dendritic patch-clamp recordings have been combined with long-duration plasticity experiments. The authors showed that LTP induction is accompanied by a persistent increase in the amplitude of back-propagating APs near the site of synaptic stimulation. This was associated with an increase in the dendritic calcium signal triggered by the back-propagating AP that was localized to a  $\sim 100$ - $\mu\text{m}$ -wide region surrounding the stimulation site (Fig. 1).

To explore the mechanisms underlying this enhancement of dendritic excitability, the authors performed cell-attached dendritic recordings of voltage-gated potassium channels, which showed a decrease in the activity of rapidly inactivating or A-type potassium channels near the resting potential after LTP induction. This was due to changes in the properties of the channels rather than a decrease in channel density, as it was associated with a hyperpo-

larizing shift in the voltage dependence of inactivation. The mechanism fits neatly with previous results from the same group showing that A-type potassium channels can regulate the size of back-propagating APs and limit dendritic excitability in general<sup>7</sup>.

These findings suggest that the induction of long-term synaptic plasticity is accompanied by a parallel memory trace, stored in the functional state of dendritic voltage-gated channels<sup>8</sup>. The idea that synaptic plasticity can go hand-in-hand with plasticity of intrinsic excitability is not unprecedented. Indeed, the first report describing LTP showed that it was accompanied by enhanced postsynaptic excitability<sup>9</sup>. This phenomenon is now known as EPSP-spike (or E-S) potentiation and has been studied intensively in recent years, primarily using somatic recordings<sup>10</sup>. A recent study<sup>11</sup> showed that induction of LTP and LTD in CA1 pyramidal cells is associated with bidirectional changes in the summation of EPSPs, with the input specificity of the effect implicating changes in dendritic channels. Another study<sup>12</sup> showed that induction of LTP in cultured pyramidal neurons is associated with increases in presynaptic excitability, indicating that potentiated synapses can trigger retrograde intrinsic plasticity. In this context, the importance of the paper by Frick and colleagues is that it is the first to show directly that LTP causes local modulation of dendritic excitability that can be traced to modulation of a specific channel subtype.

Where to next? First, the mechanisms underlying the enhanced dendritic excitabil-

ity require deeper exploration. Like the synaptic plasticity, both the enhancement of dendritic excitability and the potassium-channel modulation were blocked by NMDA receptor antagonists, consistent with the idea that the modulation of excitability depends on the induction of synaptic plasticity. However, the causality of this relationship needs to be demonstrated more directly. Furthermore, dendritic channels can be regulated by neurotransmitters independently of synaptic plasticity<sup>6</sup>—does this modulation occur via convergent or parallel second-messenger pathways? Identification of the second-messenger pathways involved should also help to clarify the factors that determine the spatial range of the plasticity. Is the observed spatial spread of the calcium signal enhancement due to messenger diffusion, or does it simply reflect the distribution of active synapses or the nonlinearity of AP back-propagation? Can the enhanced excitability ultimately be restricted to single spines? Finally, Frick and colleagues did not rule out changes in the properties or densities of other dendritic voltage-gated channels. Given recent evidence for activity-dependent modulation of dendritic calcium channels<sup>13</sup> and  $I_h$  channels (hyperpolarization-activated nonselective cation channels)<sup>11</sup>, it seems likely that synaptic plasticity may target a range of channel types, perhaps differentially with different plasticity-induction protocols.

The rich functional implications of this study are now also open for exploration. Why is such parallel memory storage mechanism necessary, and what are its benefits (and costs)? On one hand, an additional storage mechanism, particularly one that is spatially restricted, provides the neuron with many additional degrees of freedom for plasticity and enhances the storage capacity of the brain<sup>14</sup>. But the reciprocal link between the back-propagating AP and the induction of synaptic plasticity<sup>2,5</sup> also provides a sophisticated, tuneable positive feedback mechanism that can promote the induction of subsequent synaptic plasticity. Thus, dendritic excitability can be a substrate for metaplasticity, encoding the recent history of synaptic plasticity and neurotransmitter modulation. The spatial extent of the enhanced excitability also provides a means for spreading this form of metaplasticity to neighboring inactive synapses. Ultimately, however, such a form of amplification is inherently unstable and requires compensatory homeostatic mechanisms<sup>15</sup>. In that vein, it will be interesting to confirm whether LTD induction is accompanied by a corresponding downregulation of local den-

drift excitability<sup>11</sup>. Ultimately, the significance of these findings for memory storage must be evaluated in the context of behavior, where there already exists considerable evidence for changes in neuronal excitability associated with learning and conditioning in many species<sup>10</sup>.

The plasticity of dendritic excitability naturally also has important consequences for subsequent dendritic processing of synaptic inputs. The suppression of A-type potassium channels can promote EPSP summation (compare ref. 11) and regenerative synaptic interactions in dendrites, and thus enhance the impact of EPSPs on somatic output, as expected in models of E-S potentiation. Furthermore, the enhancement of the back-propagating AP can also lower the threshold for triggering dendritic calcium spikes, which

can lead to axonal burst generation<sup>3</sup>. In this way, the enhancement of dendritic excitability associated with LTP provides a means of further amplifying the impact of synaptic plasticity on neuronal output.

Finally, in a wider sense, the study by Frick and colleagues is significant because it links three flourishing fields at the heart of cellular and systems neuroscience: LTP, intrinsic plasticity and dendritic excitability. Examining the mechanisms and functional consequences of this dendritic marriage between synaptic and intrinsic plasticity promises to lead to a deeper understanding of memory storage and dendritic function in the brain.

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## Taking sides in the nervous system with miRNA

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The mechanisms by which bilateral asymmetry is established in the nervous system are poorly understood. A recent report in *Nature* describes a novel microRNA that mediates left–right asymmetry in a pair of *C. elegans* chemosensory neurons.

At first glance, the nervous systems of vertebrates and invertebrates seem bilaterally symmetrical, but on closer inspection left–right asymmetries become apparent. Humans, for example, show gross anatomical differences between right and left temporal lobes, and visual and language faculties are asymmetrically distributed between the two hemispheres. How these asymmetries arise during development remains something of a mystery (for review, see ref 1). In the nematode *Caenorhabditis elegans*, the AWC and ASE chemosensory neuron pairs are bilaterally symmetrical based on anatomical considerations, but nevertheless display asymmetrical gene expression patterns. A recent study in *Nature* by Johnston and Hobert identifies a microRNA (miRNA) as a crucial mediator of this asymmetry in the ASE neurons<sup>2</sup>.

Of the 302 neurons in the *C. elegans* hermaphrodite, 32 neurons, including 14 bilateral pairs, comprise the chemosensory system. The ASE pair mediates responses to water-soluble compounds<sup>3</sup>. Despite expressing a set of genes in common, having similar morphologies and connecting to identical sets of postsynaptic

partners, the left and right ASE neurons (ASEL and ASER) are not identical. ASEL alone expresses the transmembrane guanylyl receptor cyclase genes *gcy-6* and *gcy-7* and responds to sodium, whereas ASER expresses *gcy-5* and primarily responds to chloride and potassium<sup>4,5</sup>. *C. elegans* apparently maximizes the functionality of its limited repertoire of chemosensory neurons by further lateral differentiation.

Earlier this year, the Hobert laboratory showed that the ASEL/R asymmetry is mediated via competition between two protein complexes present in both ASEL and ASER neurons<sup>6</sup>. One complex contains the OTX-like homeodomain protein CEH-36 and the transcriptional coactivator LIN-49, and the other contains the Groucho-like transcriptional corepressor UNC-37 and the NKX6-like homeodomain protein COG-1. The outcome of this competition is biased by the expression of COG-1, which is present at far higher levels in ASER than in ASEL neurons<sup>6</sup>. Thus, the COG-1/UNC-37 complex outcompetes the CEH-36/LIN-49 complex in ASER neurons to repress ASEL-specific genes, thereby allowing the expression of ASER-specific genes. In contrast, low levels of COG-1 in ASEL allow the CEH-36/LIN-49 complex to activate the expression of ASEL-specific genes. Of course, this result immediately raised the question of

how COG-1 expression is regulated in ASEL and ASER neurons.

Enter the *lisy-6* miRNA. The miRNAs are small (~21 to 22-nucleotide) RNAs, which are processed from larger RNAs with extensive secondary structure (see ref. 7 for review). These small RNAs downregulate gene expression by base-pairing with cognate complementary sequences in the 3' untranslated regulatory regions (UTR) of target mRNAs, thereby preventing their translation. The first miRNA was identified over a decade ago in *C. elegans*<sup>8,9</sup>, but only with the recent identification of conserved miRNAs in other multicellular organisms have miRNAs evolved from being a nematode-specific oddity to representing the newest general mechanism of gene regulation. Genome mining has predicted 100–300 miRNAs in different species, and several of these are expressed in a tantalizing tissue- and developmental stage-specific manner<sup>7</sup>. However, to date, the functions of only a handful of these miRNAs have been defined, and few targets have been identified *in vivo*.

Johnston and Hobert identified *lisy-6* in their screen for mutants affecting ASEL/R asymmetry. In *lisy-6* mutants, ASEL neurons adopt ASER-like properties, whereas shared ASE-like characteristics and ASER identity are unaffected. The authors could rescue the *lisy-6*

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