Synaptic plasticity: **Regulated translation in dendrites**
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Synaptic activity can induce neurons to synthesize proteins important for cognition and brain development. Recent results suggest this activity-induced protein synthesis is partially mediated by regulated translation within neuronal dendrites.

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Some brain functions require participating neurons to synthesize new proteins. To control the production of new proteins, cells may regulate any step of the synthesis process, from transcription to translation. Although mechanisms of regulating gene transcription often receive the research spotlight, studies indicate translational control is a useful means of triggering new protein synthesis. For example, recent results [1,2] suggest that activity at brain synapses induces translation of mRNAs that are located in the postsynaptic dendrites. This temporal and spatial regulation of protein translation may play a role in mechanisms underlying memory formation and brain development.

These results bring together several observations about synaptic function. In the past few decades, researchers have discovered that synapses can increase and decrease their strength in response to different patterns of activity [3,4]. These activity-dependent synaptic modifications, generally referred to as examples of synaptic plasticity, are likely to form the basis for certain types of memory, as well as the consolidation of synaptic connections during development. The precise chain of events leading from synaptic stimulation to modification of the synapse is a subject of some controversy; nonetheless, a number of studies suggest that lasting forms of synaptic plasticity involve new protein synthesis [5].

At the same time, studies have detected the presence of protein translation machinery and mRNAs outside the neuronal cell body, specifically in dendritic processes. Using electron microscopy, Steward and Levy [6] showed that the dendrites of neurons in the hippocampus contain polyribosomes that are preferentially associated with post-synaptic structures; later studies showed hippocampal dendrites also possess the other protein and RNA components necessary for translation [7]. In addition, researchers have found high levels of certain mRNAs in cortical and hippocampal dendrites, including the transcripts for microtubule-associated protein MAP2, the α subunit of

Ca^{2+}/calmodulin-dependent kinase II (CaMKIIα), and the immediate-early gene product Arg3.1/Arc (a cytoskeleton-associated protein) [8]. Other mRNAs are present at low concentrations in dendrites [8]. While the functional relevance of these latter, low level mRNAs is uncertain, most agree that the extensive expression of certain transcripts — such as those for CaMKIIα — must serve a particular purpose. Given that translational machinery exists within dendrites, a logical hypothesis is that neurons transport specific mRNAs to dendrites to participate in the local production of new proteins.

Assuming that this idea is true, some researchers have further hypothesized that regulated translation in dendrites mediates at least some of the protein synthesis involved in synaptic plasticity. According to this view, activity at a particular synapse triggers translation of nearby, postsynaptically localized mRNAs, generating proteins that somehow modify the synapse. Compared to the alternative of making proteins in the soma and transporting them into the dendrites, local translation of dendritic mRNAs offers the potential of being faster and allowing more efficient spatial control: initiating translation on-site obviates the need to target proteins to specific synapses. Another possible reason for performing translation locally is that particular protein products may be much more difficult to transport than their mRNAs. But to confirm that localized translation participates in synaptic plasticity, it has to be shown that the translation of specific mRNAs occurs at active synapses.

Important advances in this line of research have been made recently. Several studies, for example, indicate that certain forms of synaptic plasticity do indeed depend on local, rather than somatic, protein synthesis [9,10]. In one such study, Kang and Schuman [9] took advantage of the fact that application of neurotrophins increases synaptic strength in hippocampal brain slices. They found that co-applying protein synthesis inhibitors, such as anisomyocin or cycloheximide, blocked this neurotrophin-mediated synaptic plasticity. Furthermore, when they severed the cell bodies of the presynaptic and postsynaptic neurons from the synapses, applying neurotrophins still induced a synaptic strengthening that was dependent on protein synthesis. These results imply that the protein translation needed to support this form of synaptic plasticity occurs near the synapses, rather than in the cell body.

While suggestive, such studies have not addressed specific mechanisms linking synaptic activity and local translation. An interesting step in this direction has been taken

recently by Steward *et al.* [1], who examined the distribution of *Arc* mRNA and protein after activation of synapses in hippocampal slices. Hippocampal and cortical neurons express high levels of *Arc* mRNA only after strong synaptic stimulation, which induces *Arc* transcription in the postsynaptic neuron; some of the resulting transcripts are transported into the dendrites. To examine more closely how synaptic activity influences *Arc* mRNA localization, Steward *et al.* [1] repetitively stimulated different subsets of synapses in hippocampal slices, then looked at the distribution of newly synthesized *Arc* transcripts in the slices (see Figure 1). They found that newly transcribed *Arc* mRNA concentrated in activated dendrites, bypassing non-activated dendrites of the same cells. At the same time, Arc protein also appeared in the activated dendrites, suggesting that local machinery translates the transported mRNAs. Altogether, these results present a new mechanism linking synaptic activity to dendritic targeting of newly transcribed mRNAs, which may then participate in local translation; but it remains to be seen whether such a mechanism applies to transcripts other than *Arc* mRNA.

Other studies have shed light on how neurons may recruit mRNAs that are constitutively present in dendrites to function in synaptic plasticity. The extensive expression of CaMKIIα mRNAs in dendrites is particularly interesting as there is strong evidence that this protein plays a role in certain forms of synaptic plasticity, such as long-term potentiation [11]. By immunostaining, Ouyang *et al.* [12] observed that the amount of CaMKIIα protein in dendrites increased after strong stimulation of synapses in hippocampal slices. This increase was seen specifically in activated dendrites, was blocked by protein synthesis inhibitors, and occurred within five minutes of synaptic stimulation (M.B. Kennedy and Y. Ouyang, personal communication). The speed of this increase and its spatial specificity argue for a mechanism in which synaptic activation triggers local translation of dendritic CaMKIIα transcripts.

But how might synaptic activation trigger local translation of CaMKIIα? A recent study [2] supplies this important link, showing that a mechanism of translational control found in oocytes during early development also operates in cortical dendrites. During oogenesis, the poly(A) tails of certain mRNAs are kept relatively short, rendering these transcripts translationally dormant; later, the poly(A) tails are elongated and translation begins [13]. This elongation process, called cytoplasmic polyadenylation, is controlled by two *cis*-acting sequences in the mRNA 3' untranslated region, one of which is called the cytoplasmic polyadenylation element (CPE); the cytoplasmic polyadenylation element binding protein (CPEB) binds to the CPE to induce polyadenylation of the mRNA and subsequent translation.

Wu *et al.* [2] asked whether cytoplasmic polyadenylation also operates in dendrites, particularly on dendritic CaMKIIα mRNAs. By immunostaining with an antibody

Figure 1
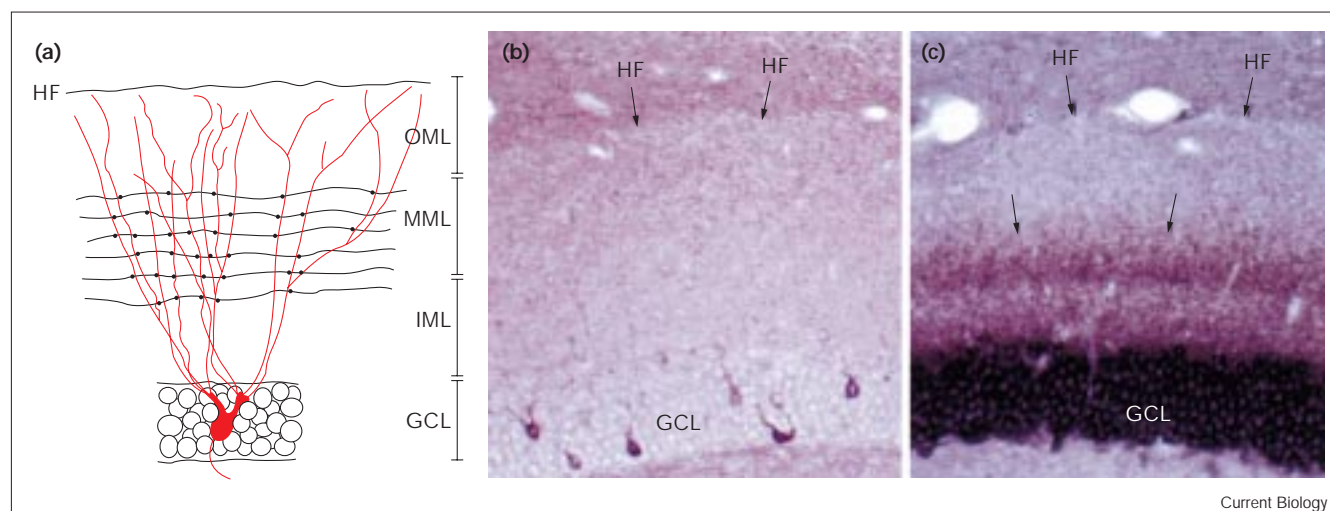
(a) The structure of the dentate gyrus in a hippocampal slice. In the dentate gyrus, granule neurons compact into the granule cell layer (GCL). Afferents onto the granule cell dendrites form synapses in different layers: the outer molecular layer (OML), the middle molecular layer (MML), and the inner molecular layer (IML). HF indicates the hippocampal fissure. (b) Photograph of the dentate gyrus in an unstimulated hippocampal slice. Staining with digoxygenin-labeled cRNA probes reveals little *Arc* mRNA in the dendrites or cell bodies. (c) Same view in a hippocampal slice after strong stimulation of synapses in MML. Stimulation induces transcription of *Arc*, and large amounts of *Arc* mRNA appear in the granule cell bodies. The mRNA is also transported into the dendrites, where it concentrates within the stimulated MML. (Figure kindly provided by O. Steward.)

against CPEB, they found that dendrites of hippocampal neurons do express CPEB, and furthermore that the protein is concentrated at synapses in cultures of hippocampal neurons. Using techniques based on the polymerase chain reaction (PCR), Wu *et al.* [2] also confirmed that CaMKIIα mRNAs have CPEs and are polyadenylated and translated when injected into *Xenopus* oocytes in which the endogenous CPEB had been activated by stimulation with progesterone. They found that, under these circumstances, CaMKIIα mRNAs gained up to 160 nucleotides and were efficiently translated.

Most intriguingly, Wu *et al.* [2] asked whether synaptic activity causes cytoplasmic polyadenylation of CaMKIIα mRNA *in vivo*. They looked at the poly(A) tails of CaMKIIα mRNA taken from rat visual cortex during the postnatal period when activity-dependent synaptic plasticity has been shown to drive the developmental organization of synaptic connections [14]. In visually inactive rats — reared in the dark — CaMKIIα mRNA taken from the visual cortex had poly(A) tails of about 200 nucleotides; in rats reared with light exposure, the mRNA had poly(A) tails of up to 1000 nucleotides. Furthermore, western blots showed that, at this time, newly synthesized CaMKIIα protein appears in the visual cortex — measured in synapse-enriched cortical fractions — specifically of light-reared rats. These results offer the first detailed evidence that a translational control mechanism operates in neuronal dendrites. This mechanism, previously identified in developing systems, may thus serve as an effector for synaptic activity to stimulate local translation of CaMKIIα.

These various studies indicate that dendrites locally synthesize CaMKIIα and Arc protein in response to synaptic activity, possibly to participate in the molecular processes underlying synaptic plasticity. More has to be done, however, before we can pronounce either case complete. For example, it remains to be directly confirmed that CPEB-induced polyadenylation of CaMKIIα mRNA occurs in dendrites and that this process underlies increased CaMKIIα activity in synapses. Also, it is not known what molecular signal links synapse activity and CPEB activation, nor what role Arc protein plays in synaptic function or plasticity. More generally, researchers must examine whether other mRNAs participate in dendritic translation and look for other mechanisms that regulate this process, as not all dendritic mRNAs appear to have CPEs. New ways of visualizing protein production and localizing mRNAs in intact neurons will undoubtedly aid the cause, and the increasing realization that mechanisms used during development may also operate in adult memory should provide this field with intellectual fodder for years to come.

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