encounter APP in the more fluid regions of the membrane.

So, how can these observations be reconciled with the effects of statins in humans? As Abad-Rodriguez *et al.* point out, most of the commonly used statins are poor penetrators of the blood–brain barrier, so their benefits might derive from anti-inflammatory or antioxidant properties rather than direct effects on brain neurons. Their new findings indicate that, rather than trying to reduce brain cholesterol, care should actually be taken to preserve the cholesterol balance in the membranes of brain neurons.

Heather Wood

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SYNAPTIC PHYSIOLOGY

Fuel for plasticity

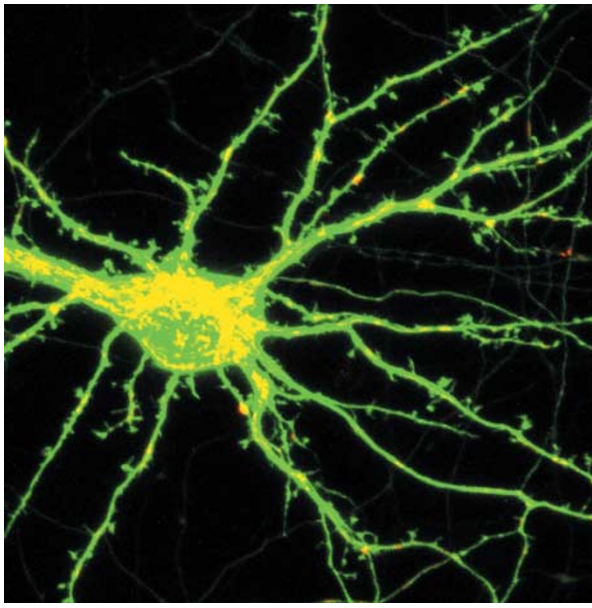
Mitochondria are the energy factories of cells. Although it is generally thought that their activity adapts to cellular physiology, the functional significance of mitochondrial distribution in the cell is largely unknown. Reporting in *Cell*, Li and colleagues show that synaptic activity and mitochondrial distribution are reciprocally regulated.

Mitochondria are abundant in the cell bodies and large-diameter proximal dendrites of cultured hippocampal neurons, but are present at much lower densities in small-diameter and distal dendrites. There is a temporal correlation between increased mitochondrial incursion into dendritic protrusions and active synapse formation, which indicates that mitochondrial function might be crucial for the development of synapses.

Repetitive depolarization of cultured hippocampal neurons, which results in the formation of new dendritic spines and morphological changes to existing ones, also leads to an increase in the proportion of dendritic protrusions that contain mitochondria. Similarly, after local synaptic stimulation of neurons in organotypic hippocampal slices, mitochondria accumulate in the vicinity of active synapses and invade enlarged spines. This process can be blocked by an NMDA (*N*-methyl-D-aspartate) receptor antagonist, which indicates that the increased mitochondrial presence is due to synaptic excitation.

To test whether mitochondria are required for synaptic development and maintenance, Li and colleagues perturbed mitochondrial distribution in clutured hippocampal neurons by overexpressing wild-type and dominant-negative mutant forms of dynamin-related protein 1 (DRP1) and optic atrophy 1 (OPA1). DRP1 and OPA1 are large GTPases of the dynamin family and are important regulators of the fission and fusion processes of mitochondria, respectively.

In neurons that were transfected with dominant-negative DRP1 (DRP1-K38A) or wild-type OPA1 — treatments that decreased the amount of mitochondria in dendrites — the density of dendritic spines was greatly reduced. By contrast, the density of dendritic spines increased almost two-fold in neurons that overexpressed wild-type DRP1. Creatine, a drug that enhances mitochondrial function, mimics the effect of DRP1 on synaptic density, indicating that the promoting effect of DRP1 on synapse formation might result from increased numbers of dendritic mitochondria. Consistent with this finding, both creatine and wild-type DRP1 enhance the synaptogenic response of neurons to repetitive stimulation.



Mitochondria (stained with MitoDsRed) are seen as yellow in the cell body and dendrites of a neuron that has been transfected with green fluorescent protein. Image courtesy of Z. Li, Massachusetts Institute of Technology, USA.

What effect does global neuronal activity have on the balance of mitochondrial fission and fusion and the motility of dendritic mitochondria? Drugs that block action potentials, such as tetrodotoxin, were shown to increase the rate of mitochondrial movement and the ratio of mitochondrial fusion/fission in cultured hippocampal neurons, whereas depolarization of neurons by KCl produced opposing effects. Overexpression of DRP1-K38A blocked the change in mitochondrial motility that was induced by tetrodotoxin, which indicates that DRP1 is required for activity-dependent regulation of mitochondrial motility. In addition, DRP1-K38A increased the ratio of mitochondrial fusion/fission in neurons, whereas wild-type DRP1 decreased it.

This study shows a structural and functional interplay between dendritic mitochondria and synapses. As abnormal mitochondrial morphology and function have been associated with neurodegenerative diseases, the findings raise the possibility that the characteristic loss of synapses in these disorders might arise, in part, from mitochondrial dysfunction.

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