This Week in The Journal

Rapamycin Restores Neurovascular Coupling in AD Mice

Candice E. Van Skike, Stacy A. Hussong, Stephen F. Hernandez, Andy Q. Banh, Nicholas DeRosa et al.

(see pages 4305–4320)

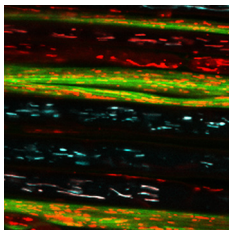
Disruption of cerebral blood flow and its regulation by neural activity (neurovascular coupling) occur early in Alzheimer's disease (AD), often before other symptoms appear. Cerebrovascular dysfunction not only deprives neurons of oxygen and glucose, but also impairs the clearance of toxic substances, including β-amyloid peptides. Consequently, vascular dysfunction may be a major contributor to cognitive decline and neurodegeneration, and reversing this dysfunction may slow AD progression. Promisingly, this might be achieved with a pharmacological agent that is already in use for other conditions, namely rapamycin.

The mechanistic target of rapamycin (mTOR) is a master regulator of cellular metabolism and aging. Reducing mTOR function with rapamycin extends life span in every animal tested so far, and it increases cerebral microvascular density, restores vasodilation initiated by endothelial nitric oxide synthase (eNOS), and prevents breakdown of the blood–brain barrier in mouse models of AD. Van Skike et al. report that rapamycin also restores neurovascular coupling mediated by neuronal nitric oxide synthase (nNOS).

In wild-type mice, neurovascular coupling is mediated by nitric oxide produced by nNOS and eNOS plus other factors released by neurons, astrocytes, or vascular cells. The nNOS-dependent component of the neurovascular response was diminished in 6-month-old mice expressing human amyloid precursor protein with AD-linked mutations (J20 mice), as revealed by smaller-than-normal increases in cerebral blood flow in the somatosensory cortex in response to whisker stimulation. This deficit was greater in 12-month-old mice, in which the NOS-independent component of the response was also diminished. Notably, nNOS expression was reduced in the hippocampus of AD patients, as well as in the microvasculature of J20 mice.

Treating mice with rapamycin for 2 months eliminated neurovascular coupling deficits by enhancing all three components of the neurovascular response. *In vitro* studies showed that rapamycin increased phosphorylation of nNOS and upregulated a protein that promotes nNOS activation. Notably, the amplitude of the neurovascular response in mice was correlated with behavioral fear responses after contextual conditioning in both wild-type and J20 mice, and rapamycin reversed memory deficits in 12-month-old J20 mice.

These data, along with previous work, suggest that rapamycin can reverse AD-related pathology and cognitive impairments. Therefore, clinical trials testing the efficacy of rapamycin in AD patients seem warranted.



Mitochondria (cyan) in saphenous nerve axons of mice fed high-fat diets have reduced membrane potential, as revealed by reduced labeling with a membrane potential indicator (red). Green labels unmyelinated Remak bundles. See Sajic, Rumora, et al. for details.

High-Fat Diet Impairs Mitochondrial Function in Neurons

Marija Sajic, Amy E. Rumora, Anish A. Kanhai, Giacomo Dentoni, Sharlini Varatharajah, et al.

(see pages 4321–4334)

Peripheral neuropathy is common in people with diabetes, but little is known about the molecular pathways linking these conditions. Diabetes is characterized by insulin resistance and hyperglycemia, but serum levels of fatty acids are also elevated in many diabetic patients. Because excessive glucose and fatty acids can overload mitochondrial metabolic pathways, mitochondrial dysfunction has been proposed to contribute to diabetic neuropathy. Consistent with this hypothesis, both glucose and palmitate (a fatty acid prevalent in plasma) disrupted mitochondrial respiration, transport, and/or membrane potential in cultured mouse dorsal root ganglia neurons. But effects produced in cultured neurons can differ from those produced *in vivo*, where axons are insulated by myelin sheaths. Therefore Sajic, Rumora, et al. asked how consumption of a high-fat diet affects mitochondria in mouse sensory axons *in vivo*.

As expected, mice fed a high-fat diet for 36 weeks had higher plasma levels of glucose, phospholipids, and cholesterol than mice fed a standard diet; the mice also developed sensory neuropathy. Unlike palmitate treatment in cultured neurons, the high-fat diet did not reduce the number of motile mitochondria in saphenous nerve axons *in vivo*. Nevertheless, after nerve stimulation to mimic activity during walking—which increases energy demand and thus stimulates mitochondrial respiration and fission—mitochondria were larger in mice fed a high-fat diet than in controls, suggesting fission was impaired. Moreover, mitochondrial membrane potential—which is essential for oxidative phosphorylation and for trafficking molecules across mitochondrial membranes—was lower than normal in mice fed a high-fat diet. Importantly, whereas nerve stimulation in control animals reduced mitochondrial membrane potential as ATP production increased, nerve stimulation did not reduce mitochondrial membrane potential further in mice fed a high-fat diet, suggesting that ATP synthesis was impaired. Likely as a result, the ability of saphenous axons to maintain spiking at high physiological frequencies was reduced and the refractory period after single spikes was lengthened in mice fed a high-fat diet.

These data indicate that consuming high-fat diets that increase plasma glucose and phospholipid levels can impair mitochondrial function in sensory axons and consequently impair nerve conduction. Future work should determine whether hyperglycemia or excess lipids are responsible for these effects, identify the molecular mechanisms, and assess whether improving mitochondrial function reverses neuropathy.

This Week in The Journal was written by Teresa Esch, Ph.D.
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