Noteworthy This Week

Papers of Note (8 December 2004)
Sci. Aging Knowl. Environ. **2004** (49), nw48. [DOI: 10.1126/sageke.2004.49.nw48]

This Week's SAGE KE News

Young at Brain Long-lived mice pump out extra neurons. M. Leslie. [Abstract] [Full Text]

MORE BREAKING NEWS

Toxic Spill Parkin protects dopamine cargo within neurons from leaking

WASHINGTON, D.C.--Rust can ruin train tracks, causing wrecks that spill toxins. Similarly, a particular insecticide splinters transportation conduits inside motor neurons, derailing containers holding a deadly chemical, according to work presented here 5 December 2004 at the American Society for Cell Biology Annual Meeting. The study also shows that parkin, a protein implicated in Parkinson's disease (PD), helps keep the tracks safe. The results could help researchers understand how PD knocks off only a subset of neurons.

Shakiness in people with PD arises from the death of brain neurons that control muscles. Rotenone, a plant-derived insecticide, gives rats parkinson-like symptoms--killing neurons that make and use dopamine in the same region of the brain that PD afflicts. Previous work has shown that rotenone somehow causes lethal oxidative damage in these neurons. Some scientists think that the pesticide mucks up mitochondria, the energy-producing organelles that pump out reactive oxygen species as a byproduct of metabolism. But the mitochondrial proteins that rotenone sticks to are found in all neurons, so Jian Feng and colleagues wondered whether the selectivity involved dopamine itself. Researchers know that the insecticide also attacks microtubule proteins--components of the tracks that carry bags of neurotransmitters within neurons. Although all neurons have these rails, only dopamine-using cells transport the neurotransmitter. The researchers speculated that faults in the lines might make their cargo cause trouble.

To find out, they doused neurons from rat embryos with rotenone and found, as expected, that 90% of the dopamine-producing neurons died. When they added taxol, which braces microtubule tracks but does not counteract oxidative damage, 50% of the neurons survived. This observation suggested that rotenone disrupts the microtubule-composed tracks and that this interference kills cells. Rotenone slayed fewer neurons when the researchers chemically blocked dopamine production. Together, these findings hint that stalled neurotransmitter containers incite problems. Rotenone-soaked cells held three times as many of the sacks as did untreated ones. Because the bags are known to leak dopamine, which oxidizes and attacks cellular contents, the team measured the amount of

oxidative damage. It doubled in the presence of rotenone but could be cut substantially by adding taxol, suggesting that the oxidative damage occurred because the tracks fell apart.

Microtubule rail lines are constantly being built and destroyed. The protein parkin tags used bits of track for disposal, and defective forms of parkin can cause PD. To test whether mutant parkin makes trouble by interfering with rail cleanup, the researchers injected healthy parkin into the neurons and found that it could cut rotenone-induced death by about 80%. Three malfunctioning forms of parkin did not protect the cells, suggesting that the inability to remove demolished microtubules allows dopamine to pile up and kill neurons.

Calling the work "intriguing," oxidative damage biologist Antony Cooper of the University of Missouri, Kansas City, says that with the rotenone-sparked microtubule demolition, the leaky neurotransmitter receptacles, and the mutant parkin, "the story fits together nicely." Some researchers think that environmental toxins cause PD, and this result helps explain how mutant parkin might render people sensitive to such poisons. If these findings hold up, perhaps researchers can find ways to subsidize the rail system in dopamine-producing neurons.

--Mary Beckman

Y. Ren, W. Liu, H. Jiang, J. Feng, Rotenone and parkin act antagonistically on microtubules to affect the survival of dopaminergic neurons. American Society for Cell Biology, 44th Annual Meeting, 4 to 8 December 2004, Washington, D.C. [Meeting Home Page]

News from the Alzheimer Research Forum

Parkinson Therapies Go Deep and Shallow
8 December 2004. Two articles from the past week describe very different approaches to therapy for Parkinson disease...

Sharpen Your Synapses with Rolipram!
3 December 2004. Among its many reputed transgressions, amyloid-β is suspected of interfering with synaptic function from the earliest stages of Alzheimer disease...

GSK-3—A Peripheral Marker for AD?
2 December 2004. Finding an easily measurable antecedent marker for Alzheimer disease would be a major development. Might glycogen synthase kinase fit the bill?...

Rifampicin for Parkinson Disease?
29 November 2004. Various antibiotics have been shown to protect against neurodegenerative diseases, not necessarily through antimicrobial action. Can one of them, rifampicin, prevent the formation of α-synuclein aggregates?...

Baited BRET—Measuring Ubiquitination/Deubiquitination in Real Time
29 November 2004. Researchers studying the ubiquitination pathway may be interested in a new technique that can measure ubiquitination—and deubiquitination—in real time...