Health & Medicine

Take Out the Trash: A Strategy to Subdue Alzheimer's

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A tidy brain is a healthy brain: to stay in working order, brain cells must continually clear out old, worn, or damaged proteins by breaking them down into smaller molecules that can be recycled. If the cellular machinery that is responsible for dismantling old proteins doesn't work efficiently, clumps of leftover proteins can accumulate inside brain cells, obstructing their function, and, say some scientists, contributing to Alzheimer's disease and other neuro-degenerative conditions.

This past fall, a team of researchers led by Columbia cell biologists Karen Duff and Natura Myeku provided the most convincing evidence yet that boosting the productivity of the brain's so-called "garbage-disposal system" could be an effective way of treating diseases like Alzheimer's, Parkinson's, and Huntington's. In a series of experiments conducted on mice that were genetically engineered to have Alzheimer's-like memory problems, the researchers showed that the drug rolipram improved the animals' cognition by accelerating the pace at which their brain cells dispensed with old proteins.

"The change we witnessed in the mice was dramatic — they went from having almost no short-term memory to perfectly normal cognition," says Duff, whose study appeared in *Nature Medicine*. "We could see this was the result of improved protein disposal because we inspected the mice's brain cells before and after the drug treatment. The cells' proteasomes, which literally chew up old proteins, were functioning much better afterward, reducing protein buildup."

Scientists have known for years that rolipram, developed in the 1990s as an antidepressant, could improve memory in mice. But the new Columbia study is the first to demonstrate that the drug achieves this effect by stimulating proteasomes. And while rolipram is inappropriate for use in humans — it was never approved for any clinical purpose because it causes severe nausea and other side effects — the

Columbia researchers are hopeful that they may soon find a safer drug that has a similarly invigorating effect on the brain’s cleanup machinery.

“This opens up a whole new strategy for treating Alzheimer’s disease and related conditions,” says Myeku. “Our strategy is unlikely to provide a cure, since neuro-degenerative conditions are extremely complex, but we believe that it holds out the possibility of at least slowing the progression of disease.”



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