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Finding key to Parkinson's

Double whammy on dopamine transport system suspected

By LOIS BAKER
Contributing Editor

Parkinson's disease may be caused by an environmental-genetic double whammy on the neurons that produce dopamine, the neurotransmitter that controls body movement, a new study has shown.

UB researchers, using cultures of rat neurons, have shown that the presence of mutated parkin genes, combined with the toxic effects of the chemical rotenone, results in a cascade of highly toxic free radicals, the destruction of microtubules that transport dopamine to the brain's movement center, and eventual death of the dopamine-producing neuron.

"This study shows how an environmental toxin and a gene linked to Parkinson's disease affect the survival of dopamine neurons by dueling on a common molecular target—microtubules—that are critical for the survival of dopamine-producing neurons," said Jian Feng, assistant professor of physiology and biophysics in the School of Medicine and Biomedical Sciences and senior author.

"Based on these findings, we have identified several ways to stabilize microtubules against the onslaught of rotenone. These results ultimately may lead to novel therapies for Parkinson's disease."

Results of the research were presented on Sunday at the American Society for Cell Biology meeting in Washington, D.C.

Researchers who study Parkinson's disease know that persons with a mutation in the parkin gene are at risk for the disease, and that exposure to agricultural chemicals, including rotenone, cause Parkinson's-like symptoms in animals. In addition, long-term epidemiological studies of Parkinson's disease patients have shown a strong link between exposure to pesticides/herbicides and increased risk of developing the disease, Feng noted.

Earlier research by several groups has shown that rotenone destroys only neurons that produce dopamine, while largely sparing neurons that produce other neurotransmitters. Feng's laboratory set out to answer the questions "Why?" and "How?"

By studying the effects of rotenone on rat neurons, they discovered that one of the targets of the pesticide was microtubules—intracellular highways for transporting various chemicals such as dopamine to the brain area that controls body movement.

Normally the enzyme parkin would protect the neuron from rotenone's assault on microtubules, Feng said.

"When microtubules are broken down by rotenone, the disassociated protein building blocks, called tubulin, are left behind," he said. "These tubulins are probably misfolded proteins. Left unattended, they could interfere with the normal assembly of microtubules. Based on our previous work that parkin marks this 'old' tubulin for rapid degradation, we theorize that parkin may thus prevent this interference."

Mutated parkin loses this protective ability, however, allowing rotenone to do its damage unchecked.

Feng and colleagues showed that rotenone damages the microtubules, which prevents dopamine from reaching the brain's movement center, causing a back-up in the dopamine transport system. Meanwhile, the backed-up dopamine accumulates in the neuron's cytoplasm and breaks down, causing a release of toxic free radicals that destroy the neuron.

Additional researchers on the study were Yong Ren, Wenhua Liu and Houbo Jiang, postdoctoral associates in the Department of Physiology and Biophysics.

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