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Parkinson's-Inducing Chemical Works by Attacking Microtubules

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By Anthony J. Brown, MD

NEW YORK (Reuters Health) Dec 03 - The pesticide rotenone has been shown to induce Parkinson's-like symptoms in laboratory animals. Now, new research suggests that it achieves this effect by damaging microtubules in dopamine-producing neurons.

As such, drugs designed to stabilize microtubules, such as paclitaxel, could offer a new therapy for Parkinson's disease. Unfortunately, simply giving this drug to patients is unlikely to work as it does not cross the blood-brain barrier. Still, the researchers are hopeful that they will uncover a chemical that can pass this barrier.

The study findings will be presented Sunday at the American Society for Cell Biology meeting in Washington, DC.

In an interview with Reuters Health, senior author Dr. Jian Feng, from the State University of New York at Buffalo, said that while "rotenone was known to destroy dopamine-producing neurons," it was unclear how it achieved this effect. In particular, how did rotenone destroy these neurons, "while largely sparing ones that produced other neurotransmitters?"

Interestingly, the idea that rotenone damages microtubules is not new. In fact, scientists "first made this observation about 30 years," Dr. Feng said. "But our study is the first to show that this known activity actually causes a selective consequence in dopaminergic neurons."

Dr. Feng explained that although the cell bodies of dopaminergic neurons lie in the substantia nigra, their axons extend into the striatum and this is where the neurotransmitter is normally released. Microtubules are important because they transfer dopamine-containing vesicles from production sites in the cell body to the axon terminus.

Rotenone damages these microtubules, leading to cellular build-up of the vesicles, which begin to leak dopamine. As it turns out, dopamine is easily oxidized, resulting in free radicals that destroy the neuron. Other neurotransmitters are not easily oxidized, which explains rotenone's selectivity for destroying dopamine-producing neurons.

The current findings compliment previous research by Dr. Feng's team showing that mutations in the parkin gene, a strong risk factor for Parkinson's disease, affect microtubule break down. With an abnormal parkin enzyme, degradation is impaired, which could interfere with new microtubule formation.

Given the shared focus on microtubules, it is likely that patients with parkin gene mutations are particularly susceptible to the neuron damage caused by rotenone, Dr. Feng noted.

Dr. Feng said that his team is currently looking for microtubule-stabilizing agents that, unlike paclitaxel, cross the blood-brain barrier.