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Buck research focuses on risk factor for Parkinson's disease

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A new study demonstrates that high levels of MAO-B, an enzyme that regulates nerve activity in the brain, cause Parkinson's-like symptoms in mice genetically engineered to overexpress the protein. Furthermore, drugs currently used as an adjunct therapy for Parkinson's in humans prevented the development of Parkinson's symptoms in these same animals. The findings, by scientists at the Buck Institute for Age Research, raise the possibility that humans could be tested to see if they have a risk factor for the progressive, incurable neurodegenerative disorder that affects 1.5 million Americans and receive preventive treatment. The study appears in the February 20 issue of the open-access, online journal, PLoS ONE.

Levels of measurable MAO-B vary 50-fold in humans and tend to increase with age. Several studies have suggested that increases in MAO-B contribute to the neurodegeneration associated with PD, but direct proof of a causative role for the enzyme has been lacking. The drug deprenyl, which inhibits MAO-B, is a longstanding therapy for Parkinson's used together with drugs that boost the level of dopamine, an important neurotransmitter that is preferentially depleted in the disease. Clinical studies that suggest that deprenyl treatment alone does not impact mortality associated with Parkinson's have cast doubt on the role of MAO-B in the disease itself.

Buck faculty member Julie Andersen, PhD, who led the study says that may not be the case. "Those studies were targeted to patients who already had symptoms of Parkinson's -- by the time Parkinson's is

symptomatically detectable, dopamine loss is usually at least 60%," said Andersen. "Therefore the lack of effectiveness of MAO-B inhibition in these patients does not negate a role for MAO-B increase in disease development." Andersen added, "We have demonstrated that elevations in MAO-B result in selective loss of neurons associated with Parkinson's in a mouse model and that the severity of this loss is age-dependent."

Tests to measure levels of MAO-B are not currently available to the general public, although enzyme levels are tracked in clinical trials. Andersen says MAO-B testing could be akin to current practices involving cholesterol, which is measured and monitored as a risk factor for cardiovascular disease. "However, it is important to note that Parkinson's is a multi-factor disease," said Andersen. "The fact that someone has high levels of MAO-B does not necessarily mean they are fated to develop Parkinson's."

Andersen said results of the study point to the need for an early diagnostic test for Parkinson's. "Currently, by the time people are diagnosed with the disease they have already lost 60% of the neurotransmitter levels implicated in Parkinson's; treatment with a drug like deprenyl would likely be most effective if taken before symptoms appear in order to halt disease progression."

The novel transgenic mouse line created for this study provides a new model for exploring molecular pathways involved in the initiation or early progression of several key features associated with Parkinson's pathology including dopaminergic midbrain cell loss. The mouse line also allows for additional therapeutic drug testing.

Source: Public Library of Science