Dementia induced and blocked in Parkinson's fly model

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Parkinson's disease is well-known for impairing movement and causing tremors, but many patients also develop other serious problems, including sleep disturbances and significant losses in cognitive function known as dementia.

Now researchers at Washington University School of Medicine in St. Louis have modeled Parkinson's-associated dementia for the first time. Scientists showed that a single night of sleep loss in genetically altered fruit flies caused long-lasting disruptions in the flies' cognitive abilities comparable to aspects of Parkinson's-associated dementia. They then blocked this effect by feeding the flies large doses of the spice curcumin.

"Clinical trials of curcumin to reduce risk of Parkinson's disease are a future possibility, but for now we are using the flies to learn how curcumin works," says author James Galvin, M.D., a Washington University associate professor of neurology who treats patients at Barnes-Jewish Hospital. "This should help us find other compounds that can mimic curcumin's protective effects but are more specific."

Galvin and senior author Paul Shaw, Ph.D., assistant professor of neurobiology, publish their results in the journal *Sleep* on Aug. 1.

Galvin is an expert in cognitive impairments in human Parkinson's disease; Shaw studies sleep and the brain in fruit flies. The researchers decided collaborate based in part on evidence that increased sleep loss in

Parkinson's patients can precede or coincide with increased severity in other Parkinsonian symptoms.

More than 74 percent of Parkinson's patients have trouble sleeping, and up to 80 percent of patients 65 and older who have Parkinson's disease for seven years will develop dementia, according to Galvin.

Shaw's lab has linked sleep loss to changes in the dopaminergic system of the brain, the part of the brain that produces the neurotransmitter dopamine and is at the center of the damage caused by Parkinson's.

"In healthy flies, sleep deprivation decreases dopamine receptor production and causes temporary learning impairments that are fully restored after a two-hour nap," Shaw says.

Shaw and Galvin studied fruit flies genetically modified to make a human protein called alpha-synuclein in their brains. Scientists don't yet know what alpha-synuclein does, nor have they found a fly counterpart for it. But they have shown that it aggregates in the brains of Parkinson's disease patients and believe the processes that cause the aggregations are harming dopamine-producing cells.

Prior studies of fruit flies with human alpha-synuclein in their brains showed that the flies, like human Parkinson's patients, also lose dopamine-producing neurons, have movement-related problems and develop alpha-synuclein aggregations. But scientists had yet to evaluate the flies for signs of dementia.

Lead author Laurent Seugnet, Ph.D., research associate at L'Ecole Supérieure de Physique Chimie Industrielles in France, first tested the flies' learning ability using a procedure he helped develop in Shaw's lab. For the test, Seugnet placed flies in a vial with two branches: one lighted branch containing quinine, a bitter-tasting substance flies prefer to avoid;

and a darkened but quinine-free branch. After a few trials, normal flies learn to suppress their natural attraction to the light and fly into the darkened vial instead to avoid the quinine.

Flies with alpha-synuclein in their brains could still learn when they were middle-aged, or about 16 to 20 days old. But when Seugnet deprived them of sleep for 12 hours, he found that their ability to remember was more severely impaired than that of young healthy flies that had also been sleep-deprived.

"This was still true even 10 days later, so it seemed to be a lasting effect," says Seugnet.

Galvin had earlier found that curcumin, a derivative of the spice turmeric, blocks alpha-synuclein aggregation in cell models of Parkinson's disease. Based on this, Seugnet fed curcumin to a new batch of flies, repeated the tests and found middle-aged flies with alpha-synuclein retained their ability to learn as well as normal young flies.

"Thanks to this model our labs have created, Dr. Galvin and I can not only quickly test potential new treatments for these symptoms of Parkinson's, we can also move up our treatments in terms of the timeline along which the disorder develops," says Shaw. "That may give us a real chance to change the course of the disease."

More information: Seugnet L, Galvin JE, Suzuki Y, Gottschalk L, Shaw PJ. Persistent short-term memory defects following sleep deprivation in a Drosophila model of Parkinson disease. *Sleep*, Aug. 1, 2009

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