Caffeine-based compounds show promise against Parkinson's disease

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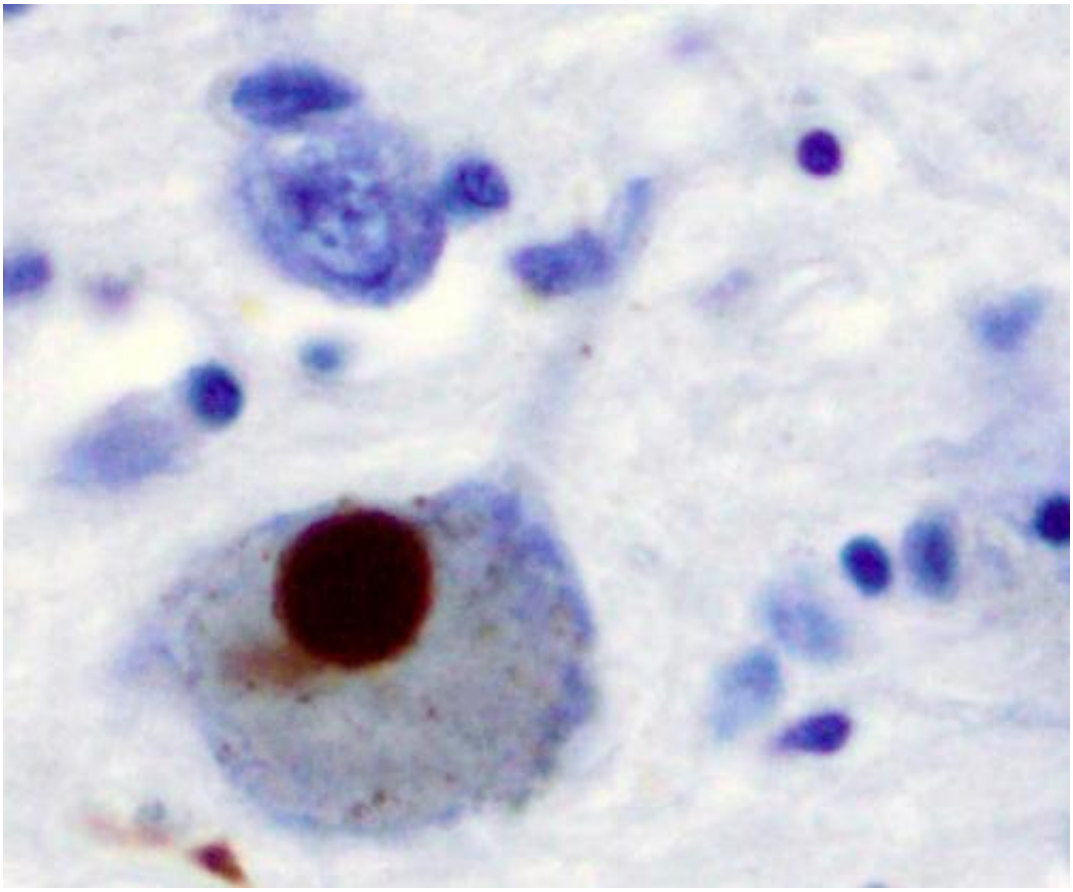

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A team of researchers from the University of Saskatchewan has

developed two caffeine-based chemical compounds that show promise in preventing the ravages of Parkinson's disease.

Parkinson's disease attacks the nervous system, causing uncontrolled shakes, muscle stiffness, and slow, imprecise movement, chiefly in middle-aged and elderly people. It is caused by the loss of brain cells (neurons) that produce dopamine, an essential neurotransmitter that allows neurons to "talk" to each other.

The team focused on a protein called α-synuclein (AS), which is involved in dopamine regulation.

In Parkinson's sufferers, AS gets misfolded into a compact structure associated with the death of dopamine-producing neurons. Worse, AS appears to act like a prion disease (for example, variant Creutzfeldt-Jacob or "mad cow"). In prion diseases, one mis-folded protein triggers mis-folding in others, spreading like falling dominos.

Jeremy Lee, a biochemist from the U of S College of Medicine, and Ed Krol from the College of Pharmacy and Nutrition led the team, which included researchers Troy Harkness and Joe Kakish from the U of S College of Medicine, as well as Kevin Allen from the Drug Discovery and Research Group in the College of Pharmacy and Nutrition.

"Many of the current therapeutic compounds focus on boosting the dopamine output of surviving cells, but this is effective only as long as there are still enough cells to do the job," Lee said. "Our approach aims to protect dopamine-producing cells by preventing α-synuclein from mis-folding in the first place."

Although the chemistry was challenging, Lee explained the team synthesized 30 different "bifunctional dimer" drugs, that is, molecules that link two different substances known to have an effect on dopamine-

producing cells. They started with a caffeine "scaffold," guided by literature that shows the stimulant has a protective effect against Parkinson's. From this base, they added other compounds with known effects: nicotine, the diabetes drug metformin, and aminoindan, a research chemical similar to the Parkinson's drug rasagiline.

Using a yeast model of Parkinson's disease, Lee and his team discovered two of the compounds prevented the AS protein from clumping, effectively allowing the cells to grow normally.

"Our results suggest these novel bifunctional dimers show promise in preventing the progression of Parkinson's disease," Lee said.

The team's findings are published in the journal *ACS Chemical Neuroscience*.

More information: Joe Kakish et al. Novel Dimer Compounds That Bind α-Synuclein Can Rescue Cell Growth in a Yeast Model Overexpressing α-Synuclein. A Possible Prevention Strategy for Parkinson's Disease., *ACS Chemical Neuroscience* (2016). DOI: 10.1021/acschemneuro.6b00209

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