Understanding how chemical changes in the brain affect Alzheimer's disease

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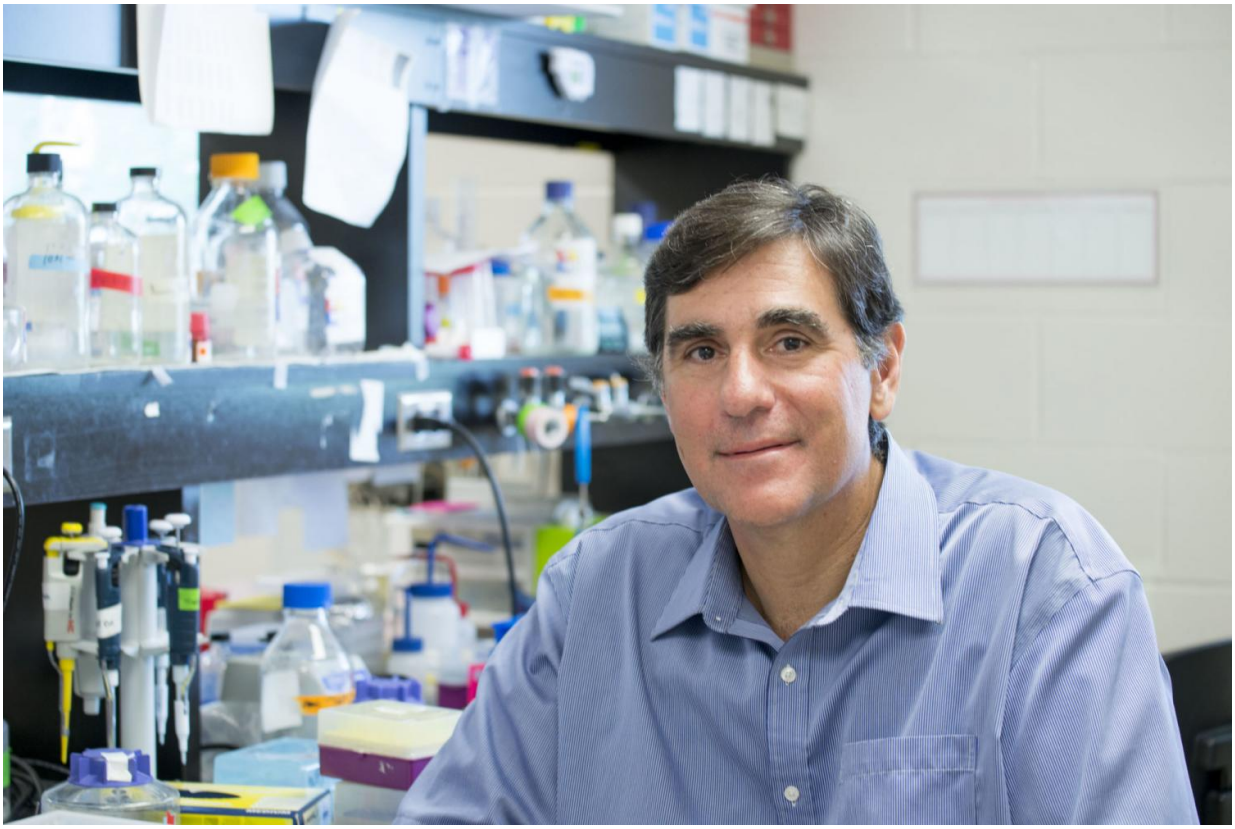

Credit: University of Western Ontario

A new study from Western University is helping to explain why the long-term use of common anticholinergic drugs used to treat conditions like allergies and overactive bladder lead to an increased risk of developing

dementia later in life. The findings show that long-term suppression of the neurotransmitter acetylcholine - a target for anticholinergic drugs - results in dementia-like changes in the brain.

"There have been several epidemiological studies showing that people who use these drugs for a long period of time increase their risk of developing dementia," said Marco Prado, PhD, a Scientist at the Robarts Research Institute and Professor in the departments of Physiology and Pharmacology and Anatomy & Cell Biology at Western's Schulich School of Medicine & Dentistry. "So the question we asked is 'why?'"

For this study, published in the journal *Cerebral Cortex*, the researchers used genetically modified mouse models to block acetylcholine in order to mimic the action of the drugs in the brain. Neurons that use acetylcholine are known to be affected in Alzheimer's disease; and the researchers were able to show a causal relationship between blocking acetylcholine and Alzheimer's-like pathology in mice.

"We hope that by understanding what is happening in the brain due to the loss of acetylcholine, we might be able to find new ways to decrease Alzheimer's pathology," said Prado.

Prado and his partner Dr. Vania Prado, DDS, PhD, along with PhD candidates Ben Kolisnyk and Mohammed Al-Onaizi, have shown that blocking acetylcholine-mediated signals in neurons causes a change in approximately 10 per cent of the Messenger RNAs in a region of the brain responsible for declarative memory. Messenger RNA encodes for specific amino acids which are the building blocks for proteins and several of the changes they uncovered in the brains of mutant mice are similar to those observed in Alzheimer's disease.

"We demonstrated that in order to keep neurons healthy you need acetylcholine," said Prado. "So if acetylcholine actions are suppressed,

brain cells respond by drastically changing their messenger RNAs and when they age, they show signs of pathology that have many of the hallmarks of Alzheimer's disease." Importantly, by targeting one of the messenger RNA pathways they uncovered, the researchers improved pathology in the mutant mice.

The study, conducted at Western's Robarts Research Institute, used human tissue samples to validate the mouse data and mouse models to show not only the physical changes in the brain, but also behavioral and memory changes. The researchers were able to show that long-term suppression of acetylcholine caused brain cell to die and as a consequence decrease memory in the aging mice.

"When the mutant mice were old, memory tasks they mastered at young age were almost impossible for them, whereas normal mice still performed well," said Kolisnyk.

The researchers hope their findings will have an impact on reducing the burden of dementia by providing new ways to reverse the loss of acetylcholine.

More information: Benjamin Kolisnyk et al, Cholinergic Surveillance over Hippocampal RNA Metabolism and Alzheimer's-Like Pathology, *Cerebral Cortex* (2016). DOI: 10.1093/cercor/bhw177

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