

Genetically-modified mice reveal another mechanism contributing to heart failure

February 1 2010

Scientists at the Robarts Research Institute at The University of Western Ontario, working in collaboration with researchers in Brazil, have used a unique genetically-modified mouse line to reveal a previously unidentified mechanism contributing to heart failure. The study, led by Marco Prado, Robert Gros and Vania Prado of London, Canada and Silvia Guatimosim of Brazil, shows how the decreased release of the neurotransmitter acetylcholine, a chemical messenger which slows cardiac activity, contributes to heart failure.

Heart failure affects close to a half million Canadians, often as a result of conditions including coronary disease, [high blood pressure](#), diabetes and high alcohol or drug consumption. Cardiac output is controlled using two opposing divisions of the [autonomic nervous system](#): the [sympathetic nervous system](#) which boosts the heart rate and the parasympathetic system which slows it by releasing acetylcholine.

"Lots of people have studied the system that increases the [heart rate](#) and that has been the hallmark; we know there's an increase in the sympathetic nervous system in people who have [heart failure](#)," explains Gros, a cardiovascular researcher and assistant professor in the Departments of Physiology & Pharmacology and Medicine at Western's Schulich School of Medicine & Dentistry.

"What we're now showing with this mouse model is that even if you have a functional sympathetic nervous system, if the other system, the parasympathetic system is dysfunctional or works less optimally than

normal, you still end up with a sick heart. This opens up a whole new avenue that people have missed in the past."

Marco and Vania Prado genetically modified a line of mice with decreased secretion of acetylcholine originally for use in studying neuronal function in diseases such as Alzheimer's. But they found these mice, over time, developed changes in their hearts that progressively decreased their ability to pump blood, similar to what occurs with heart failure in humans.

"There are other mouse and rat models of heart failure, but what we haven't had before is a model where we specifically target this chemical messenger, acetylcholine," says Marco Prado, a professor in the Departments of Physiology & Pharmacology and Anatomy & Cell Biology. "One striking finding in this study is that heart dysfunction in these mice could be corrected by treating the animals with an existing drug which increases acetylcholine levels. Although it requires further study, this could provide a novel opportunity for treating failing hearts." The drug, Pyridostigmine, is currently approved for use in treating certain cases of muscle weakness.

More information: The study is published online in *Molecular and Cellular Biology* at

<http://mcb.asm.org/cgi/content/abstract/MCB.00996-09v1>

Provided by University of Western Ontario

Citation: Genetically-modified mice reveal another mechanism contributing to heart failure (2010, February 1) retrieved 6 February 2023 from

<https://medicalxpress.com/news/2010-02-genetically-modified-mice-reveal-mechanism-contributing.html>

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