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GDNF not needed by the midbrain dopamine system

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A key factor in the motor symptoms associated with Parkinson's disease is the gradual destruction of dopamine neurons. The glial cell-derived neurotrophic factor, or GDNF, has been proven to protect dopamine neurons in test tube conditions and in test animal models for Parkinson's disease. GDNF and its close relative, neurturin, have also been used in experimental treatments of patients with severe Parkinson's disease. The results have been promising, but vary widely in terms of efficacy. At the moment, two companies are conducting tests to determine the clinical effects of GDNF on Parkinson's sufferers.

According to an article published in *Nature Neuroscience* in 2008, removing GDNF from adult mice through gene technology causes significant damage to the midbrain dopamine system as well as triggers motor disorders. The article concluded that GDNF is vital to the maintenance and function of dopamine neurons.

At the same time, Academy of Finland Research Fellow Jaan-Olle Andressoo, from Professor Mart Saarma's research group at the Institute of Biotechnology, had developed a mouse model that was equivalent to the model used in the other study, with minor technical differences. In Andressoo's model, GDNF was removed from the central nervous system towards the end of the fetal period through gene deletion, and the mice remained healthy until high age. They studied the brains of the GDNF knockout mice together with the research group of University Lecturer Petteri Piepponen, based in the Faculty of Pharmacy.

"We decided to confirm the previous result using the mouse model Andressoo developed, and noticed that the complete absence of GDNF did not cause significant changes to the amount or function of dopamine neurons. Since the result surprised us, we wanted to verify it using two alternative methods, one of which was identical to the method in the previously published article," explains Dr Jaan-Olle Andressoo.

In addition, some of the experiments were conducted in parallel at Professor Anders Björklund's laboratory at Lund University. The Lund tests similarly indicated no changes to the dopamine systems or the behaviour of the mice. This clearly established that GDNF is not a necessary component of the dopamine system.

The manuscript including the new research results was approved for publication in the same series as the previous study. However, the study was subjected to even closer scrutiny than is associated with the normal publication procedure.

"The editors considered the manuscript to be a correction, so in addition to the normal peer review, they sent it to the researchers who published the previous results for comments. Ultimately, our results were deemed indisputable," Dr Petteri Piepponen says.

More information: Kopra J, Vilenius C, Grealish S, Härma M-A, Kä Varendi K, Lindholm J, Castrén E, Võikar V, Björklund A, Piepponen TP, Saarma M, Andressoo J-O. "GDNF is not required for catecholaminergic neuron survival in vivo." *Nature Neuroscience* 18, 319–322 (2015), DOI: 10.1038/nn.3941

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