Signaling Ret-receptors protect the live of nerve cells in the aging brain

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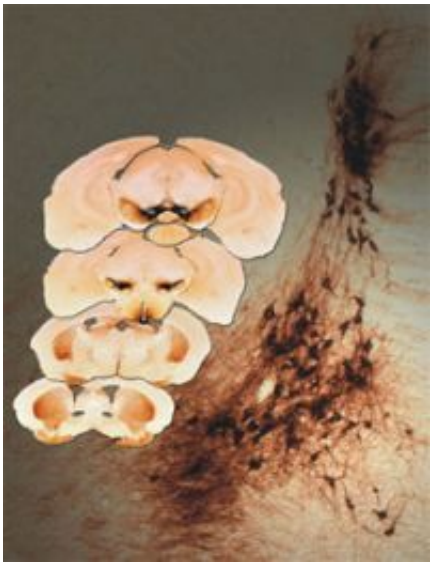

To the left several cross sections of a mouse brain are shown. In the dark labeled areas the scientists of the Max Planck Institute were able to selectively eliminate the receptor for a specific neurotrophic factor. In the background neurons that would also die due to Parkinson's disease, but have been positively affected by GDNF and its receptor, are shown. Image: Max Planck Institute of Neurobiology

Uncontrolled neuronal death in the brain often gives rise to neurodegenerative illnesses like Parkinson or Alzheimer disease. Whether or not neurons have a long and healthy life is, apart from other factors, determined by the presence of neurotrophic factors. Scientists of the Max Planck Institute of Neurobiology have now provided unambiguous proof that the presence of the neurotrophic factor GDNF

and its receptor Ret are essential for the survival of neurons in a specific brain region.

In mice the researchers inactivated the receptors of two neurotrophic factors in the substantia nigra, an area in which early cell death gives rise to Parkinson disease. The brains of these mice developed normally, however in the adult animal a significant decrease of dopaminergic neurons was observed over time, similar to what is seen in patients suffering form Parkinson disease. (*PLoS Biology*, March 5, 2007).

Parkinson patients suffer from loss of dopaminergic neurons in a certain region of the brain, the substantia nigra. Several experiments seem to indicate that the neurotrophic factor GDNF and its receptor might prevent an early, uncontrolled death of these neurons. The international team consisting of Edgar Kramer, Liviu Aron, Sabine Seitz und Rüdiger Klein of the Max Planck Institute of Neurobiology has now shown that neurons of the substantia nigra lacking the Ret-receptor indeed suffer an earlier death compared to normal control neurons. Loss of nerve cells and axons in this brain region is typical for Parkinson disease.

The disappearance of neurons lacking the Ret-receptor in this brain area has now for the first time been observed in mice, since the scientists were able to eliminate the receptor specifically in neurons of this brain region. The mice thus altered are viable and live as long as their normal relatives. "For the first time it was now possible to study the effects of missing GDNF signals on the establishment and maintenance of the nigrostriatal pathway (a neural pathway connecting the substantia nigra with the striatum)", stated Rüdiger Klein, Director at the Max Planck Institute of Neurobiology and head of the research team. Animals that lack GDNF and its receptor in all neurons are not viable and therefore it was not possible to investigate the precise role of GDNF and its receptor in the adult and aging brain.

"Surprisingly even without the Ret- receptor the nigrostriatal system developed normally", remarked Edgar Kramer, one of the leading scientists of the study. Only in adulthood the inability of these neurons to receive GDNF due to the missing receptor became evident and the older the animals grew, the more nerve cells died.

Worldwide more than 100 million especially older people suffer from diseases of the brain that are characterized by a gradual loss of neurons. Depending on which region of the brain is affected the symptoms vary, e.g. Alzheimer patients suffer from a progressive loss of memory whereas in Parkinson disease failures of the motor system are most evident. However, the characteristic muscle shaking and the inability to initiate movement of Parkinson's disease, from which also prominent people like Muhammed Ali and Michael J. Fox suffer, only become apparent after more than 50 percent of the neurons have died.

"Our results will help us to understand which factors nerve cells fated to die in Parkinson's patients need to survive" Rüdiger Klein stated. The published results are therefore of importance for promoting therapeutic approaches against Parkinson's disease.

Citation: Edgar R. Kramer, Liviu Aron, Geert M.J. Ramakers, Sabine Seitz, Xiaoxi Zhuang, Klaus Beyer, Marten P. Schmidt & Rüdiger Klein, Absence of Ret signaling in mice causes progressive and late degeneration of the Nigrostriatal system, *PLOS Biology* 2007, March 5, 2007

Source: Max Planck Institute of Neurobiology

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