Parkinson's disease: Iron accumulation to the point of demise

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Neurons that produce the neurotransmitter dopamine are the cerebral cells that most commonly die-off in Parkinson's disease. The cells in the so-called substantia nigra, which contain the dark pigment neuromelanin, are affected. It is also known that the iron content of these cells increases during the course of Parkinson's disease.

A team of researchers from the University of Bochum working under the auspices of Prof. Katrin Marcus and in close collaboration with colleagues in Munich and Wurzburg studied this process in greater depth. They have managed to make a first-time decisive observation, namely to provide evidence of ferritin in the neuromelanin granules in the affected brain cells. Ferritin is an iron depot protein that had only been proven in the supporting cells of the brain to date, but not in neurons. The scientists have published their results in *Molecular & Cellular Proteomics*.

Dark cerebral matter fades in Parkinson’s disease

Investigation of the human brain discloses a distinct dark discoloration of the substantia nigra and locus coeruleus within parts of the brainstem. This is due to the bluish to brown-black pigment neuromelanin, which is only present in the human brain and that of a few other mammals (primates, cows, horses, some breeds of sheep). Research into neuromelanin is particularly interesting because the substantia nigra of patients with PD fades in colour during the course of the disease. The

pigment is most common in dopaminergic neurons, which mostly die-off in PD patients. Dopamine is an important neurotransmitter. Motor control is impaired if dopaminergic cells decay. This in turn results in the symptoms typical of Parkinson's disease such as resting tremor, increasing postural instability and poor coordination of general movements.

Protective effect due to the "interception" of iron

After the researchers from Bochum and Würzburg had been able to clarify the composition and production of the neuromelanin granules four years ago, they began investigating the inner life of neuromelanin granules in greater detail. The significance of the currently obtained data is that the selective necrosis of the dopaminergic neurons in the substantia nigra is accompanied by an accumulation of ferrous ions (Fe^{3+}). The homeostasis of the iron content is evidently damaged and this intensifies as the disease progresses. Elevated quantities of free Fe^{3+} result - inter alia - in an increased formation of cell-damaging free radicals which ultimately leads to necrosis of the cells. Neuromelanin is capable of bonding ferrous ions (and other heavy metals). For many decades, it had been uncertain whether the cells are protected by the pigment "intercepting" ferrous ions, or whether the accumulation of the iron was actually responsible for damaging the cells. Data gained during the past few years indicates that neuromelanin primarily plays a protective role for the neurons.

Additional iron accumulation mechanism

During the current study, the scientists thus investigated whether there could be a further mechanism for the accumulation of iron in the substantia nigra over and above the direct binding of the Fe^{3+} to neuromelanin. For the first time, they were now able to supply evidence

of ferritin in the neuromelanin granules using a combination of diverse techniques (one-dimensional SDS gel electrophoresis, targeted mass spectrometry, western blot analysis, as well as immune transmission electron microscopy). To date, this important iron depot protein had only been proven in glia but not in neurons.

New hypothesis on the development of Parkinson's disease

Prof. Katrin Marcus concludes that - in the opinion of her research team - ferritin in the neuromelanin granules is a further significant element in the homeostasis of the iron content in the substantia nigra. This first direct proof of ferritin in neuromelanin granules in dopaminergic neurons is an important step towards an improvement in the comprehension of the iron metabolism in the human substantia nigra. It moreover supplies arguments for new hypotheses concerning the mechanisms of the iron-regulated degeneration of the substantia nigra in Parkinson's disease. Currently the scientists are investigating further unclarified issues, such as how the composition of the neuromelanin granules changes with increasing age and during the course of the disease. Moreover, they are trying to elucidate the exact function of the neuromelanin in the cell, and why only the neuromelanin-containing cells in the substantia nigra die-off.

Source: Ruhr-Universitaet-Bochum (news : web)