New animal model gives insights into mechanisms of Parkinson's disease pathogenesis

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In Parkinson's disease, the protein "alpha-synuclein" aggregates and accumulates within neurons. Specific areas of the brain become progressively affected as the disease develops and advances. The mechanism underlying this pathological progression is poorly understood but could result from spreading of the protein (or abnormal forms of it) along nerve projections connecting lower to upper brain regions. Scientists at the German Center for Neurodegenerative Diseases (DZNE) in Bonn have developed a novel experimental model that reproduces for the first time this pattern of alpha-synuclein brain spreading and provides important clues on the mechanisms underlying this pathological process. They triggered the production of human alpha-synuclein in the lower rat brain and were able to trace the spreading of this protein toward higher brain regions. The new experimental paradigm could promote the development of ways to halt or slow down disease development in humans.

The research team headed by Prof. Donato Di Monte presents these results in the scientific journal *EMBO Molecular Medicine*.

Parkinson's disease is a disorder of the nervous system. It typically manifests itself with motor disturbances, such as an uncontrollable trembling of the limbs, as well as non-motor symptoms, including sleep disorders and depression.

At the present, no cure exists for Parkinson's disease, although symptomatic intervention, including treatment with dopamine agonists, can alleviate patients' motor impairment. Parkinson's is the second most common neurodegenerative disorder, after Alzheimer's disease; it is estimated that 100,000 to 300,000 patients are affected by Parkinson's disease in Germany alone.

In a small percentage of cases, Parkinson's disease is due to genetic abnormalities carried within families. For the vast majority of patients, however, the cause of the disease remains unknown; the development of this sporadic form of the disease is likely promoted by both environmental and genetic risk factors. An intriguing characteristic of the brain of patients with sporadic Parkinson's disease is the progressive accumulation of intraneuronal inclusions that were first described by a German neurologist, Friedrich Lewy, and are therefore called Lewy bodies.

"A major discovery in the late 90's was that Lewy bodies are formed when the protein alpha-synuclein becomes aggregated," says Di Monte. "Since then, it was also found that aggregates of alpha-synuclein are progressively accumulated within the patients' brains during the course of the disease".

Pathology studies from human brains show that the deposits usually start forming in the lower part of the brain, in an area named "medulla oblongata". In subsequent disease stages, alpha-synuclein aggregates are observed in progressively higher (more rostral) brain regions, including the midbrain and cortical areas.

"This spreading appears to follow a typical pattern based on anatomical connections between regions of the brain," says the neuroscientist. "For this reason, it has been hypothesized that alpha-synuclein or abnormal forms of it can be transferred between two interconnected neurons and hence migrate throughout the brain. But until now, there was no way of targeting the medulla oblongata to reproduce this spreading of alpha-synuclein in the laboratory. It is also unclear what conditions could trigger the inter-neuronal passage of the protein or its aggregates. We have now developed a new

experimental paradigm which enables investigations on these fundamental issues."

From the neck into the brain

The researchers' concept is based on reproducing alpha-synuclein spreading in rats: for this, they transferred the blueprint of the human form of alpha-synuclein into the rat brain. The blueprint was transported by specifically engineered viral particles that the scientists injected into nerve fibres in the neck of the animals. The genetic code for the protein passed along these fibres into the medulla oblongata, where transfected rat neurons began producing high quantities of human alpha-synuclein.

"We have good reasons to believe that the medulla oblongata is a primary site of early disease development. This is why we wanted to activate production of alpha-synuclein specifically in this part of the brain. The medulla oblongata is difficult to reach via surgical procedures. For this reason, we injected the viral particles into the vagus nerve. This is a long nerve stretching from the abdomen via the neck to the medulla oblongata. The nerve consequently served as an entrance into the brain and, in particular, the medulla oblongata," Di Monte explains.

A migrating protein

The researchers monitored the production and localization of human alpha-synuclein in rats' brains over a period of four and a half months after injection of the viral particles. As predicted, the exogenous protein was synthesized only within neurons of the medulla oblongata connected to the vagus nerve. Starting at two months, however, human alpha-synuclein was observed also in brain areas more and more distant from the medulla oblongata (see figure). Caudo-rostral spreading involved inter-neuronal passage of the protein along specific nerve tracts and was accompanied by morphological alterations (such as swellings) of the neuronal projections taking up human alpha-synuclein.

The study, sponsored in part by the Blanche A. Paul Foundation, bears a number of critical implications. It reproduces a pattern of protein propagation that resembles the progressive spreading of pathological alpha-synuclein in Parkinson's disease. As importantly, the process of protein transmission was triggered by overproduction of alpha-synuclein within a specific brain region.

"Overproduction of alpha-synuclein accompanies a variety of conditions, such as aging, neuronal injury or genetic polymorphisms, that could promote the development of Parkinson's disease." concludes Di Monte. "Thus, our results suggest a mechanistic link between disease risk factors, enhanced levels of alpha-synuclein, spreading of the protein and its pathological accumulation."

Insight into the early stages of Parkinson's

The new model mimics events that likely occur in the early stages of alpha-synuclein pathology in the absence of overt behavioural (in rats) or clinical (in patients) manifestations. "It will therefore become a valuable tool to investigate early mechanisms of disease pathogenesis that could be targeted for therapeutic intervention. Early intervention would have a greater probability to prevent or halt the spreading of pathology and progression of the disease," says Di Monte.

More information: "Caudo-rostral Brain Spreading of ?-Synuclein through Vagal Connections", Ayse Ulusoy, Raffaella Rusconi, Blanca I. Pérez-Revuelta, Ruth E. Musgrove, Michael Helwig, Bettina Winzen-Reichert, Donato A. Di Monte *EMBO Molecular Medicine* (2013), DOI: 10.1002/emmm.201302475

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