Identification and treatment of neural mechanisms underlying early behavioral symptoms in Parkinson's disease

Parkinson's disease is the most common neurodegenerative disease after Alzheimer's disease. The disease is characterized from the histopathological perspective by the degeneration of neurons that produce dopamine and the presence of Lewy bodies, protein aggregates that contain mainly alpha-synuclein. Recent studies have shown that an increase in the amount of alpha-synuclein in the brain is sufficient to induce the death of dopaminergic neurons. The death of dopaminergic neurons in the midbrain leads to a reduction in the quantity of dopamine released in the striatum and consequent motor impairment. However, when motor symptoms occur, the degeneration is already excessively extended, which makes compelling the need to identify early symptoms and the biological mechanisms underlying them for commencing restorative therapies.

One of the research lines of our laboratory aims at identifying early alterations of Parkinson's disease and associated symptoms to develop therapeutic strategies that can slow down the disease course. Among these early symptoms, there are motor learning deficits in complex tasks, alterations in working memory and more recently it has been noted that specific vision deficits can also be a warning bell.

In our lab we study the physiology of motor memory; motor memory is characterized by a slow and progressive learning that requires massive training until movements become automatic. The striatum is crucial for motor learning; however, it is not clear, how practice modify the striatal cells activity to progressively reach plateau performance.

Using a protocol of behavioral metaplasticity, which consists of identifying the synaptic signature of behavioral experiences, we found that if we apply an electrical stimulus to the striatum neurons in untrained animals, they give an inhibitory response; if the same stimulus is applied to animals subjected to the first learning sessions, the neurons respond by getting excited, identifying a new form of cellular memory stored in striatal cells. However, once the motor exercise is perfectly learned and the movement is performed automatically, the neurons return to give an inhibitory response to the electrical stimulus. From biochemical analysis we found that this mechanism of metaplasticity is regulated by the dopamine transporter, DAT. Using alpha-synuclein over-expression models, we then discovered that long before the death of dopaminergic neurons, the excess of alpha-synuclein led to a transcriptional reduction of DAT and stopped the animals from performing the learned movements automatically. These results identify for the first time a very early clinical manifestation in motor learning prior to the death of neurons in Parkinson’s disease. Low levels of DAT, measured by imaging methods in patients, are used in the clinic to predict the level of neurodegeneration, based on the assumption that striatal DAT is reduced due to the degeneration of dopaminergic cells in the midbrain. The results of this research suggest that low levels of DAT do not necessarily represent the death of dopaminergic neurons, but may instead indicate a sinucleinopathy, a diagnostic hypothesis that deserves targeted investigation with genetic investigations and cerebrospinal fluid sampling, in order to predict its evolution.

We then observed similar defects in Parkinson's disease models generated by directly injecting into the striatum aggregates of alpha-synuclein protofibrils, that in an early stage lead to specific visual-spatial cognitive defects and synaptic plasticity defects that depend on the amount of aggregates. We are using these models to verify the efficacy of monoclonal antibodies to inhibit alpha-synuclein and other new generation treatments.

More recently we've started to study visual defects in Parkinson's disease and we have discovered that intra-vitreus alpha-synuclein over-expression in healthy mice, induces at an early stage the death of dopaminergic neurons of the retina, the amacrine cells, visual acuity defects and altered adaptation to darkness measured by electroretinogram. We are using this model to understand if the retina can be used as one of the models of choice to test new cell therapies for Parkinson's disease.


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