A Possible Role of Neural Gap Junctions in Parkinson's Disease Pathology

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Research question and background

The pathology of Parkinson's disease (PD) is characterized by modified behavior of neuronal networks in the basal ganglia after loss of dopamine. Parkinsonian states show bursting neural activity and high synchronization among neurons as well as altered frequency bands in local field potentials. These network modifications are often assumed to be directly related to PD motor symptoms such as akinesia and bradykinesia. However, it is still a matter of debate what triggers and stabilizes the pathological behavior.

We hypothesized that neural gap junctions are involved in this process. Gap junctions in the retina have been shown to be depressed by dopamine. If this holds true for gap junctions in the basal ganglia, depression of gap junctional coupling could contribute to the effects of L-Dopa medication.

Methods and tissues used:

We investigated the occurence of neural gap junctions by immunohistochemistry and confocal imaging in human post-mortem tissue, including tissues from the subthalamic nucleus (STN), putamen as well as external and internal part of the globus pallidus (GPe and GPi, respectively). Gap junctional coupling and Cx36 expression in putamen is well described in literature and served here as a positive control. The tissues were labeled with markers for Connexin-36 (Cx36), GABAergic neurons and cell nuclei. All images were processed offline. To quantify the occurence of Cx36, we segmented the Cx36 signal with an adaptive threshold based on noise and signal intensities. Segmented dots with an area typical for gap junctions were counted.

Results and conclusion

In the first two control subjects and the first two PD patients, we did not detect Cx36 in the subthalamic nucleus. This lead to the further exclusion of STN tissues from the study. However, we could detect Cx36 in the putamen, GPe and GPi of all twelve subjects and patients. Although there was a high inter-subject variability, PD patients showed a significantly higher level of Cx36 than control subjects.

The occurence of Cx36 in GPe and GPi suggests the possibility of gap junctional coupling in these nuclei. Due to dopamine depletion and injury, this coupling may be increased in PD, as also indicated by higher levels of Cx36 in PD. Increased gap junction coupling may have pronounced effects on synchrony in the basal ganglia.