POSSIBLE ROLES OF NEURAL GAP JUNCTIONS IN PARKINSON'S DISEASE PATHOLOGY

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ABSTRACT

The pathology of Parkinson's disease (PD) is characterized by modified behavior of neuronal networks in the basal ganglia after depletion of dopamine. PD states show bursting neural activity and high synchronization among neurons as well as altered oscillations in local field potentials. These network modifications are thought to be directly related to PD motor symptoms such as tremor, akinesia and bradykinesia.

Computational models of the basal ganglia can reproduce physiological and pathological neuronal behavior depending on certain parameter values [1]. However, it is still a matter of debate what triggers and stabilizes the pathological behavior and how deep brain stimulation (DBS) influences it. In particular, computational models suffer from a lack of experimental data on structure and function. They commonly estimate the degree and course of chemical synapses and do not take electrical synapses (neuronal gap junctions) into account.

Gap junctions (GJs), constructed out of connexins (Cxs), are direct electrical connections between cells. In different parts of the brain, neuronal gap junctions have been shown to be able to lead to synchronization, bursting and oscillations. They are remodeled in a number of different diseases and can change their conductance under the influence of neurotransmitters such as dopamine [2]. Current research also demonstrated activity-dependent plasticity of GJs [3].

In our experiments, we look for the occurence of Cx36, a neuronal Cx, by immunohistochemistry and confocal microscopy in rat tissue of the subthalamic nucleus (STN), globus pallidus external segment (GPe) and internal segment (GPi). We found spots of

Cx36 in all three nuclei at a level that is roughly comparable to the Cx36 level in the striatum, where coupling of neurons via gap junctions is well described in literature.

We investigated the impact of gap junctions in a computational model of the basal ganglia, the Rubin-Terman-Model [4] including STN, GPe and GPi. Gap junctions between neighboring neurons were implemented as ohmic resistors inside the three nuclei. At low conductances of the gap junctions, the network showed irregular (physiological) states. After uprising gap junction conductance, STN and GPe showed bursting and the firing rate of the GPi increased. In all neurons, synchronization was enhanced. These states are in high accordance with experimental measurements of neural activity in PD patients and animal models of PD.

Our results strongly suggest a role of neuronal gap junctions in PD pathology. The modulation of gap junctions by dopamine might be a candidate for the remodeling of oscillations, synchronization and bursting. A better understanding of these basic processes can in later stages lead to improved therapies such as refined stimulation protocols for DBS or novel medications.

Currently we are extending our experiments to human post-mortem tissue of PD patients and controls. The aim is to quantify differences in Cx36 expression and adjust the computational model to these changes.

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