An investigation into the effect of activity-dependent mitochondrial trafficking on neuronal morphology

Bachelor Thesis

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Complex neuronal morphology, which consists of highly branched dendrites and an axon, is necessary for the correct function of neurons as it determines how neurons convey information. The formation of these complex structures is a highly energy demanding process and therefore energy supply could regulate and be limiting for the development of correct morphology.

As mitochondria are the major producer of energy, it is likely that mitochondrial transport to growth points is important for the correct formation of dendritic structures. The transport of mitochondria along microtubules is mediated by kinesin and dynein motor proteins. It is regulated by adaptor proteins, such as the atypical Rho GTPase Miro, which links kinesin motor proteins to mitochondria. Moving mitochondria can be stopped by Ca^{2+} binding to the EF hand domains of Miro and therefore respond to increased calcium levels. Altered mitochondrial transport through the overexpression of Miro1 WT and Miro1 ΔEF, a mutant version of Miro1 which cannot bind calcium and therefore is not able to respond to neuronal activity, causes increased mitochondrial movement into dendrites and an inability to stop mitochondria in ΔEF mutants. These changes in mitochondrial trafficking could affect neuronal morphology by varying the energy supply.

In addition to the role of Miro as adaptor to kinesin motor proteins, it is also suggested that it plays a role in dynein-mediated movement. To investigate this, the interaction between Miro and dynein motor proteins was characterized. Co-immunoprecipitation studies presented no direct Miro1-dynein interaction, why it was assumed that overexpression of Miro only affects kinesin-mediated movement of mitochondria.

The effects of overexpression of Miro1 WT and Miro1 ΔEF were investigated in hippocampal neurons by quantifying their dendritic complexity in view of branch points, total dendritic length and order of dendrites. Miro1 WT and ΔEF expressing neurons presented a significant increase in branching, which could be caused by an elevated transport of mitochondria into dendrites and therefore increased energy supply for branching. Comparing Miro1 WT and ΔEF expressing cells, different locations of branch points over the whole dendritic field suggest the importance of activity-dependent mitochondrial stopping for the locations of branch points.

In conclusion, this study gave an indication that the regulation of mitochondrial transport by Miro is essential for the growth of correct neuronal morphology in vitro. It also suggests that energy supply by mitochondria could be regulating for branching of dendrites.