The endolysosomal system in neuronal physiology and pathology

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SUMMARY

The first aim of this thesis was to study the role of endosomal sorting in presynaptic terminals (**Chapter 2** and **Chapter 3**)**.** We used a shRNA approach to evaluate the impact of depleting key endosomal sorting proteins in the presynaptic terminals of mouse primary neurons. In **Chapter 2**, we show for the first time that VPS35 is present at the mammalian presynaptic terminal. VPS35 depletion did not affect neuronal morphology (neurite length and synapse number), presynaptic ultrastructure, and synaptic vesicle release and retrieval. In **Chapter 3**, we first set out to perform basic characterizations of SNX4 localization in neurons. We developed a novel antibody against SNX4 for western blot, immunocytochemistry and immunoelectron microscopy. SNX4 was present in neurons and it accumulated in synapses, mainly at presynaptic terminals. SNX4 depletion downregulated synaptic communication-related proteins without affecting presynaptic ultrastructure or neuronal morphology. Three shRNAs against SNX4 drastically impaired synaptic vesicle release. However, this phenotype was not restored by expressing a SNX4 variant resistant to the shRNAs. In **Chapter 2** and **Chapter 3**, the identification of VPS35 and SNX4 as presynaptic proteins indicated a selective demand for endosomal sorting in presynaptic boutons.

The second aim of this thesis was to investigate if the endolysosomal aberrations observed in the Alzheimer's disease (AD) brain can be a consequence of the seeding of tau pathology (**Chapter 4**). In iPSC-derived human neurons, the seeding of tau pathology decreased the number, size and EEA1 labelling intensity of early endosomes, and increased the levels of the endosomal sorting proteins VPS35 and SNX4. The seeding of tau pathology did not morphologically change late endosomes and lysosomes but lysosomal proteolytic activity appeared to be reduced. Thus, the seeding of tau pathology causally affects the endolysosomal system, which may play a role in neurodegeneration in AD.