Section: neurobiology of disease

Drosophila acyl-CoA synthetase long-chain family member 4 regulates axonal transport of synaptic vesicles and is required for synaptic development and transmission

Abbreviated title: ACSL4 regulates axonal transport and synaptic function

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Abstract

Acyl-CoA synthetase long-chain family member 4 (ACSL4) converts long-chain fatty acids to acyl-CoAs that are indispensable for lipid metabolism and cell signaling. Mutations in ACSL4 cause non-syndromic X-linked mental retardation. We previously demonstrated that *Drosophila* dAcsl is functionally homologous to human ACSL4, and is required for axonal targeting in the brain. Here we report that *Drosophila dAcsl* mutants exhibited distally-biased axonal aggregates that were immunopositive for the synaptic-vesicle proteins synaptotagmin (Syt) and cysteine-string protein (CSP), the late endosome/lysosome marker LAMP1, the autophagosomal marker Atg8, and the multivesicular body marker Hrs. In contrast, the axonal distribution of mitochondria and the cell-adhesion molecule Fas II was normal. Electron microscopy revealed accumulation of prelysomes and multivesicle bodies. These aggregates appear as retrograde instead of anterograde cargos. Live imaging analysis revealed that *dAcsl* mutations increased the velocity of anterograde transport but reduced the flux, velocity, and processivity of retrograde transport of Syt-eGFP labeled vesicles. Immunohistochemical and electrophysiological analyses showed significantly reduced growth and stability of neuromuscular synapses, and impaired glutamatergic neurotransmission in *dAcsl* mutants. The axonal aggregates and synaptic defects in *dAcsl* mutants were fully rescued by neuronal expression of human ACSL4, supporting a functional conservation of ACSL4 across species in the nervous system. Together our findings demonstrate that dAcsl regulates axonal transport of synaptic vesicles and is required for synaptic development and function. Defects in axonal transport and synaptic function may account, at least in part, for the pathogenesis of ACSL4-related mental retardation.