UKE Paper of the Month März 2014

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GRIP1 interlinks N-Cadherin and AMPA receptors at vesicles to promote combined cargo transport into dendrites

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ABSTRACT: The GluA2 subunit of AMPA-type glutamate receptors (AMPARs) regulates excitatory synaptic transmission in neurons. Also the trans-synaptic cell adhesion molecule N-Cadherin controls excitatory synapse function and stabilizes dendritic spine structures. At postsynaptic membranes GluA2 physically binds N-Cadherin, underlying spine growth and synaptic modulation. We report that N-Cadherin binds to PDZ2 of the glutamate receptor interacting protein 1 (GRIP1) through its intracellular C-terminus. N-Cadherin and GluA2-containing AMPARs are presorted to identical transport vesicles for dendrite delivery and live imaging reveals cotransport of both proteins. The kinesin KIF5 powers GluA2/N-Cadherin codelivery by employing GRIP1 as a multi-link interface. Notably, GluA2 and N-Cadherin use different PDZ domains on GRIP1 to simultaneously bind the transport complex and interference with either binding motif impairs the turnover of both synaptic cargoes. Depolymerisation of microtubules, deletion of the KIF5 motor domain or specific blockade of AMPAR exocytosis impacts delivery of GluA2/N-Cadherin vesicles. At the functional level, interference with this cotransport reduces the number of spine protrusions and excitatory synapses. Our data suggest the concept that the multi PDZ-domain adaptor protein GRIP1 can act as a scaffold at trafficking vesicles in the combined delivery of AMPARs and N-Cadherin into dendrites.

STATEMENT: *Basic neuroscience is the basis for breakthroughs in clinical research and drug development. Our work constitutes a great example of how the UKE not only facilitates clinical but also basic research in order to gain and transfer knowledge into clinical applications in future. In the brain, the efficacy of synaptic transmission critically depends on the number of proteins located at synapses. In turn, modulation of protein delivery displays a fundamental mechanisms to adapt neuronal excitability during learning and memory processes. Hence, malfunctions in protein trafficking underly several neuropathological conditions. Two key players in this context are AMPA receptors (AMPARs) and the cell adhesion molecule N-Cadherin. Our work identifies that AMPARs and N-Cadherin are concentrated within one distinct class of transport vesicles through a previously unknown vesicular scaffold. This cell biological concept advances our understanding of motor protein dependent vesicle trafficking in neurons. Importantly, we find that this concentrated delivery of synaptic key proteins impacts neuronal connectivity, and therefore opens a chance to better understand learning and memory processes. As AMPARs clearly govern the majority of excitatory signaling in brain, their vesicular synapse trafficking represents a tempting target for drug development efforts with respect to attention deficit hyperactivity disorder (ADHD), status epilepticus, migraine pain, Alzheimer's disease and others.*

BACKGROUND: This study was mainly carried out in the Department of Molecular Neurogenetics (ZMNH, University of Hamburg Medical School) and its head Prof. Dr. Matthias Kneussel. Together with the two first authors, Dr. Frank Heisler and Dr. Han Kyu Lee, Prof. Kneussels team has particular interests in active, intracellular transport at the molecular level, focusing on its contribution to learning and memory processes in a higher order context. Dr. Frank Heisler is currently supported by an UKE FFM fund (Forschungsförderung der Medizinischen Fakultät). The work was further funded and part of the DFG research training group 1459 at the UKE (chair Prof. Dr. Thomas Braulke, Children´s Hospital), DFG grants KN556/4-2 and "neurodapt" to Prof. Matthias Kneussel. Within the UKE, other cooparation partners include Dr. Michaela Schweizer, who interdisciplinary contributed to the project with her electron-microscopical expertise.