CICLO DE SEMINARIOS 2012

SMAT-C Soft Matter Research and Technology Center

"LOCATION MATTERS: PROTEIN TRAFFICKING AND EARLY SECRETORY ORGANELLES IN DENDRITES AND AXONS"

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Neurons are highly polarized cells with dendrites and axons extending long distances from the cell body, and synapses constituting functional specializations that mediate neuronal communication. The trafficking of membrane lipids and proteins throughout the neuron is essential for the establishment and maintenance of cell morphology and synaptic function. However, the dynamic shape and spatial organization of secretory organelles, and their role in defining neuronal polarity and the composition of synapses are not well delineated. In particular, the structure/function relations of the continuous and intricate network of the endoplasmic reticulum (ER) in neurons remain largely unknown. We have studied GABAB receptors (GABABRs) and voltage-gated ion channels (NaVs) to understand the contribution of the dendritic and axonal ER to local trafficking and its potential implications for synaptic plasticity and pathology.

GABABRs are heteromers (GABABR1 and GABABR2) that regulate the efficacy of synaptic transmission throughout the brain. Using fixed and live-cell imaging in cultures of rat hippocampal neurons under control conditions or after blockade of intracellular trafficking we have determined that dendritic GABABR1 localizes preferentially to the ER and moves in manner dependent on themolecular motor Kif5. GABABRs traffic through satellite Golgi outposts and insert *de novo* throughout the somatodendritic domain. Axonal GABABRs require the Golgi apparatus for plasma membrane delivery but axonal sorting and targeting of GABABR1a operate in a pre-Golgi compartment. GABABR1a subunits are also enriched in the ER, and their dynamic behavior and colocalization with other secretory organelles like the ER-to-Golgi intermediate compartment (ERGIC) suggest that they negotiate the secretory pathway using a local route. The transport of axonal GABABR1a is microtubule-dependent and Kif5 determines axonal localization. We conclude that GABABRs utilize a non-canonical secretory route in dendrites and axons and uncover a novel role for Kif5 in the long-range transport of cargo along the ER.

NaVs are responsible for the generation and propagation of action potentials and are mostly concentrated in the axon initial segment and the Nodes of Ranvier. Despite their fundamental role, little is known about the intracellular trafficking mechanisms that govern their availability. The presence of the ER has been documented in peripheral axons, but it is unclear whether this or other local secretory organelles participate in the delivery of NaVs. We hypothesized that trafficking through the local ER is necessary for the delivery of NaVs to the nodes of Ranvier in axons of dorsal root ganglion neurons. By evaluating the distribution of NaVs by immunofluorescence in dissociated axons after local *in vivo* manipulations we have demonstrated that blockade of ER to Golgi trafficking produced a local redistribution of NaVs at the nodes. Our data suggest that local early secretory organelles have a central role in the distribution of NaVs at the nodes of Ranvier in peripheral axons.

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