DZNE German Center for Neurodegenerative Diseases within the Helmholtz Association

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

NEUROCURE Cluster of Excellence

EINSTEIN CENTER Neurosciences

Einstein Center for Neurosciences Berlin

Neuroscience Colloquium

Winter Semester 2017/2018

Lectures are held Thursdays, 5 p.m.
Venue: Paul-Ehrlich Lecturehall, Virchowweg 4, next to CCO

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Mechanisms of SNARE- and synaptotagmin dependent vesicle priming and fusion.

Regulated exocytosis involves several steps, including vesicle priming and fusion triggering. Priming is the process that makes the vesicle release-competent, and it was shown to be Ca^{2+}-dependent in the sub-μM range 25 years ago. Molecularly, it involves the assembly of the N-terminal end of the SNARE-complex between vesicle and plasma membrane with the help of Munc18 and Munc13 isoforms. Fusion triggering is also Ca^{2+}-dependent (in the several-μM range), and it requires Ca^{2+}-binding to synaptotagmins (in chromaffin cells synaptotagmin-1 and synaptotagmin-7), and is assisted by the cytosolic protein complexin.
I am going to discuss two questions. First: how is priming made Ca^{2+}-dependent? Ca^{2+}-dependent priming in chromaffin cells potentially allows circulating hormones that release Ca^{2+} from intracellular stores (e.g. histamine), to increase primed vesicle pool size, and act synergistically with neuronal stimulation to boost release. We have found that when present alone synaptotagmin-1 and synaptotagmin-7 both act autonomously in exocytosis triggering, with synaptotagmin-1 being the faster sensor. However, when present together, synaptotagmin-7 and synaptotagmin-1 take over different functions: synaptotagmin-7 now acts to decrease unpriming (the opposite reaction to priming), whereas synaptotagmin-1 acts to trigger fast release. I will discuss how these different functions might result from isoform competition in the presence of a conserved mechanism for synaptotagmin action.
The second question is: what is the nature of the interaction between the SNAREs, synaptotagmins and membranes which makes fusion Ca^{2+}-dependent? This involves experiments performed in autaptic glutamatergic neurons. Using mutagenesis, we find that fusion triggering is limited by an electrostatic energy barrier, which is influenced by charges on the outside of the SNARE-bundle. This energy barrier for release is increased in amplitude by negative charges and decreased by positive charges. This makes it possible for Ca^{2+} to trigger release in a fraction of a millisecond by throwing an electrostatic switch.

Location: Paul Ehrlich-Hörsaal,
Charité – Universitätsmedizin Berlin, Campus Mitte
Virchowweg 4, next to CCO

Date: **Thursday, November 2nd, 5 p.m.**

Host: Alexander Walter / Christian Rosenmund

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