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SFB 1089

Bonn Lecture Series in Neuroscience

Regulation of Exocytosis by inhibitory GPCRs and Gβγ subunits

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Friday, July 15th 2016, 15:00h
Life & Brain, Seminar Room, Ground Floor

Complex regulatory mechanisms converge on the exocytotic apparatus to regulate transmitter release and ensure precise control of signaling events. One mechanism by which presynaptic GPCRs have been shown to modulate synaptic transmission is through fast, membrane-delimited inhibition of exocytosis such as that occurring through the direct interaction between Gβγ subunits and SNARE proteins. SNAP25 is a key downstream effector of G protein βγ subunits; we have shown that proteolytic cleavage of SNAP25 by botulinum toxin A (BoNT/A) reduces the ability of Gβγ to compete with the calcium sensor synaptotagmin 1(Syt1) for binding, to SNAP-25 in a calcium-dependent manner. These truncated SNAP25 proteins sustain a low level of exocytosis but are unable to support serotonin-mediated inhibition of exocytosis in lamprey spinal neurons. Mutagenesis studies narrowed down the final 3 amino acids on SNAP25 as critical for Gβγ binding and inhibition of exocytosis. A transgenic mouse containing the SNAP25Δ3 mutation was generated using CRISPR/Cas9 technology. We have found a variety of behavioural abnormalities in these mice, suggesting that inhibition of exocytosis through this mechanism is widespread and pervasive. We postulate that this dynamic regulation of vesicle fusion properties plays an important role in presynaptic integration.

Selected Publications

Zurawski Z, Rodriguez S, Hyde K, Alford S, **Hamm HE**. (2016) Gβγ Binds to the Extreme C Terminus of SNAP25 to Mediate the Action of Gi/o-Coupled G Protein-Coupled Receptors. *Mol Pharmacol*, 89: 75-83.

Friedman EA, Texeira L, Weeke PE, Delaney J, Lynch DR, Kasasbeh E, Denny JC, **Hamm HE**, Song Y, Harrel FE, Roden DM, Cleator JH. (2016) Evaluation of the F2R IVS-14A/T PAR-1 Polymorphism with Subsequent Cardiovascular Events and Bleeding in Patients who have undergone Percutaneous Coronary Intervention. *J. Thrombosis and Thrombolysis*, 41(4): 656-662.

Lokits A, Leman JK, Kitko K, Alexander NS, **Hamm HE**, J Meiler. (2015) A survey of conformational and energetic changes in G protein signaling. *AIMS Biophysics*, 2(4): 613-631.

Duvernay MT, Matafonov A, Lindsley CW, **Hamm HE**. (2015) Platelet Lipidomic Profiling: Novel Insight into Cytosolic Phospholipase A(2)α Activity and Its Role in Human Platelet Activation. *Biochemistry*, 54: 5578-5588.

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