GPCR and Gβγ mediated inhibition of exocytosis through direct interaction with the SNARE complex

Heidi E. Hamm, Department of Pharmacology, Vanderbilt University

$G_{i/o}$-coupled G protein coupled receptors modulate secretion through inhibition of exocytosis. We discovered a Gβγ-mediated inhibitory mechanism downstream of calcium entry, Gβγ binding to SNARE complexes. We created a transgenic mouse via CRISPR-Cas9 partially deficient in this interaction by premature truncation of the SNAP25 carboxy terminus by three residues. The SNAP25Δ3 mutation results in inhibited Gβγ-SNARE binding and diminished ability of Gβγ to compete with synaptotagmin 1 for binding sites on SNARE complexes. SNAP25Δ3 homozygote animals are viable, with a normal appearance, and have normal presynaptic inhibition by $GABA_B$ receptors that inhibit voltage gated calcium channels. Despite this, they exhibit deficits in inhibition of secretion by receptors that work directly on the SNARE complex such as 5-HT_{1b} and α_{2a} adrenergic receptors. The SNAP25Δ3 homozygote exhibits a number phenotypes. We have found that the mice are resistant to diet induced obesity and have enhanced insulin sensitivity. I'll discuss our exploration of the mechanisms of this interesting phenotype and the possibility of harnassing it for treatment of obesity.