Physiological roles for neuromodulation via $G_{i/o}$ GPCRs working through Gβγ–SNARE interaction

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Activation of presynaptic $G_{i/o}$-coupled receptors by hormones, neurotransmitters (NT) and neuromodulators leads to decreased neurotransmission. This decreased release provides an important control mechanism for autoreceptors to guard against over-activation, and an important homeostatic mechanism. For heteroreceptors, it is a critical component of synaptic integration mediating circuitry-level effects. Fast membrane-delimited inhibition of secretion may occur via Gβγ regulation of voltage-dependent Ca^{2+}channels (VDCCs). However, a direct interaction between Gβγ and soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins also leads to inhibition of exocytosis downstream of Ca^{2+} entry [1]. This mechanism is not only more acute and direct in controlling evoked release, leaving secondary effects of presynaptic Ca^{2+} unaffected, but is also able to modify components of exocytosis not available to mechanisms that control release probability. These include modifying the concentration of neurotransmitter released [2] by interacting with a region of the SNARE complex that controls fusion rate, but also modifying spontaneous release, which has important roles in its own right. The same synapses can have different $G_{i/o}$-GPCR-triggered modulation of neurotransmitter release by different mechanisms. For example, in hippocampal neurons, $GABA_B$ receptors cause decreased Ca^{2+} entry and $5HT_{1b}$ receptors inhibit exocytosis by directly acting on SNAREs at the same synapse: this allows for presynaptic neural integration [3]. What could be the mechanistic basis of this specificity? There is considerable evidence that unique Gβγ isoforms play specific roles in mediating interactions with both receptors and effectors. Our recent *in vivo* proteomic studies of Gβγ specificity suggest that it might come from receptor selection of particular Gβγ subunits [4], and the affinity of those Gβγ's for the SNARE complex (unpublished).

Understanding of the physiological role of Gβγ-SNARE interaction has lagged because of a lack of tools. But recent progress in understanding the molecular basis of this interaction, in particular a target for Gβγ at the C-terminal of SNAP25 [5] has yielded a transgenic SNAP25Δ3 mouse with a selectively disturbed Gβγ–SNARE interaction. This mouse has normal evoked exocytosis and normal GABAergic inhibition of VDCC, but disturbed inhibition of exocytosis through Gβγ–SNARE interaction. The SNAP25Δ3 mouse provides clear evidence that the Gβγ–SNARE locus is physiologically important for regulation, because it has a number of interesting phenotypes both central and peripheral, including elevated stress-induced hyperthermia, impaired supraspinal nociception, defective spatial learning, impaired gait, and depressive-like behavior [6].

Most interestingly, the two Gβγ-mediated inhibitory mechanisms, co-occurring at the same synapse, are synergistic with each other: a completely unexpected result. This observation suggests that combinations of neurotransmitters may shape neuromodulation, potentially giving rise to novel effects on circuits. Thus, synaptic integration can occur as much presynaptically as postsynaptically. The specificity of the two mechanisms raises the possibility that targeting the Gβγ-SNARE interaction may be a therapeutic strategy, and, further, that therapeutic pairing of drugs that affect each mechanism may themselves work synergistically, an exciting possibility.

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ADDITIONAL INFORMATION

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