Activation of presynaptic GABA(B(1a,2)) receptors inhibits synaptic transmission at mammalian inhibitory cholinergic olivocochlear-hair cell synapses

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Title Activation of presynaptic GABA(B(1a,2)) receptors inhibits synaptic transmission at mammalian inhibitory cholinergic olivocochlear-hair cell synapses
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The synapse between olivocochlear (OC) neurons and cochlear mechanosensory hair cells is cholinergic, fast, and inhibitory. The inhibitory sign of this cholinergic synapse is accounted for by the activation of Ca(2+)-permeable postsynaptic alpha9alpha10 nicotinic receptors coupled to the opening of hyperpolarizing Ca(2+)-activated small-conductance type 2 (SK2)K(+) channels. Acetylcholine (ACh) release at this synapse is supported by both P/Q- and N-type voltage-gated calcium channels (VGCCs). Although the OC synapse is cholinergic, an abundant OC GABA innervation is present along the mammalian cochlea. The role of this neurotransmitter at the OC efferent innervation, however, is for the most part unknown. We show that GABA fails to evoke fast postsynaptic inhibitory currents in apical developing inner and outer hair cells. However, electrical stimulation of OC efferent fibers activates presynaptic GABA(B(1a,2)) receptors [GABA(B(1a,2))Rs] that downregulate the amount of ACh released at the OC-hair cell synapse, by inhibiting P/Q-type VGCCs. We confirmed the expression of GABA(B)Rs at OC terminals contacting the hair cells by coimmunostaining for GFP and synaptophysin in transgenic mice expressing GABA(B1)-GFP fusion proteins. Moreover, coimmunostaining with antibodies against the GABA synthetic enzyme glutamic acid decarboxylase and synaptophysin support the idea that GABA is directly synthesized at OC terminals contacting the hair cells during development. Thus, we demonstrate for the first time a physiological role for GABA in cochlear synaptic function. In addition, our data suggest that the GABA(B1a) isoform selectively inhibits release at efferent cholinergic synapses.
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