Inhibitory presynaptic cholinergic modulation on synaptic transmission at the Calyx of Held Synapses

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Acetylcholine (Ach) is considered as an excitatory neurotransmitter in the peripheral and central nervous systems and significantly functions in sleep, wakefulness, attention, learning, memory, and sensory information processing. This study investigates the presynaptic regulation of Ach at the Calyx of Held synapse in medial nucleus of trapezoid body of the mice auditory brainstem.It was shown that application of Ach or nicotine induced depolarization at calyceal terminals, indicating the existence of presynaptic nicotinic Ach receptors (nAchR) in the calyx of Held synapses. Postsynaptical recording showed that the application of Ach or nicotine could increase of the frequency of miniature excitatory postsynaptic currents (mEPSC) but significantly reduce the amplitude and total charge of excitatory postsynaptic currents (EPSC). Furthermore, paired-pulse ratio (PPR) was found increased, displaying the presynaptic inhibitory effect of Ach on the synaptic transmission. By taking advantage of the giant size of presynpatic terminal of the Calyx of Held synapses, we observe the action potentials at presynaptic terminals with and without Ach application. It was found that Ach-induced depolarization significantly reduced the action potential amplitude at the presynaptic terminals and thus decreased calcium ion influx to cause down-regulation of the glutamatergic vesicle release from the calyceal terminals. Our study suggests that Ach can play an inhibitory role on presynaptic transmitter release via axo-axonic nicotinic synapse although nAchRs are traditionally considered to mediate excitatory signaling.