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Schwann cells sense and control acetylcholine spillover at the neuromuscular junction by α7 nicotinic receptors and butyrylcholinesterase

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Abstract

Terminal Schwann cells (TSCs) are key components of the mammalian neuromuscular junction (NMJ). How the TSCs sense the synaptic activity in physiological conditions remains unclear. We have taken advantage of the distinct localization of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) at the NMJ to bring out the function of different ACh receptors (AChRs). AChE is clustered by the collagen Q in the synaptic cleft and prevents the repetitive activation of muscle nicotinic AChRs. We found that BChE is anchored at the TSC by a proline-rich membrane anchor, the small transmembrane protein anchor of brain AChE. When BChE was specifically inhibited, ACh release was significant depressed through the activation of α7 nAChRs localized on the TSC and activated by the spillover of ACh. When both AChE and BChE were inhibited, the spillover increased and induced a dramatic reduction of ACh release that compromised the muscle twitch triggered by the nerve stimulation. α7 nAChRs at the TSC may act as a sensor for spillover of ACh adjusted by BChE and may represent an extrasynaptic sensor for homeostasis at the NMJ. In myasthenic rats, selective inhibition of AChE is more effective in rescuing muscle function than the simultaneous inhibition of AChE and BChE because the concomitant inhibition of BChE counteracts the positive action of AChE inhibition. These results show that inhibition of BChE should be avoided during the treatment of myasthenia and the pharmacological reversal of residual curarization after anesthesia.

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Keywords

Acetylcholinesterase, Glia, Muscle, Neuromuscular disease, Synaptic homeostasis