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Regulation of acetylcholinesterase activity by nitric oxide in rat neuromuscular junction via N-methyl-d-aspartate receptor activation

Petrov K., Malomouzh A., Kovyazina I., Krejci E., Nikitashina A., Proskurina S., Zobov V., Nikolsky E.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Acetylcholinesterase (AChE) is an enzyme that hydrolyses the neurotransmitter acetylcholine, thereby limiting spillover and duration of action. This study demonstrates the existence of an endogenous mechanism for the regulation of synaptic AChE activity. At the rat extensor digitorum longus neuromuscular junction, activation of N-methyl-d-aspartate (NMDA) receptors by combined application of glutamate and glycine led to enhancement of nitric oxide (NO) production, resulting in partial AChE inhibition. Partial AChE inhibition was measured using increases in miniature endplate current amplitude. AChE inhibition by paraoxon, inactivation of NO synthase by Nω-nitro-l-arginine methyl ester, and NMDA receptor blockade by dl-2-amin--5-phosphopentanoic acid prevented the increase in miniature endplate current amplitude caused by amino acids. High-frequency (10 Hz) motor nerve stimulation in a glycine-containing bathing solution also resulted in an increase in the amplitude of miniature endplate currents recorded during the interstimulus intervals. Pretreatment with an NO synthase inhibitor and NMDA receptor blockade fully eliminated this effect. This suggests that endogenous glutamate, released into the synaptic cleft as a co-mediator of acetylcholine, is capable of triggering the NMDA receptor/NO synthase-mediated pathway that modulates synaptic AChE activity. Therefore, in addition to well-established modes of synaptic plasticity (e.g. changes in the effectiveness of neurotransmitter release and/or the sensitivity of the postsynaptic membrane), another mechanism exists based on the prompt regulation of AChE activity. NO molecules depress AChE activity in the neuromuscular junction thereby enhancing endplate current amplitude. Endogenous glutamate, released into the synaptic cleft as a co-mediator of acetylcholine, is capable of triggering the NMDA receptor-/NO synthase-mediated pathway that modulates synaptic AChE activity. In addition to well-established modes of synaptic plasticity another mechanism exists based on the prompt regulation of AChE activity. © 2012 Federation of European Neuroscience Societies and Blackwell Publishing Ltd.

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Keywords

Acetylcholine, Glutamate, Mammalian cholinergic synapse, Nitric oxide synthase