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Dynamic Modulation of AMPA Receptor-Mediated Synaptic Transmission by Polyamines in Principal Neurons. Focus on "Polyamines Modulate AMPA Receptor-Dependent Synaptic Response in Immature Layer V Pyramidal Neurons"

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Activity-dependent enhancement (facilitation) of synaptic transmission for hundreds of milliseconds after a train of action potentials is a fundamental property of many synapses throughout the CNS. For many years, this type of short-term synaptic plasticity was attributed to increased neurotransmitter release caused by elevated Ca^{2+} concentration at presynaptic release sites (Zucker 1999). Although a postsynaptic mechanism, polyamine-dependent facilitation of AMPA receptor (AMPAR)-mediated excitatory transmission has been described, it was restricted to a relatively small population of mammalian GABAergic interneurons and tectal neurons in retino-tectal synapses of *Xenopus* tadpoles that express Ca^{2+}-permeable, polyamine-sensitive AMPARs (Aizenman et al. 2002; Rozov and Burnashev 1999). Therefore this mechanism of facilitation was considered rather exotic. The study by Shin et al., appearing in this issue of *The Journal of Neurophysiology* (p. 2634–2643), extends this mechanism to principal pyramidal neurons in mammalian neocortex (Shin et al. 2005). In a series of elegant experiments, they show that in immature brain (<P14) excitatory synaptic transmission in neocortical layer V pyramidal neurons mediated by polyamine-sensitive, Ca^{2+}-permeable AMPARs (Kumar et al. 2002) undergoes facilitation in response to presynaptic burst activity.

Polyamines (PAs), such a putrescine, spermine, and spermidine, are ubiquitous intracellular factors with low molecular mass and multiple positive charges. They are expressed in almost every cell type. In addition to their important role in protein synthesis, cell division, and cell growth, they interact with a number of different types of ion channels (for review, see Williams 1997). Blockade of Ca^{2+}-permeable AMPARs (lacking GluR2 subunits) by intracellular PAs generates inward rectification of the current-voltage (*I-V*) relation. However, as a membrane potential becomes sufficiently positive, PAs can permeate the AMPAR channel so that ion flux is restored resulting in so called doubly rectifying *I-V* relation. During repetitive activity PA block can be relieved, inducing facilitation of the AMPAR-mediated current (Rozov et al. 1998).

Shin et al. show that synthesis of PAs in pyramidal neurons is developmentally regulated. In young animals, levels of spermine and its key metabolic enzyme ornithine decarboxylase are increased, and this high expression of PAs coincides in time with expression of PA-sensitive AMPARs. Is this just coincidence? In the view of the Shin et al. study, the exact timing of expression of polyamine-sensitive AMPARs and increase of PA synthesis, which has been shown to be driven by physiological stimuli (Aizenman et al. 2002), may be potent mechanisms for controlling the efficacy of synaptic transmission in the immature brain. This would result in greater plasticity at the early developmental stages when most neuronal circuitry is being built.

The unique frequency dependence of the PA-dependent facilitation [a stronger facilitation at higher frequencies (Rozov and Burnashev 1999)] suggests that synapses expressing PA-sensitive AMPARs may serve as high-pass filters to enhance synaptic gain during enhanced sensory experience. Under certain pathological conditions when Ca^{2+}-permeable subunits of AMPARs are overexpressed or GluR2 subunit expression is downregulated, the PA-dependent facilitation may contribute to overexcitability of principal neurons and may thus play a role in the development of epilepsy. Indeed, genetically manipulated mice in which AMPARs were modified to be Ca^{2+} permeable and polyamine sensitive showed an epileptic phenotype (Feldmeyer et al. 1999; Krestel et al. 2004).

Finally in view of the findings of Shin et al., the pervasive notion that paired-pulse facilitation is a purely presynaptic phenomenon will have to be reconsidered.

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