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Polyamine-dependent facilitation of currents through Ca^{2+}- permeable AMPAR channels: a novel post-synaptic mechanism for short-term plasticity

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This study has been performed on recombinant and synaptically located α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor (AMPAR) channels, using two types of preparations (HEK 293 expressing AMPAR subunits and acute brain slices) and numerous electrophysiological techniques (fast agonist application, paired whole-cell recordings from synaptically connected neurons, intracellular dialysis and others). The following results were obtained:

In outside-out patches excised from HEK 293 cells expressing Ca^{2+}-permeable, polyamine-sensitive AMPAR channels, currents activated by 1 ms glutamate pulses at negative membrane potentials facilitated during and following a repetitive (2 to 100 Hz) agonist application. The degree of

facilitation depended on subunit type, membrane potential and stimulation frequency being antagonized by a slow recovery from desensitization.

Activity-dependent current facilitation occurred in Ca^{2+}-permeable but not in Ca^{2+}-impermeable AMPAR channels. Current facilitation, however, does not depend on Ca^{2+} flux. Rather it reflects a relief from the block of Ca^{2+}-permeable AMPARs by intracellular polyamines since facilitation occurred only in the presence of polyamines and since facilitated currents had a nearly linear current-voltage relation.

Relief from polyamine block was use-dependent and occurred mainly in open channels. The relief mechanism was determined primarily by membrane potential rather than by current flow.

In closed channels the degree of polyamine block was independent of membrane potential. The voltage dependence of the rate of relief from the block in open channels rather than the voltage dependence of the block underlies the inwardly-rectifying shape of the I-V at negative potentials.

Polyamine-dependent facilitation contributes to the short-term plasticity in local circuits formed by presynaptic pyramidal neurons and postsynaptic multipolar interneurons in layer 2/3 of rat neocortex.

Activity-dependent relief from polyamine block of postsynaptic Ca^{2+}-permeable AMPARs in the interneurons either reduces the rate of paired-pulse depression in a frequency-dependent manner or, at a given stimulation frequency, induces facilitation of synaptic response that otherwise would depress.

Concentration of endogenous polyamines is sufficient to induce facilitation of currents through synapticaly located AMPARs.

It is concluded that a use-dependent relief from polyamine block during consecutive AMPAR channel openings underlies current facilitation. This polyamine-dependent facilitation represents a novel entirely entirely postsynaptic mechanism of dynamic regulation of synaptic gain that may determine target-cell-specific differences of synaptic transmission in neuronal circuits. In addition to this important functional consideration, this significant post-synaptic influence on paired-pulse ratios means that previous assumptions concerning the pre-synaptic locus of such changes must be reconsidered in synapses where polyamine-sensitive AMPA receptors are expressed.