Regulation of AMPA receptors in synaptic plasticity.

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Dynamic changes in synaptic strength underlie various brain functions, such as memory formation, developmental plasticity, restoration of function after injury, and drug addiction. The best understood models of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). It is now recognized at a molecular level that plasticity of excitatory synaptic transmission is mediated, at least in part, by regulation of AMPA-type glutamate receptor function. We have previously demonstrated that LTP and LTD are accompanied by changes in phosphorylation of AMPA receptor GluR1 subunit, at two specific phosphorylation sites: serine 831 and serine 845. GluR1 S831 is phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC), while S845 is a protein kinase A (PKA) substrate. Alterations in these two phosphorylation sites on GluR1 are known to affect AMPA receptor mediated current.
To specifically test whether the two phosphorylation sites on GluR1 are necessary for LTP and LTD, we recently generated several lines of mice that lack specific phosphoylation sites on GluR1 subunit. In one line of mice, both S831 and S845 were mutated to alanines to prevent phosphorylation. In these "double" phosphomutants, we found a reduction in LTP and a lack of LTD. To further dissect out which of the two phosphorylation sites are necessary to support LTP and LTD, we looked at mice that lack only S831 or S845. In mice that have S845A mutation, we found that LTP is normal, but LTD is lacking. However, in mice that have S831A mutation, we found that both LTP and LTD are normal. Our results demonstrate that LTD is critically dependent on GluR1 S845 phosphorylation site. On the other hand, LTP is partially dependent on the two GluR1 phosphorylation sites, and only one of the phosphorylation sites needs to be intact to support LTP.

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