The administration of glycine induces the dephosphorylation of AMPA receptors and attenuates fear memory of the contextual fear conditioning.

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In the central nervous system, glycine plays an excitatory role via binding to the NMDA receptors (NMDARs) and an inhibitory role via binding to the glycine receptors (GlyRs). Recently, it has been found that upon the increase of glycine concentration in the synaptic cleft, glycine binds to the GlyRs, mainly expressed in the extrasynapse, and introduces LTD. In addition, NMDARs and AMPA receptors (AMPARs) involve in this type of LTD. To elucidate the mechanisms underlying glycine-dependent LTD, we examined the phosphorylation of AMPARs under excess amount of glycine. Furthermore, we hypothesized that the administration of high-dose glycine would attenuate hippocampal- dependent fear memory, known to require the phosphorylation of AMPARs.

We performed biochemical analysis to examine the phosphorylation status of AMPARs in the hippocampus under different doses of glycine. Glycine decreased the phosphorylation of serine 845 of GluA1 subunit of AMPARs dose-dependently. Furthermore, high-dose glycine co-incubated with strychnine, AP5 and FK506 did not show the reduction in the phosphorylation of serine 845 of GluA1, suggesting that this effect of glycine was mediated by not only GlyRs but also NMDARs. Interestingly, the high-dose administration of glycine to the rats before fear conditioning reduced the freezing behavior during the test. Moreover, this effect was eliminated by co-administration of strychnine.

In this study, we revealed that LTD required the dephosphorylation of serine 845 of GluA1 and this type of LTD could attenuate contextual fear memory.