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Emotional intelligence

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A neurotransmitter involved in emotional arousal enhances learning by phosphorylating glutamate receptors.

Do you remember the song that was playing during your first kiss? Both positive and negative emotions influence learning and memory but researchers have not determined the mechanism. Now Hu *et al.* report that the neurotransmitter norepinephrine regulates glutamate receptor trafficking in a recent article in *Cell*.

Axon terminals containing norepinephrine synapse in the hippocampus and amygdala, which are important in emotional memory. In the hippocampus, norepinephrine reduces the threshold for long-term potentiation (LTP), which is thought to be a substrate of memory. Norepinephrine acts at -adrenergic receptors, where it activates cAMP-dependent protein kinase (PKA) and calcium/calmodulin-dependent protein kinase II (CaMKII). These kinases phosphorylate serines 845 and 831, respectively, in the AMPA glutamate receptor type 1 (GluR1). The authors proposed that norepinephrine regulates learning by phosphorylating AMPA receptors.

Norepinephrine increased GluR1 phosphorylation at serines 831 and 845, which was blocked by the -adrenergic receptor inhibitor propanolol. The PKA inhibitor KT57 blocked norepinephrine-induced phosphorylation of serine 845 but not serine 831, and the CamKII inhibitor KN-93 blocked norepinephrine-induced phosphorylation of serine 831 but not serine 845. Does norepinephrine induce GluR1 phophorylation *in vivo*? Peripheral injection of epinephrine induces norepinephrine release in the central nervous system. Peripheral epinephrine treatment increased hippocampal GluR1 phosphorylation. Exposure to urine from foxes, a natural predator of mice, increased the phosphorylation of serines 831 and 845 in GluR1. Propanolol blocked GluR1 phosphorylation and freezing behavior, suggesting that norepinephrine induces GluR1 phosphorylation following exposure to stressful stimuli.

Relative to electrical stimulation alone, norepinephrine increased tetanic stimulus-induced LTP. Norepinephrine alone did not affect LTP, consistent with a role in enhancing synaptic connections during learning, according to the authors. The time courses of norepinephrine-induced GluR1 phosphorylation and LTP facilitation were similar, suggesting that norepinephrine-induced GluR1 phosphorylation affects synaptic transmission.

AMPA receptors are tetramers composed of combinations of GluR1-4 subunits. Cells with homomeric GluR1 channels show rectification (reduced conductance at positive membrane potentials). Norepinephrine coupled with tetanic stimulation increased rectification in hippocampal neurons expressing exogenous GluR1, suggesting that norepinephrine induced the

trafficking of AMPA receptors to the membrane. In contrast, norepinephrine and tetanic stimulation reduced AMPA currents in neurons expressing GluR1 with serine-to-alanine mutations, which prevent phosphorylation, relative to control neurons, suggesting that the mutant AMPA receptors act in a dominant-negative fashion, reducing the membrane incorporation of GluR1.

Mice expressing phosphomutant GluR1 show deficits in norepinephrine-enhanced LTP and learning. Norepinephrine increased LTP in wild-type but not phosphomutant mice, suggesting that GluR1 phosphorylation is necessary for norepinephrine facilitation of LTP. Epinephrine increased fearful freezing in wild-type but not phosphomutant mice trained to associate a context with a shock, suggesting that GluR1 phosphorylation is necessary for emotion-enhanced memory.

If these mechanisms are also found in people, perhaps targeted phosphatase treatment could prevent or diminish persistent troubling memories in those at risk for developing posttraumatic stress disorder.

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1. Hu, H. *et al.* Emotion enhances learning via norepinephrine regulation of AMPA-receptor trafficking. *Cell* **131**, 160–173 (2007). | Article | PubMed |