ION CHANNELS

Small conductance, big effects

Emotionally salient memories are better remembered than neutral ones, probably because they activate the amygdala; however, the cellular and molecular mechanisms that lead to memory formation in the amygdala are not well understood. Faber *et al.* now provide evidence that activation of β-adrenoceptors in the basolateral amygdala triggers the modulation of SK channels, which in turn leads to enhanced long-term potentiation (LTP).

The stress hormone noradrenaline activates β-adrenoceptors in the basolateral amygdala and contributes to fear learning, enhancing the induction of LTP at glutamatergic synapses. Small-conductance Ca^{2+}-activated K^+ (SK) channels are activated by Ca^{2+} influx through NMDA (*N*-methyl-D-aspartate) receptors. Previously, the authors had shown that activated SK channels reduce excitatory postsynaptic potentials (EPSPs) . Conversely, synaptic transmission was enhanced when SK channels were blocked by apamin. Here, the authors set out to identify the molecular components of fear learning in the lateral amygdala.

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First, they applied the β-adrenoceptor agonist isoprenaline in rat brain slices. This enhanced EPSPs owing to a postsynaptic effect mediated by β-adrenoceptors. Apamin also enhanced synaptic transmission, but when applied after isoprenaline it had no further enhancing effect. The same was observed for isoprenaline treatment that followed apamin treatment, suggesting that the activation of β-adrenoceptors might increase excitatory synaptic transmission by reducing the activity of SK channels.

As G-protein-coupled receptors, β-adrenoceptors signal through the classical pathway of adenylyl cyclase, cyclic AMP and protein kinase A (PKA). Using pharmacological interventions, the authors established that direct activation of PKA or adenylyl cyclase precluded the subsequent enhancement of EPSPs by apamin. Next they used SK channels tagged with an extracellular myc epitope and, using immunohistochemistry, showed that application of forskolin, an activator of adenylyl cyclase, reduced the number of SK channels at excitatory synapses in the lateral amygdala.

Lastly, the authors examined whether isoprenaline enhanced synaptic plasticity through SK channel modulation. Tetanic stimulation of excitatory inputs to principal neurons in the lateral amygdala caused LTP of EPSPs that was further enhanced in the presence of isoprenaline. The authors had previously shown that apamin increases LTP at these synapses. However, no further enhancement occurred when apamin was applied with isoprenaline, suggesting that isoprenaline enhances LTP through the regulation of SK channels.

Integrating these findings, the authors propose a model for the enhanced learning of emotional memories. According to this model, stress hormones act through β-adrenoceptors to remove SK channels from postsynaptic sites, thereby potentiating synaptic transmission. Understanding the molecular mechanisms of emotional memories is key for developing efficient treatments for anxiety-related disorders, such as post-traumatic stress disorder.

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ORIGINAL RESEARCH PAPER Faber, E. S. L. *et al.* Modulation of SK channel trafficking by beta adrenoceptors enhances excitatory synaptic transmission and plasticity in the amygdala. *J. Neurosci.* **28,** 10803–10813 (2008)