These findings show that, in the medial CeA, oxytocin and vasopressin modulate activity in opposite ways. Through the activation of distinct elements of this inhibitory network, the two neuropeptides can integrate the different signals entering the CeA into a single output to the autonomic nervous system, thereby regulating the expression of fear. The authors argue that the distribution of oxytocin and vasopressin receptors throughout the larger, extended amygdala indicates that this system might also be involved in the control of anxiety, stress, motivation and addiction in mammals. Furthermore, they suggest that these neuropeptide receptors could be future targets for the pharmacological treatment of stress and anxiety in humans.

David Stevens

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NEUROTRANSMITTER RECEPTORS

A new role for stargazin

Two recent studies have revealed that the protein stargazin, which is involved in the trafficking of glutamate receptors, can also influence their functional properties. This finding offers new insights into how receptor function can be regulated at excitatory synapses.

Stargazin, which interacts with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors (AMPARs), is a member of the TARP (transmembrane AMPAR regulatory proteins) family. The interaction of stargazin with AMPARs is important for the correct localization of the receptors at synapses, and this process is involved in synaptic plasticity. The authors of these two studies investigated whether stargazin also influences the gating of AMPARs.

Both Tomita *et al.* and Priel *et al.* used co-expression of glutamate receptor subunits and stargazin in cells such as *Xenopus laevis* oocytes to investigate this question. They found that, as well as increasing the surface expression of AMPARs, stargazin reduced the desensitization and deactivation of the receptors, and speeded up their recovery from desensitization. Stargazin thereby increased the response of cells that expressed AMPARs to glutamate. In addition, the co-expression of stargazin with AMPARs greatly increased the sensitivity of these receptors to the partial agonist, kainate. Tomita and colleagues used this potentiation to quantify the effects of stargazin on channel properties.

Tomita *et al.* then went on to investigate the mechanism by which stargazin influences AMPAR function. They generated stargazin mutants in which specific domains of the protein were substituted with the equivalent domains from another TARP, γ-5, which does not enhance the receptor's response to glutamate or its trafficking. Whereas the trafficking functions of stargazin are mediated by its cytoplasmic tail, they found that an extracellular loop of stargazin was crucial for its effects on AMPAR channel properties.

How does the extracellular domain of stargazin mediate these effects? Tomita and colleagues used a fast glutamate perfusion system to investigate the effects of stargazin on the channel kinetics of AMPARs. In patches from cells transfected with the GluR4 subunit, stargazin greatly increased the steady-state current that could be evoked by glutamate, and specifically increased the frequency of large single-channel openings and the duration of channel bursts. The fundamental effect of stargazin on AMPAR function seems to involve an increase in the rate constant for channel opening.

Finally, Tomita *et al.* investigated whether these biophysical effects of stargazin are physiologically relevant at synapses. They expressed a stargazin–γ-5 chimaera that does not affect channel gating in neurons to disrupt the effects of the endogenous TARP. Overexpression of this chimaera reduced the peak amplitude and increased the decay rate of miniature excitatory postsynaptic potentials, which indicates that stargazin does regulate glutamatergic transmission in intact neurons.

The finding that a receptor trafficking protein can also influence the biophysical properties of AMPARs adds new complexity to the regulation of synaptic responses in the nervous system. The functional importance of this effect, and the molecular mechanisms by which it is mediated, will undoubtedly come under scrutiny in the near future.

Rachel Jones

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