MOLECULAR NEUROSCIENCE

Right time, right place

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors (AMPARs) mediate most excitatory transmission in the CNS, and thus their export from the endoplasmic reticulum (ER) and trafficking to the plasma membrane have to be carefully regulated. Two papers in *J. Neurosci.* describe different mechanisms through which this might be achieved.

GABA (γ-aminobutyric acid)-ergic interneurons have a key role in synchronizing neural activity in the cortex and have been implicated in regulating working memory. Dopamine signalling through D_1 and D_2 receptors has been shown to influence the function of these cells, but the role of the highly expressed dopamine D_4 receptor was unknown. Yuen and Yan found that D_4 activation suppressed AMPA-mediated glutamatergic transmission in the prefrontal cortex. This effect was due to a decrease in the trafficking of AMPARs to synapses that resulted from an alteration to actin- and myosin V-mediated transport, as pharmacological disruption of actin dynamics or inhibition of myosin V activity occluded the effect of D_4 activation. Furthermore, they showed that, by activating calcineurin, D_4 receptors activate the phosphatase slingshot (also known as SSH1), which in turn increases the activity of the actin-depolymerizing protein cofilin. Thus, by regulating actin depolymerization, D_4 receptors decrease AMPAR trafficking, decrease the excitation of GABAergic interneurons and relieve inhibition in the prefrontal cortex. These findings might explain why impaired D_4 function has been implicated in attention-deficit hyperactivity disorder and schizophrenia.

Previous studies have shown that the agonist-binding domain of AMPARs is required for receptor biogenesis. Keinanen and colleagues examined the fate of receptors bearing point mutations in this domain (at positions R507 and E727) that directly alter glutamate binding. Using electrophysiology and immunofluorescence, they demonstrated that glutamate binding is essential for AMPAR trafficking to the cell surface of cortical neurons. Further analysis in HEK293 cells showed that this effect is independent of the transmembrane and cytoplasmic domains of the receptor; moreover, the transmembrane AMPAR-regulatory protein stargazin (also known as CACNG2) was able to rescue the transport defect of the mutant receptors. The mechanism through which stargazin helps mutant receptors exit the ER remains to be determined.

These studies highlight the importance of glutamate binding for the vesicular trafficking of AMPARs — it is possible that agonist-induced closure of the binding site functions as a quality-control step that allows ER export — and outline a molecular pathway involving actin dynamics through which another neurotransmitter system can regulate AMPAR trafficking and modulate a neuron's excitability.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPERS Coleman, S. K. *et al.* Agonist occupancy is essential for forward trafficking of AMPA receptors. *J. Neurosci.* **29**, 303–312 (2009) | Yuen, Y. & Yan, Z. Dopamine D_4 receptors regulate AMPA receptor trafficking and glutamatergic transmission in GABAergic interneurons of prefrontal cortex. *J. Neurosci.* **29**, 550–562 (2009)