HIGHLIGHTS

CELL BIOLOGY OF THE NEURON

Primed and ready to go

Moving receptors to and from the postsynaptic membrane is a potentially important way for cells to control the strengths of individual synapses — the more receptors there are, the stronger the signal will be. NMDA (*N*-methyl-D-aspartate) receptors are more 'stable' than some others, but they can still be internalized by the cell, and work published in *Nature* by Nong *et al.* gives some insight into how this process is controlled.

NMDA receptors are activated by glutamate or NMDA, but this process also requires a 'co-agonist', glycine. When acutely isolated cells are exposed to relatively large concentrations of the two agonists in a process known as conditioning, the currents produced by stimulation of NMDA receptors drop sharply and then continue to fall more gradually. Nong *et al.* found that this process could be prevented by treating the cells with a protein that blocks clathrin-dependent endocytosis, indicating that the depression of NMDA receptor-mediated currents results from clathrin-dependent internalization of the receptors. They then set out to investigate how NMDA and glycine cause the receptors to be internalized.

When the authors applied the NMDA blocker AP5 at the same time as the conditioning treatment, they found that the immediate sharp drop in current was prevented, but there was still a gradual decrease after treatment. Using glycine alone (rather than glycine with NMDA) as the conditioning treatment had the same

effect, indicating that the progressive decline in current depended on conditioning with glycine but did not require conditioning with NMDA. But when test applications of smaller concentrations of NMDA and glycine after conditioning (to measure the size of NMDA receptor-mediated currents) were delayed, the authors found that the progressive decline in current did not begin until the cells were stimulated with NMDA.

So, it seems that both NMDA and glycine are needed for internalization, but that glycine alone can 'prime' the receptors so that they become internalized when later stimulated with both co-agonists. How is this priming achieved? Conditioning with glycine increased the co-precipitation of NMDA receptors with adaptin β2, a component of the AP2 complex, which is involved in clathrin-dependent endocytosis. So the authors conclude that stimulation of the glycine site on NMDA receptors initiates a signalling process that recruits the endocytic machinery to the receptors, without causing endocytosis. The receptors are then primed so that subsequent receptor activation causes them to be internalized.

These findings open up many possibilities for the future study of how glycine signals through the NMDA receptors and regulates the strength of synaptic transmission by these receptors. As NMDA receptors are particularly important for synaptic plasticity, changes in glycine levels could have lasting consequences for neuronal circuits.

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References and links

ORIGINAL RESEARCH PAPER Nong, Y. *et al.* Glycine binding primes NMDA receptor internalization. *Nature* **422**, 302–307 (2003)
FURTHER READING Carroll, R. C. *et al.* Role of AMPA receptor endocytosis in synaptic plasticity. *Nature Rev. Neurosci.* **2**, 315–324 (2001) | Choquet, D. & Triller, A. The role of receptor diffusion in the organization of the postsynaptic membrane. *Nature Rev. Neurosci.* **4**, 251–265 (2003)