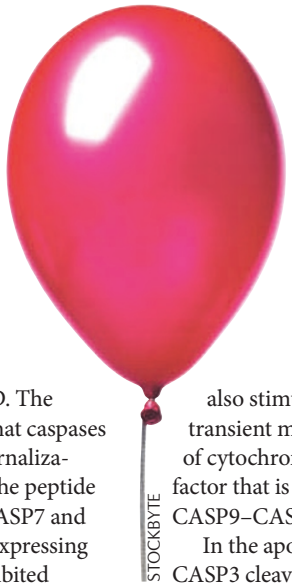
STOCKBYTE

SYNAPTIC PLASTICITY

Depress or die

Caspases are well known for their role in apoptosis, but their involvement in synaptic plasticity had not been investigated. Sheng and colleagues now show that NMDA (*N*-methyl-D-aspartate) receptor-dependent activation of caspase 3 (CASP3) and CASP9 through the mitochondrial pathway plays a key part in the internalization of AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors (AMPARs) and hence long-term depression (LTD).

The authors investigated the role of caspases in synaptic plasticity at the Schaffer collateral–CA1 synapse in acute hippocampal slices. The application of peptide inhibitors of CASP3, CASP7 and CASP9 specifically blocked the induction of LTD by low-frequency stimulation without affecting long-term potentiation (LTP). LTD was also blocked by overexpression in CA1 neurons of the genes encoding the caspase inhibitors BCL-XL and X-linked inhibitor of apoptosis (XIAP) — both of which inhibit the mitochondrial pathway of apoptosis. Furthermore, low-frequency stimulation failed to induce LTD in slices from *Casp3*-knockout mice. These findings suggest that CASP3, CASP7 and CASP9, which might be activated by the mitochondrial apoptotic pathway, have a role in LTD.

Internalization of AMPARs from the postsynaptic membrane is a prerequisite for LTD. The authors hypothesized that caspases might regulate this internalization. Indeed, applying the peptide inhibitors of CASP3, CASP7 and CASP9, as well as overexpressing *XIAP* and *BCL-XL,* inhibited NMDA-stimulated internalization of AMPARs in dissociated hippocampal neurons. Moreover, AMPAR internalization was abolished in *Casp3*-knockout neurons. As CASP7 is expressed at very low or non-detectable levels in the brain, the authors proposed that CASP3 and CASP9 are likely to be key factors in LTD and AMPAR internalization.

CASP9 is known to be an upstream activator of CASP3 in the apoptotic response. Therefore, the authors focused on CASP3 and investigated the mechanistic link between CASP3 and AMPAR internalization. Treatment of cultured neurons with NMDA led to AMPAR internalization and resulted in a rapid and transient increase in the levels of activated CASP3 and CASP9, which peaked 30 minutes after NMDA treatment. This change is different from the staurosporin-induced delayed and sustained accumulation of activated caspases that leads to neuronal apoptosis, indicating that transient and low increases in caspase activity might be sufficient to induce AMPAR internalization without inducing apoptosis. Interestingly, treatment with NMDA also stimulated the rapid and transient mitochondrial release of cytochrome *c*, a pro-apoptotic factor that is known to activate the CASP9–CASP3 cascade.

In the apoptotic response, CASP3 cleaves AKT1, a pro-survival protein kinase that also inhibits glycogen synthase kinase 3β (GSK3β), an enzyme that is required for LTD induction. The authors identified a mutant form of AKT1 that was resistant to cleavage by CASP3 but able to phosphorylate GSK3β. When they expressed this mutant AKT1 in CA1 neurons of hippocampal slice cultures, LTD — but not LTP — was abolished, suggesting that other components of the apoptotic signalling cascade are involved in the regulation of LTD.

These findings reveal an unexpected and crucial role of CASP3 and CASP9, activated through the mitochondrial apoptotic signalling pathway, in synaptic depression. It will be intriguing to identify the mechanistic differences between the signalling cascades that lead to apoptosis and LTD.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Zheng, L. *et al.* Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. *Cell* **141**, 859–871 (2010)

FURTHER READING Galluzzi, L., Blomgren, K. & Kroemer, G. Mitochondrial membrane permeabilization in neuronal injury. *Nature Rev. Neurosci.* **10**, 481–494 (2009)