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SYNAPTIC PLASTICITY

Finely tuning caspase function

Caspase function is not limited to the realm of apoptosis: in rodent hippocampal neurons, for example, long-term depression (LTD) of synaptic transmission requires active caspase 3. How caspases are activated in non-apoptotic processes is unclear, as is why they do not induce cell death. Now, Jiao and Li show that caspase 3 activation in LTD involves pro-apoptotic signalling proteins, and that the function of this protease is determined by its level of activation.

BCL2 antagonist of cell death (BAD) and apoptosis regulator BAX are pro-apoptotic factors belonging to the BCL2 protein family. In apoptosis, BAD is dephosphorylated and translocates to mitochondria where it promotes BAX-mediated cytochrome c release, leading to caspase 3 activation.

Jiao and Li showed that BAD–BAX signalling also activates this protease during LTD. Electrophysiological experiments on hippocampal slices from *Bad*$^{-/-}$ or *Bax*$^{-/-}$ mice revealed that the absence of one or other of these proteins blocked NMDA-mediated LTD. Moreover, NMDA stimulation caused an increase in active caspase 3 in hippocampal slices from wild-type mice but not from *Bad*$^{-/-}$ or *Bax*$^{-/-}$ animals.

To explore how BAD–BAX signalling mediates such different functional outcomes, the authors treated cultured cortical neurons with NMDA or actinomycin — which induces apoptosis — and examined changes in these proteins. Desphosphorylated and mitochondria-associated BAD levels were higher following actinomycin treatment than after NMDA stimulation, as were mitochondrial and total BAX levels, suggesting differences between BAD–BAX signalling in apoptosis and LTD. Interestingly, these differences were reflected in caspase 3 activity: NMDA stimulation caused transient, moderate activation of this caspase, whereas actinomycin treatment led to sustained, robust caspase 3 activation.

These findings led the authors to examine the hypothesis that the duration and intensity of caspase 3 activation determines its function. In support of this assertion, they found that robust activation of caspase 3 with high NMDA concentrations induced cell death in cultured hippocampal neurons, whereas low-level activation of this protease following a low dose of actinomycin failed to induce apoptosis. Prolonged activation of caspase 3 with low doses of NMDA also induced some apoptosis.

These results show that variation in BAD–BAX signalling alters the level of caspase 3 activation and determines the function of this protease. Similar mechanisms might underlie the functional diversity of other caspases.

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ORIGINAL RESEARCH PAPER Jiao, S. & Zheng, L. Nonapoptotic function of BAD and BAX in long-term depression of synaptic transmission. *Neuron* **70**, 758–772 (2011)