NEUROTRANSMITTER RECEPTORS

Location, location, location — a matter of life and death

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N-methyl-D-aspartate receptors (NMDARs) are the Jekylls and Hydes of neuronal receptors — their activation promotes either survival or cell death. It was previously unknown whether this depends upon the location of these receptors (synaptic or extrasynaptic) or on different degrees of their activation. Bading and colleagues provide evidence that the location of NMDARs is crucial and that upon receptor activation, specific gene expression programmes guide survival or death.

NMDARs are Ca^{2+}-permeable ion channels. As calcium signals can influence the gene expression pattern of cells, Bading and co-workers used DNA microarrays to investigate the transcriptome of hippocampal cell cultures after two different stimulation protocols: stimulating only synaptic NMDARs promoted neuronal survival, whereas stimulating all NMDARs in a glutamate bath initiated cell death. Using NMDAR blockers in combination with both protocols allowed the identification of genes that are specifically controlled by NMDAR activity.

The authors identified almost 170 genes that are either induced or repressed through activation of NMDARs. Surprisingly, synaptic and extrasynaptic NMDARs have largely separate pools of gene targets. Synaptic NMDARs activate the expression of 106 and repress the expression of 34 genes, whereas extrasynaptic NMDARs activate 11 genes and repress one.

Genes that are regulated by Ca^{2+} entry through synaptic, but not extrasynaptic NMDARs could have a role in neuroprotection. From the database, the authors identified two genes with previously unknown functions in neuronal cells, *Btg2* and *Bcl6*. They investigated these genes by expressing them in hippocampal neurons or by using RNA interference (RNAi). The results clearly showed that *Btg2* and *Bcl6* have a central role in neuroprotection, as their expression had a robust neuroprotective effect whereas inhibition of expression by RNAi eliminates neuroprotection after stimulation with the survival protocol. In addition, the authors showed that the expression of *Btg2* and *Bcl6* is coupled to nuclear Ca^{2+} signals and may be controlled by CREB, a well known transcription factor in neuroprotection.

Extrasynaptic NMDARs couple to the expression of — among other genes — *Clca1*, a putative calcium-activated chloride channel and pro-death gene. *Clca1* is the first gene to be identified that is specifically induced by extrasynaptic NMDAR activity. Expression of *Clca1* in hippocampal neurons was sufficient to kill cells, and therefore it is very likely that *Clca1* has a role in death-signalling pathways.

In this elegant study, the authors demonstrated that activation of synaptic or extrasynaptic NMDA receptors induces specific genetic responses that promote survival or neuronal cell death, respectively, and therefore that the location of these receptors determines the physiological outcome of their activation. Future studies might use the pool of identified genes as a basis to expose the molecular mechanisms and signalling pathways involved in survival or death programs.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Zhang, S.-J. *et al.* Decoding NMDA receptor signaling: identification of genomic programs specifying neuronal survival and death. *Neuron* **53**, 549–562 (2007)