DEVELOPMENT

Circuit building

Representative three-dimensional serial reconstructions of two mossy fibre synaptic complexes taken before (top) and during (bottom) the stereotyped pruning of infrapyramidal bundle mossy fibres, which originate from the dentate gyrus of the mouse hippocampus. Before stereotyped pruning (top), a large mossy fibre presynaptic terminal (green) is seen associating with several postsynaptic densities (yellow) on multiple dendritic spines (purple) of a CA3 pyramidal cell. During stereotyped pruning, the synaptic complex is much smaller and less complex in shape (bottom) as a presynaptic terminal (green) is seen to associate with a single postsynaptic density (yellow) on a small dendritic shaft (purple) of a CA3 pyramidal cell. Image courtesy of H.-J. Cheng, Center for Neuroscience, University of California, Davis, USA.

Collateral branch connections of axons are issued during development to ensure that all potential postsynaptic targets are covered. However, the exact cellular mechanisms underlying the pruning of inappropriate connections continue to elude developmental neuroscientists. Writing in *The Journal of Neuroscience*, Liu, Low and colleagues shed light on how these connections are eliminated.

It takes hundreds of thousands of synaptic connections to create the intricate circuitry of the CNS, and, to ensure that all synaptic targets are covered, some of the early connections are imprecise and axonal projections are often too long. How this rough draft of the CNS is subsequently refined is still not fully understood, but it seems that different neuronal populations use various processes to prune and remodel axons.

Focusing on the hippocampal mossy fibre system, Liu *et al.* investigated pruning in the synaptic complex, which is formed by mossy

fibres of the infrapyramidal bundle that transiently make contact with basal dendrites of CA3 pyramidal cells. The authors considered three potential pruning methods: axon retraction (axon contents are recycled); Wallerian degeneration (axon fibres are atrophic and destroyed after injury); and axosome shedding (axonal contents are discharged from the terminal and the remnants are engulfed by glial cells).

Immunocytochemistry and electron microscopy analysis showed that a transient contact was formed between the mossy fibre boutons and the basal dendrites. But, as pruning progressed, both the size and complexity of the transient synaptic complex diminished. Because no axonal degeneration or glial cell engulfment was detected, the authors concluded that axonal retraction was occurring during stereotyped pruning, a process that is thought to be triggered by plexin A3 signalling.

It has been suggested that plexin A3 signalling initially disrupts the

GLIA

From kiss-and-run to crosstalk

Astrocytes can respond to neuronal activity and actively modulate neurotransmission by releasing glial transmitters such as glutamate, ATP and D-serine. Two recent studies have taken important steps in understanding the mechanisms of glial transmitter release and the role of gliotransmission in regulating synaptic strength and plasticity.

The calcium-dependent vesicular release of gliotransmitters in response to membrane receptor activation is thought to depend on SNARE proteins, but many questions remain about the mode of gliotransmitter exocytosis.

Chen *et al.* used electrochemical amperometry and frequency-modulated (fluorescent) single-vesicle imaging to look at the kinetics of stimulus-evoked vesicular release from cultured and freshly isolated rat hippocampal astrocytes. In response to strong, non-physiological stimulation, astrocytes adopted a permanent fusion mode, in which most of the vesicle contents were secreted. As expected,

stimulus-induced quantal secretion was SNARE dependent in these glial cells. To their surprise, the researchers found that physiological stimulation caused astrocytes to release their contents by a kiss-and-run mechanism, in which only ~10% of the vesicle contents were released during a brief opening of the 'fusion pore' — a channel that connects and spans the vesicle and plasma membranes. In neurons, the fusion pore can switch on and off many times in a process known as 'flickering'; however, kiss-and-run in astrocytes appeared to involve just a single 'kiss' or 'flicker'.

Pascual and colleagues exploited the SNARE dependence of glial transmitter release to investigate the role of gliotransmission in synaptic networks. To block gliotransmitter release, the researchers generated transgenic mice that expressed a dominant-negative (dn)SNARE domain in astrocytes. They studied synaptic transmission and long-term potentiation (LTP) in acutely isolated hippocampal slices from these animals. By releasing ATP, which

is rapidly hydrolysed to adenosine, Pascual *et al.* found that astrocytes can tonically suppress excitatory synaptic transmission by activating A1 adenosine receptors. And by regulating the strength of basal synaptic transmission, it seems that these glial cells can enhance the available range for synaptic plasticity, the magnitude of LTP being significantly reduced in dnSNARE mice. Because ATP can diffuse to distant sites before adenosine begins to accumulate, the synaptic activation of astrocytes provides a mechanism for crosstalk to distant synapses.

These studies add to a burgeoning literature on the active roles of astrocytes in synaptic networks. It will be interesting to learn whether differences in the characteristics of kiss-and-run exocytosis in neurons and glia are related to differences in the fusion proteins expressed by these cell types. We look forward with interest to the next steps in our understanding of the regulatory functions of astrocytes in synaptic transmission.

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References and links

ORIGINAL RESEARCH PAPERS Chen, X. *et al.* "Kiss-and-run" glutamate secretion in cultured and freshly isolated rat hippocampal astrocytes. *J. Neurosci.* **25**, 9236–9243 (2005) | Pascual, O. *et al.* Astrocytic purinergic signalling coordinates synaptic networks. *Science* **310**, 113–116 (2005) | **FURTHER READING** Volterra, A. & Meldolesi, J. Astrocytes, from brain glue to communication elements: the revolution continues. *Nature Rev. Neurosci.* **6**, 626–640 (2005)