not entirely normal: precursor neuroblasts had slightly longer cell cycles and some had bent spindles. Though, neither problem prevented mitosis. The need for APC in some neurons but not others seems to reflect a requirement for Wnt signaling. As well as its cytoskeletal role, APC is a downstream regulator of Wnt, and while medulla neurons need Wnt for axon growth, the other types of neurons did not. It will be of interest to check whether hippocampal neurons, where the dominant-negative experiments were carried out, are also Wnt responsive.

Rusan, N.M., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200807079.

Astrocyte’s clean up job

By mopping up excess neurotrophic factor from neuronal synapses, astrocytes may finely tune synaptic transmission to affect processes such as learning and memory, say Bergami et al.

The major cellular events of learning and memory are long-term potentiation (LTP) and long-term depression (LTD), both of which affect neurons’ ability to communicate with one another. Neurons that have undergone LTP display a stronger electrical response to the same level of a stimulus, whereas neurons that have gone through LTD display a weaker response. These changes are thought to result from modifications of the neuronal synapses, such as alterations in the density of postsynaptic receptors, or downstream signaling events.

Secretion of the neurotrophic factor BDNF (brain-derived neurotrophic factor) has been implicated in long-term synaptic modification, and the function of BDNF on synaptic strength depends on its particular form: in its pro-BDNF form it is believed to promote LTD, and in its mature form it prompts LTP. Neurons were thought to secrete pro-BDNF, which then matured into BDNF in the synaptic space. However, a recent study suggests that only mature BDNF is secreted, pro-BDNF being processed intracellularly.

To get to the bottom of things, Bergami et al. investigated the fate of both forms after LTP induction in brain slices from the rat cortex. By fluorescent immunohistochemistry they showed that that neurons indeed secrete both mature and pro-BDNF, but that a large amount of the pro-BDNF is immediately taken up by astrocytes.

Astrocytes, previously thought to be unimportant in neuronal transmission, have recently been implicated in long-term modulation of neuronal synapses. For example, they release the neurotransmitter glutamate into the synapse prompting LTP. By specifically mopping up pro-BDNF, astrocytes seem to have another means to assist in LTP. However, while it’s likely that most pro-BDNF gets degraded inside astrocytes, say the authors, some gets recycled and re-released, suggesting that astrocytes in fact fine-tune synaptic plasticity.

Bergami, M., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200806137.

Microdomain switching is a bad move for APP

Amyloid precursor protein (APP), whose cleavage product, amyloid-β (Aβ), builds up into fibrous plaques in the brains of Alzheimer’s disease patients, jumps from one specialized membrane microdomain to another to be cleaved, report Sakurai et al.

Although there is no definitive evidence that Aβ plaques are the direct cause of Alzheimer’s disease, there is much circumstantial evidence to support this. And working on this hypothesis, scientists are investigating just how the plaques form and what might be done to stop or reverse their formation.

APP, a protein of unknown function, is membrane associated and concentrates at the neuronal synapse. Certain factors such as high cellular cholesterol and increased neuronal or synaptic activity are known to drive APP cleavage, and Sakurai and colleagues’ paper pulls these two modes of Aβ regulation together.

APP associates with membrane microdomains high in cholesterol (lipid rafts). These lipid rafts can also contain the enzyme necessary for APP cleavage, BACE. Synaptic activity is known to involve a very different type of membrane microdomain high in an excytosis-promoting factor called syntaxin. Sakurai et al. now show that although APP preferentially associates with syntaxin microdomains, upon neuronal stimulation APP instead associates with microdomains that contain BACE.

It’s unclear why APP should be associated with syntaxin, though it might suggest a role for APP in vesicle trafficking and exocytosis. Also unclear is why neuronal activity should cause APP to jump from syntaxin domains to BACE domains. What is clear, however, is that the process is an active one, requiring a kinase called cdk5. Furthermore, treating neurons with a cdk5 inhibitor called roscovitine, which is currently in trials for cancer treatment, reduced APP’s association with BACE microdomains and reduced APP cleavage.

Sakurai, T., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200804075.