

## NEURODEGENERATIVE DISEASES

# From amyloid- $\beta$ to receptor endocytosis

Another piece has been added to the puzzle of how the amyloid- $\beta$  peptide, which accumulates in the brains of patients with Alzheimer's disease, might cause neurological damage and memory loss. Writing in *Nature Neuroscience*, Snyder and colleagues describe how amyloid- $\beta$  can influence the removal of NMDA (*N*-methyl-D-aspartate)-type glutamatergic receptors from cortical synapses.

In patients with Alzheimer's disease, the levels of amyloid- $\beta$  in the brain are higher than normal, and amyloid- $\beta$  forms extracellular plaques and intracellular inclusions. However, memory impairments and synaptic abnormalities are found in animal models of Alzheimer's disease before the plaques begin to form, which has led to speculation that soluble extracellular amyloid- $\beta$  might be responsible for these pathological effects. But how amyloid- $\beta$  might cause pathogenic changes in Alzheimer's disease has remained unclear.

As amyloid- $\beta$  can reduce long-term potentiation (LTP) — a type of lasting synaptic plasticity that is thought to be associated with memory formation — Snyder *et al.* investigated whether amyloid- $\beta$  alters signalling through NMDA receptors, which are needed for most types of LTP. In cultured cortical neurons, amyloid- $\beta$  reduced the number of NMDA receptors on the cell surface at synapses, without altering the overall levels of these receptors. The reduction in receptors at the synapse was the result of an increase in endocytosis that was caused by treatment with amyloid- $\beta$ .

To investigate whether a similar effect occurs *in vivo*, the authors

looked at NMDA receptors in neurons from a mouse model of Alzheimer's disease. They found that surface expression of the NR1 subunit of NMDA receptors was much lower in cortical neurons from these mice than in neurons from control mice.

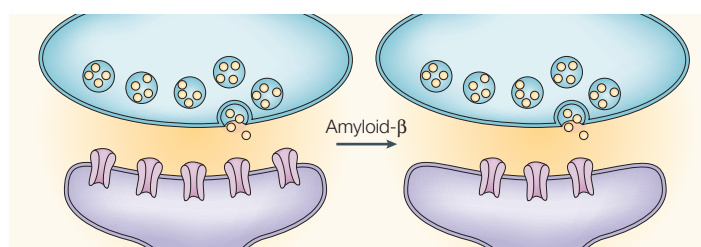
How could amyloid- $\beta$  regulate the endocytosis of NMDA receptors? Amyloid- $\beta$  binds to  $\alpha$ -7 nicotinic receptors, which are found at more than 70% of cortical glutamatergic synapses, and these receptors can activate protein phosphatase 2B (PP2B). Inhibiting either  $\alpha$ -7 nicotinic receptors or PP2B reduced the ability of amyloid- $\beta$  to promote the endocytosis of NMDA receptors. One target of PP2B is the striatal enriched phosphatase (STEP), and treatment with amyloid- $\beta$  reduced the phosphorylation of STEP. The authors used a dominant-negative fusion protein to provide further evidence that amyloid- $\beta$  dephosphorylates and activates STEP, which can dephosphorylate NMDA receptor subunits and thereby promote their endocytosis.

Further work will be needed to pin down the exact mechanism by which amyloid- $\beta$  can regulate the synaptic expression of NMDA receptors, and whether this accounts fully for the synaptic abnormalities that are found in Alzheimer's disease. Nevertheless, this finding could provide important new insight into the pathogenesis of Alzheimer's disease, as well as pointing towards potential new therapeutic targets.

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## References and links

**ORIGINAL RESEARCH PAPER** Snyder, E. M. *et al.* Regulation of NMDA receptor trafficking by amyloid- $\beta$ . *Nature Neurosci.* **8**, 1051–1058 (2005)



## IN BRIEF

### NEUROTECHNIQUES

Organically modified silica nanoparticles: a nonviral vector for *in vivo* gene delivery and expression in the brain.

Bharali, D. J. *et al.* *Proc. Natl Acad Sci. USA* **28** July 2005 (10.1073/pnas.0504926102)

Bharali *et al.* show that silica nanoparticles carrying binding sites for DNA can transfect neuronal cells with genes for enhanced green fluorescent protein (EGFP) or the nucleus-targeting fibroblast growth factor receptor type 1 (FGFR1). Transfection with FGFR1 caused reduced incorporation of bromodeoxyuridine into the DNA of cells in the subventricular zone and rostral migratory stream, which showed that the transfection controlled proliferation in these areas. Nanoparticles such as these might offer an alternative to viral vectors for gene delivery to the brain.

### TRANSPORTERS

Allelic heterogeneity at the serotonin transporter locus (*SLC6A4*) confers susceptibility to autism and rigid-compulsive behaviors.

Sutcliffe, J. S. *et al.* *Am. J. Hum. Genet.* **77**, 265–279 (2005)

Human serotonin transporter variants display altered sensitivity to protein kinase G and p38 mitogen-activated protein kinase.

Prasad, H. C. *et al.* *Proc. Natl Acad Sci. USA* **29** July 2005 (10.1073/pnas.0501432102)

Serotonin (5-hydroxytryptamine or 5-HT) transporters are an important target of drugs that are used to treat a number of disorders, including mood disorders and neurodevelopmental conditions, such as autism. Following on from findings that have implicated the gene for the 5-HT transporter (*SLC6A4*) in the aetiology of autism, Sutcliffe *et al.* find that multiple rare alleles at *SLC6A4* show significant linkage to and association with autism, which indicates that these alleles might cause an increased risk of the disorder. In another study, Prasad *et al.* show that different coding variants of the transporter gene have significant functional differences — in particular, they show variations in sensitivity to protein kinases that normally regulate the transporters. Altered 5-HT signalling could, therefore, contribute to an increased risk of psychiatric conditions.

### NEURODEVELOPMENT

Cellular mechanisms of dendrite pruning in *Drosophila*: insights from *in vivo* time-lapse of remodeling dendritic arborizing sensory neurons.

Williams, D. W. & Truman, J. W. *Development* **132**, 3631–3642 (2005)

Williams and Truman use multiphoton time-lapse imaging to study two types of dendritic pruning — local degeneration and branch retraction — that take place during early metamorphosis in *Drosophila melanogaster*. Local degeneration involves the severing of a branch after disruption of the microtubule cytoskeleton, whereas retraction occurs at the tips of branches or in stumps after severing. Local degeneration depends on the steroid ecdysone, and phagocytes are also important for severing branches.