reduces the expression of genes that are regulated by the transcription factors DAF-16 and HSF-1, resulting in a shortened lifespan. By knocking down *daf-2* in *C. elegans* that expressed human $A\beta_{1-42}$, the researchers showed that worms with longer lifespans had reduced toxic aggregation — late onset is therefore due to a compromised detoxifying activity rather than a stochastic accumulation. Double knockdown of *daf-2* with either *daf-16* or *hsf-1*, however, reversed this effect.

So, how do DAF-16 and HSF-1 inhibit the toxicity of protein aggregation? Examining the amounts of high molecular weight $A\beta_{1-42}$ aggregates and small $A\beta_{1-42}$ aggregates, Cohen and colleagues made several interesting findings. First, HSF-1 regulates the disaggregation of $A\beta_{1-42}$ aggregates, but DAF-16 does not. By contrast, DAF-16 mediates the formation of high molecular weight $A\beta_{1-42}$ aggregates, but these aggregates do not correlate with toxicity. Last, small $A\beta_{1-42}$ aggregates correlate with toxicity.

Together, these results are indicative of a mechanism that links ageing with late-onset AD. As aggregates develop, HSF-1 activity mediates their disaggregation. DAF-16 activity supports an alternative pathway (which perhaps functions as a back-up pathway) that mediates the formation of low toxicity, high molecular weight aggregates from high toxicity small aggregates. Because both detoxification pathways are mediated by the ageing-related insulin signalling pathway, both can become compromised with ageing, leading to aggregate build-up.

Interestingly, as the insulin signalling pathway is also associated with the formation of other toxic aggregates, such as those responsible for Huntington's disease, further research into this pathway could yield therapeutic targets for the general prevention of late-onset aggregation-linked neurodegenerative diseases.

Asher Mullard, Copy Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPER Cohen, E. *et al.* Opposing activities against age onset proteotoxicity. *Science* 10 August 2006 (doi:10.1126/science.1124646)

of proliferating cells in the ventricular zone (detected by BrdU labelling) was reduced in mutant brains, but the amount of cell death was unchanged, suggesting that extracellular glutamate concentration modulates neurogenesis at E16.

A laminar organization of the neocortex is usually seen by E16, but this pattern was severely disturbed in the brains of mutant mice, suggesting an impairment of cortical cell migration from the ventricular zone to other layers. BrdU labelling confirmed the presence of migration defects. Moreover, antibody staining revealed a disruption of radial glial fibres, which normally guide postmitotic neurons during migration. Neuronal tracing experiments with a fluorescent dye showed that these guidance defects resulted in severe disruptions to corticothalamic and thalamocortical pathways.

To confirm the involvement of excess glutamatergic signalling in these developmental defects, the authors administered antagonists of NMDA (*N*-methyl-D-aspartate receptors) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors to mutant mice. Treatment resulted in a partial restoration of the neocortical laminar structure, suggesting that signalling through these receptors does indeed modulate early brain developmental processes, but also that other mechanisms are important for these processes.

It will be interesting to determine which other neurotransmitter systems have a role in early brain development and to unravel the separate contributions of neuronal activity and genetic programming. The use of excess stimulation, in addition to genetic ablation, of neurotransmitter pathways might be one way to answer these questions.

Daniel McGowan

ORIGINAL RESEARCH PAPER Matsugami, T. R. *et al.* Indispensability of the glutamate transporters GLAST and GLT1 to brain development. *Proc. Natl Acad. Sci. USA* **103**, 12161–12166 (2006)

IN BRIEF

NEUROTRANSMITTERS

Deletion of the $GABA_A$ receptor α1 subunit increases tonic $GABA_A$ receptor current: a role for GABA uptake transporters.

Ortinski, P. I. *et al. J. Neurosci.* **26**, 9323–9331 (2006)

Mice lacking the gene for the α1 GABA (γ-aminobutyric acid) receptor subunit type A ($GABA_A$), a crucial component of $GABA_A$-mediated synaptic neurotransmission, exhibit remarkable functional compensation: despite missing more than half the normal number of $GABA_A$ receptors they show no overt phenotype. Ortinski *et al.* now show the mechanism of compensation to be an increase in 'tonic' $GABA_A$ receptor-mediated current through high-affinity non-α1-containing receptors. The abundance of these receptors was unchanged, but the level of extrasynaptic GABA was increased owing to a decrease in GABA transporter activity.

NEUROGENESIS

Neocortical neurogenesis in humans is restricted to development.

Bhardwaj, R. D. *et al. Proc. Natl Acad. Sci. USA* **103**, 12564–12568 (2006)

Debate over the existence of adult-born neurons in the neocortex is compounded by difficulties in assessing neurogenesis in humans. Now, evidence has emerged showing that, in the human cortex, no new neurons are added after birth. The authors employed a technique that takes advantage of changing levels of atmospheric ^{14}C during the twentieth century. From 1955 to 1963, ^{14}C levels increased owing to nuclear bomb testing, then rapidly declined. These changes are reflected in the ^{14}C content of DNA in cells becoming postmitotic during these periods. In post-mortem brain tissue, all neocortical neurons examined were demonstrated to have been present at birth, although the authors note that neurogenesis contributing to less than 1% of the total neocortical population would not have been detected by this method. These findings, together with evidence from BrdU studies, provide further evidence to suggest that neurons are not normally generated in the adult neocortex.

NEURODEGENERATIVE DISEASES

Ubiquitin hydrolase Uch-L1 rescues β-amyloid-induced decreases in synaptic function and contextual memory.

Gong, B. *et al. Cell* **126**, 775–788 (2006)

The ubiquitin–proteasome pathway is known to have a role in the pathogensis of Alzheimer's disease (AD). It now seems that inhibiting the activity of a component of this pathway, ubiquitin C-terminal hydrolase L1 (Uch-L1), is associated with impairments in long-term potentiation in slice cultures treated with oligomeric Aβ. Increasing Uch-L1 activity through treatment with exogenous Uch-L1 reversed this effect in the hippocampal slice cultures and in slices from *App/PS1* mice. Moreover, in *App/PS1* mice, exogenous delivery of Uch-L1 led to an improvement in contextual memory. Further work showed that the effect of Uch-L1 on synaptic function depended on the protein kinase A (PKA)-cyclic AMP response element binding (CREB) protein pathway. These findings highlight a potential therapeutic target for the memory difficulties in AD.