IN THE NEWS

Smart drugs

According to *BBC Online* (8 July), "A drug developed to help ward off the progress of dementia could increase the mental power of people without the illness." The story was reporting the results of a study carried out by Jerome Yesavage of Stanford University. He and his colleagues found that airline pilots performed better on a complex flight-simulator test after taking Aricept for a month than after taking a placebo.

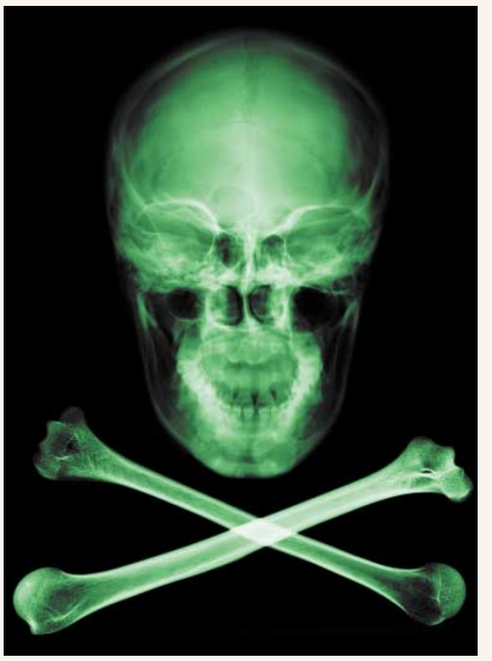
Aricept is an acetylcholinesterase inhibitor that is used to delay the progression of Alzheimer's disease. The results of the study indicate that it might also be a potential 'smart drug' — one that could increase memory or cognitive performance in people without Alzheimer's or other diseases.

Such a suggestion is highly controversial. The idea that students might take it during their degree courses, or that parents could use it to improve their childrens' performance on school tests, has led to debates about whether smart drugs are ethical or desirable. It is feared, for example, that the availability of such drugs — at a cost — could widen the gap between rich and poor. But the effects found in the study were small — Yesavage told the *New York Times* (9 July), "It's not something where people will jump up after a month and say, 'I'm a heck of a lot smarter.'"

Rachel Jones

NEURODEGENERATIVE DISORDERS

The one-hundred faces of neuronal death



The expansion of a CAG trinucleotide in a variety of genes results in the so-called polyglutamine diseases, a group of disorders that includes Huntington's disease and several forms of spinocerebellar ataxia (SCA). How this expansion leads to the neuropathological changes that characterize such diseases is less clear. Three recent papers illustrate this fact by identifying different ways in which expanded polyglutamine stretches can lead to neurotoxicity.

Aggregation of the affected proteins seems to be a prerequisite for their deleterious effects, and Meriin *et al.* report that a prion protein participates in the aggregation process. They developed a yeast model of polyglutamine toxicity, expressing huntingtin fragments with expanded glutamine stretches of different lengths. Such a model could potentially be an efficient system for the pharmacological and genetic screening of modifiers of aggregation and toxicity. The authors screened for the contribution of several chaperones to the effects of huntingtin, and identified two classes of proteins in which deficiencies led to a suppression of the initiation and the expansion of aggregates, respectively. But as some of these chaperones also participate in prion propagation in yeast, the authors wondered whether a prion protein might be involved in aggregation. Indeed, they found that eliminating the prion protein Rnq1 from wild-type yeast suppressed huntingtin aggregation. This raises the intriguing possibility that a prion-like protein might be similarly involved in the polyglutamine disorders.

Once the aggregates are formed, their toxicity might depend on mechanisms such as oxidative stress, mitochondrial dysfunction and proteasomal dysfunction. Nishitoh *et al.* added another possibility to this list by showing that polyglutamine aggregates induce endoplasmic reticulum (ER) stress. They investigated the effect of expressing a polyglutamine fragment of ataxin-3, a protein that is involved in the pathogenesis of SCA3. They reasoned that if the aggregates affected proteasomal function, this might influence the degradation of unfolded proteins that are produced at a normal rate. As unfolded proteins accumulate in the ER, Nishitoh *et al.* tested whether expression of the mutant ataxin-3 in PC12 cells and neurons led to ER stress. They found that the activity of IRE1 and PERK, two kinases that mediate ER stress responses, was elevated after expression of the mutant protein, an effect that was associated with proteasomal dysfunction, and that ultimately led to cell death. Importantly, ER stress also activated the apoptosis-signal-regulating kinase ASK1, and the authors provided evidence that this protein might serve as a link between IRE1 and downstream apoptotic pathways. ASK1 might therefore be a new target for the treatment of polyglutamine disorders.

But not all of the literature agrees on the idea that polyglutamine disorders result from toxicity of the aggregates. Some authors have even proposed that the aggregates might represent a protective mechanism — an attempt of the cell to sequester the mutant protein to reduce its intrinsic toxicity. In a third study, Watase *et al.* provided evidence in support of this idea by introducing an expanded polyglutamine stretch into the endogenous mouse ataxin-1 in an attempt to generate a new model of SCA1. The mutant mice showed many of the symptoms that characterize SCA1, including loss of motor coordination and Purkinje cell degeneration. But strikingly, the authors found that the mutant ataxin-1 was most soluble in the brain regions that were most vulnerable to deterioration; Purkinje cells did not form aggregates until advanced stages of the disease. So, the neurons that cannot capture the mutant protein in aggregates suffer the worst functional damage in this model.

Although these papers highlight the many routes to cell death in polyglutamine disorders, they also remind us that these diseases form a heterogeneous group, and that a universal remedy for such conditions might not exist.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPERS Meriin, A. B. *et al.* Huntingtin toxicity in yeast model depends on polyglutamine aggregation mediated by a prion-like protein Rnq1. *J. Cell Biol.* **157**, 997–1004 (2002) | Nishitoh, H. *et al.* ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev.* **16**, 1345–1355 (2002) | Watase, K. A long CAG repeat in the mouse *Sca1* locus replicates SCA1 features and reveals the impact of protein solubility on selective neurodegeneration. *Neuron* **34**, 905–919 (2002)
FURTHER READING Gusella, J. F. & MacDonald, M. E. Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease. *Nature Rev. Neurosci.* **1**, 109–115 (2000)