Alzheimer's disease – a metallic problem

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Scientists in Australia and the USA believe they can prevent the deposition of β-amyloid (Aβ) protein and dissolve the amyloid plaques characteristic of Alzheimer's disease (AD). Ashley Bush (Massachusetts General Hospital East, MA, USA) and colleagues at the University of Melbourne (Melbourne, Australia) propose that oxidative damage in the neocortex associated with AD is potentiated by a build-up of metal ions, in particular, copper[1]. Moreover, they believe that chelation of these ions will reduce the oxidative burden, lower Aβ levels and improve the symptoms of AD. Currently, they and colleagues at Prana Biotechnology (Melbourne, Australia) are evaluating the clinical effects of the targeted delivery of the copper and zinc ion chelator PBT1 (clioquinol), a molecule currently used in antifungal preparations (Fig. 1).

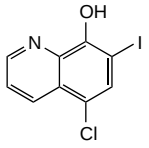

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Figure 1. Chemical structure of clioquinol.

Aβ plaques are characteristic of AD and, until recently, were seen as permanent features of the disease. 'In the past, these plaques were considered to be the cause of AD, but now we think they are like bomb craters in a war; they represent battles but not the cause of the war,' says Bush. The emphasis in AD research has been on limiting the build-up of these plaques, but research by Bush and colleagues suggests that it might be possible to block the vicious cycle of

oxidative damage that leads to plaque deposition (Bush, A.I. *et al*. *In vivo* inhibition of Aβ amyloid formation in a transgenic mouse model for Alzheimer's disease following oral treatment with a copper/zinc chelator. *Society for Neuroscience 30th Annual Meeting*, New Orleans, LA, USA, 7 November 2000, http://www.sfn.org/).

Oxidative burden

Aβ is a metalloprotein that binds copper and iron, explains Bush. It converts molecular oxygen into hydrogen peroxide by reducing copper or iron although, he says, it binds particularly strongly to copper. Hydrogen peroxide is a pro-oxidant that might be responsible for much of the oxidative damage in the brains of people with AD, including the deposition of amyloid plaques[2]. Therefore, accumulation of Aβ is both a result and a cause of oxidative stress: 'It is a chicken-and-egg situation and we do not yet know what triggers the problem,' says Bush. 'My suspicion is that an event, such as reduced blood perfusion caused by stroke or head injury, causes oxidative stress and triggers this vicious circle of activity.'

According to Bush, similarly abnormal reactions between proteins and metal ions underlie several neurological disorders, including AD, prion diseases and Parkinson's disease[3]. He proposes that these diseases share three common features: oxidation of neural tissue mediated by an interaction between a redox-active metal ion and a target protein, protein aggregation in that tissue, followed by functional decline[3].

Metal ion chelation

PBT1 chelates copper and zinc but chelates copper by a couple of orders of magnitude more strongly, explains Bush. Its ability to chelate copper enables it to inhibit the production of hydrogen peroxide by Aβ, diminishing the oxidative burden. However, an accumulation of zinc in amyloid plaques appears to be the brain's way of reducing the oxidative burden caused by Aβ (Ref. 4). Zinc levels are extremely high in amyloid plaques and Bush and colleagues propose that the metal acts as an antioxidant and precipitates Aβ deposition in plaques to stop hydrogen peroxide production.

'These plaques are associated with activation of the microglial system,' explains Bush. 'We think that the microglial system releases zinc and causes Aβ to be deposited. Because zinc shuts down hydrogen peroxide formation in Aβ, this could be a successful if incomplete defence mechanism,' he says. In theory, chelation of zinc by PBT1 could negate the beneficial effects of copper chelation, but Bush believes: 'The ability to chelate copper trumps this potential disadvantage.'

Bush and colleagues evaluated PBT1 in transgenic mice that over-produce Aβ and possess deposits in the brain similar to those seen in people with AD. After 12 weeks of treatment, established amyloid deposits disappeared from some mice and were reduced in others (Bush, A. *et al.*, http://www.sfn.org/). In a subsequent study, treatment induced a 50%

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reduction in total Aβ levels and a reduction in plaque surface area (Bush, A. *et al.*, http://www.sfn.org/).

Clinical studies

PBT1 is now in Phase II clinical trials in 50 patients with mild-to-moderate AD at the Health Research Institute of Victoria and the University of Melbourne. So far, 15 patients have been recruited to the 6-month study that is expected to report results in about a year's time. Results from earlier studies are expected to be submitted for publication in early 2001.

Most (80%) Aβ in the brain is present in an insoluble, diffuse form, a further 2% being soluble. The rest is in plaques. 'We are targeting the soluble and diffuse deposits and are indifferent to the plaque deposits, although they do seem to be reduced with treatment,' says Bush. He believes that this approach has advantages over others, such as blockade of the secretase enzyme involved in Aβ deposition and immunological approaches, in that it effectively leaves Aβ alone; 'We do not assume that Aβ is of no use,' he says.

PBT1 is targeted at the brain and therefore should not affect copper and ion levels in the rest of the body. Carol A. Scorer, Head, Alzheimer's Disease Research at GlaxoWellcome (Stevenage, UK) will be interested to see if metal chelation in the brain proves to be safe and tolerable, given the need for tight homeostatic regulation of metal ion levels in the body. In light of the evidence that Aβ trapped in plaques appears to be less toxic than the soluble or diffuse form of the protein, she also questions the safety of dissolving the plaques and releasing Aβ: 'It is possible that it could be harmful to solubilize a large quantity of deposited amyloid within the brain,' says Scorer. 'The key issue will be whether the solubilized amyloid is rapidly and harmlessly cleared,' she adds. This is a question that presumably will be answered in forthcoming publications from the research group.

References

1 Huang, X. *et al.* (1999) Cu(II) potentiation of Alzheimer Aβ neurotoxicity. *J. Biol. Chem.* 274, 37111–37116

2 Huang, X. *et al.* (1999) The Aβ peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry* 38, 7609–7616

3 Bush, A.I. (2000) Metals and neuroscience. *Curr. Opin. Chem. Biol.* 4, 184–191

4 Cuajungco, M.P. *et al.* (2000) Evidence that the β-amyloid plaques of Alzheimer's disease represent the redox-silencing and entombment of Aβ by zinc. *J. Biol. Chem.* 275, 19439–19442

Immunization blocks gastrin's ability to promote tumour cell division

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A novel immunotherapy to target gastrointestinal cancers has now reached Phase III clinical trials. Patients with Stages III and IV pancreatic cancer and Stage IV stomach cancer are currently being recruited to test a vaccine-like therapy that blocks the action of gastrin. In the UK/Europe multicentre trial, the Phase III study will compare the anti-G17 immunogen, developed and produced by Aphton Corporation (Miami, FL, USA) with gemcitabine, the best chemotherapeutic agent available for pancreatic cancer. In the US-based trial, anti-G17 will be given in combination with gemcitabine and compared with a group receiving gemcitabine only, both for ethical reasons (gemcitabine is the approved drug for pancreatic cancer in the US) and to investigate a possible synergy between the two treatments.

Gastrin as a growth factor

During the past 10–15 years, gastrin has been identified as the central trophic factor for gastrointestinal cancers and has therefore emerged as a potential anticancer target. There are several forms of gastrin; the precursor molecule preprogastrin is cleaved by an endopeptidase to progastrin, which is further processed to glycine-extended gastrin 34 and to

gastrin 34. These 35- and 34-amino acid peptides can be cleaved to form glycine-extended gastrin 17 and gastrin 17, respectively. Cells with gastrin receptors can respond to mature amidated forms

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