News in brief

CNS disorders

Fruitful research for Alzheimer's

Scientists have identified a new way in which Alzheimer's disease (AD) kills brain cells [1]. The research, conducted at the Department of Neurology, University of California at Los Angeles (UCLA; CA, USA), used genetically engineered fruit flies to imitate the molecular symptoms of human dementia.

Some neurodegenerative disorders, such as AD, progressive supranuclear palsy and frontotemporal dementia, are a result of abnormal 'tangles' in the brain, caused by the microtubule-associated protein tau; magnification of these tangles shows that the tau protein is altered by phosphorylation. George Jackson, Principal Investigator and UCLA Professor of Neurology, said: 'Does the altered tau cause the tangles – or do the tangles cause the alteration? We created a fruit fly model to find out.'

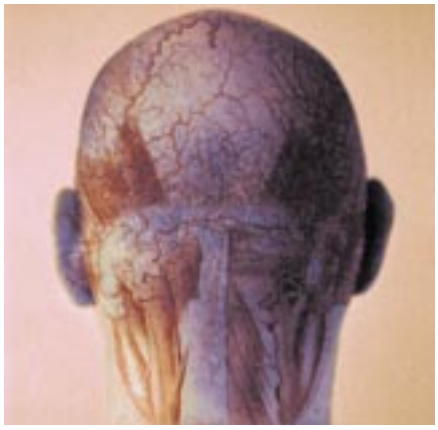
The UCLA researchers engineered flies that produced human tau in their eyes; the cells were observed to develop abnormally and die rapidly. 'The retina opens a window into the brain,' said Jackson. 'These findings imply that there is indeed a causal relationship between tau modification and cell death.'

While searching for a genetic pathway that could serve as a potential drug target, the scientists evaluated the influence of other proteins on the death of the nerve cells. It was found that manipulation of the 'wingless' pathway, which is a cluster of genes responsible for early brain development in both humans and flies, affected cell degeneration. The gene 'shaggy', in particular, demonstrated the most effect. Daniel Geschwind, UCLA Assistant Professor of Neurology and co-author of the study, said: 'We found that increasing the amount of shaggy worsened degeneration of nerve cells.'

This increase in expression of shaggy led to a breakthrough result. The appearance of tau-laced tangles that resemble those found in AD brains began to appear in the flies' eyes. 'We think this discovery could provide an important tool for testing future therapies to treat Alzheimer's and other neurodegenerative disorders,' said Geschwind. These findings could lead to an inexpensive way to speed up drug development for AD.

1 Jackson, G.R. *et al.* (2002) Human wild-type tau interacts with *wingless* pathway components and produces neurofibrillary pathology in *Drosophila*. *Neuron* 34, 509–519

Homocysteine: a culprit in brain atrophy and vascular disease



Elevated levels of the amino acid homocysteine have been significantly linked to brain atrophy and vascular disease and could be involved in the onset of neurodegenerative diseases such as Alzheimer's disease (AD) [2]. In a study of 36 healthy, elderly individuals, blood levels of homocysteine were measured and compared with magnetic resonance imaging (MRI) scans showing the amount of brain atrophy. Homocysteine was found to have a significant positive relationship with measurements of central atrophy.

In contrast to previous work, a related study of 43 people with AD and 37 healthy, elderly individuals showed that elevated levels of homocysteine are related to vascular disease but not directly to AD pathology [3]. This was concluded from data showing that the relationship between levels of homocysteine and vascular disease were only significant in two subjects with AD. Furthermore, patients with AD were found to be 12 times more likely to have low plasma homocysteine levels. These findings suggest that low levels of homocysteine might contribute to the vascular disease that could mediate AD, and that depletion of vitamin B_6, which determines homocysteine levels, could also be involved in the onset of the disease. If these results can be confirmed by other studies, the promise of preventing AD simply by taking supplements of vitamin B_6 and/or homocysteine could be a reality.

2 Sachdev, P.S. *et al.* (2002) Relationship between plasma homocysteine levels and brain atrophy in healthy elderly individuals. *Neurology* 58, 1539–1541

3 Miller, J.W. *et al.* (2002) Homocysteine, vitamin B6 and vascular disease in AD patients. *Neurology* 58, 1471–1475

Inflammatory protein implicated in AD and vascular dementia

Elevated levels of the inflammatory signalling protein, high-sensitivity C-reactive protein (hsCRP), have been shown to correspond with an increased risk of developing either AD or vascular dementia [4]. Analysis of the stored blood of 214 Japanese–American men with dementia and 828 without dementia from the ongoing Honolulu–Asia Aging Study showed that middle-aged men who had elevated levels of hsCRP had a three-fold risk for developing either of the two diseases.

'This is the first study to show that markers of inflammation are raised long before clinical dementia appears,' said Lenore J. Launer, a researcher at the National Institute for Aging (Bethesda, MD, USA). These findings correlate with previous studies that implicate inflammatory processes in the development of AD, but the mechanism of this is not yet understood.

4 Schmidt, R. *et al.* (2002) Inflammation and dementia: a 25-year follow-up of the Honolulu–Asia Aging study. *Ann. Neurol.* 10.1002/ana.10265 (www.interscience.wiley.com)

Cardiovascular disease

Hypertension drug can reduce pulse pressure and reverse vessel stiffness

Omapatrilat, a vasopeptidase inhibitor currently in clinical trials for hypertension, has been shown to reduce pulse pressure

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and vessel stiffness in large arteries, an effect that would be desirable in the control of hypertension [5]. Vessel stiffness causes an increase in systolic blood pressure, the pressure that occurs when the heart contracts, and affects 90% of the 50 million people with hypertension in the USA. Until now, the stiffening of large central arteries was thought to be an irreversible effect of aging but now researchers at Cardiovascular Engineering (Holliston, MA, USA) have shown that the first of a new class of vasopeptidase inhibitor drugs is more effective at reducing vessel stiffness than the well known hypertension drugs, angiotensin-converting enzyme (ACE) inhibitors.

In a 12-week, double-blind trial called Conduit Hemodynamics of Omapatrilat International Research Study (CHOIRS), 167 patients with moderately high blood pressure were treated with either enalapril (an ACE inhibitor) or omapatrilat. As well as blocking production of the vasoconstricting hormone angiotensin, omapatrilat also increases the levels of vasodilatory peptides, such as the natriuretic peptides (NPs). It is thought that NPs act favourably on arteries and might prevent them becoming stiff.

The group used a measurement of pulse pressure to compare the two treatments. Pulse pressure is the difference between the systolic and diastolic blood pressure values, and elevated pulse pressure is an indication of stiffening in large central blood vessels such as the aorta. Omapatrilat was significantly more effective than the ACE inhibitor at reducing both peripheral blood pressure and pulse pressure, and this reduction in pulse pressure is thought to be attributable to the observed reduction in stiffness of the aorta. It is hoped that the magic combination of decreased vasoconstriction and enhanced vasodilation mediated by omapatrilat will translate into improved clinical outcomes.

5 Mitchell, G.F. *et al.* (2002) Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension. *Circulation* 10.1161/01.CIR.0000020500.77568.3C (http://circ.ahajournals.org)

Tea – good for the heart?

A recent report [6] suggests that drinking caffeinated tea on a regular basis could help protect patients who have suffered a heart attack.

Tea has long been studied for its benefits to health, partly because it contains flavonoids and other antioxidants that have been hypothesized to prevent cardiovascular disease (CVD). For example, flavonoids inhibit the oxidation of low-density lipoprotein cholesterol, and could therefore lower the atherogenicity of the compound. However, epidemiological evidence for the effects of tea or flavonoid consumption is conflicting.

A new study, led by Kenneth J. Mukamal (Beth Israel Deaconess Medical Center, Boston, MA, USA), tested the hypothesis that tea consumption in patients who have previously suffered a heart attack leads to better long-term survival. Patients were questioned four days after they had suffered a heart attack. The researchers then followed up the 1900 patients 3.8 years after their attack, and found that those who were classed as heavy tea drinkers (>14 cups of tea a week) had 'a significantly lower mortality rate than non tea-drinkers'.

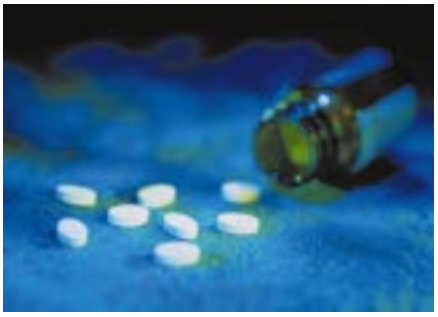
Mukamal is quick to point out that these differences could also be accounted for by differences in life style, although the study did control for differences where possible. He cautions that controlled clinical studies are needed to be able to establish a firm link between tea consumption and reduced mortality, but these results do suggest that the humble cuppa might be more than it seems.

6 Mukamal, K.J. *et al.* (2002) Tea consumption and mortality after acute myocardial infarction. *Circulation* 105, 2476–2481

Aspirin and the vascular system

The beneficial effects of aspirin are again in the spotlight with recent reports that aspirin can protect blood vessels from the effects of even mild inflammation [7].

Researchers led by Patrick J.T. Vallance (University College, London, UK) generated an inflammatory response using a typhoid vaccine in 17 healthy volunteers, 12 of whom had been given either a placebo or 1.2 g of aspirin two hours before vaccination. They then measured the levels of interleukin 1 (IL-1), an inflammatory factor, and found that, in the placebo group, IL-1 levels peaked at three hours and remained elevated until eight hours after vaccination, whereas there was no change from baseline in the group who had received aspirin before vaccination. The researchers also recorded the ability of the blood vessels to expand, by measuring the flow of blood in an arm of each volunteer once a drug affecting the endothelium had been injected into the same arm. Eight hours following vaccination, those volunteers who had received placebo had a decreased flow of blood, indicating a temporary stiffening of their arteries; by comparison, those who had received aspirin showed no decrease in blood flow, thus indicating that aspirin might be having a protective effect.



It seems, therefore, that there might be more to the humble aspirin that just its blood-thinning properties. 'This is an exciting opportunity to rethink how we use aspirin and whether there are situations in which we should be giving aspirin to reduce cardiovascular risk', says Vallance.

On a slightly different note, researchers have found that if ibuprofen is taken before aspirin [8], it reduces the ability of aspirin to stop platelets clumping. Although the

researchers suggest that ibuprofen taken occasionally is unlikely to hinder the beneficial effects of aspirin, it might be better to use a different form of painkiller if it is taken on a regular basis for weeks or months.

7 Kharbanda, R.K. *et al.* (2002) Prevention of inflammation-induced endothelial dysfunction: a novel vasculo-protective action of aspirin. *Circulation* 105, 2600–2604

8 Burnakis, T.G. *et al.* (2002) Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N. Engl. J. Med.* 346, 1589–1590

Cancer targets and mechanisms

Clues to how vitamin E protects the prostate

Vitamin E has long been implicated in the prevention of prostate cancer, however the mechanism of its protective action is not fully understood. Scientists at the University of Rochester (Rochester, NY, USA) have now shown that exposure of prostate cancer cells to vitamin E succinate (VES) suppresses the expression of prostate specific antigen (PSA) – a marker of prostate cancer – by as much as 90% and also suppressed expression of the androgen receptor (AR), which is a key signalling molecule in the progression of the disease [9].

VES inhibition of the AR was by transcriptional and post-transcriptional modification and was shown to be selective because VES does not suppress other nuclear receptors. Researchers also observed a 25–50% decrease in the number of cancer cells, a more significant decrease than that caused by the antiandrogen, hydroxyflutamide, which is the current treatment for prostate cancer. When hydroxyflutamide and VES were added simultaneously to cancer cells, an additive cytotoxic effect was observed. These findings suggest that VES might suppress androgen/AR mediated cell growth and expression of PSA by inhibited AR, and the knowledge of this mechanism could lead to new therapeutic approaches against prostate cancer.

9 Zhang, Y. *et al.* (2002) Vitamin E succinate inhibits the function of androgen receptor and the expression of prostate-specific antigen in prostate cancer cells. *Proc. Natl. Acad. Sci. U. S. A.* 99, 7408–7413

Resurrection for old cancer drugs?

A group of anti-cancer drugs that were unsuccessful in clinical trials might still be useful in the fight against the disease. Maytansinoids were first discovered in the 1970s but were found to be too potent and toxic for use. However, researchers at the University of Washington (Seattle, WA, USA) have identified a cluster of genes that could enable them to modify the structure of maytansinoids through genetic engineering [10].

Tim-Wein Yu and colleagues cloned two gene clusters that are essential for the biosynthesis of the maytansinoid, ansamitocin, from a cosmid library of *Actinosynnema pretiosum*. They identified a set of genes that are involved in biosynthesis of the starter subunit, 3-amino-5-hydroxybenzoic acid (AHBA). The discovery of two AHBA synthase gene homologues is thought to be of note because it suggests that each homologue might have a different role in the formation of the starter subunit.

In addition to these genes of interest, the team identified several other genes encoding enzymes for each step of the biosynthesis pathway, as well as some open reading frames (ORFs) thought to be involved in postsynthetic modifications such as methylation, epoxidation and the introduction of acyl and carbamoyl groups. Work is already under way to confirm the functions of these genes so that the group can begin to modify the structure of these highly potent compounds.

10 Yu, T-W. *et al.* (2002) The biosynthetic gene cluster of the maytansinoid antitumor agent ansamitocin from *Actinosynnema pretiosum*. *Proc. Natl. Acad. Sci. U. S. A.* 99, 7968–7973

Miscellaneous

Barr challenges patents protecting Remeron™ SolTab®

Barr Laboratories (Pomona, NY, USA) is being sued by Akzo Nobel (Arnhem, Netherlands) and Organon (West Orange, NJ, USA), thereby initiating Barr's challenge to the patent held by Akzo protecting its product, Remeron™ SolTab®, an orally disintegrating tablet formulation of mirtazepine. The suit, filed on 3 May 2002, aims to prevent Barr from commercializing their generic version of the anti-depressive drug.

'We continue to focus on challenging patents where we believe an invalid or non-infringed patent unnecessarily prevents consumers from enjoying the benefits of a more affordable version of a brand product,' said Bruce L. Downey, Chairman and CEO of Barr. Remeron™ SolTab® has annual sales of approximately US$59 million.

Pharmaceutical market still growing despite gloom

The pharmaceutical market grew 12% in 2001 despite a downturn in the world economy and gloom about the industry from financial analysts, according to figures from IMS Health (Fairfield, CT, USA).

Profit warnings from major players Merck (Whitehouse Station, NJ, USA), Bristol-Myers Squibb (New York City, NY, USA) and Eli Lilly (Indianapolis, IN, USA), as well as the growing threat of patent expiry and increased political pressure to lower the cost of drugs had led to a pessimistic outlook. However, in 2001 sales grew 17% in the crucial US market and 10% in Europe, taking the market's total global worth to US$364.2 billion per year.

'It is normal for individual companies to go through ups and downs,' said Joe Zammit-Lucia, President of Cambridge Pharma Consultancy (Cambridge, UK), which is owned by IMS. 'But this is still a very good industry for investors,' he said.

In the same time period, Pfizer's cholesterol-lowering drug Lipitor displaced Prilosec (AstraZeneca) as the world's top-selling drug, with sales rising by 31% to US$7 billion. Four of the top-ten therapeutics categories for drugs (cholesterols, antipsychotics, diabetes treatments and antihistamines) increased sales by more than 20%. However, these levels of growth are not expected to continue with levels for next year predicted at 11–12%.

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