memory in rats by the lead compound, CX516 [Fig. 1; 1-(1,3-benzodioxol-5-yl-carbonyl)piperidine]. In the short-term memory test, trained male rats were initially allowed to retrieve rewards from four arms of an eight-arm maze with the other arms blocked. Four hours later the rats were released into the same maze, with all arms unblocked, and the number of 'incorrect' entries measured. Medium-term memory was tested using a two-odour discrimination task in which mature male rats were rewarded for selecting the 'correct' odour four days after initial training. In each case, rats that had been injected with CX516 before the initial training session performed significantly better than controls.

In another example, similar rats were injected with CX516 or vehicle on alternate days[5]. Their performance in a delayed nonmatch-to-sample (DNMS) test was shown to increase over a period of 32 days. Control rats that received only vehicle showed no improvement throughout the trial. Interestingly, the improvement in the experimental group continued on the days when they only received vehicle.

Human studies

The term 'age-associated memory impairment' covers a spectrum of conditions, ranging from normal memory decline to dementia. CX516 has been shown to improve recall of nonsense syllables in a double-blind trial in normal elderly volunteers[6]. Volunteers were aged 65–76 years and were tested in groups of ten (six placebo and four drug) over a period of three months. On average, volunteers taking the highest concentration of drug (900 mg) recalled over twice as many nonsense syllables after 5 min as those receiving placebo.

The upcoming trial of CX516, funded by the Institute of Aging, focuses on a group intermediate between these volunteers and AD patients: individuals with MCI. Patients diagnosed with MCI perform worse in memory tests than normal individuals of similar ages and educational levels, but are otherwise cognitively normal[7]. Although MCI has many possible causes, approximately 15% of patients with this condition develop AD every year.

Ronald C. Peterson, a neurologist at the Mayo Clinic (Rochester, MN, USA) and a key researcher in this field, says 'If we could cut this number [of MCI patients progressing to AD] in half using medications, there would be positive implications for quality of life.' The US government is already funding an evaluation of Vitamin E and Pfizer's Aricept (which is already licensed for mild to moderate AD) in slowing the progression of MCI patients to dementia.

Simmon is optimistic about the prospects for Ampakines for this group of individuals: 'We believe that it will be possible to improve memory in patients with MCI, rather than just slowing its decline.' More potent and specific AMPA modulating agents in this series, which are still in preclinical development, could be even more promising as treatments for this and other memory disorders.

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Clare Sansom

News in brief

More reasons not to eat those chips!

Recent research at the Case Western Reserve University School of Medicine and University Hospitals of Cleveland (Cleveland, OH, USA) indicated that eating a high-fat diet in early and mid-adulthood might increase the probability of developing Alzheimer's disease in later life. This work, reported at the recent *World Alzheimer Congress 2000*, showed that the risk is increased in individuals with the ApoE-e4 allele marker, which is known to be linked to the development of Alzheimer's disease.

Researchers retrospectively analyzed foods consumed by 304 individuals (~70 years of age): 72 had Alzheimer's, 232 were healthy. Individuals with the ApoE-e4 allele who ate a higher-fat diet increased the risk of developing Alzheimer's by seven-fold, relative to those who did not possess this marker and ate a lower-fat diet.

It was found that 40–59 year-olds with the ApoE-e4 allele consuming high-fat diets (40% calories from fat) had a 29-fold increased risk of developing

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Alzheimer's relative to those without this allele who consumed similar diets. Those with a lower-fat diet (<35% fat) had only a four-fold increase in risk of developing Alzheimer's compared with those without ApoE-e4 who ate a similar diet.

These results support the idea that systems that influence the onset of Alzheimer's disease can occur in early adulthood.

NMI870 combats impotence in post-menopausal women

The female sexual arousal disorder (FSAD) drug NMI870 has shown positive Phase II clinical results. These results were recently announced by the University of Texas (Austin, TX, USA) psychologist, Cindy Meston at the *UT Academy of Sex Research Conference* in Paris, France. The therapy, a nitric oxide-enhanced compound of the α_2-adrenoceptor antagonist, yohimbine, increased vaginal blood flow in post-menopausal women suffering from FSAD. The study, a randomized, double-blind, placebo-controlled, three-way crossover clinical trial, used 24 post-menopausal FSAD sufferers and compared the effects of orally administered NMI870 with yohimbine alone and with placebo. The response of the patients was measured using vaginal photoplethysmography, a proven psychophysiological sexual arousal evaluation technique.

Emerging HIV drug resistance in Africa

HIV drug resistance monitoring systems (Virco, Durban, South Africa) have identified the development of substantial HIV drug resistance in African countries, where antiretrovirals were first used in the African continent.

Two studies were conducted in association with the UNAIDS Drug Access Initiative. In Uganda, it was shown that 78% of patients administered 3TC were infected with a drug resistant virus, and 20% of those treated with AZT were resistant. In Cote d'Ivoire, HIV resistance to AZT was present in 43% of patients, and 15% were resistant to 3TC.

The UNAIDS Drug Access Initiative was launched in 1997, and is developing healthcare infrastructure and HIV drug delivery in Cote d'Ivoire, Uganda, Vietnam and Chile.

'Inevitably, where HIV is treated, resistance will follow,' said Brendan Larder, Vice President of R&D at Virco, 'The worrying aspect of these studies is that resistance appears to be developing very quickly, and this raises concern about the way drugs should be used.'

Eat chocolate to stay healthy

Workers at the University of California (Davis, CA, USA) have recently concluded that cocoa-enriched beverages inhibit platelet activation for up to 6 h after ingestion. The results of the research, carried out using healthy, non-smoking adults, suggest that moderate intake of cocoa-containing foods could, in the long-term, reduce the risk of developing heart disease. Heart disease is caused by unwanted blood clots preventing the smooth flow of blood around the body. It is thought that cocoa, a rich source of the natural plant antioxidant flavanoids, could inhibit platelet aggregation using a similar mechanism to aspirin and red wine.

Brain abnormalities detected by radiology in children with BPAD

A radiological approach has been used at the University of North Carolina (NC, USA) to detect brain abnormalities in children with bipolar affective disorder (BPAD). If such abnormalities are found to be characteristic of BPAD, this method could be used to test for BPAD or to facilitate its clinical diagnosis.

A recent report described the examination of ten children with BPAD using proton MR spectroscopy[1]; they found increased levels of glutamate and glutamine metabolites, and increased lipid levels, compared with healthy individuals. The authors propose that an increase in metabolite concentration indicates irregular neurotransmitter activity in the brain, and this could be responsible for the complexity experienced in the treatment of BPAD with drugs.

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Combating cancer with coffee

Oncology Sciences Corporation (OSC; Austin, TX, USA) have announced a novel patent-pending method of roasting coffee beans that increases the availability of polyphenols, which are antioxidants known to inhibit cancer tumours. Polyphenols occur naturally in coffee and tea, and offer protection against cardiovascular and inflammatory diseases, immune dysfunction and other degenerative diseases.

Roasting, which gives coffee its flavour and smell, involves heating green coffee beans to 204.4°C, at which point they darken and oils appear. However, during the traditional roasting process, ~70% of polyphenols are destroyed. OSC say that with their new process, the flavour remains the same but there is a 35% increase in the availability of residual polyphenols.

OSC and AMC Cancer Research Center (Denver, CO, USA) are carrying out further research on this novel process, and anticipate producing coffee that contains 200% more polyphenols than traditional coffee. 'Relative to cancer, there is an inverse association between the intake of polyphenols and the incidence of all cancers,' said Thomas Slaga, President and CEO of AMC.

Focus turns from human genome to determination of gene function

Over one-third of the mouse genome has now been altered by way of 'gene knockout' in an effort to facilitate the determination of individual gene function.

The work, carried out by Lexicon Genetics (The Woodlands, TX, USA), rests on the similarity of the mouse genome to that of humans. It is hoped that experimenting with knockout-mice gene models will provide insight into how individual genes function in the human body, and possibly help improve current methods of drug discovery. It is also hoped that some of these knockout-validated genes might themselves encode for therapeutic proteins.

Effect of cocaine and alcohol worse together

Patients ingesting cocaine and alcohol in tandem exhibit more impulsive decision-making and poorer performance in tests of learning and memory than those who take only one of the drugs, concluded a recent study[2]. The study, carried out by Jean Luc Cadet of National Institute on Drug Abuse (Baltimore, MD, USA) and Karen Bolla of John Hopkins Medical Institute (Baltimore, MD, USA), examined 56 cocaine users who also regularly consume at least ten alcoholic drinks per week. The participants were then asked to abstain from both drugs for a month, and had their general intelligence, verbal memory, learning, attention, planning and mental flexibility tested at the beginning and end of this period. The results of the study indicated that a cumulative level of impaired mental ability persists for a month after abuse stops.

'[The test] has significant implications for drug abuse treatment, which involves learning and remembering concepts that help recovering drug abusers to change behaviours and avoid situations where they might use drugs', said Alan Leshner, National Institute on Drug Abuse Director.

2 Bolla, K.I. *et al.* (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology* 54, 2285–2292

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