Furberg goes over the top on calcium channel antagonists

In March 1995, Dr Bruce Psaty (University of Washington, Seattle, USA) shook the world of cardiology when he presented a case control study at a meeting in San Antonio in which it was claimed to show that, compared with other agents, calcium channel antagonists (CCAs) are associated with a higher risk of heart attack when used to treat hypertension. The matter has been debated in the literature ever since, and one of the main critics of CCA safety has been Curt Furberg, Professor of Public Health, Bowman Gray School of Medicine, Winston-Salem, NC, USA. Consequently, one of the hottest items at the *45th Annual Scientific Session of the American College of Cardiology*, held in Orlando in March 1996, was a debate on this topic between Professor Furberg and Dr Robert Roberts (Baylor College of Medicine, Houston, TX, USA).

An audience of about 3,000 attendees assembled for the start of the debate at 8.30 am, probably helped by the rumour that Furberg was going to present some fresh information. The initial sessions in which Furberg presented his thesis and Roberts attempted to demolish it were relatively uneventful and revisited information published in the literature in the previous 12 months. Briefly, Furberg maintains that there are no good long-term safety data on CCAs and he sees them as, at best, third-line treatments and, if indicated, he believes verapamil may be better than dihydropyridines such as nifedipine. He also slated what he saw as an unhealthy relationship between doctors and the pharmaceutical industry, citing the latter's sponsorship activities in areas such as research and conferences. Roberts countered these claims, suggesting that case-control studies were the lowest form of epidemiological tool, usually only useful to generate and test hypotheses. He cited a number of distinguished cardiologists who have criticized the Psaty study and some, such as Dr Franz Messerli (Ochsner Medical Clinic, New Orleans, LO, USA) have even found methodological errors in the way in which it was performed.

However, it was only when Furberg was given a few minutes to reply to these criticisms that he really pulled out the stops. He showed a slide which described how calcium was involved in a number of physiological and pathological processes, such as apoptosis, and suggested that CCAs may produce adverse effects in diseases where calcium plays an important role, such as cancer, AIDS and Parkinson's disease. None of these claims was supported with evidence, and it was hard to decide what the audience thought of it. Cardiologists tend to be fairly polite, and no questions were allowed from the floor. However, it is hard not to believe that pharmacologists would have had a field day if they had been unleashed.

One thing is certain – the debate will continue, but Furberg has done his case a lot of harm unless he can quickly produce supporting evidence.

David B. Jack

Cystic fibrosis: new strategies for drug therapy

It has been more than six years since the discovery of the genetic defect that causes cystic fibrosis (CF); the defect is located on a gene that encodes a membrane protein now known as the CF transmembrane conductance regulator (CFTR). This key protein is a chloride channel that regulates the flow of water and salt across epithelial tissues and thus controls the degree of hydration of bodily secretions. Its discovery provided an explanation for the presence of poorly hydrated airway mucus and associated life-threatening bacterial infections of the lung that are characteristic of the disease. Many different genetic defects have now been discovered on the same gene, each of which alters the function of CFTR to a different degree. This heterogeneity of genetic defects presumably accounts for the wide diversity in the severity of CF.

Consequently, many scientists and clinicians considered gene therapy to be the most promising solution to the most common genetic disease of the Caucasian population. It was anticipated that reengineered adenoviruses would be the ideal vector to deliver the wild-type CFTR gene to the airways of CF patients. The new gene would reverse the susceptibility of CF patients to lung infections irrespective of the position of the gene defect on CFTR. So far the promise is unfulfilled, and in the past two years, clinical trials have exposed fundamental problems with the adenoviral vector. In some cases, the vector caused an unexpected inflammatory reaction, but the major problem is the lack of efficiency of infection. Airway cells appear much more resistant to adenoviral infection than anyone ever expected, making it impossible to deliver sufficient amounts of the wild-type gene.

As a result, gene therapists are busy redesigning vectors, while other scientists are focusing on more traditional drug therapies for treating the disease.

An intriguing new suggestion for drug therapy is the use of aminoglycoside antibiotics to override premature stop codons on the CFTR gene – a class of mutations that account for approximately 5% of the cases of CF. Drs Marybeth Howard, Raymond A. Frizzell and David M. Bedwell at the University of Alabama (Birmingham, AL, USA) report that when the aminoglycoside antibiotic G-418 is administered to HeLa cells containing transfected CFTR genes with a premature in-frame ochre (UGA) stop codon in place of a codon for glycine, the cells expressed the full-length CFTR protein [*Nature Medicine* (1996) 2, 467–469]. Moreover, the full-length protein exhibited chloride channel activity. Such activity was not a foregone conclusion because the amino acid inserted in place of the stop codon was most likely not the glycine found in the wild-type protein.

All aminoglycoside antibiotics do not possess equal ability to suppress the premature stop codons. There was little or no full-length CFTR produced when the investigators used tobramicin and gentamicin – drugs frequently prescribed for lung infections in CF patients – in place of G-148. However, treatment with gentamicin caused chloride channel activity to appear. Undoubtedly many different aminoglycosides are available in pharmaceutical libraries. A systematic effort to sort through such compounds for those that are most efficient in suppressing premature stop codons might yield an important new class of compounds for treating some forms of CF.

Another promising approach is the design of chaperone molecules targeted to CFTR that will stabilize the biologically active conformation of the mutant protein. The major gene defect accounting for most cases of CF is the ΔF508 mutation, which allows the synthesis of a full-length CFTR protein but disrupts folding of the protein. The pre-Golgi protein synthesis machinery apparently recognizes the misfolded protein as aberrant and tags it for degradation. As a result, the plasma membrane is devoid of CFTR protein and chloride channel activity.

Dr Ron Kopito and coworkers (Stanford University, CA, USA) recently found that inclusion of 10% glycerol in the cell culture growth media induces the ΔF508 CFTR to fold correctly *in vivo* and results in the appearance of chloride channels [*J. Biol. Chem.* (1996) 271, 635–638]. Others had already shown that lowered temperatures also induce the mutant protein to fold into its functional conformation [Denning, G.M. *et al. Nature* (1992) 358, 761–764]. Drs Stephen J. Delaney and Brandon J. Wainwright at the Centre for Molecular and Cellular Biology at the University of Queensland (Brisbane, Australia) believe that these observations suggest that drugs acting as 'synthetic chaperones' might be found that could stabilize the wild-type conformation of the mutant CFTR molecule and restore chloride function to most CF patients [*Nature Medicine* (1996) 2, 392–393]. A molecular screen to uncover such molecules might produce an exciting and new class of therapeutics.

Robert W. Wallace

Scots search for slimmers' holy grail

Big may be beautiful for some, but obesity is now a common condition in all affluent countries, and it is now estimated that 10% of the UK population are frankly obese. There is good evidence that it is a chronic condition, and it is associated with a significantly higher mortality and morbidity resulting from an increased incidence of coronary heart disease, hypertension, stroke, type II diabetes, sexual dysfunction, colonic cancer, arthritis and pulmonary problems. A wide range of treatments has been tested, but none has been shown to produce a sustained loss in weight.

Scotland tops the world league for the incidence of heart disease in men, and this is attributable to factors such as the soft water, poor diet, smoking and alcohol consumption. Small wonder, then, that scientists at the Strathclyde Institute for Drug Research (SIDR), Glasgow, have become interested in this area. During their research into novel hypoglycaemic agents, they included different types of plant extract in the diet of mice. One plant was found to lower blood glucose but, to their surprise, there was a marked reduction in the weight of genetically obese, hyperglycaemic animals compared with controls. Initially they attributed this simply to loss of appetite, but the weight reduction was maintained when the animals began to eat normally – even when they began to eat more than the controls.

The active ingredient has now been extracted from the plant and found to be a small organic molecule with a molecular weight of less than 200. It has been synthesized and its activity confirmed *in vivo*. SIDR have filed a preliminary patent application and, according to Professor Alan Harvey, Director of SIDR, they are now looking for a commercial sponsor to allow them to accelerate the R&D programme for this agent in exchange for commercial rights.

The SIDR track record is impressive. Since it was set up in 1988, it has generated an extensive natural product library through developing a collaborative natural product network stretching from South America, across Africa to South-East Asia. It has also developed a series of ventures with industrial partners distributed almost equally between Europe, the USA and Japan and its total income for the financial year 1994 was more than £1.1 million.

David B. Jack