been developed by Dr J.C. Hall at North Carolina State University (Raleigh, NC, USA) in an attempt to develop a novel male contraceptive. According to Hall, this substrate analog is a highly effective oral contraceptive in rats. He says "the analog appears to have a short onset of action, negligible effects on the libido and no residual effect on the rat's fertility after the dosage has been discontinued". He points out that a major advantage of targeting the hexosaminidase is that its inhibition does not cause disruption of the hormonal balance. Hall's research describing the quantification and localization of the enzyme in the male rat's reproductive tract will be published in the March issue of *Biology of Reproduction*. A patent application has been made.

DNA mimic of bacterial tRNA

Dr P.F. Agris and coworkers at North Carolina State University (Raleigh, NC, USA) have recently reported the design of a DNA mimic of a bacterial phenylalanine tRNA molecule that specifically blocks microbial protein synthesis [*Nature Structural Biology* (1996) 3(1), 38–44]. Agris reported that the molecule inhibits translation by 50% when present at a concentration eightfold greater than the total number of ribosomes. The DNA molecule mimics the anticodon loop of the a normal phenylalanine tRNA, but does not contain the remainder of the molecule. Although it slips into the small subunit of the ribosome when a codon signal for phenylalanine comes along on the mRNA, the DNA mimic is incapable of delivering phenylalanine to the growing peptide chain, bringing protein synthesis to a halt. Agris believes that the significant differences in the structure of tRNA between bacterial and mammalian species will allow for disruption of microbial protein synthesis, while leaving protein synthesis in mammalian cells intact.

Agris believes that the DNA molecules will provide proof of principle studies and a critical assay for future discovery efforts. He envisions the discovery of a small organic molecule through high-throughput screening of compound libraries that will act at the same site on the small subunit of the ribosome. This molecular target is less likely to elicit resistance because it is the actual codon on the messenger RNA that is being targeted. According to Agris, "a mutation that alters the codon is likely to prove lethal". He is currently talking to pharmaceutical companies regarding a possible collaboration and a patent application has been submitted.

Dopamine D_1 receptor

The D_1 receptor plays a critical role in cognitive function by modulating working memory, according to research conducted by Dr P. Goldman-Rakic (Yale University, New Haven, CT, USA). She has reported that dopamine, working through the D_1 receptor, modulates working memory in primates [*Nature* (1995) 376, 572–575)] and has found a window in the amount of D_1 receptor occupancy required to achieve optimal activity of the neurons involved in working memory function. Too little or too much D_1 receptor occupancy caused a decline in neuronal activity. In normal conditions, there appeared to be too high a level of D_1 receptor occupancy; neuronal activity increased significantly when a small dose of the highly specific D_1 antagonist SCH 39166 (Schering Plough) was administered by iontophoresis directly onto the working memory neuron.

Goldman-Rakic has administered SCH 39166 to primates and found an improvement of some 15–25% in cognitive function tests. Although dopamine receptors are certainly not new targets, this work should stimulate interest in targeting the D_1 receptor for the development of a drug to increase cognitive function in humans.

Robert W. Wallace

Corticotropin-releasing factor and Alzheimer's disease

Corticotropin-releasing factor (CRF) is a 41-amino acid neuropeptide that is released from the hypothalamus under stress and initiates a cascade of endocrine responses. Lightman, S.L. [*Nature* (1995) 378, 233–234] has eloquently reviewed both the existing literature in this field and two recent studies published in the same issue. The first publication by Vaughan, J. and coworkers [*Nature* (1995) 378, 287–292] describes a new peptide, urocortin, which is structurally similar to CRF but has different efficacies at the two CRF receptor subtypes. Intravenous administration of urocortin causes a decrease in blood pressure in rats, and immunoreactivity data indicate that the peptide may occur both peripherally and in the CNS. Lightman therefore suggests that the cardiovascular and immunological effects of exogenous CRF may be attributable to the action of endogenous urocortin.

Evidence suggests that memory loss associated with Alzheimer's disease may be attributable to a decrease in CRF [De Souza, E.B. *et al. Nature* (1986) 319, 593–595]. CRF is also known to have a cognitive enhancing effect in rats but produces undesirable side-effects, such as anxiety, which limits the possible use of CRF analogues as therapeutic agents. However, under normal conditions, much of the CRF in the CNS is bound to a CRF-binding protein. In the second publication, Behan, D.P. and coworkers [*Nature* (1995) 378, 284–287] describe an investigation of the displacement of CRF from a binding protein as a possible treatment for Alzheimer's disease. These studies involved the administration of a truncated CRF peptide that has no intrinsic activity at CRF receptors but is able to displace bound CRF. This treatment was found to induce memory enhancement in rats without the associated anxiogenic side-effects.

Lightman suggests that the identification of a second CRF agonist may herald the discovery of other CRF-like peptides. Furthermore, the future development of chemical entities which can efficiently displace CRF from the CRF-binding protein may offer therapeutic potential for the treatment of Alzheimer's disease.