New genes reveal major role for iron in neurodegeneration

The discovery that mutations in two genes lead to iron deposition in the basal ganglia has provided a huge leap in knowledge for two rare genetic neurodegenerative disorders. "We have gone, almost overnight, from clinical and pathologic descriptions to being able to delineate sound and testable hypotheses for disease pathogenesis and to propose possible therapies", says Susan Hayflick (Oregon Health and Science University, Portland, OR, USA), author of one of the studies.

John Burn (Institute of Human Genetics, Newcastle-upon-Tyne, UK) and colleagues have shown that neuroferritinopathy, a dominantly inherited late-onset basal ganglia disease, is due to a mutation in the gene for ferritin light polypeptide, a component of the main iron storage protein. The disease presents with involuntary movements in people aged 40–55 years old; symptoms of extrapyramidal dysfunction follow but are not accompanied by cognitive decline. Patients have abnormal aggregates of iron and ferritin in the brain, and low serum ferritin concentrations. Genetic analysis of an affected family from Cumbria, UK, revealed an adenine insertion at position 460–461 that is predicted to alter the carboxy-terminal residues of the gene product (*Nat Genet* 2001; **28:** 350–54, DOI 10.1038/ng571).

"This new information suggests that we may be able to treat patients with desferrioxamines to try to chelate the iron out of brain tissue", says Burn. In the longer term an important step will be to develop a mouse model deficient in the L chain of ferritin to understand the pathophysiology of the disease.

Kay Double (Prince of Wales Medical Research Institute, Sydney, NSW, Australia) welcomes the study. "This has far-reaching implications beyond this single gene disorder", she says, pointing out that basal ganglia diseases such as Parkinson's, that do not follow a dominant inheritance pattern, are also characterised by changes in iron homeostasis. Shai Shoham (Sarah Herzog Memorial Hospital, Jerusalem, Israel) agrees and notes that "it is possible that environmental agents that affect iron storage in ferritin may interact with genetic background to induce neurodegenerative disorders in specific individuals."

In the second study, Hayflick and colleagues have identified the genetic basis for Hallervorden–Spatz syndrome (HSS). This childhood disease is caused by a defect in a pantothenate kinase gene, *PANK2*. They found missense mutations in 32 of 38 subjects with HSS. Pantothenate kinase is an essential regulatory enzyme in the biosynthesis of coenzyme A (coA). *PANK2* mutations are predicted to block a metabolic pathway in the brain, causing cysteine accumulation in cells in regions of the brain where iron tends to accumulate, resulting in free radical formation and cytotoxicity (*Nat Genet* 2001; **28:** 345–49, DOI 10.1038/ng572). "This pathway may be common to other neurodegenerative disorders such as Alzheimer's disease and Parkinson's", says Hayflick. The discovery of the gene defect suggests therapeutic possibilities. "If we can design drugs to deliver phosphopantothenate to cells and bypass the defective enzyme, we may be able to prevent some disease complications."

Kathryn Senior

Small part of cannabis puzzle solved by animal studies

Researchers studying the cannabinoid signalling system may have identified a new target for the treatment of pain. Benjamin Cravatt (Scripps Research Institute, La Jolla, CA, USA) and colleagues report that fatty acid amide hydrolase (FAAH) is a key in-vivo regulator of anandamide, an endogenous cannabinoid receptor ligand. "We have many more experiments to do", cautions Cravatt, "but our results indicate that it might be possible to develop FAAH inhibitors to prime the endogenous cannabinoid system so that it responds selectively in neural pathways that are stimulated by pain."

Anecdotal evidence indicates that cannabis can control chronic pain in conditions such as multiple sclerosis. But because cannabis use is illegal in many parts of the world, discussion of medical marijuana is controversial. A better understanding of the endogenous cannabinoid signalling pathway may indicate targets for new pain-killing drugs and so circumvent the debate on medical marijuana, say some researchers.

Cravatt and co-workers are studying anandamide, a fatty acid amide that behaves like a cannabinoid in vitro but has weak, transient in-vivo behavioural effects. "We postulated that rapid degradation of anandamide in vivo could explain its lack of effect compared with tetrahydrocannabinol (THC), marijuana's active component", says Cravatt. In 1996, the team cloned FAAH, an enzyme that degrades anandamide and they have now bred mice lacking the *FAAH* gene. These mice "cannot effectively degrade anandamide so they have 15-fold higher endogenous levels than wild-type mice", adds Cravatt. Nevertheless, the mice seem normal until injected with anandamide. Then, they show behaviour similar to that seen with THC. The knockout mice, even without anandamide treatment, have reduced pain sensitivity that can be reversed by a cannabinoid receptor antagonist, indicating that increased endogenous anandamide in FAAH knockout mice affects their pain pathways (*Proc Natl Acad Sci* 2001; 98: 9371–76). "If in-vivo FAAH inhibitors can be developed, they may provide a selective way to use the cannabinoid signalling system for chronic pain relief", suggests Cravatt.

Robert Harding

An alternative to cannabis for pain relief?

"This is another interesting part of the puzzle", comments William Notcutt (James Paget Hospital, Great Yarmouth, UK). "However, the philosopher's stone of something that mimics the good effects of cannabis without having the bad effects may be an impossible goal. We've tried that approach unsucessfully with morphine." Instead, says Notcutt, more effort should go into clinical testing of defined cannabis extracts. "Chronic pain is a complex phenomenon and there is a huge amount of work waiting to be done with existing agents", he concludes.

Jane Bradbury