NEURODEGENERATIVE DISEASE

COX-2 on the brain

Despite intensive research efforts, the pathogenic events underlying Parkinson's disease (PD), which is characterized by the loss of nigrostriatal dopaminergic neurons, remain elusive. There are, however, a number of clues, one of which has emerged from epidemiological studies indicating a link between inflammation and a number of neurodegenerative diseases. In support of this link, elevated levels of the inflammation-associated enzyme cyclooxygenase-2 (COX-2) — and those of its product, prostaglandin E_2 (PGE_2) — have been implicated in neurodegeneration.

Following this lead, Przedborksi and colleagues, reporting in the 29 April issue of the *Proceedings of the National Academy of Sciences*, have asked whether, and how, COX-2 levels contribute to PD. The group found that in post-mortem PD specimens COX-2 expression was induced specifically within substantia nigra pars compacta (SNpc) dopaminergic neurons. The same was found in mice treated with 2-methyl 1-4-phenyl-1,2,3,6-tertrahydropyridine (MPTP), a chemical commonly used to model the loss of nigrostriatal dopaminergic neurons seen in PD.

So what leads to elevated COX-2 levels, and how do these contribute to PD? Teismann *et al.* found that COX-2 induction after MPTP administration is mediated through a JUN N-terminal kinase/c-JUN-dependent pathway, and further that neurodegeneration could be reduced by COX-2 inhibitors. Moreover, it was shown that the catalytic activity of COX-2 is crucial to the neurodegenerative process in SNpc dopaminergic neurons in the MPTP model, and by extension probably in PD also. By contrast, the inhibition of COX-1 provided no protective effects against MPTP. Two possible explanations for the effects of COX-2 were proposed. Neurons overexpressing COX-2 could cause their own death, by synthesizing excess amounts of PGE_2 that result in the production of micro-glial-derived mediators, which then aid the killing of the neurons. Alternatively, COX-2 could cause cell death in a cell-autonomous manner through the production of reactive oxygen species generated by the catalytic activity of COX-2, which in turn can result in oxidants such as dopamine-quinone. The authors suggest that the neuroprotective effect of COX-2 inhibition could result from mitigating the oxidative damage caused by dopamine-quinone, which has previously been implicated in PD. These results are obviously of relevance to the further investigation of targets for PD therapeutics.

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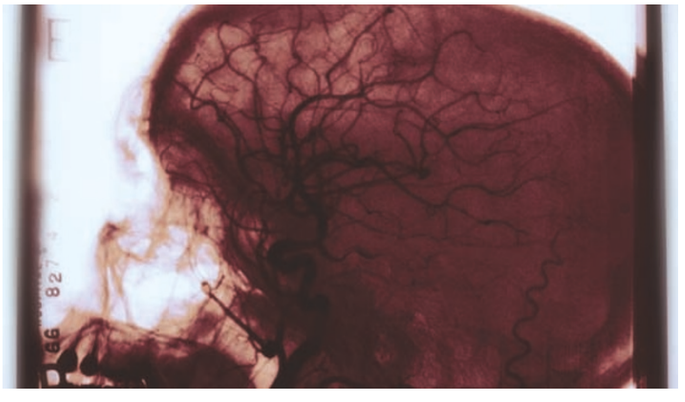
References and links

ORIGINAL RESEARCH PAPER Teismann, P. *et al.* Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proc. Natl Acad. Sci. USA* **100**, 5473–5478 (2003)

FURTHER READING Lotharius, J. & Brundin, P. Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. *Nature Rev. Neurosci.* **3**, 932–942 (2003)



IN BRIEF

ADME

A model for predicting likely sites of CYP3A4-mediated metabolism on drug-like molecules.

Singh, S. B., Shen, L. Q., Walker, M. J. & Sheridan, R. P. *J. Med. Chem.* **46**, 1330–1336 (2003)

Oral bioavailability of a drug depends largely on its ability to withstand degradation by intestinal and hepatic metabolizing enzymes, such as cytochrome P450s (CYPs), and there is considerable interest in computational approaches that can efficiently predict compound susceptibility to metabolism. Sheridan and colleagues have developed a model that can rapidly and accurately predict likely sites of metabolism for compounds that could be substrates of CYP3A4.

ANTICANCER DRUGS

PPAR-γ receptor ligands: novel therapy for pituitary adenomas.

Heaney, A. P., Fernando, M. & Melmed, S. *J. Clin. Invest.* **111**, 1381–1388 (2003)

Pituitary tumours cause considerable morbidity as a result of local invasion and hormonal hypersecretion, but in many cases there is no suitable drug treatment. Heaney and colleagues found that a nuclear receptor known as peroxisome-proliferator-activated receptor-γ (PPAR-γ) is abundantly expressed in human pituitary tumours, and showed that thiazolidinediones — PPAR-γ ligands that are used for treating type 2 diabetes — inhibit pituitary tumour growth and hormone secretion. These drugs could therefore represent a novel treatment for this cancer.

CARDIOVASCULAR DISEASE

Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia. A prospective, randomized, double-blind trial.

Ballantyne, C. M. *et al. Circulation* Apr 28 (2003)
doi: 10.1161/01.CIR.0000068312.21969.C8

Although the efficacy of statins in reducing levels of low-density lipoprotein cholesterol (LDL-C) is well established, many patients do not achieve recommended LDL-C goals for several reasons, including increased risk of adverse effects with high statin doses. The results of this trial indicate that co-administration of atorvastatin and ezetimibe — the first in a new class of cholesterol-lowering drugs — is significantly more effective in reducing LDL-C than either drug alone.

ANTICANCER DRUGS

Treatment-specific changes in gene expression discriminate *in vivo* drug response in human leukemia cells.

Cheok, M. H. *et al. Nature Genet.* **34**, 85–90 (2003)

To elucidate how cancer cells respond to chemotherapies, Cheok *et al.* analysed the effects of treatment with methotrexate and mercaptopurine alone or in combination on more than 9,600 human genes in acute lymphoblastic leukaemia cells. Their results indicate that changes in gene expression are treatment-specific and that treatment-induced changes in gene expression might provide a basis for optimizing combination chemotherapy.