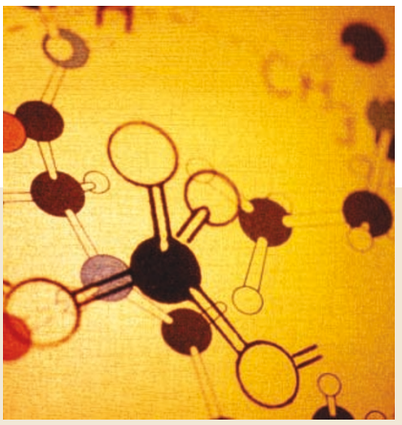
NSAIDS

Better design through chemistry



Clinical observations and studies that found that taking common non-steroidal anti-inflammatory drugs (NSAIDs) was linked to a lower risk of certain cancers was good news for many companies, as it bucked the trend at that time of creating anticancer therapies by rational design. And when a next-generation NSAID, the cyclooxygenase-2 (COX2) inhibitor Celebrex (celecoxib), was approved for familial adenomatous polyposis — an inherited predisposition to colorectal cancer — in 1999, there was hope that other COX2 inhibitors would also prove to be safe and powerful anticancer treatments.

However, further studies showed that not all COX2 inhibitors are created equal. The antitumour effects — thought to occur by sensitizing tumour cells to apoptosis — of other equally powerful COX2 inhibitors, such as Vioxx (rofecoxib), were much lower than celecoxib, which implied that the antitumour effects of these drugs are distinct from their effects on COX2 inhibition.

So, Chen and colleagues went back to basics and looked for structural differences between celecoxib and rofecoxib that could explain this discrepancy. They used a systematic chemical approach to modify the structures of both celecoxib and rofecoxib to produce 50 compounds, and then tested them for their ability to induce apoptosis in human prostate cancer cells. The pathways through which apoptosis acts was monitored and molecular models were used to identify the key structural elements involved in COX2-mediated apoptosis.

The results, published in the *Journal of the National Cancer Institute*, confirm that the structural requirements for the induction of apoptosis are distinct from those that mediate COX2 inhibition. The induction of apoptosis required a bulky terminal ring, a heterocyclic system with negative electrostatic potential and a benzenesulphonamide or benzenecarbonamide moiety. To prove their observations, Chen and colleagues modified the structure of rofecoxib to create four compounds that mimicked the surface electrostatic potential of celecoxib — one of which showed a substantial increase in apoptotic activity.

The researchers found that apoptosis was mediated by downregulating the production of AKT and ERK2, which are essential to cancer cell survival. Interestingly, the crucial role that AKT and ERK2 also have in angiogenesis, taken together with previous observations that celecoxib can inhibit angiogenesis, indicates that these anti-angiogenic effects could be mediated by a similar mechanism to that which induces apoptosis. To investigate this further, Chen and colleagues are now looking at the relative contributions of the apoptotic and anti-angiogenic mechanisms to the *in vivo* effects of celecoxib and its derivatives on tumour growth, and are also assessing the pharmacokinetic, pharmacodynamic and toxicity profiles of the apoptosis-inducing agents.

Simon Frantz

References and links

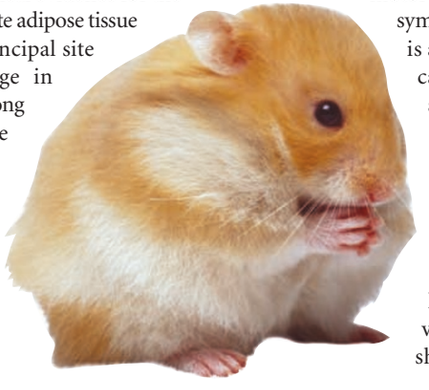
ORIGINAL RESEARCH PAPER Zhu, J. *et al.* Using cyclooxygenase-2 inhibitors as molecular platforms to develop a new class of apoptosis-inducing agents. *J. Natl Cancer Inst.* **94**, 1745–1757 (2002)

FURTHER READING Gupta, R. A. & DuBois, R. N. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. *Nature Rev. Cancer* **1**, 11–21 (2001)

OBESITY

It goes straight to my hips

The distribution and utilization of fat in different body compartments is subject to exquisite regulation, and it is hard to conceive how this might be achieved purely by the local effects of circulating humoral factors such as insulin. Many other body systems are controlled by the antagonistic arms of the autonomic nervous system, so why not fat metabolism too? Although histological evidence for the innervation of white adipose tissue (WAT) — the principal site for energy storage in mammals — has long existed, extensive sympathetic innervation of WAT was confirmed only recently (see further reading). Now, in the November issue of the *Journal of Clinical Investigation*, Kreier *et al.* demonstrate for the first time that WAT receives parasympathetic innervation.



Using a transneuronal retrograde tracer — pseudorabies virus (PRV) — in combination with selective sympathetic denervation, Kreier *et al.* revealed that fat pads receive direct parasympathetic innervation from the vagal motor nuclei in the brain stem. The sympathetic innervation of WAT is active when the body is in a catabolic, energy-spending state, and the authors hypothesized that parasympathetic control might take over during anabolic states, thereby controlling the build-up of adipose tissue. In keeping with this idea, local parasympathetic denervation by vagotomy was shown to reduce the levels of insulin-mediated glucose and free-fatty-acid uptake by the vagotomized retroperitoneal fat pads by 33 and 36%, respectively. It was also shown to increase the activity of hormone-sensitive lipase, a catabolic enzyme responsible for hydrolysing triglyceride in adipose tissue, and to lead to a decrease in the level of leptin mRNA.

In an extension of the retrograde labelling technique, Kreier *et al.* were able to demonstrate somatotopy within the projections of the autonomic nervous system to WAT. So, it seems not only that parasympathetic innervation of adipocytes can directly promote energy storage, but furthermore that the selective activation of somatotopically defined pathways might be able to direct storage to specific locations. The challenge will now be to see whether therapeutic strategies might be devised that can selectively regulate the balance of autonomic control in diseases involving obesity.

Adam Smith

References and links

ORIGINAL RESEARCH PAPER Kreier, F. *et al.* Selective parasympathetic innervation of subcutaneous and intra-abdominal fat — functional implications. *J. Clin. Invest.* **110**, 1243–1250 (2002)

FURTHER READING Bamshad, M. *et al.* Central nervous system origins of the sympathetic nervous system outflow to white adipose tissue. *Am. J. Physiol.* **275**, R291–R299 (1998)