CARDIOVASCULAR DISEASE

Oestrogen activates COX2 pathway

Heart disease and atherosclerosis is more pronounced in men than in women, but this difference is reduced after menopause. Although some studies have shown that the female hormone oestrogen slows heart disease in mouse models, the underlying mechanism is largely unknown. In *Science Express*, FitzGerald and colleagues show that female mice are protected from hardening of the arteries as a result of oestrogen activation of the cyclooxygenase (COX)-2 enzyme, which causes an increase in the amount of the atheroprotective molecule prostacyclin, PGI_2.

During inflammation, phospholipase enzymes convert membrane phospholipids to arachidonic acid. Arachidonic acid is the precursor for prostaglandins, such as PGI_2, and thromboxanes, which are derived from the COX1 and COX2 pathways. The COX prostaglandin products are acted on by thromboxane synthase (in platelets) or prostacyclin synthase (in endothelium) to form thromboxanes or PGI_2, respectively. PGI_2 has an important and beneficial role in vascular function, as it inhibits platelet adhesion to the vascular endothelium and is a strong vasodilator. The COX pathway is inhibited by aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Newer anti-inflammatory drugs selectively target the inducible isoform COX2 and have fewer gastrointestinal side effects than the non-selective COX inhibitors such as aspirin and ibuprofen.

Mice deficient in the low-density lipoprotein (LDL) receptor were used to investigate the role of PGI_2; LDL-deficient male mice develop atherosclerosis more rapidly than females. Knocking out the prostacyclin receptor (IP) in these female mice took away the atheroprotective effect of oestrogen. These mice also showed increased oxidative stress. By removing the ovaries of female LDL-deficient mice, the authors were able to identify the direct effects of oestrogen. Administration of oestrogen to ovariectomized mice increased PGI_2 synthesis. Furthermore, PGI_2 synthesis was also increased after administration of oestrogen to female mice deficient in the oestrogen receptor β, but not the α-receptor, showing that PGI_2 biosynthesis occurs by activation of the α-receptor. In LDL- and IP-deficient female mice, administration of oestrogen did not confer protection from atherosclerosis compared with LDL-deficient mice alone.

ANTIVIRAL DRUGS

Blocking the route to infection

A promising approach to developing agents that can prevent HIV transmission is described in a recent report in *Proceedings of the National Academy of Sciences*. Furthermore, the medicinal chemistry strategy used by Offord and co-workers to improve the pharmacological properties of a natural protein that blocks HIV entry could also be applicable to other therapeutic proteins.

The entry of HIV into target cells involves the CD4 protein, as well as the CC-chemokine receptor 5 (CCR5), which is especially important in the early stages of the disease. Natural ligands of CCR5 — such as RANTES, a small human protein of the chemokine family — can block the entry of HIV strains that require CCR5 to enter the target cells.

Optimizing such proteins to make them more potent inhibitors of HIV entry could lead to agents that effectively prevent HIV transmission. Small proteins have traditionally been modified using mutagenesis, but this approach is limited to natural amino acids; now, however, techniques are available for the rapid chemical synthesis of large numbers of analogues of small natural proteins, which allows non-natural amino acids to be incorporated that might improve the therapeutic properties of the analogues.

Previously, Offord and co-workers synthesized a RANTES analogue — AOP-RANTES — that was more effective at blocking HIV entry into target cells than natural RANTES. In AOP-RANTES, a serine residue was replaced with the non-natural amino acid aminooxypentane oxime on the amino terminus to increase its hydrophobicity. In the current study, the authors systematically determined the structure–activity relationships of analogues of AOP-RANTES, which led to the generation of several more potent inhibitors of HIV in mice. The analogues were further optimized by replacing the amino acids at the two adjacent positions to the original amino acid that was modified. One derivative of AOP-RANTES, termed PSC-RANTES, was 50 times more potent than the starting molecule.

These RANTES analogues are thought to be successful at inhibiting HIV entry into target cells because they trigger the intracellular sequestration of CCR5. Offord and co-workers reported a correlation between potency and capacity to induce CCR5 sequestration.

However, contrary to earlier predictions that this capacity relates to increased affinity for the receptor, there was no correlation between affinity and potency. Future studies might shed light on the mechanism by which these modifications lead to intracellular sequestration of CCR5, and could lead to the development of clinically effective inhibitors of HIV transmission.

Alison Rowan

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Because of the direct link between oestrogen and the protective COX2 pathway, this study raises a number of concerns about the use of selective COX2 inhibitors in premenopausal women. It also raises the possibility of an interaction between hormone replacement therapy and drugs that inhibit COX2, including traditional NSAIDs. In light of the recent studies linking long-term use of COX2 inhibitors with increased cardiovascular risk, this study provides some insight into how this risk might occur, and identifies potential biomarkers of this evolving risk. Although there is considerable interest in the further potential clinical use of COX2 inhibitors, interest in therapeutic target selection is shifting downstream in the prostaglandin biosynthetic/response pathway, towards specific prostaglandin synthases and receptors.

Melanie Brazil

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MEDICINAL CHEMISTRY

Some things never change…

The balance between polar and nonpolar drug properties is an important and unchanging feature of oral drug molecules, suggests a recent extensive analysis of drugs launched over more than two decades published in the *Journal of Medicinal Chemistry*. The study, by Leeson and Davis at AstraZeneca, also investigates time-related differences in the physicochemical properties of drugs grouped by therapeutic area.

Retrospective analyses of known drugs and agents in development have had a considerable influence on our view of what types of compounds are 'drug-like' and are therefore anticipated to have a greater chance of becoming future drugs. A notable outcome of one such analysis is the Lipinski 'Rule of 5', which is widely used to aid in the assembly of chemical libraries for high-throughput screening. This rule links limits on simple properties — molecular mass, lipophilicity and number of hydrogen-bond donors and acceptors — to the likelihood of a given compound having appropriate pharmacokinetic properties to be used as an oral drug. Numerous further analyses have identified more complex properties to aid in predicting drug-likeness, but there are no generally applicable means of differentiating drugs from non-drugs.

Leeson and Davis set out to investigate the most important properties of oral drugs by comparing the physicochemical properties of all the drugs launched between 1983 and 2002 (a total of 329) with those launched before 1983 (a total of 864). Mean values of lipophilicity, percent polar surface area and number of hydrogen-bond donors were the same in both sets of drugs, and so the authors propose that these are the most important oral-drug-like physicochemical properties, and should therefore be most carefully controlled in oral drug discovery programmes. Mean values of other properties assessed, such as molecular mass, have generally increased in the more recent set of drugs.

It has also been recognized that the physicochemical properties of drugs can be affected by the therapeutic area they are intended for. So, to assess this issue the authors compared the profiles of drugs launched in several major therapeutic areas from 1983 to 2002. Nervous system drugs have significantly reduced molecular mass, polar properties and rotatable bonds relative to other classes, which the authors point out as being consistent with the established importance of limited polar surface area and molecular size for blood–brain barrier penetration. And apart from anti-infective drugs, all the classes show similar distributions of lipophilicity, emphasizing the importance of this property irrespective of therapeutic area.

Finally, there has been no significant change in molecular mass with year of launch from 1983 to 2002 in each therapeutic area, with the exception of cardiovascular drugs, which have shown an increase in molecular mass. The authors propose that this is because most cardiovascular drugs approved during this period are in a small number of established classes, such as statins, and so what is being observed is an optimization of an initial 'breakthrough' structure, which tends to result in increased size. This is consistent with the well-known tendency for molecular mass to increase during lead optimization, and provides support for the trend in lead discovery to aim to keep key physicochemical properties of leads below the limits of drug-like properties, and thereby provide scope for increases in these properties during lead optimization.

Peter Kirkpatrick

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