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

References and links

ORIGINAL RESEARCH PAPER Egan, K. M. *et al.* Cox-2 derived prostacyclin confers atheroprotection on female mice. *Science Express* 2004 November 18 (doi:10.1126/science.1103333)

FURTHER READING FitzGerald, G. A. COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nature Rev. Drug Discov.* **2**, 635–645 (2003) | Wallace, J. L., Ignarro, L. J. & Fiorucci, S. Potential cardioprotective action of NO-releasing aspirin. *Nature Rev. Drug Discov.* **1**, 375–382 (2002)

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

References and links

ORIGINAL RESEARCH PAPER Leeson, P. D. & Davis, A. M. Time-related differences in the physical property profiles of oral drugs. *J. Med. Chem.* **47**, 6338–6448 (2004)

FURTHER READING Rees, D. *et al.* Fragment-based drug discovery. *Nature Rev. Drug Discov.* **3**, 660–672 (2004)