PERSPECTIVES: BIOMEDICINE

Back to an Aspirin a Day?

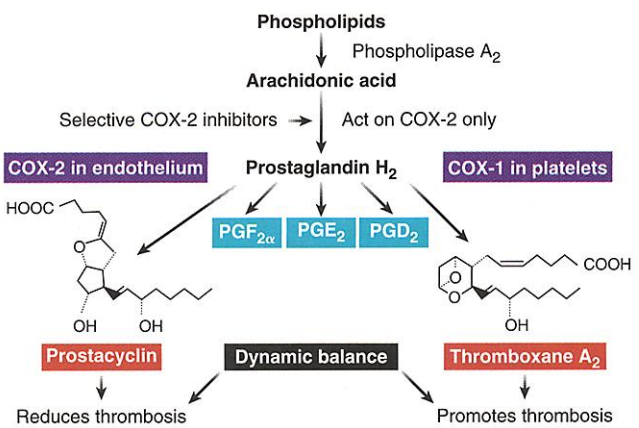
John R. Vane

It is almost 20 years since Bunting, Moncada, and Vane proposed that a balance between the eicosanoids prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) contributes to homeostasis of the circulatory system (*1*). A report by Cheng *et al.* (*2*) on page 539 of this issue now examines this balance in more detail and sheds light on the surprising thrombotic side effects observed in a recent clinical trial of a new anti-inflammatory drug.

The group of chemical mediators known as the eicosanoids (because they contain 20 carbon atoms) are crucial players in many physiological processes. In activated platelets, TxA_2 is produced by the enzyme thromboxane synthetase. This eicosanoid not only causes platelet aggregation, but also is a potent vasoconstrictor (that is, it promotes contraction of blood vessels). In contrast, in vascular endothelial cells PGI_2 is produced by prostacyclin synthase. This prostacyclin not only prevents platelet action and clumping, but also is a powerful vasodilator. Both eicosanoids are synthesized from a precursor, prostaglandin PGH_2, which is made by two isoforms of the enzyme cyclooxygenase, COX-1 and COX-2 (see the figure). Platelets contain only COX-1, whereas endothelial cells contain primarily COX-2 (which may be induced by the shear stresses arising from the pulsatile pressure as blood flows through the vasculature). Intriguingly, biosynthesis of PGI_2 is increased in patients with platelet activation syndromes, reinforcing the notion that the balance between PGI_2 and TxA_2 constitutes a homeostatic regulator of the circulation (*3*). Inhibition of one COX isoform would theoretically leave the PGH_2 substrate available for catabolism by the other isoform.

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin inhibit both COX-1 and COX-2. Patients undergoing coronary angioplasty are given aspirin because it reduces TxA_2 production and platelet clumping and hence the chance of myocardial infarction. Now there is a new generation of NSAIDs that primarily block COX-2 in the endothelium, reducing PGI_2 production but leaving platelet COX-1 free to synthesize TxA_2 (*4*, *5*). But which NSAIDs belong to this new generation? In the UK, the National Institute for Clinical Excellence (NICE) has classified four drugs as selective COX-2 inhibitors: celecoxib (Celebrex), etodolac (Lodine), meloxicam (Mobic), and rofecoxib (Vioxx). Clinical trials and postmarketing surveillance show that these drugs all have fewer gastrointestinal side effects than the traditional NSAIDs, which inhibit both COX isoforms (*6*). The VIGOR clinical trial—which compared the selective COX-2 inhibitor rofecoxib with a comparator drug, the traditional NSAID naproxen—surprisingly showed a fivefold increase in myocardial infarction among patients treated with rofecoxib compared with the naproxen group (*7*). There could be three reasons for this: (i) A chance effect or (ii) naproxen protects the cardiovascular system because it blocks TxA_2 production or (iii) rofecoxib has a deleterious cardiovascular effect because it does not block and may even enhance TxA_2 production.

Using genetically engineered mice, Cheng *et al.* (*2*) set out to discover which of these hypotheses accounted for the results of the VIGOR trial. Their engineered mice lacked receptors for either PGI_2 or TxA_2, or for both eicosanoids. They examined the proliferative response of vascular smooth muscle cells in the mice after inflicting injury on the carotid artery with a catheter. The authors found that mice lacking the PGI_2 receptor (IP) showed enhanced cellular proliferation and increased platelet activation in response to injury. This seemed to be due to increased production of TxA_2 as indicated by increased excretion of TxA_2 metabolites in mouse urine. In contrast, mice lacking both IP and TxA_2 receptors (TP) showed abrogation of the enhanced proliferative and platelet response to vascular injury. Mice lacking TP receptors or IP-deficient mice treated with a TP antagonist exhibited a decreased proliferative and platelet response after injury to the carotid artery. These results provide clear evidence that PGI_2 modulates the cardiovascular actions of TxA_2 in vivo. They further reinforce the notion that the balance between these two eicosanoids maintains cardiovascular homeostasis.



The cardiovascular effects of COX-2 inhibitors. A dynamic balance between PGI_2 production in vascular endothelial cells and TxA_2 production in platelets may maintain cardiovascular homeostasis (*1*). Production of both PGI_2 and TxA_2 depends on the COX enzyme, which synthesizes the prostaglandin precursor PGH_2. Traditional NSAIDs, such as aspirin, inhibit COX-1 and to varying degrees COX-2. Thus, NSAIDs reduce the propensity of platelets to form TxA_2 and to aggregate. In contrast, the newer selective COX-2 inhibitors reduce PGI_2 formation, thereby potentially boosting TxA_2 production by platelets, which may explain the thrombotic side effects associated with use of these drugs.

But was it an imbalance between PGI_2 and TxA_2 that led to the increased thrombotic events associated with rofecoxib in the VIGOR trial? Rofecoxib is the most selective COX-2 inhibitor available on the market (*8*). In the VIGOR clinical trial (*7*), there were five times as many thrombotic events in the rofecoxib group as in the group receiving naproxen. Interestingly, there is no published evidence for a cardiovascular hazard associated with the other COX-2 inhibitors celecoxib, etodolac, or meloxicam (*7*–*9*). Furthermore, a recent epidemiological analysis failed to detect a reduction in myocardial infarction among patients prescribed naproxen (*10*). If the "balance hypothesis" is correct, why is there no evidence of a class effect involving all COX-2 inhibitors? One explanation could be differences in the physicochemical or pharmacokinetic properties among the selective COX-2 inhibitors. It is also possible that aspects of the trial design, particularly the patient population and exclusion of concomitant aspirin administration, were relevant to the outcome of the VIGOR trial. In mice, IP deletion does not cause spontaneous thrombosis, but only enhances the response to thrombotic stimuli (*11*).

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For now, it remains unproven which hypothesis—"balance" or "naproxen"—accounts for the increased thrombotic events associated with rofecoxib treatment. As Cheng and colleagues point out, these two hypotheses are in fact mutually compatible. Large-scale clinical trials of these compounds need to be instigated with patients suffering from cardiovascular disease. Because of continuing concerns, Merck will enroll about 30,000 subjects in trials to resolve questions about the cardiovascular safety of both rofecoxib and the newly announced selective COX-2 inhibitor, Arcoxia (etoricoxib) (*12*). Perhaps an academic group, such as the Oxford-based Antithrombotic Trialists' Group (*13*), will take an interest in resolving the present imbalance between perception and evidence of a cardiovascular hazard from selective inhibitors of COX-2.

References and Notes

1. S. Bunting, S. Moncada, J. R. Vane, *Br. Med. Bull.* **39**, 271 (1983).
2. Y. Cheng *et al.*, *Science* **296**, 539 (2002).
3. G. A. FitzGerald *et al.*, *N. Engl. J. Med.* **310**, 1065 (1984).
4. B. F. McAdam *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 272 (1999).
5. F. Catella-Lawson *et al.*, *J. Pharmacol. Exp. Ther.* **289**, 735 (1999).
6. S. S. Jick, *Pharmacotherapy* **20**, 741 (2000).
7. C. Bombardier *et al.*, *N. Engl. J. Med.* **343**, 1520 (2000).
8. G. A. FitzGerald, C. Patrono, *N. Engl. J. Med* **345**, 433 (2001).
9. A. S. Reicin *et al.*, *Am. J. Cardiol.* **89**, 204 (2002).
10. W. A. Ray *et al.*, *Lancet* **359**, 118 (2002).
11. T. Murata *et al.*, *Nature* **388**, 678 (1997).
12. F-D-C Reports *The Pink Sheet* (17 December 2001).
13. Antithrombotic Trialists' Collaboration, *Br. Med. J.* **324**, 71 (2002).
14. J.R.V has received payment to act as a consultant and/or to speak at conferences in the past 3 years from Boehringer Ingelheim, Merck Inc., Parke-Davis, Rhone-Poulenc Rorer, and Shire Pharmaceuticals.

PERSPECTIVES: GEOLOGY

Osmium Remembers

Richard W. Carlson

On page 516 of this issue, Meibom and Frei (*1*) report isotopic analyses of mineral grains picked from stream deposits in Oregon and California. From these data, they derive conclusions about geochemical processes that occurred long ago in Earth's core. How can minute crystals found in a riverbed provide information on Earth's deep interior?

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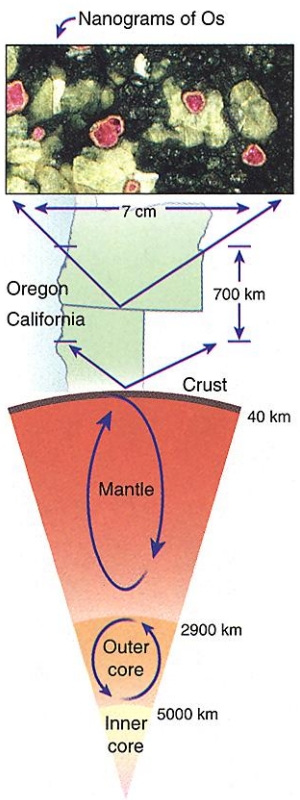
Less than 50 years ago, plate tectonic theory delivered the realization that Earth's interior is not rigid but is in continual motion driven by thermal convection. The data reported by Meibom and Frei provide further evidence that convection in Earth's interior has caused at least some portions of the mantle to circulate to its two thermal boundary layers (the crust and the core) not once, but several times over Earth's history. Reading the "core signal" in their samples, the authors suggest that the solid inner core began to form within 250 million years of Earth's formation. This conclusion has far-reaching implications for the history of the magnetic field and the thermal evolution of Earth.

Meibom and Frei examined the isotopic composition of osmium (Os) in rare Os-metal alloy grains, which had been weathered from mantle rocks now exposed in the crust of Oregon and northern California (see the figure). Some of the osmium is formed via the decay of two radioactive elements. The rhenium isotope ^{187}Re (half-life, 41.6 billion years) decays to ^{187}Os, and the platinum isotope ^{190}Pt (half-life, 449 billion years) to ^{186}Os. Osmium is present at only parts per billion levels in the mantle, but it is highly concentrated into mineral phases such as iron-nickel-sulfide and the Os-metal alloys studied by Meibom and Frei. Consequently, these Os-rich minerals are exceedingly rare and well-separated spatially from one another in the mantle.

Because of the separation between these minerals and the strong chemical affinity Os has for them, diffusion is ineffective in mixing Os isotopic composition across any substantial distance in the mantle. In this respect, the osmium system differs from other radiometric systems, such as rubidium-strontium and samarium-neodymium, which have been used for decades to study the melting history of Earth's mantle. These elements are widely distributed throughout the silicate minerals that make up the majority of the mantle. Because of diffusion at high mantle temperatures, the isotopic consequences of small-scale chemical heterogeneity are averaged out in these radiometric systems. The record of discrete events in the chemical differentiation of the mantle is smoothed as a result.

In contrast, the grains studied by Meibom and Frei show a wide range of Os isotopic compositions, which can be translated into formation ages for the individual grains. The resulting ages range from 256 to 2644 million years ago. The rocks from which these minerals were presumably derived were added to North America between 160 and 500 million years ago. The wide range of Os model ages most likely reflects the inability of convective stirring and diffusion to homogenize Os isotopic composition in the mantle. In essence, the Os isotopic system records multiple events in the chemical differentiation history of the mantle.

A particularly intriguing aspect of the data presented by Meibom and Frei is that their samples have higher ^{186}Os/^{188}Os ratios but generally lower ^{187}Os/^{188}Os ratios, in comparison to the average mantle. Low ^{187}Os/^{188}Os ratios are a common feature of mantle regions from which partial melts have been extracted (*2*). They result from removal of Re, which preferentially partitions into the melt while Os stays behind in the solid. But because Pt follows Re



Connecting sand grains in Oregon to the inner core. Meibom and Frei measured the isotopic composition of osmium extracted from millimeter-sized grains weathered from bodies of mantle rock (7-cm-wide section of rock shown) tens of kilometers in size, accreted to the Oregon-California crust by collision between North America and the oceanic crust of the Pacific. In this collision, most of the oceanic plate sank and became involved in a mantle convection system that reaches from Earth's crust to the core. The chemical history of crystallization of the inner core, recorded in the composition of the outer core, is transferred to the mantle by material exchange across the core-mantle boundary. This "core signal" will be brought back to the surface as mantle convection circulates the lowermost mantle to the surface.

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