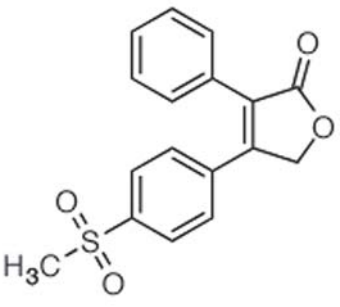
Do COX-2 the shades of gray

By Kathleen Jacobs



▲ The chemical structure of rofecoxib, more popularly known as Vioxx.

In the midst of a promising study analyzing its effects on cancerous polyps, rofecoxib (Vioxx) was pulled off the prescription drug market after evidence came to light that long-term use doubles the risk of heart attack and stroke. Since its recall, Vioxx and other drugs like it, collectively called COX-2 inhibitors, have been labeled as failures of the federal drug maintenance system and dismissed as having no further potential in medicine (1). But

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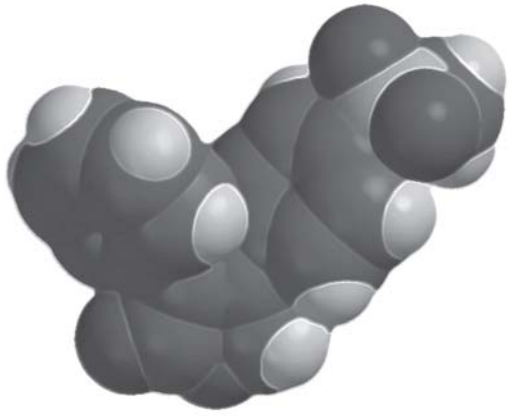
Inhibitors Have a Future?

in the past decade, research has shown that COX-2 inhibitors could be the next step in cancer treatment. Despite the potential cardiovascular risks, researchers still see COX-2 inhibitors as viable drugs in the treatment of illnesses such as cancer, in which the benefits clearly outweigh the potential negatives. Research is once again starting to investigate the workings behind COX-2 inhibitors and their possible applications (2).



▲ A three dimensional space filling model of Vioxx

Out with the Old, In with the New

Vioxx belongs to a class of drugs called cyclooxygenase-2 (COX-2) inhibitors. This class of drugs includes other popular analgesics like Bextra and Celebrex, the only COX-2 inhibitor currently available on the market. The development of COX-2 inhibitors began with their predecessors, traditional non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide the same degree of pain relief and inflammatory suppression for arthritis patients as COX-2 inhibitors, but have harsh side effects, including stomach ulcers (3).

NSAIDs work by non-selectively suppressing both the COX-1 and COX-2 enzymes, both of which catalyze the arachidonic acid pathway but which have different expression levels and tissue specificities (4). Arachidonic acid is a fatty acid released by cell membranes in virtually all tissues (Figure 1). The COX enzymes convert this acid into prostaglandins, which can serve a number of purposes in the body, including modulating blood pressure and muscle activity and mediating immune reactions (5). COX-1 is expressed constitutively throughout the body and mediates the production of protective prostaglandins such as thromboxane A_2, a platelet activator (6). Aspirin is an example of an NSAID that, by inhibiting COX-1 enzymes, prevents platelet aggregation and thereby promotes cardiovascular health (7). At the same time, inhibition of COX-1 reduces the levels of gastrointestinal protective proteins, resulting in stomach bleeding and irritation (6). These side effects are the main limitations of NSAIDs.

For over two decades, researchers believed that COX enzymes were expressed at equal levels throughout the whole body (8). In 1990, however, a novel form of COX was discovered in monocytes, which play a key role in inflammation and in our immune system (9). Further research demonstrated that mouse models of acute inflammation, which were characterized by swelling of the footpads, showed an overexpression of COX-2 mRNA in the inflamed footpads, while the expression level of COX-1 did not change (8). Unlike COX-1, COX-2 produces pro-inflammatory prostaglandins after being stimulated by toxins, antigens, and cytokine signaling molecules. What makes NSAIDs effective medicines for patients with chronic inflammatory conditions such as rheumatoid arthritis is that they inhibit the production of these pro-inflammatory prostaglandins (10).

Based on the dichotomy of NSAID drug action, researchers deduced that the therapeutic properties of NSAIDs were derived from suppression of COX-2 while the undesirable side effects were derived from inhibition of COX-1. With the discovery of the second COX enzyme, drug companies rushed to develop a drug that would specifically inhibit COX-2. The idea behind Vioxx and drugs like it was simple: inhibit COX-2 enzymes but not COX-1 enzymes, and you get a drug that has the benefits of non-selective NSAIDs without the harsh gastrointestinal side effects (3).

The Rise and Fall of COX-2 Inhibitors

After the release of COX-2 inhibitors to the market, doctors were hesitant to prescribe these new medications because their therapeutic benefits were unverified. But with the publication of two key clinical research studies, *CLASS* and *VIGOR*, sales of COX-2 inhibitors skyrocketed (11). Both studies demonstrated that COX-2 inhibitors greatly decreased gastrointestinal side effects while remaining potent relievers of pain and inflammation (6). By October 2000, less than a year after being introduced, Celebrex and Vioxx had sales of over 3 billion dollars in the United States alone and accounted for over 100 million prescriptions filled (11). However, in September 2004, the success of COX-2 inhibitors came to an end.

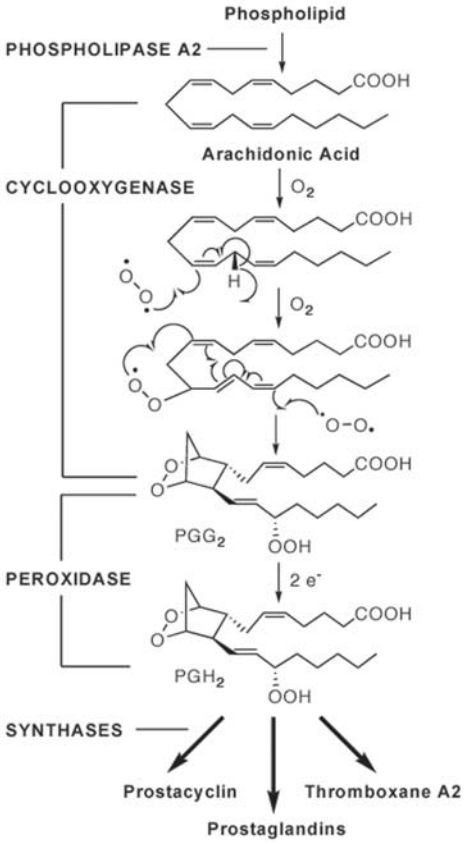


Figure 1. Synthesis of prostaglandins from arachidonic acid. COX-1 and COX-2 enzymes mediate the production of prostaglandins, such as thromboxane and prostacyclin, from arachadonic acid released from cellular membranes.

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By 2004, numerous papers had hypothesized that COX-2 inhibitors could cause cardiovascular damage, citing the previous *VIGOR* trial, which showed an increase in the rate of heart attacks and strokes. The distributor of Vioxx, Merck, attributed this increase to the heart-protective nature of naproxen, an NSAID given to the control group in the study (12). At this stage, the effect of COX-2 inhibitors on the heart was still unknown, but could be postulated since COX-2 produces prostacyclin, a prostaglandin that inhibits platelet production and dilates blood vessels. Therefore, inhibition of COX-2 could cause excess platelet aggregation, lead-

ing to thrombotic events such as heart attacks or strokes. Inhibition of COX-1 would cause the exact opposite—it would inhibit a blood clotting protein, thromboxane, thereby helping blood flow through the body. NSAIDs balance these two opposing side effects and therefore do not cause an overall problem. Indeed, they could actually help the heart, depending on the drug (6). The cardiovascular side effects of COX-2 inhibitors did not gain attention until the Merck study analyzing the effects of Vioxx on cancerous polyps showed that the risk of heart attack and stroke was more than doubled after long-term use beyond 18 months.

The question that remains to be answered is: are these cardiovascular side effects a class effect? In other words, do all COX-2 inhibitors behave the same way? It is currently unknown whether or not all COX-2 antagonists increase the risk of cardiovascular disease. The *CLASS* clinical trial, which was performed in 1999 on Celebrex, did not indicate any increase in heart problems. However, *CLASS* has since lost credibility because of poor implementation. Despite the potential health risks, cancer researchers are looking to COX-2 inhibitors as the next promising cancer therapy (12).

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Looking Ahead

Although the exact roles of COX-2 enzymes in tumor growth and maintenance are still largely unknown, numerous experiments and clinical studies have shown that NSAIDs, and especially highly selective COX-2 inhibitors, are strong chemopreventive drugs. The discovery of abnormal COX-2 expression in cancerous cells was the first indication of COX-2 inhibitors' potential chemotherapeutic benefits. The role played by COX-2 in cancer cells may again involve the pro-inflammatory prostaglandins, which are also present at abnormally high levels in tumors. These prostaglandins could support tumor growth by inducing the development of blood vessels that oxygenate and sustain tumor cells (13). In rodent models of FAP, a genetic disease that leads to colon cancer, deletion of the gene thought to encode COX-2 reduced the number and size of cancerous intestinal polyps (14). Similarly, COX-2 inhibitors can prevent tumor growth by blocking formation of new blood vessels (13).

Another possible mechanism of tumor cell death induced by COX-2 inhibitors may involve the accumulation of arachidonic acid. Recall that the function of COX enzymes is to metabolize arachidonic acid and produce prostaglandins as products. In experiments that combined the addition of arachidonic acid with COX-2 inhibitor treatment, a greater percentage of cancer cells died compared to the percentage that died when treated only with COX-2 inhibitors (15).

Research has so far shown that COX-2 inhibitors are best used in conjunction with other cancer drugs. A clinical trial that administered Vioxx in addition to common chemotherapy drugs indicated a higher response rate compared to the group treated only with chemotherapy drugs. This study lasted for a year and there were no occurrences of cardiovascular events. Therefore, COX-2 inhibitors could be very safe chemotherapy drugs if not taken for long periods of time (16).

Immediately after the Vioxx controversy, a large number of clinical trials testing COX-2 inhibitors as cancer drugs were halted in light of the potential harm to trial participants, a move indicative of the trend to discourage the use of COX-2 inhibitors. However, COX-2 inhibitors still have many unknown variables and may be much more complex than is currently believed. If researchers better understood how they work throughout the body, harmful side effects such as stroke and heart attack could be avoided. In addition, COX-2 inhibitors may open the door to other realms of research and insight into the functioning of the human body, much like they already have in cancer and immunology research. H

—Kathleen Jacobs '08 is a Biochemical Sciences concentrator in Pforzheimer House.

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