Vioxx: What Went Wrong?

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Arthritis is one of the most common medical problems in the world. Nearly four million Canadians are affected with arthritis and other rheumatic conditions; these numbers are expected to escalate as the population continues to age (PHAC, 2003). At present there exists only treatments for arthritis, but no cure.

Osteoarthritis is a degenerative form of arthritis which occurs when the cartilaginous lining that cushions the ends of bones in joints deteriorates, leaving bones to rub against one another (Hunder, 1999). Rheumatoid Arthritis (RA), on the other hand, is not associated with wear and tear. It is thought to be an autoimmune disease in which an unidentified agent stimulates an immune response in the joint capsule (Hunder, 1999). The ensuing inflammatory response results in the thickening of the joint capsule synovium. If untreated, inflammatory mediators digest cartilage, bone, tendons and ligaments.

Given the aforementioned etiology of RA, treatment regimens have focused primarily upon reducing the auto-Inflammatory response associated with the disease. This has led to the utilization and development of various families of anti-Inflammatory drugs – one of which are the Non-Steroidal Anti-inflammatory Drugs (NSAIDs). This class of drugs, of which aspirin is a member, inhibits inflammation by interfering with an inflammatory mediator known as cyclo-oxygenase (COX). Clinical trials demonstrate that although NSAIDs are effective in alleviating symptoms associated with RA, they present a marked increase in gastrointestinal ulceration (Kremer, 2000). These findings led to the development of NSAIDs that specifically inhibit the one isozyme of COX which is involved in inflammation, COX-2, but left the other isozyme (COX-1) untouched. These COX-2 specific NSAIDs exhibit the same anti-inflammatory potential as their traditional counterparts without the adverse gastrointestinal complications (Bombardier et al., 2000). Perhaps the most prominent of the COX-2 specific inhibitors is Vioxx. Despite these advantages, Vioxx was verified to increase risk of heart attack, stroke, and serious cardiovascular events by greater than 50% (Bombardier et al., 2000); these findings resulted in a nationwide recall of the pharmaceutical drug.

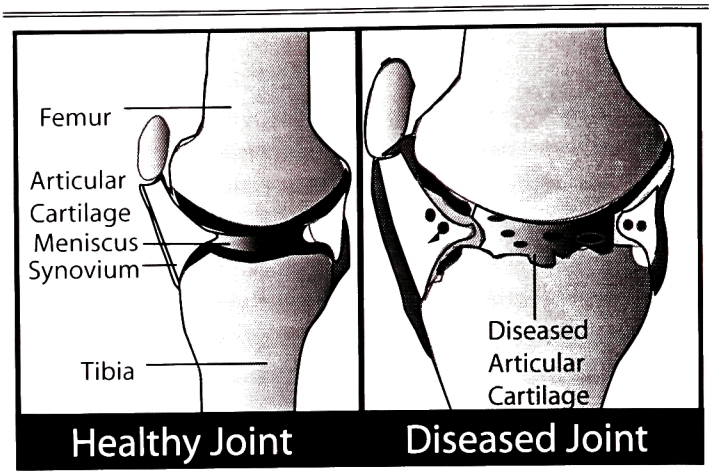

Figure 1: Inflammation of the joint capsule results in destruction of the articular cartilage and meniscus separating the two bones. If untreated, inflammatory mediators will continue to digest synovium, bones, ligaments and tendons.

Physiological Function Of Cyclo-Oxygenase (COX)

Cyclo-oxygenase (COX) plays an important role in the production of prostaglandins. Prostaglandins are a family of chemical messengers which allow for local signaling within tissues. The effects of the signal are highly dependent upon both the specific type of prostaglandin as well as the

Prostaglandin	Physiological Function(s)
Thromboxane A_2 (TXA_2)	Platelet Aggregation (blood clot formation) & Vasoconstriction
Prostacyclin (PGI_2)	Anti-aggregation (blood thinning) & Vasodilation
PGE_2	Induce immune response, Vasodilation, Protect gastric mucosa

Table 1: Prostaglandin Functions

properties of the target tissue cells. For instance, the same prostaglandin may have different effects when acting upon the endothelial cells of the gastrointestinal tract than on the vasculature of inflamed tissue. Prostaglandins participate in a variety of physiological mechanisms, including:

- Activation of an inflammatory response
- Haemostatic mechanisms: formation or destruction of blood clots depending on the type of prostaglandin
- Dilation or constriction of blood vessels
- Production of the protective mucosal layer which lines the inside of the gut and inhibition of gastric acid secretion
- Regulation of blood supply to the kidneys

All members of the prostaglandin family (Table 1) are enzymatically produced products of arachidonic acid. Arachidonic acid is a dietary unsaturated fat which is metabolized from phospholipid membrane of cells. The first stage of prostaglandin synthesis is the transformation of arachidonic acid into cyclic endoperoxide intermediates; this pathway is catalyzed by the COX enzymes (Pairet & van Ryn, 2004).

PROSTAGLANDIN SYNTHESIS PATHWAY

Protaglandin synthesis proceeds via two primary stages:

1) COX catalyzes the breakdown of Arachidonic Acid into a cyclic endoperoxide intermediate in a two step process that ultimately produces Prostaglandin H_2 (PGH_2).

2) Downstream of COX action, a range of tissue-specific synthases transform PGH_2 into the different prostaglandins.

SUBTYPES OF COX

There are two isozymes, or forms, of the COX enzyme, designated COX-1 and COX-2. The first, COX-1, has been demonstrated to be constitutive in most cells; in other words, it is present at a fairly constant level regardless of physiological demand (Pairet & van Ryn, 2004). Conversely, very little COX-2 is found in resting cells. However, it is powerfully induced in fibroblasts, endothelial cells and vascular smooth muscle by cytokines and in macrophages by lipopolysacharide (Pairet & van Ryn, 2004). These observations have led to the hypothesis that the constitutively expressed COX-1 is involved in

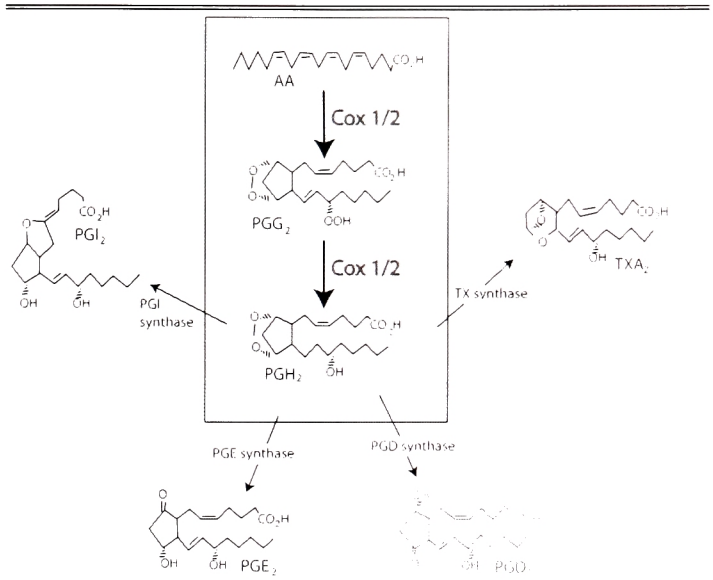

Figure 2: Cyclo-oxygenase (COX) enzymes convert the membrane lipid Arachidonic Acid (AA) into a prostaglandin intermediate, PGH_2. Tissue specific synthases then proceed to convert this intermediate into the various prostaglandins.

the production of prostaglandins which mediate normal physiological processes. This includes the prostaglandin thromboxane A_2 involved platelet aggregation, and prostaglandin PGE_2 which protects the gastric mucosa from ulceration. The inducible COX-2, on the other hand, is believed to be primarily responsible for the production of prostaglandins in inflamed tissues.

ADVERSE GASTROINTESINAL EFFECTS OF NSAIDS

Traditional NSAIDs function by non-selectively inhibiting both isozymes of COX. Therefore, while the inhibition of COX-2 results in a reduced inflammatory response, the inhibition of COX-1 interferes with essential physiological processes. One such compromised process is the protection of the gastric mucosa from ulceration. Therefore treatment of arthritis with non-selective NSAIDs, such as aspirin, contributes to gastrointestinal morbidity.

COX-2 SPECIFIC INHIBITORS

Although the active sites of COX-1 and COX-2 are similar, there are structural differences. The NSAID binding pocket on COX-2 is larger than that of COX-1. The important consequence of this difference is that COX-2 binds more readily to bulkier inhibitors (Smith et al., 2000). This has served as the framework for the development of COX-2 selective NSAIDs.

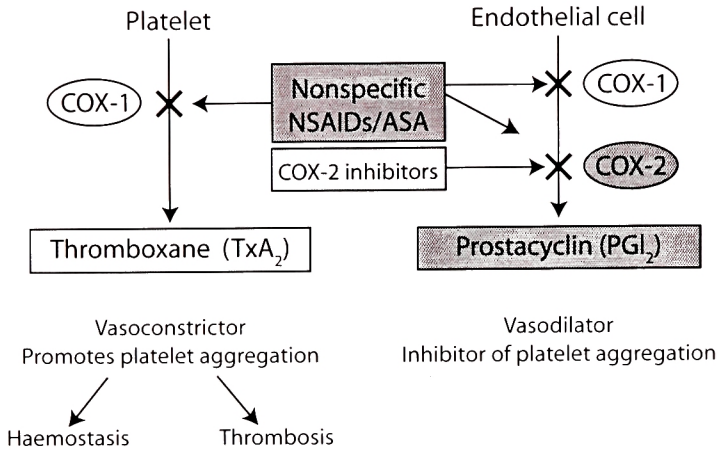

Figure 3: Traditional Non-specific NSAIDs and aspirin inhibit both COX-1 and COX-2 activity, preventing the production of both Thromboxane A_2 and Prostacyclin (PGI_2); therefore, the effects on haemostasis (blood clotting) are balanced. COX-2 specific inhibitors inhibit only Prostacyclin (PGI_2) production causing a shift towards increase vasoconstriction and blood clotting. (Clark, 2004)

Adverse Cardiovascular Effects Of COX-2 Inhibitors

Aside from inflammation, one fundamental physiological function of prostaglandins is haemostasis, maintaining a balance between liquid and solid (clotting) blood. In particular, it is thromboxane A_2 (TXA_2) which initiates platelet aggregation and clot formation, and prostacyclin (PGI_2) which serves as an anti-aggregatory blood thinner (Clark, 2004). TXA_2 production in platelets is mediated by COX-1, while PGI_2 production in vascular endothelial cells is mediated by COX-2. Traditional non-selective NSAIDs inhibit both COX-1 and COX-2 and therefore the effects on haemostasis are counterbalanced. However, COX-2 specific NSAIDs inhibit PGI_2 production only; this shifts the haemostatic balance towards increased platelet aggregation and vasoconstriction of blood vessels (Clark, 2004). These two conditions lead to the increased cardiovascular complications found in patients using Vioxx.

The results of the VIGOR (VIOXX Gastrointestinal Outcomes Research) in 2000 revealed that while Vioxx demonstrated less gastrointestinal toxicity than the comparative non-selective NSAID, it also led to a marked increase in adverse cardiovascular events (Bombardier et al. 2000). However, it was not until four years later when the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial confirmed these cardiotoxicity findings that Vioxx was recalled.

Drugs, Tea and Curry: The Means to Finding a Cure for Alzheimer's Disease?

Danny Ricci

There is no known cure for Alzheimer's disease, but certain substances and drugs have shown promising results in treating this neural degenerative disorder.

Alzheimer's disease is a neural degenerative disorder that affects 11% of the population over the age of 65 (Tortora & Grabowski, 2003). A German physicist, Alois Alzheimer, discovered Alzheimer's disease in 1906, after his study of a 51-year old woman who had various abnormalities in the brain, particularly the cerebral cortex (Kolb & Whishaw, 2001). Individuals with Alzheimer's disease become forgetful, confused, disoriented and may experience paranoia and delirium. As the brain deteriorates, they lose the ability to read, speak, eat, walk and write. Alzheimer's disease leads to dementia, the permanent or progressive loss of intellectual abilities, including the impairment of judgment, abstract thinking and memory. The causes of Alzheimer's disease are still unknown, though evidence suggests that the disease results from a combination of genetic and environmental factors, as well as the aging process (Tortora & Grabowski, 2003). Researchers have been studying the neuronal abnormalities that occur during Alzheimer's disease and also new methods to treat the disease.

Plaque Deposits In The Cerebral Cortex

One of the changes that occurs in the brain during Alzheimer's disease is the development of plaques in the cerebral cortex (Kolb & Whishaw, 2001). The plaques are