S36. The fundamentals: How Aspirin and NSAID's work

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Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse group of compounds that share the ability to inhibit the enzymatic activity of cyclooxygenases (COX). Their main pharmacological effects come from blocking the first step in the metabolism of arachidonic acid through the COX pathway, thereby inhibiting the formation of several tissue-specific signaling lipids such as prostaglandins, prostacyclin, and thromboxane A_2. The downstream products of the COX pathway vary and have different effects in different tissues. For example, thromboxane (TXA_2) in platelets promotes the aggregation of platelets and hemostasis; prostacyclin (PGI_2) in vascular endothelial cells causes vasodilatation and inhibits platelet aggregation. Prostaglandin E_2 (PGE_2) in gastric epithelium protects the gastric mucosa against acid, whereas PGE_2 in inflammatory tissues promotes inflammation, wound healing, and neoplasia. Due to these diverse and tissue-specific biological effects, the consequences of inhibiting COX activity can be therapeutic, toxic, or both depending on the dose, drug, and patient characteristics.

Several strategies have been used in efforts to improve the selectivity and minimize the potential toxicity of NSAIDs. One approach, based on the discovery in 1991 that there are two distinct isoforms of the COX enzyme, was to develop drugs and treatment regimens that more or less selectively inhibit COX-1 or COX-2. COX-1 is expressed constitutively in virtually all cells of the body; whereas COX-2 is upregulated by cytokines and growth factors in inflammation and in the development of some cancers. Aspirin at low doses ($\leqslant$100 mg daily) selectively inhibits COX-1, whereas at anti-inflammatory doses, Aspirin and other traditional NSAIDs (tNSAIDs) such as ibuprofen, naproxen, indomethacin and piroxicam non-selectively inhibit both COX-1 and COX-2. A number of newer drugs such as rofecoxib, celecoxib, valdecoxib (collectively called coxibs) were developed to inhibit COX-2 more selectively with the goal of minimizing gastrointestinal toxicity from inhibition of COX-1. However, the cardiovascular toxicity of the selective COX-2 inhibitors, resulting from their inhibition of prostacyclin in vascular endothelium, essentially precludes their long term use for cancer prevention.

A unique advantage of Aspirin, with respect to the prevention of thrombotic cardiovascular events, is that it irreversibly inhibits the production of thromboxane (TXA_2) in platelets by binding covalently to the active site of COX-1. This is accomplished at low doses ($\leqslant$100 mg daily) as platelets pass through the enterohepatic circulation. The effect is specific to platelets, because platelets lack a nucleus and have limited ability to synthesize protein, and because the concentrations of Aspirin are considerably higher in the enterohepatic circulation than after the first pass through the liver. While it would be fortuitous if prophylactic use of low dose Aspirin were effective for cancer prevention as well as for cardiovascular disease, this remains unresolved. Low dose Aspirin has no systemic effects on COX-2. It remains unclear what dose of Aspirin may be optimal for the prevention of colorectal or other cancers.