COX-1 and COX-2 Enzymes Synthesize Prostaglandins and Are Inhibited by NSAIDS (Nonsteroidal Anti-inflammatory Drugs)

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Abstract

Prostaglandins are molecules involved in signaling pain and maintaining the lining of the stomach. Inhibitors of COX-1 and COX-2 are used to relieve pain and reduce inflammation. The two enzymes are structurally similar but differ in their active sites, allowing selective inhibition of COX-2.

Introduction

COX-1 and COX-2 are enzymes that synthesize prostaglandins. Prostaglandins are responsible for fever, pain, and inflammation, but also the maintenance of the lining of the stomach and prevention of ulcers. COX-1 is found mainly in the gastrointestinal lining, and COX-2 is found in response to inflammation. NSAIDS (Nonsteroidal Anti-Inflammatory Drugs) such as aspirin, ibuprofen, naproxen, and flurbiprofen inhibit both COX-1 and COX-2 and are regularly used by over 33 million Americans for pain and inflammation. Some 15%–30% of these users suffer gastrointestinal side effects from the inhibition of COX-1 which protects the stomach lining. To solve this problem, a series of drugs were created that inhibited only COX-2: Vioxx, Bextra, Celebrex, and Advil. These drugs do not have the gastrointestinal side effects, but some have been linked to increased numbers of heart attacks and strokes. We are studying the interaction of COX enzymes with NSAIDS and COX inhibitors to see how the enzymes are inhibited from catalyzing prostaglandins. We are also studying models of the normal COX substrate, arachidonic acid, and NSAIDS and COX-2 inhibitors. We are designing models of the active sites of COX-1 and COX-2 using pdb files 1Q4G and 1PX, as well as models of the normal COX substrate (arachidonic acid), NSAIDS and COX-2 inhibitors to better understand the actions and side effects of NSAIDS and COX-2 inhibitors.

Structure

Cyclooxygenase are dimers (consisting of two identical individual proteins) that attach to each other by the hydrophobic knobs on their surfaces. The proteins are embedded in the endoplasmic reticulum membrane, anchored by hydrophobic knobs. The enzyme has two active sites. Located deep inside the enzyme is the cyclooxygenase active site, which the substrate enters through a tunnel that extends down into the plasma membrane. When the first reaction has occurred, the product of the reaction moves to the second site (near the Heme molecule) where the peroxidate reaction occurs. The product of this reaction is then released into the cytosol.

COX-1 vs. COX-2 Structure

Phospholipids in the membrane are broken down by phospholipase A2 when triggered by first messengers, including neurotransmitters, neuromodulators, and neurohormones. One of the products of this break down is arachidonic acid. In the picture above, COX-1 (orange) and COX-2 (lavender) are superimposed around SC-558. SC-558 (Celebrex [celecoxib]) is shown bound to COX-2 (carbon, green; nitrogen, blue; sulfur, yellow; oxygen, red; fluorine, dark brown; bromine, magenta) which is super-imposed on structurally homologous residues of COX-1 from its complex with flurbiprofen (omitted for clarity). The blue ribbon is the carbon backbone. The larger NSAID binding pocket in COX-2 is clearly visible. Access to this ‘side pocket’ is restricted in COX-1 because of the isoleucine at 523.

Cyclooxygenase Active Sites

In the pictures below, the heme is orange, the hydrophobic knob is yellow, and the amino acids in the Cyclooxygenase active site are colored in CPK (red for oxygen, blue for nitrogen, and gray for carbon). Cyclooxygenase with its normal substrate arachidonic acid (purple)

Chemical Process

1. Phospholipids in the membrane are broken down by phospholipase A2 when triggered by first messengers, including neurotransmitters, neuromodulators, and neurohormones. One of the products of this break down is arachidonic acid.
2. Assist by side chains located within the channel, arachidonic acid enters COX through the hydrophobic knob that anchors the protein into the membrane.
3. The arachidonic acid goes into the cyclooxygenase active site, which adds two oxygen molecules to the arachidonic acid, turning it into prostaglandin endoperoxide (PGG2).
4. Prostaglandin endoperoxide (PGG2), after having one oxygen atom removed, becomes prostaglandin H2 (PGH2) which leaves the COX enzyme and regulates blood clots, pain sensitivity, and allergic reactions.

Conclusion

• COX-1 and COX-2 are enzymes that synthesize prostaglandin, a molecule involved in signaling pain and maintaining the lining of the stomach.
• The enzymes are 60-65% similar and create identical prostaglandins, but they are expressed in different areas of the body.
• The slight difference between the enzymes allows certain drugs to be selective for one and not the other, inhibiting COX-2 (which would otherwise promote inflammation) and ignoring COX-1 (which protects the gastrointestinal lining).
• The reason Vioxx causes heart attacks and strokes isn’t certain. The COX-1 enzyme encourages blood clotting while the COX-2 enzyme inhibits clotting. Drugs like Vioxx block COX-2 enzymes and allow COX-1 enzymes may increase blood clotting, an excess of which can lead to coronary events like heart attacks and strokes.

Drugs

The three drugs below are all nonsteroidal anti-inflammatory drugs (NSAIDS). The first two NSAIDS, aspirin and ibuprofen, are called nonselective COX inhibitors since they affect both COX-1 and COX-2 similarly (note their high COX-2/COX-1 effect ratios). The third, Vioxx, is a type of NSAID called a selective inhibitor since it targets only the COX-2 enzyme (note its low effect ratio).

Supporting Information

NSAIDS and How They Inhibit COX

COX-2 Specific Celecoxib (celecoxib)

Celecoxib, a selective COX-2 inhibitor developed in the 1990’s by G.D. Searle & Co. and Pfizer Inc., is a type of NSAID called a selective inhibitor since it targets only the COX-2 enzyme (note its low effect ratio). Celecoxib exploits the fact that the active site of COX-2 is about 20% larger than that of COX-1.