The Effects of COX-1 Enzyme Inhibitions by NSAIDs

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Introduction:

The inhibition of the cyclooxygenase-1 enzyme with nonsteroidal anti-inflammatory drugs, also known as NSAIDs, diminishes the mucous layer in the stomach resulting in gastric ulcers. Cyclooxygenase-1, abbreviated as COX-1, is a prostaglandin-endoperoxide synthase encoded in the PTSG1 gene (1). It is a necessary enzyme for the biosynthesis of prostaglandins, which are naturally occurring chemicals responsible for promoting inflammation throughout the body. NSAIDs inhibit these enzymes, restricting inflammation, in turn allowing the stomach's acid to digest itself without the protection of the gastric mucosa.

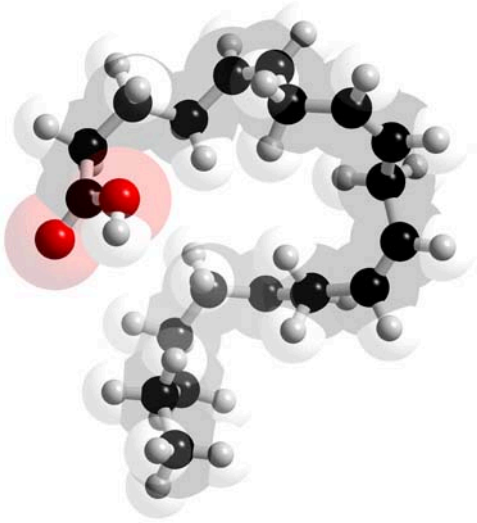

Figure 1: The structure of a molecule of arachidonic acid.

Prostaglandins are produced when specific cell-surface receptors are stimulated, activating the phospholipase A_2 to release arachidonic acid from the cell membrane (2). Arachidonic acid ($C_{20}H_{32}O_2$) is a polyunsaturated fatty acid, meaning it has more than one double bond in its chemical structure, creating a long hydrocarbon chain with kinks in it from the different arrangements. These kinks prevent the molecules from packing tightly together, lowering intermolecular forces, allowing the arachidonic acid to withstand the temperature of the body and remain a liquid. These arachidonic acid molecules fit into the active site of COX-1 by utilizing its carboxyl group to bond to the amino acid hydrogen-bonding network at the base of the active site. This network is comprised of Arg-120, Tyr-355, and Glu-524 (3). The cis double bonds within arachidonic acid promote flexibility through the disruption of a straight hydrocarbon chain, allowing it to fit into the L-shaped active site of COX-1.

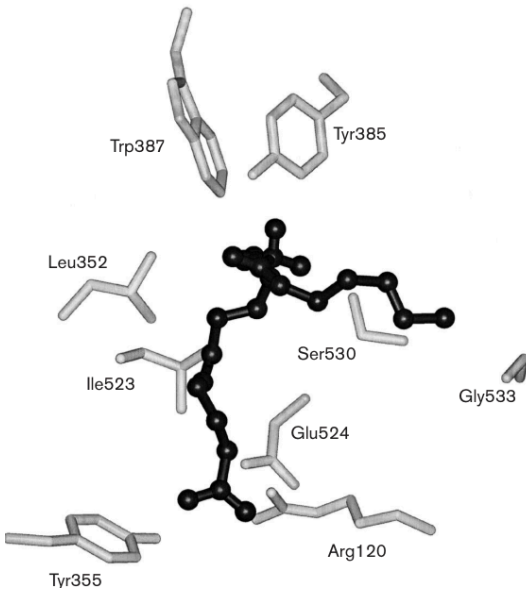

Figure 2: Arachidonic acid bound to the active site of the COX-1 enzyme

The COX-1 enzyme has a heme group with a central atom of iron. This atom becomes oxidized by a hydroperoxy functional group (-OOH) in a redox reaction where Fe^{3+} is oxidized into Fe^{4+} paired with an oxygen from the ROOH. The generation of the ferryl-oxo complex (Fe^{4+}=O), the first intermediate produced in this cycle, is a thermodynamically favorable process with a redox potential of approximately 1V. It donates one electron to Tyr-385 which is ideally positioned between the heme group and COX active site, increasing binding success between substrate and enzyme through increased orientation correctness, forming a tyrosyl radical in an exothermic process. The decay of the ferryl-oxo complex's visible absorbance concurs with the production of the tyrosyl radical, which means kinetically that the rate of decay of ferryl-oxo complex is directly proportional to the rate of formation of the tyrosyl radical, implying a coupled or sequential reaction mechanism. The instability of radicals from their unpaired electron causes them to be extremely reactive, and they can act as either reducing agents or oxidizing agents depending on if they donate their extra electron or gain another one to fulfill the pair respectively.

The redox potential of the resting ferric state (Fe^{3+}) in the COX-1 enzyme is -167mV, meaning it is thermodynamically unfavorable, and the iron atom in the heme group can not oxidize Tyr-385 into a tyrosyl radical without being oxidized itself, or without an external energy source to drive the reaction in favor of its products.

The tyrosyl radical then removes a hydrogen from arachidonic acid, highly reactive due to the hydrogen being situated between two double bonds, in the simplified reaction initiating the COX catalytic cycle:

Tyrosyl Radical + Arachidonic Acid → Tyrosine + Arachidonic Acid Radical

(Tyrosyl-O$\cdot$ +H-C=CH-CH$_2$-CH=CH → Tyrosyl-OH+C=CH-CH$\cdot$ -CH=CH)

The creation of the radical leaves an unpaired electron on the carbon from which the hydrogen was removed, forming a pentadienyl radical, or a five carbon chain with two double bonds and a radical. The overlapping p-orbitals from the carbons allow for the electron to

delocalize, like in metals, creating a conjugated diene. Delocalization occurs because it lowers the energy and increases the stability of a system, and it allows for the radical to be oxidized by oxygen due to the increased availability of electrons for bonding, resulting in a peroxyl radical. One atom of oxygen within the oxygen molecule reattaches itself to another carbon in the structure because it increases stability through a more favorable geometry that optimizes electron-electron repulsion in the electron clouds of different atoms, and it allows for more electron delocalization through the creation of a cyclic peroxide.

The tyrosine formed from the addition of a hydrogen from arachidonic acid to the tyrosyl radical donates its hydrogen in another redox reaction to form prostaglandin G_2, which is an intermediate of prostaglandins, and it reforms the tyrosyl radical to continue the COX catalytic cycle and abstract a hydrogen from another arachidonic acid molecule (4).

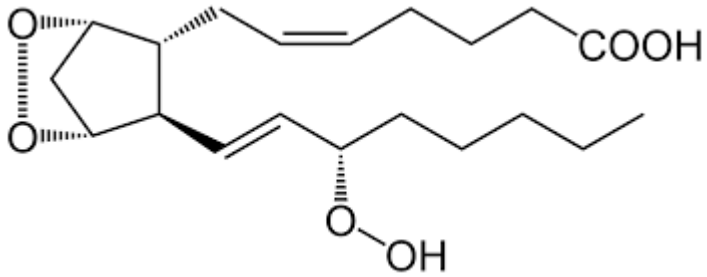

Figure 3: Arachidonic acid after transformation into prostaglandin G_2 by COX-1 enzyme

PGG_2 (prostaglandin G_2), however, is an unstable intermediate due to its peroxide group (O-O), which is highly reactive and prone to decomposition into more stable products due to the weak bond between oxygens. The COX-1 enzyme mediates the transformation of PGG_2 by a two electron reduction into PGH_2, which is more stable (5).

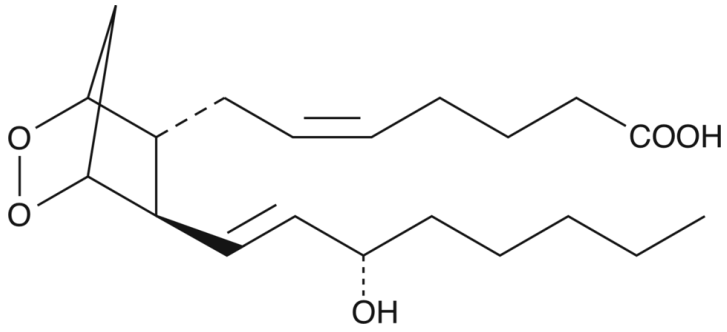

Figure 4: Prostaglandin G_2 after peroxide decomposition into prostaglandin H_2

PGH_2 undergoes more transformations as it enters the specialized active sites of different prostaglandin synthases, where it undergoes modifications to evolve into an array of specific

prostaglandins, each serving a purpose surrounding physiological regulation. PGE_2 specifically focuses on all pertaining physiological functions of the gut, such as mucosal protection and gastrointestinal secretion and motility (6). PGI_2 focuses on vasodilation, which increases blood flow to the stomach lining, increasing nutrients and oxygen to mucosal cells for repair, and the inhibition of platelet aggregation, ensuring proper blood flow (7). These two derivatives of PGH_2 maintain and protect the stomach's gastric lining from its harmful acid, promoting a healthy gastrointestinal tract free from ulcers.

Conclusion:

NSAIDs are orally ingested and absorbed into the bloodstream through the gastrointestinal tract. They are carried throughout the body, reaching inflamed tissues and the stomach lining, where they bind to the active site of COX-1 using hydrogen bonds with amino acid residues and intermolecular forces. They inhibit arachidonic acid from bonding instead, preventing the production of PGG_2 and PGH_2 as well their transformations into PGE_2 and PGI_2, in turn diminishing the gastrointestinal protection and allowing the stomach's acid to digest itself, creating gastric ulcers.

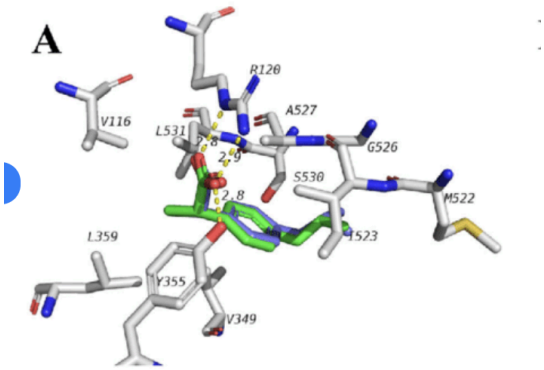

Figure 5: Ibuprofen (green) inhibiting the active site of COX-1

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