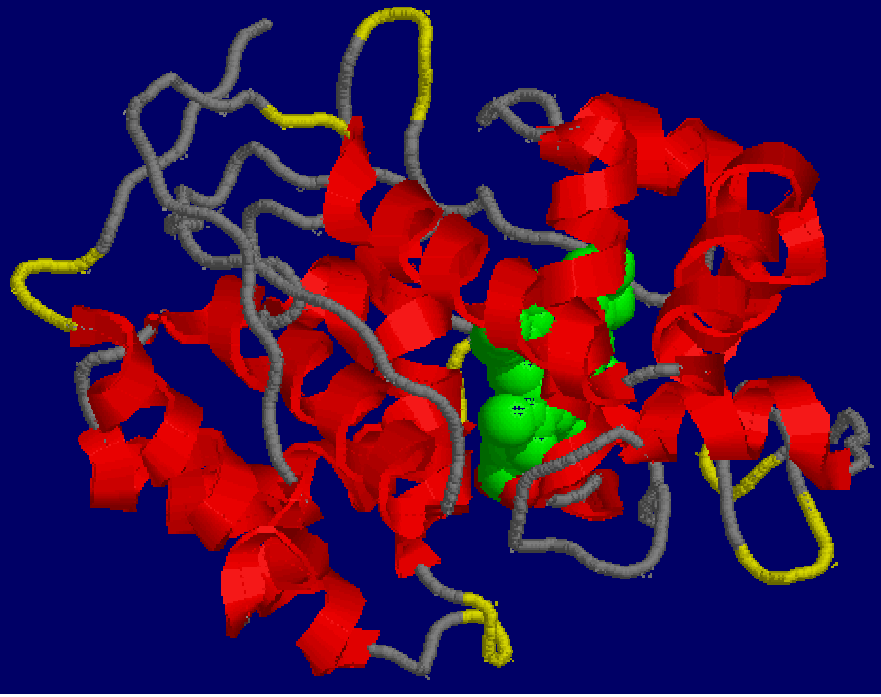
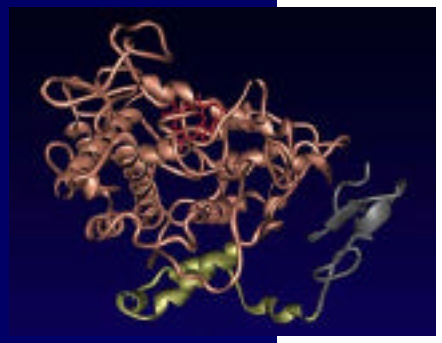
Cyclooxygenase and NSAIDs

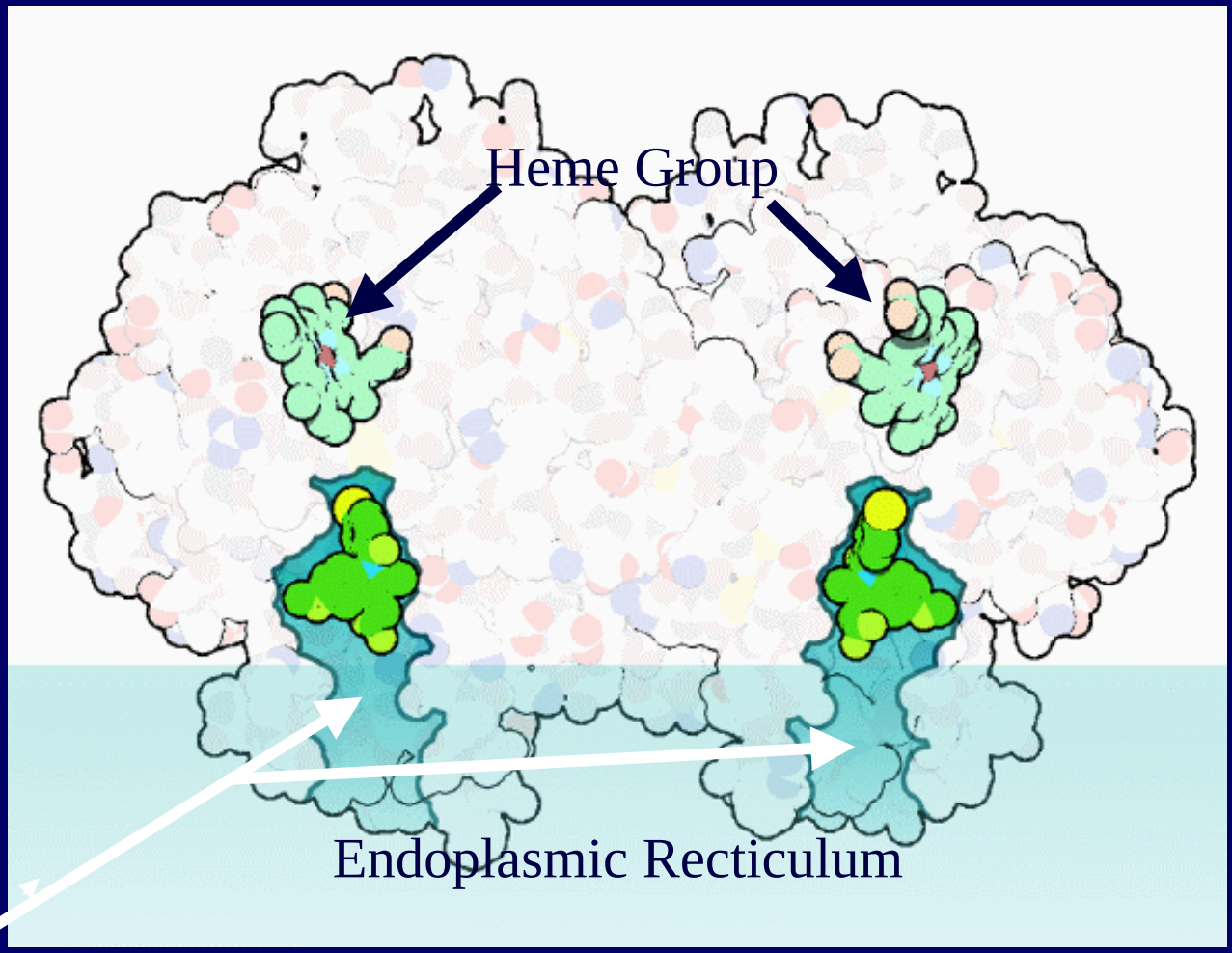


Cyclooxygenase



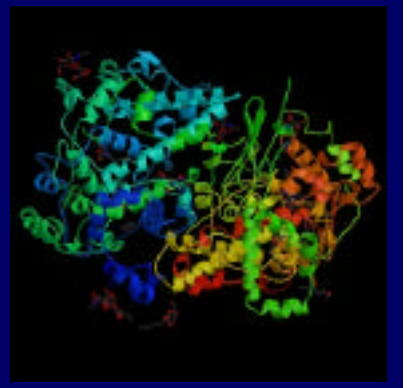
- An enzyme responsible for the production of prostaglandins
- Two forms, COX1 and COX2
- Contains two separate active sites for prostaglandin synthase
- One side contains the cyclooxygenase active site
- The opposite side contains the peroxidase active site which is involved in activating the heme group necessary for cyclooxygenase reaction
- Complex composed of identical dimers (2 cyclooxygenase sites and 2 peroxidase active sites)
- Each subunit has a carbon rich knob involved in anchoring the complex to the ER
- Knobs contain funnels to active sites responsible for guiding arachidonic acid from the ER to the enzyme

COX Enzyme Structure



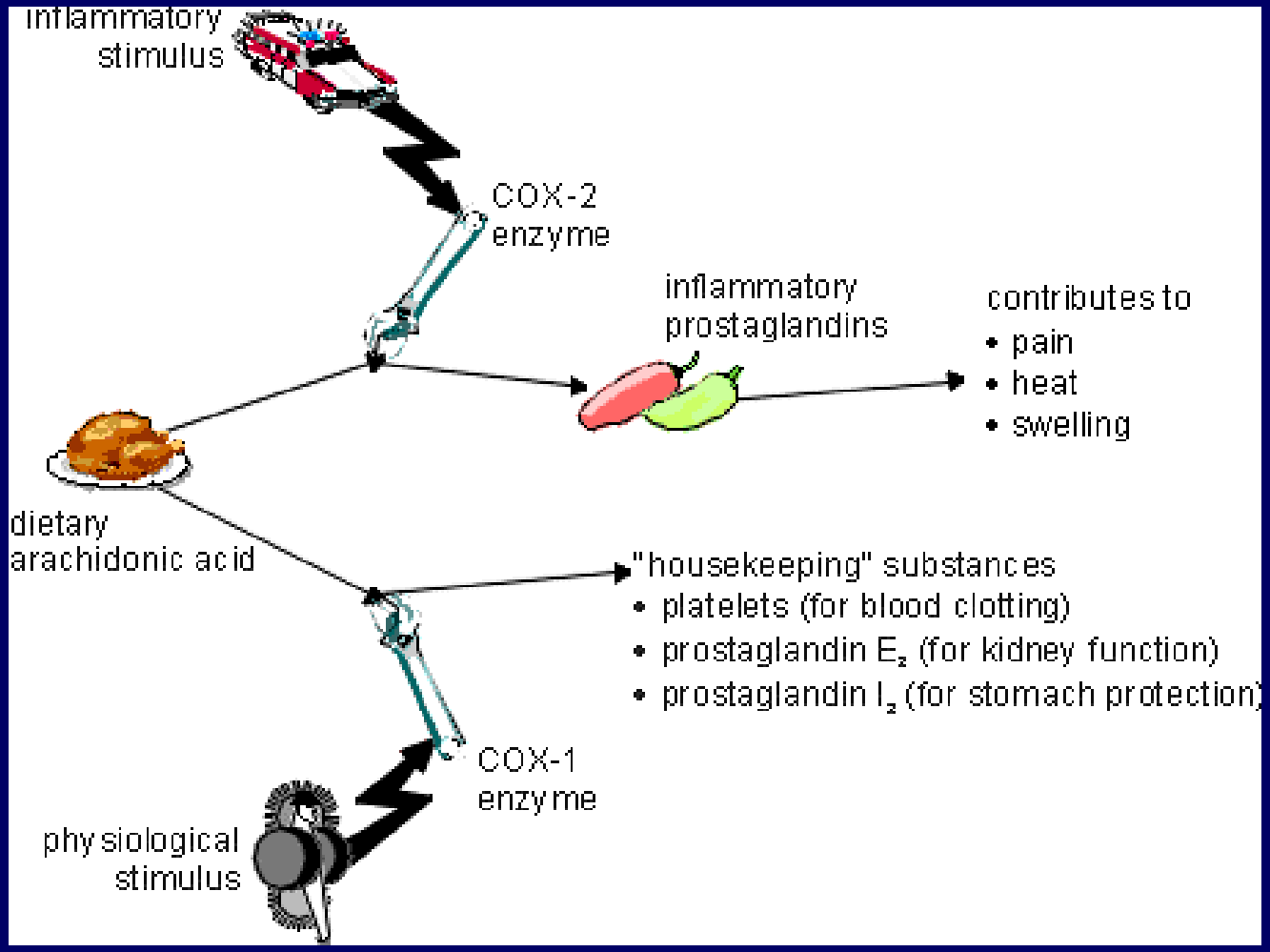
Active Sites

COX 1 and COX 2



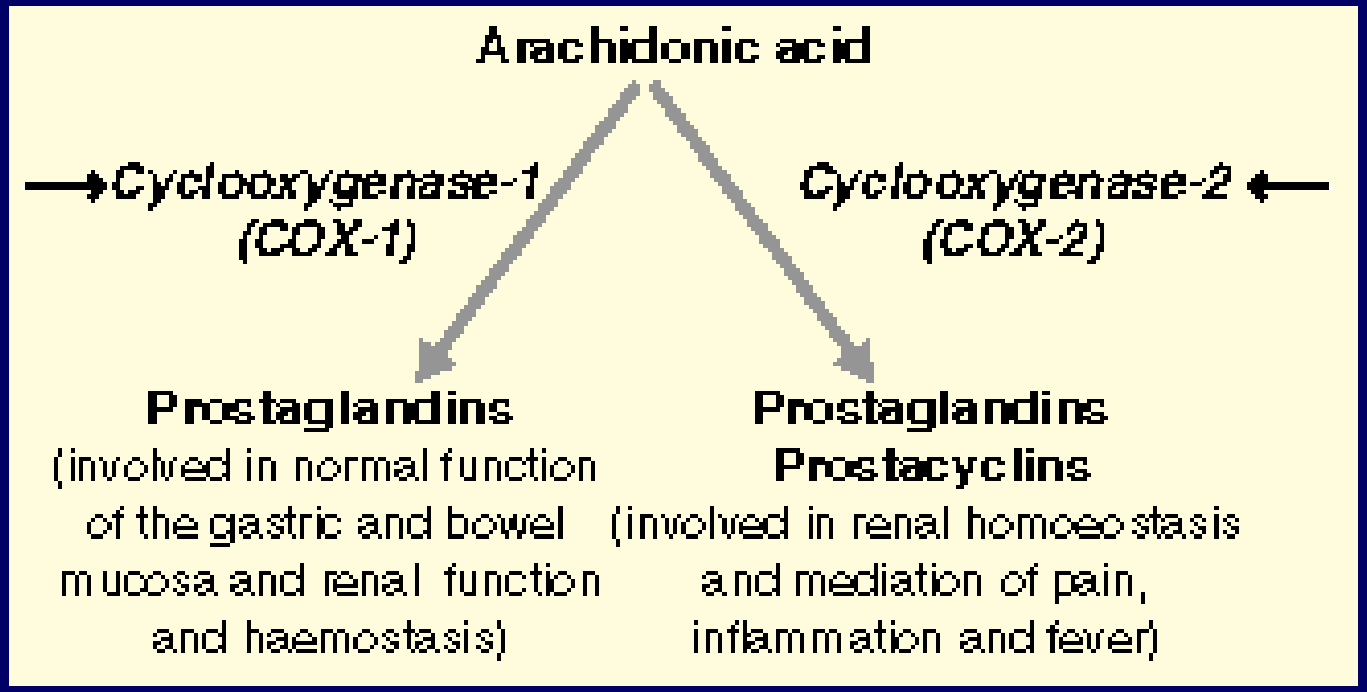
- COX1
  - Continuously stimulated by the body
  - Constitutive (Its concentration in the body remain stable)
  - Creates prostaglandins used for basic house keeping throughout body
  - Prostaglandins stimulate normal body functions such as stomach mucous production, regulation of gastric acid and kidney water excretion
- Cox 2
  - Induced (normally not in present in cells)
  - Built only in special cells (EX a549 lung cells)
  - Used for signaling pain and inflammation
  - Produces prostaglandins for inflammatory response
  - Stimulated only as part of immune response
  - Production is stimulated by inflammatory cytokines and growth factors

Different pathways for Cox1 and Cox 2



Cox 1 and 2 continued

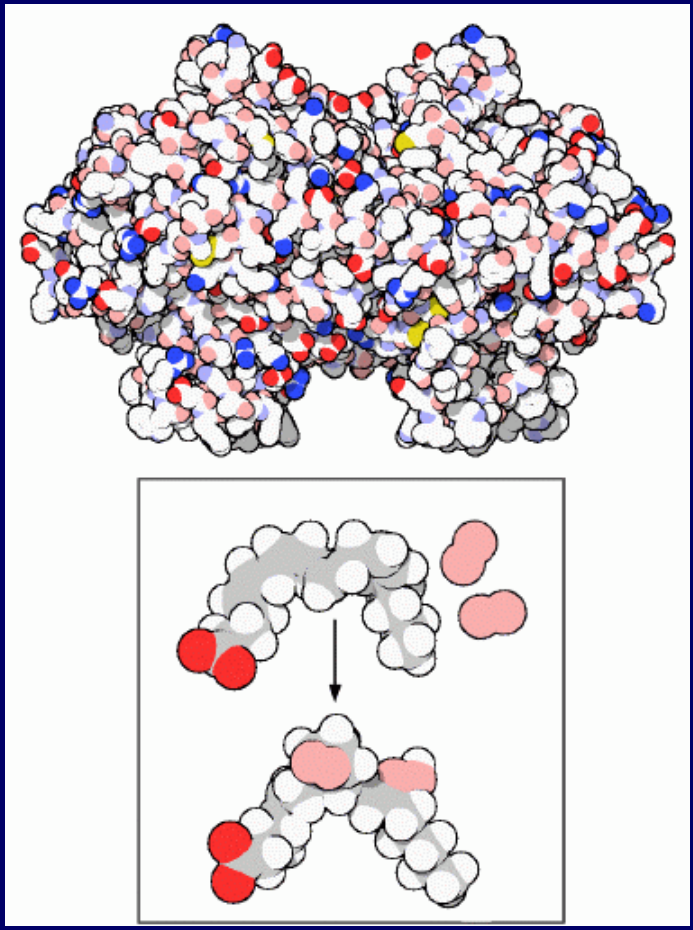
- **Each Form of COX catalyzes arachidonic acid to form its own prostaglandins**



Prostoglandins

- Created from common precursor molecule cyclooxygenase
- Key hormones used to carry local messages
- Created by local cells instead specialized glands like most hormones
- Acts in local area of cells
- control processes including constriction of muscle and blood vessels, aggregation of platelets and constriction of the uterus
- Deliver and strengthen pain signals and induce inflammation

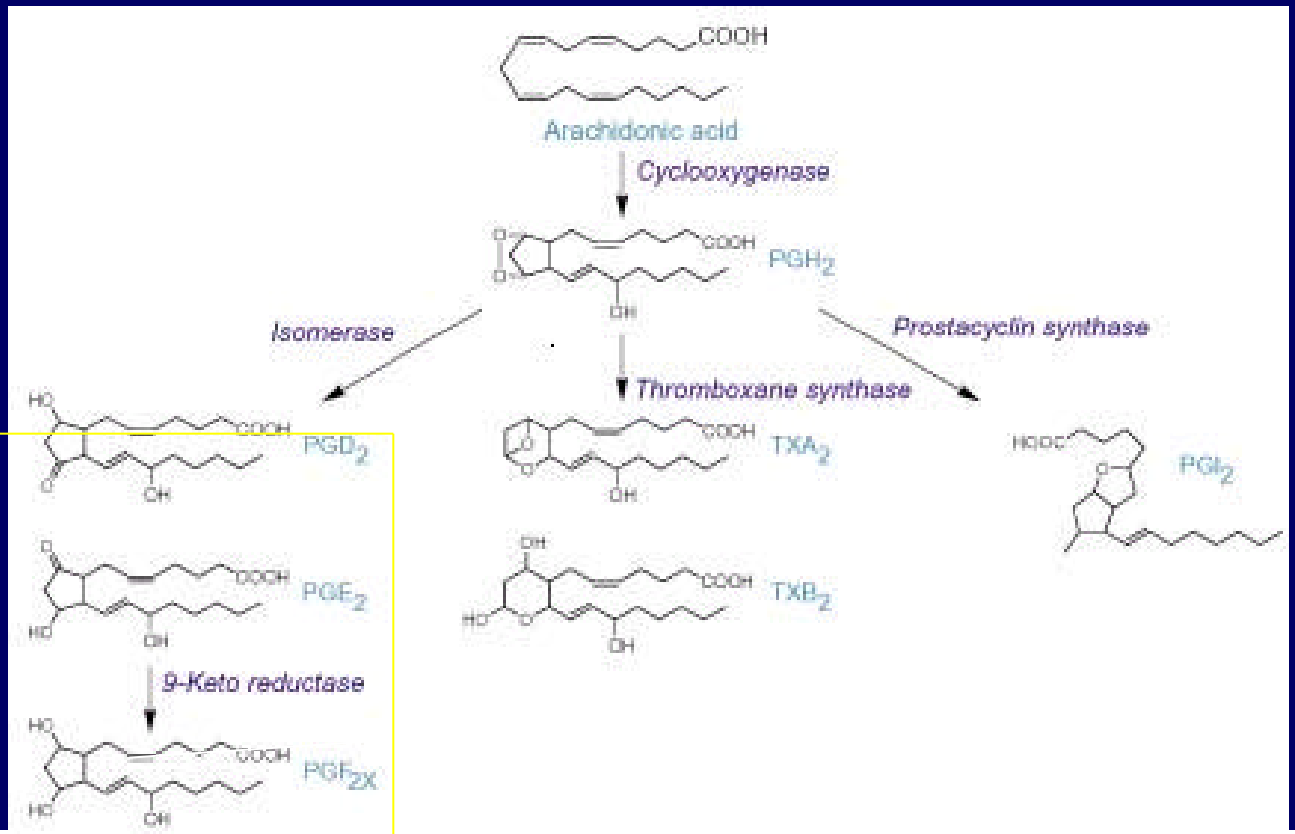
Prostaglandins continued…



- Cyclooxygenase performs the first step in prostaglandins creation
- Cyclooxygenase adds 2 O molecules to Arachidonic Acid to form Prostaglandin H2

Still more prostaglandins...

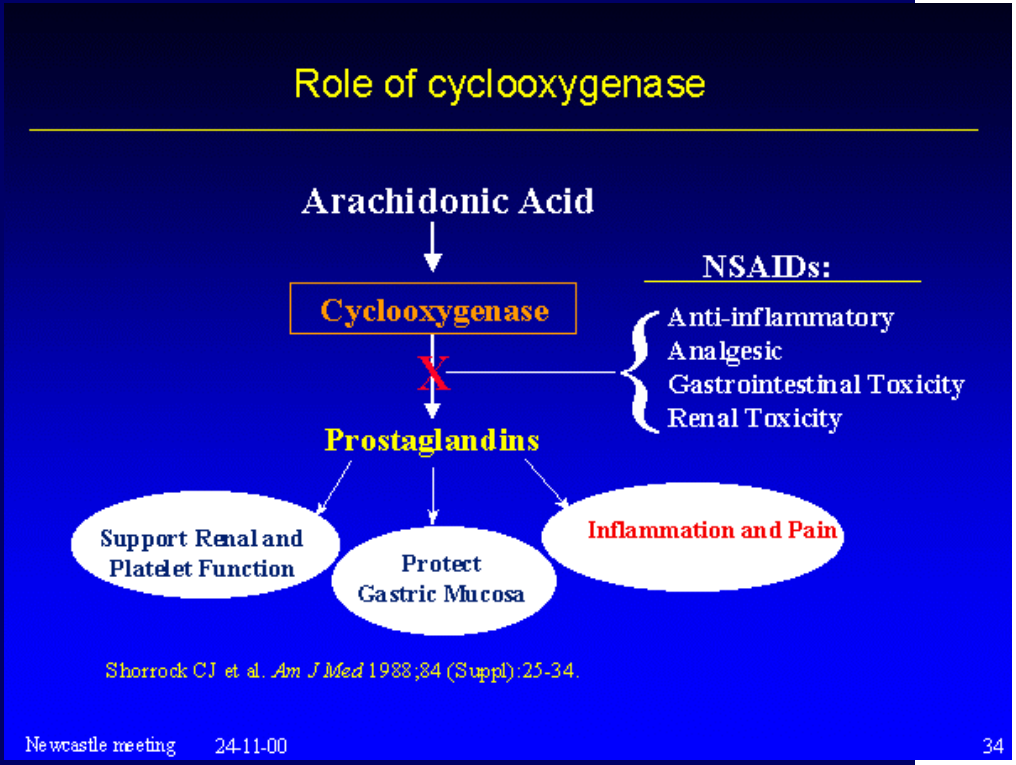
- **Prostagalndin H2 is the precursor for D,E and F**
- **Production of PGE2 is the type of prostaglandin most associated with inflammation**



- Since COX has such an influence on metabolic function and inflammatory response, finding ways to regulate inflammation without interrupting the the normal body process has become difficult. Thus finding drugs that have selective reactions towards COX2 and not COX1 has become a hot topic.

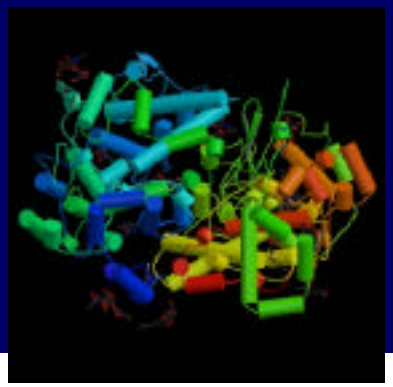
NSAIDS

- Finding ways of reducing pain and inflammation are key roles of NSAIDs
- The mechanism of these drugs is due to their binding ability to the active sites of COX , preventing the catalysis of Arachidonic acid to prostaglandins

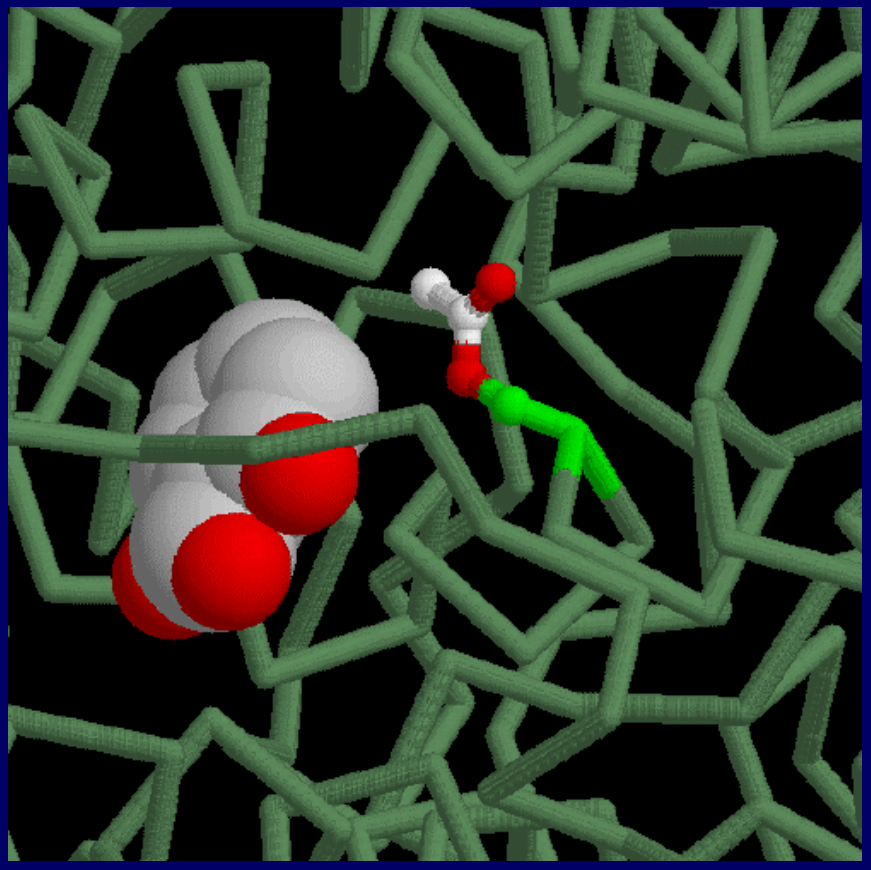


Non Steroidal Anti-Inflammatory drugs

- Most NSAIDs currently used today shows no selectivity to COX1 and COX2 (ex Aspirin)
- This non selectivity leads to various side effects
- Aspirin and other similar NSAIDs lead to excessive production of stomach acid as well as ulceration and gastrointestinal bleeding
- This is due to the inhibiting of COX1's house keeping role as well as COX2's inflammatory response
- Resent research has been directed at the selectivity of COX2 over COX1



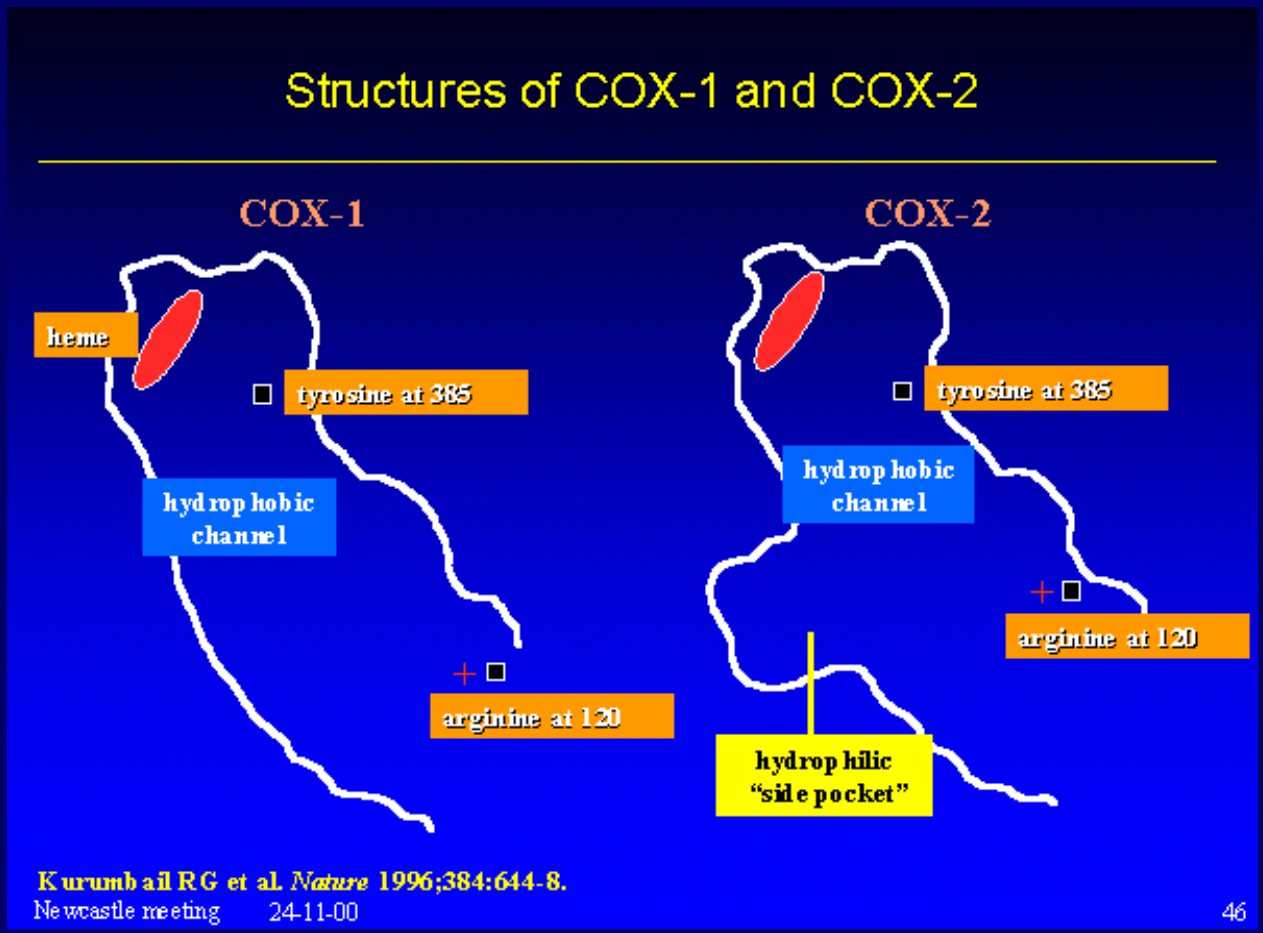
Aspirins Effect on COX



- Aspirin irreversibly acetylates the COX binding site preventing formation of prostaglandins
- Binding to COX1 inhibits its prostaglandin production responsible for assisting platelet formation thus causing the blood to thin and less clotting
- Binding COX2 lessens inflammatory response

Selectivity of NSAIDs

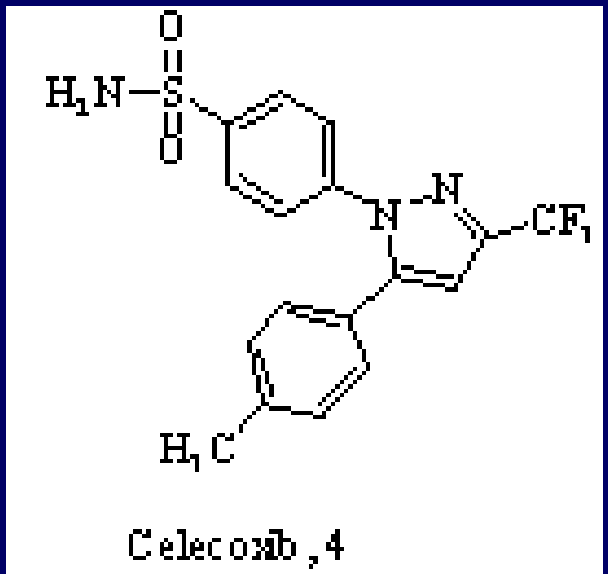
- COX 1 and COX2 vary slightly in their structure
- Finding drugs selective to COX2 requires the utilization of the hydrophilic side pocket



Kurumbail RG et al. *Nature* 1996;384:644-8.

NSAIDs effects on COX

- Since aspirin is nonselective to both COX1 and COX2 it shows duel effects
- A current new drug called celecoxib shows selectivity to COX2 thus inhibiting only the inflammatory prostaglandins and not the COX1 house keeping prostaglandins

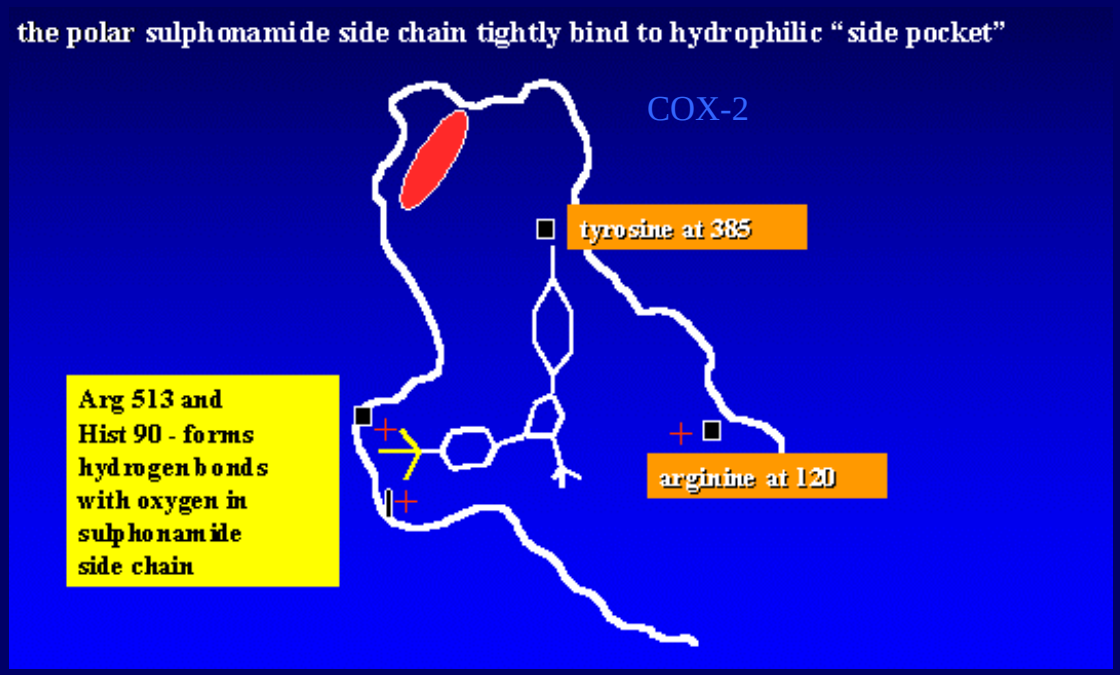


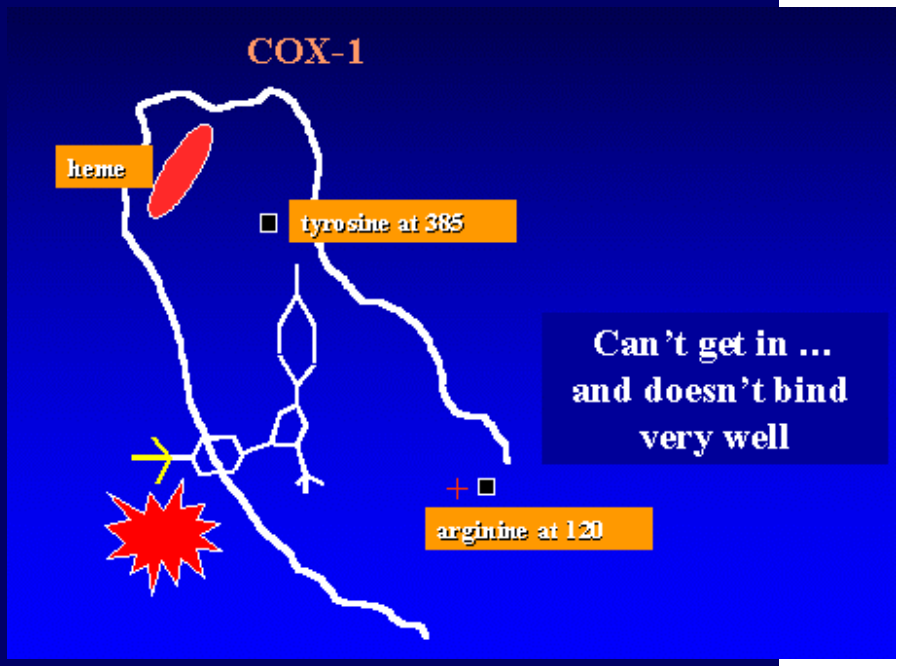
Celecoxib ,4

- WHY IS CELECOXIB SELECTIVE TO COX2?

Celecoxib effects on COX2

- **While aspirin can bind to COX1 and COX2, celecoxib binds only to COX2 due to COX2's hydrophilic side pocket**





Future Uses of Selective NSAIDs

- In addition of COX2 inhibiters to control pain and inflammation, research suggests that further uses of these drugs can have beneficial effects
- Research has shown that there is a link to COX2 and cancer. Thus the effects of selective NSAID to COX2 can reduce the occurrence of certain kinds of cancer
- Other studies have also connected COX2 inhibiters to have reduced Alzheimer's disease though the mechanism is unknown