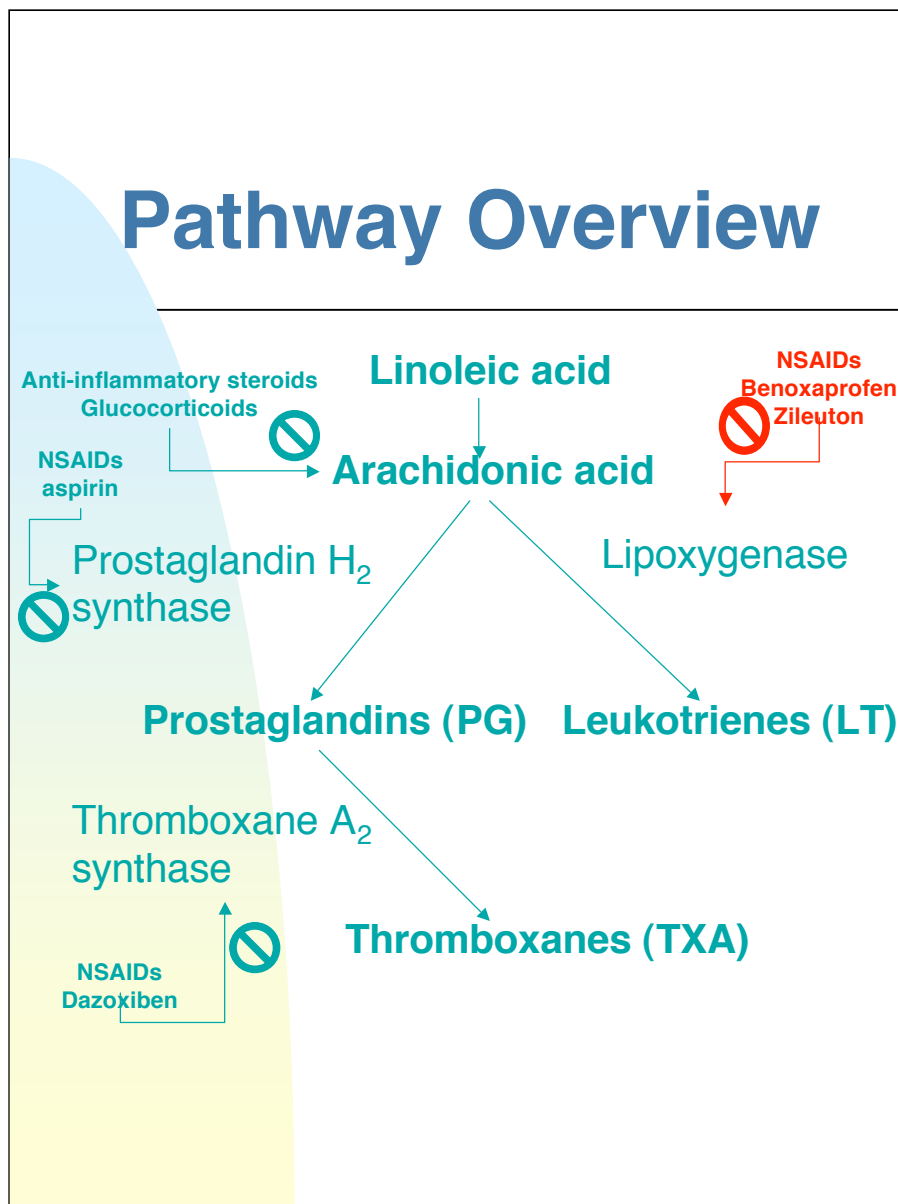


## **Prostaglandin, Leukotriene, and Thromboxane Synthesis**

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- **Pathway overview**
- **Prostaglandin receptors**
- **Pathway details**
- **Differential actions of cyclooxygenases**
- **COX-1 and COX-2 comparison**
- **COX-1 specificity of common NSAIDs**
- **Tissue comparison**

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**PG:** prostaglandins - PGG<sub>2</sub>, PGH<sub>2</sub> (constriction), PGD<sub>2</sub> (constriction or vasodilation), PGE<sub>1</sub> (vasodilation), PGE<sub>2</sub> (vasoconstriction/dilation), PGF<sub>2α</sub> (constriction), PGI<sub>2</sub> (prostacyclin, dilation, inhibition of platelet adhesion)

**LT:** leukotrienes - LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub> (multiple roles, microvascular vasoconstriction)

**TBX:** thromboxanes - TXA<sub>2</sub> (constriction, platelet adhesion), TXB<sub>2</sub> (constriction)

**NSAIDs:** nonsteroidal anti-inflammatory drugs, aspirin, ibuprofen, acetaminophen (not really an NSAID); anti-inflammatory steroids work by boosting levels of lipocortin (an annexin, Ca<sup>2+</sup>-dependent inhibitor protein/enzyme that inhibits phospholipase A<sub>2</sub>); lipocortin-1 = annexin-1

Most of the enzymes are located in the smooth endoplasmic reticulum

Brain/nerves - PGD<sub>2</sub>, PGE<sub>2</sub>, and PGF<sub>2α</sub>

Kidneys - PGE<sub>2</sub> and PGI<sub>2</sub>

Lungs - PGD<sub>2</sub>

Synovial cells - PGE<sub>2</sub> and PGI<sub>2</sub> when stimulated by interleukin-1

Vascular beds - PGE<sub>2</sub> and PGI<sub>2</sub> & PGH<sub>2</sub> and TXA<sub>2</sub>

# Prostaglandin Receptors

Receptor (PG)	Signal Transduction	Distribution
DP <sub>1</sub> (PGD <sub>2</sub> )	AC↑, [cAMP]↑	Platelets, VSM, nervous tissue, retina, small intestine, ileum, lung, stomach, uterus
DP <sub>2</sub> (PGD <sub>2</sub> )	Mobilize intracellular [Ca <sup>2+</sup> ]	Eosinophils, basophils, Th2 cells
EP <sub>1</sub> (PGE <sub>2</sub> )	phosphoinositol turnover↑, [Ca <sup>2+</sup> ]↑	Kidney, lung, spleen, skeletal muscle, testis uterus
EP <sub>2</sub> (PGE <sub>2</sub> )	AC↑, [cAMP]↑	Lung, placenta
EP <sub>3</sub> (PGE <sub>2</sub> )	Most receptors AC↓, [cAMP]↓, some AC↑ and [cAMP]↑	Kidney, stomach, uterus, pancreas, adrenal, testis, ovary, small intestine, brain, spleen, colon, heart, liver, skeletal muscle, lung, thymus, ileum
EP <sub>4</sub> (PGE <sub>2</sub> )	AC↑, [cAMP]↑	Small intestine, lung, thymus, kidney, uterus, pancreas, spleen, heart, stomach, brain, ileum, peripheral blood mononuclear cells
FP (PGF <sub>2</sub> )	phosphoinositol turnover↑, [Ca <sup>2+</sup> ]↑	Corpus luteum, uterus, stomach, kidney, heart, lung, eye, liver
IP (PGI <sub>2</sub> )	AC↑, [cAMP]↑	Platelets, VSM, kidney, thymus, liver, lung, spleen, skeletal muscle, heart, pancreas
TP (TXA <sub>2</sub> )	phosphoinositol turnover↑, [Ca <sup>2+</sup> ]↑	Platelets, VSM, thymus, spleen, lung, kidney, heart, uterus

<http://www.caymanchem.com/app/template/scientificIllustrations%2Cillustration.vm/illustration/2018/a/z>

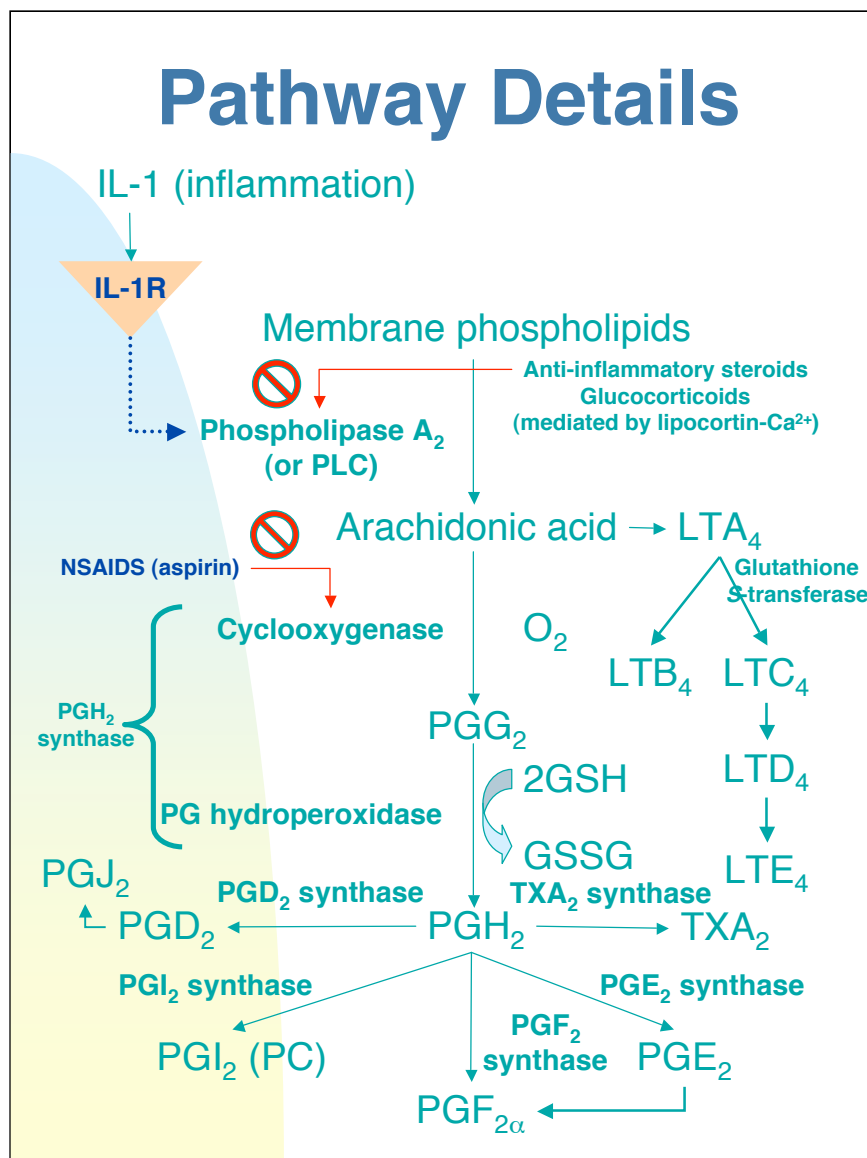
**PG:** prostaglandin

**cAMP:** cyclic adenosine monophosphate

**TXA<sub>2</sub>:** thromboxane A<sub>2</sub>

**AC:** adenylyl cyclase

**VSM:** vascular smooth muscle



**IL:** interleukin-1

**IL-1R:** interleukin-1 receptor

**NSAIDs:** nonsteroidal anti-inflammatory drugs, aspirin (irreversible inhibitor of COX-1), ibuprofen (lesser ratio of COX-1/COX-2), acetaminophen (Tylenol, does not affect COX-1 or COX-2 but may indicate presence of a COX-3 or PCOX-1a or PCOX-1b isoforms that are not involved in PG synthesis but address fever and pain); anti-inflammatory steroids boost levels of Ca<sup>2+</sup>-dependent inhibitor protein lipocortin

**PG:** prostaglandin

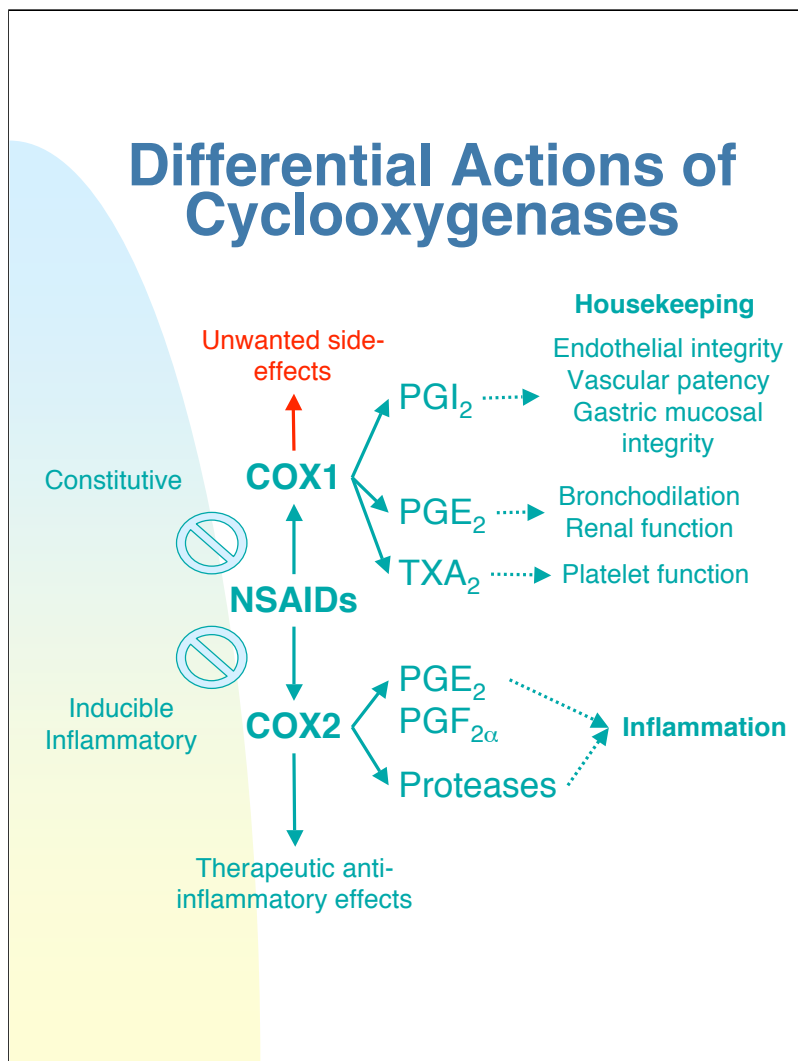
**GSH:** glutathione (reduced form)

**GSSG:** glutathione disulfide (oxidized form)

**PC:** PGI<sub>2</sub> or prostacyclin

PGE<sub>2</sub> synthase is also denoted PG endoperoxidase E isomerase, microsomal form is key enzyme

Recall that most of the enzymes are located in the smooth endoplasmic reticulum



**COX:** cyclooxygenase, COX1 constitutive (endoplasmic reticulum), COX2 inducible (perinuclear envelope), COX3 brain

**NSAIDs:** nonsteroidal anti-inflammatory drugs, aspirin, ibuprofen, acetaminophen

**PG:** prostaglandins (PGI<sub>2</sub> = prostacyclin, endothelial cells)

**TX:** thromboxane (TXA<sub>2</sub> = thromboxane, platelets)

COX-1 and COX-2 serve identical functions in catalyzing the conversion of arachidonic acid to prostanoids. The specific prostanoid(s) generated in any given cell is determined by which distal enzymes in the prostanoid synthetic pathways are expressed. For example, stimulated human synovial cells synthesize small amounts of PGE<sub>2</sub> and prostacyclin but not thromboxane or PGD or PGF<sub>2α</sub>. Following exposure to interleukin-1, synovial cells make considerably more PGE<sub>2</sub> and prostacyclin, but they still do not synthesize PGD, TXB<sub>2</sub> or PGF<sub>2α</sub>. The IL1-induced increase in PGE<sub>2</sub> and prostacyclin is mediated through COX-2.

Thus, while the species of prostanoid synthesized in a cell is dependent upon the specific distal synthetic enzyme(s) expressed, the amount synthesized is determined by the amount of COX — 1 and —2 activities expressed. COX-1 is expressed in nearly all cells (except red cells) in their basal (unstimulated) state. COX-1 mediated production of thromboxane in platelets promotes normal clotting. And COX-1 mediated synthesis of prostaglandins in the kidney appears to be responsible for maintaining renal plasma flow in the face of vasoconstriction.

## COX-1 and COX-2 Comparison

<u>Parameter</u>	<u>COX-1</u>	<u>COX-2</u>
Regulation	usually constitutive	<b>inducible</b>
Range of gene induction	2 to 4-fold	<b>10 to 80-fold</b>
Rate of gene activation	24 h	<b>0.5 to 4 h</b>
Effect of glucocorticosteroids	<b>inhibits expression</b>	<b>inhibits expression</b>
Relative size of active site	smaller	larger
Rate of arachidonic acid consumption	34 nmol/min/mg	39 nmol/min/mg
Effect of aspirin on COX activity	<b>inhibited</b>	affected

<http://elfstrom.com/arthritis/nsaids/actions.html>

Aspirin will inactivate COX-1. Its effects take longer to wear off because it takes 24 hours for new enzyme synthesis.

Aspirin will acylate COX-2, but the larger active site can still bind arachidonic acid and may produce other mediators.

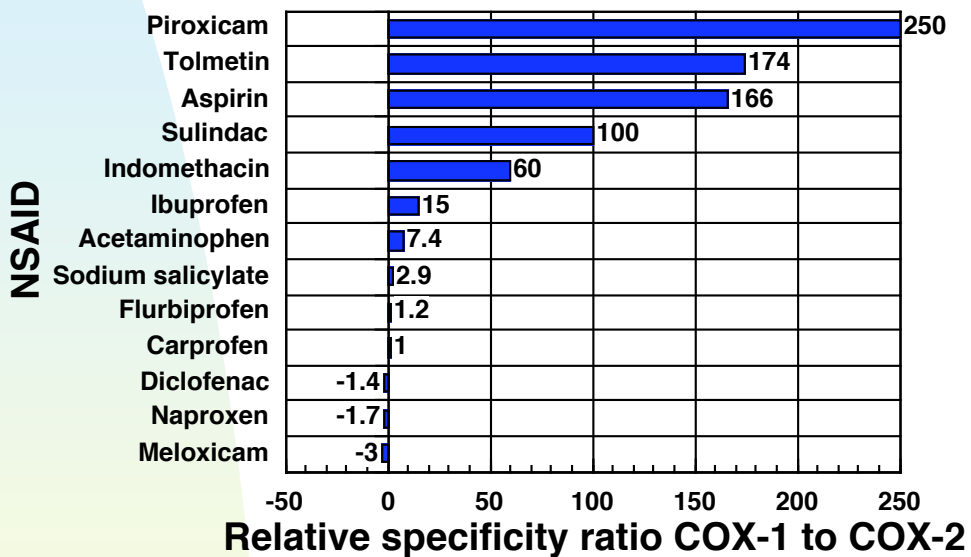
Glucocorticosteroids have effects at both the gene and protein level.

Recall that COX-1 is found primarily in the endoplasmic reticulum and COX-2 is located in the perinuclear envelope.

There is recent work suggesting that inducible NO synthase activates COX-2 (no effect on COX-1). NO synthase and COX-2 enhances cPLA2 activity.

Oxidized low-density lipoprotein (LDL) appear to increase gene expression of COX-2.

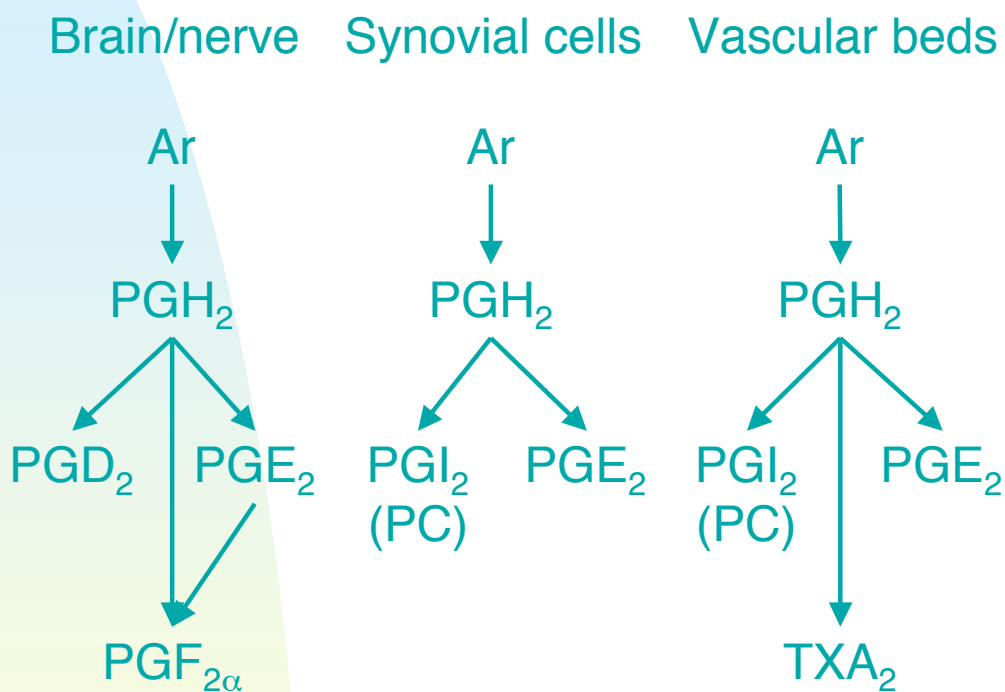
# COX-1 Specificity of Common NSAIDs



Generally, the more selective for COX-1, the more serious side-effects appear

<http://elfstrom.com/arthritis/nsaids/actions.html>

# Tissue Comparison



So what would happen if we gave a patient a large dose of aspirin or Coxib to reduce inflammation/pain in these tissues?

**Ar:** arachidonic acid

**PC:** prostacyclin

**PG:** prostaglandin

**TX:** thromboxane

# Review Questions

- **How are prostaglandins, leukotrienes, and thromboxanes synthesized (substrates, enzymes, cofactors)?**
- **What is the nomenclature for prostaglandin receptors?**
- **How do NSAIDs work?**
- **How do steroids work?**
- **What are the important characteristics of COX-1 and COX-2?**