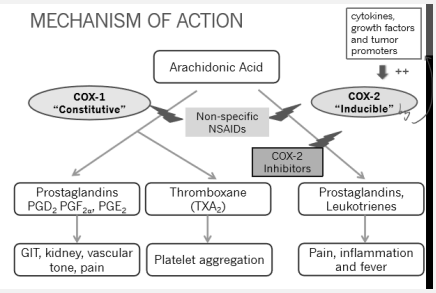
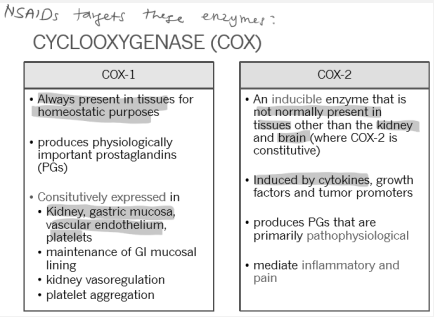
MOA



Enzyme targets by NSAIDs



NSAIDs targets these enzymes:

CYCLOOXYGENASE (COX)

COX-1	COX-2

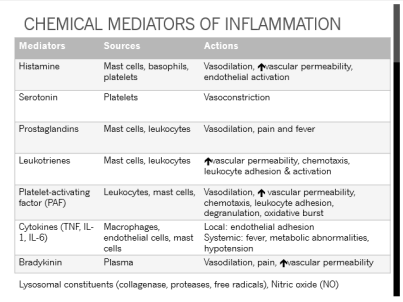
• Always present in tissues for homeostatic purposes
• produces physiologically important prostaglandins (PGs)
• Consitutively expressed in
  • Kidney, gastric mucosa, vascular endothelium, platelets
  • maintenance of GI mucosal lining
  • kidney vasoregulation
  • platelet aggregation
	• An inducible enzyme that is not normally present in tissues other than the kidney and brain (where COX-2 is constitutive)
	• Induced by cytokines, growth factors and tumor promoters
	• produces PGs that are primarily pathophysiological
	• mediate inflammatory and pain

REMEMBER

COX-2
= C = K = Kidney
= 2 = B = Brain

COX-1 = 1 = Number 1 so good at affecting everything else

Chemical mediators of inflammation



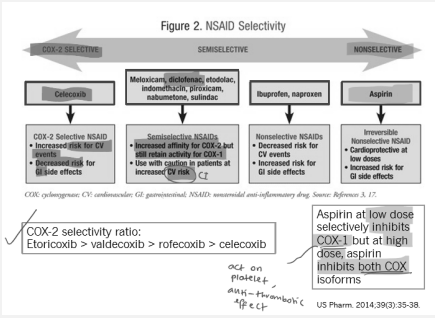
CHEMICAL MEDIATORS OF INFLAMMATION

Mediators	Sources	Actions
Histamine	Mast cells, basophils, platelets	Vasodilation, ↑vascular permeability, endothelial activation
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain and fever
Leukotrienes	Mast cells, leukocytes	↑vascular permeability, chemotaxis, leukocyte adhesion & activation
Platelet-activating factor (PAF)	Leukocytes, mast cells,	Vasodilation, ↑vascular permeability, chemotaxis, leukocyte adhesion, degranulation, oxidative burst
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial adhesion Systemic: fever, metabolic abnormalities, hypotension
Bradykinin	Plasma	Vasodilation, pain, ↑vascular permeability

Lysosomal constituents (collagenase, proteases, free radicals), Nitric oxide (NO)

extra information

Common NSAIDs



NOTES:
* Cannot take other NSAIDs before taking aspirin because they may prevent aspirin action
* COX-2 selective has less AE of GI
* Naproxane less CVS effect dt antithrom-boxane

REMEMBER:

"ABCDiN"
- Aspirin
- iBuprofen, Naproxen
- COX-2 selective
- Diclofenac

COX-2 Selective, remember **"-coxib"**
main: Celecoxib

Beneficial effects of inhibition PG synthesis

Analgesia

↓Bradykinin, 5-HT (serotonin)

Antipyretic

↓ IL-1, reset thermostat

Anti-inflammatory

↓ PGE2, PGI1

Antithrombotic

by aspirin at low dose (permanent acetylation, inhibit platelet activation)

Arteriosus (NSAIDs for closure of patent ductus arteriosus)

Adverse effect

nSAIDS

Allergy
Impaired
Renal function
Damage stomach wall (ulcer)

Contraindication

Bleeding

Avoid in patient:
-Anticoagulants
-Pregnancy 3rd trimester (premature close DA, risk bleeding)
Inhibit platelet cycloxygenase (COX), thereby **blocking the formation of thromboxane A2 (TXA2)** and impairing TXA2 dependent platelet aggregation

Asthma

Inhibition of COX pathway shifts the arachidonic acid metabolism to **Lipoxy-genase (LOX) pathway** leading to **increased leukotriene synthesis**

Allergy

Stomach (Peptic ulcer, gastritis)

Mucosal damage by –
COX-1 inhibition: Reduced blood flow
Topical irritation: Epithelial damage
COX-2 inhibition: Leukocyte adherence
*Can prescribe PPI for gastro-protection

CVS event

angina, recent cardiac bypass usrgery, MI, any CV events

REMEMBER
CBARS

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