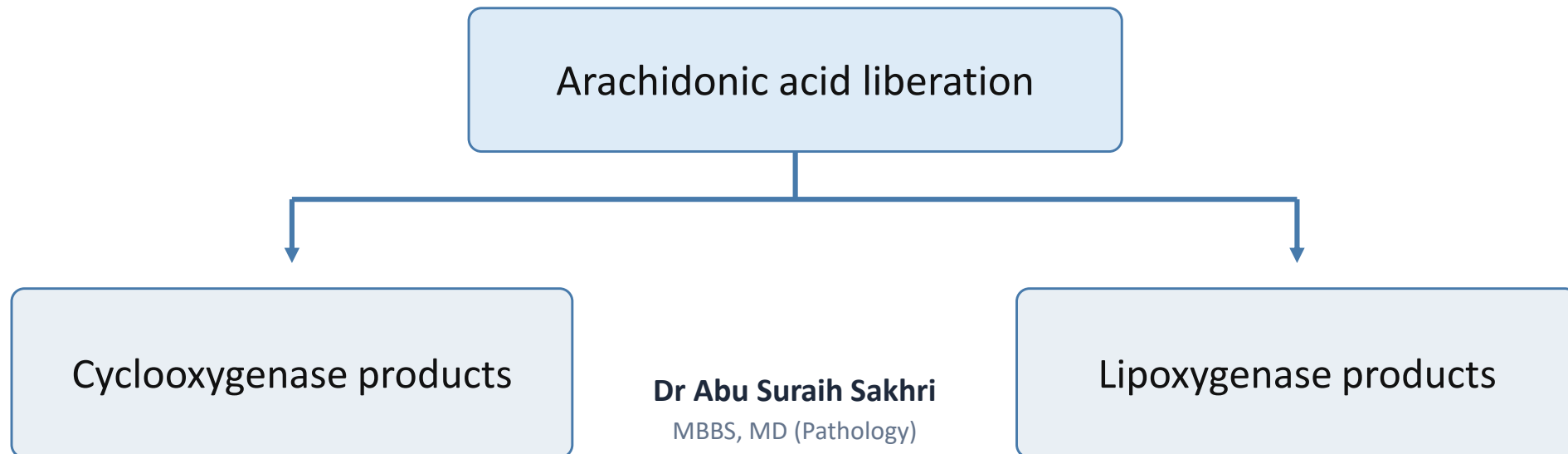


Arachidonic Acid Metabolites

Prostaglandins • Leukotrienes • Lipoxins

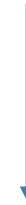


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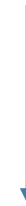
Learning objectives

- Trace liberation of arachidonic acid from membrane phospholipids
- Distinguish cyclooxygenase and lipoxygenase products
- Explain each major mediator's effects in acute inflammation
- Locate anti-inflammatory drug actions on the pathway

Substrate and enzymes



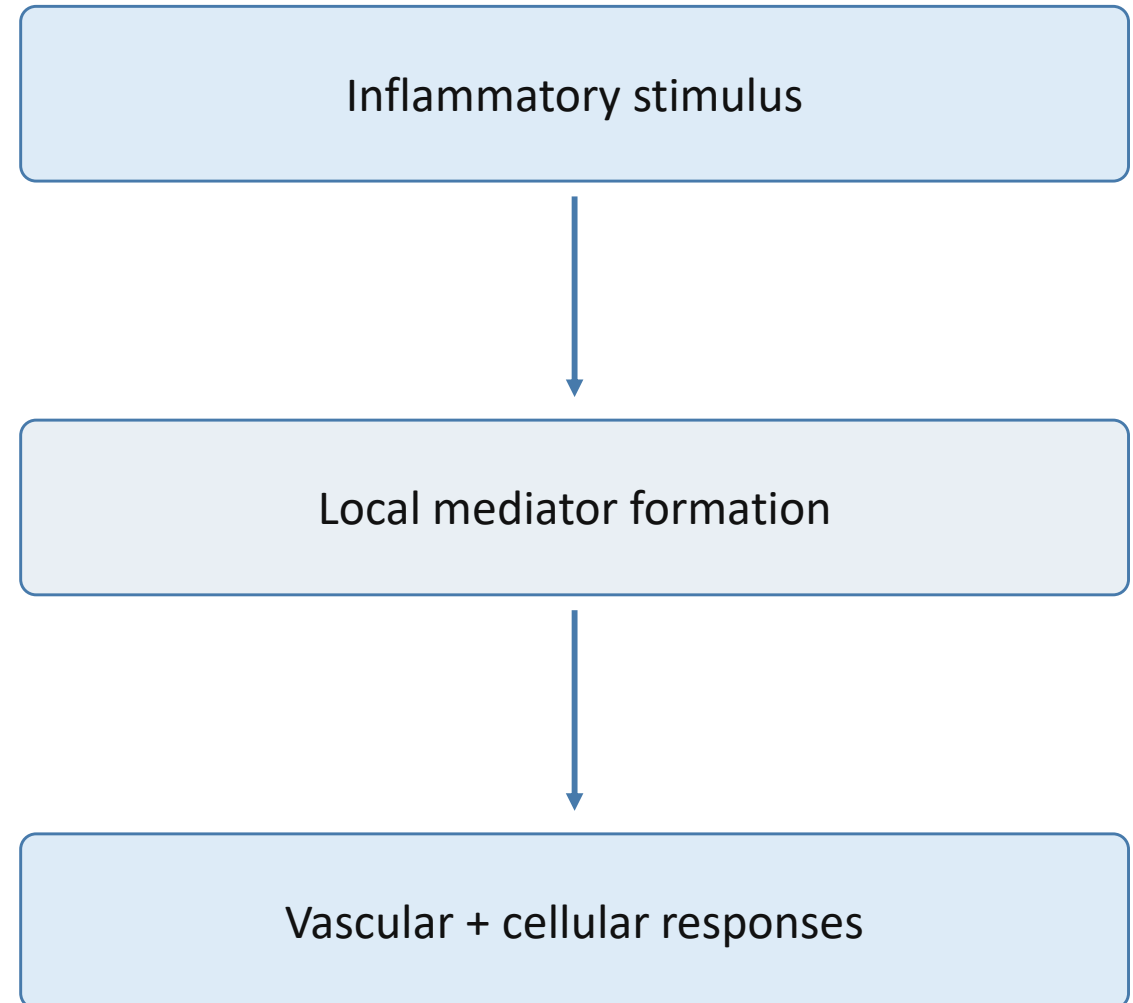
Mediator actions



Therapeutic inhibition

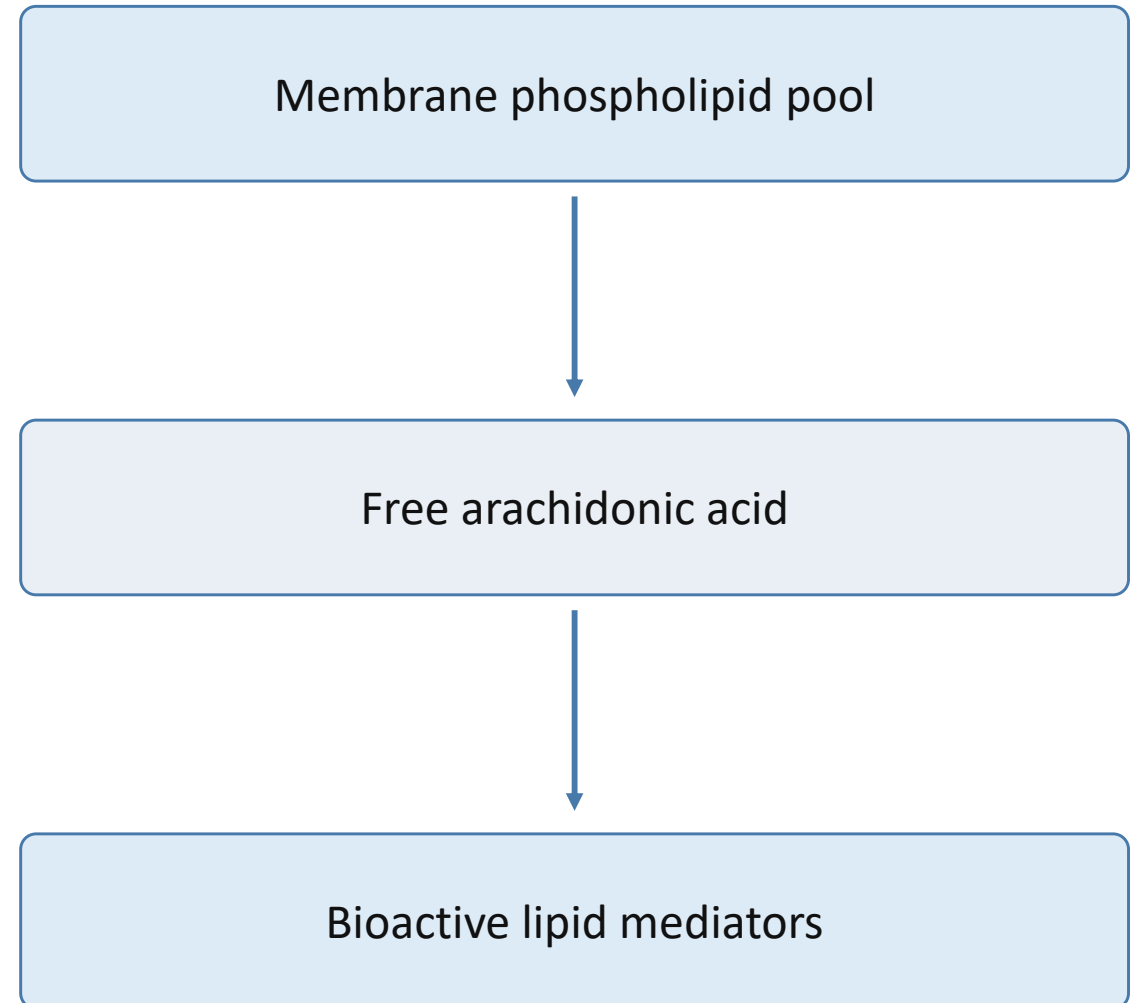
Where eicosanoids fit in inflammation

- They are locally generated lipid mediators of acute inflammation
- They regulate vascular caliber, permeability, and leukocyte responses
- They complement, rather than replace, amines and cytokines



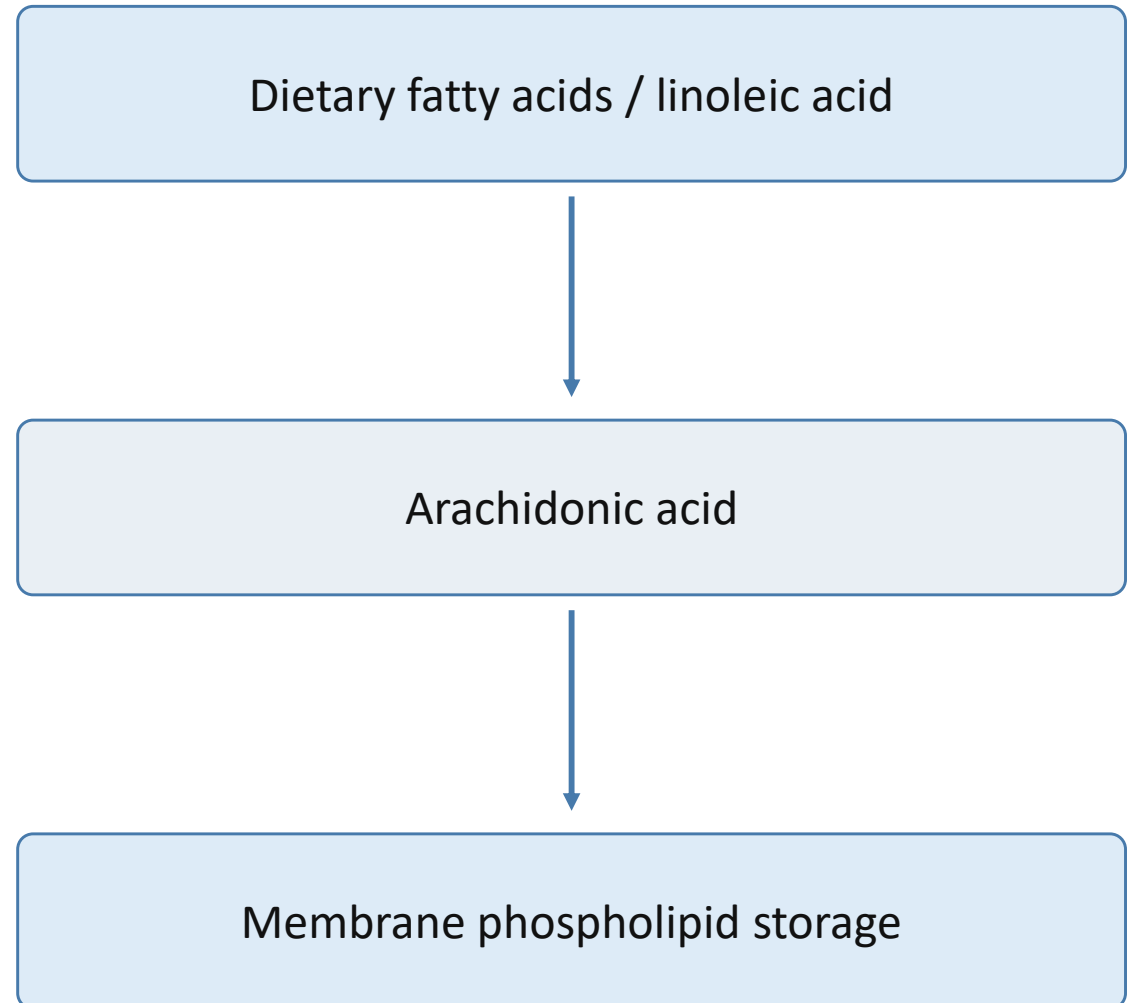
Arachidonic acid is a membrane-derived substrate

- Arachidonic acid (AA) is a 20-carbon polyunsaturated fatty acid
- It is incorporated in cellular membrane phospholipids
- Release of AA provides substrate for several mediator families



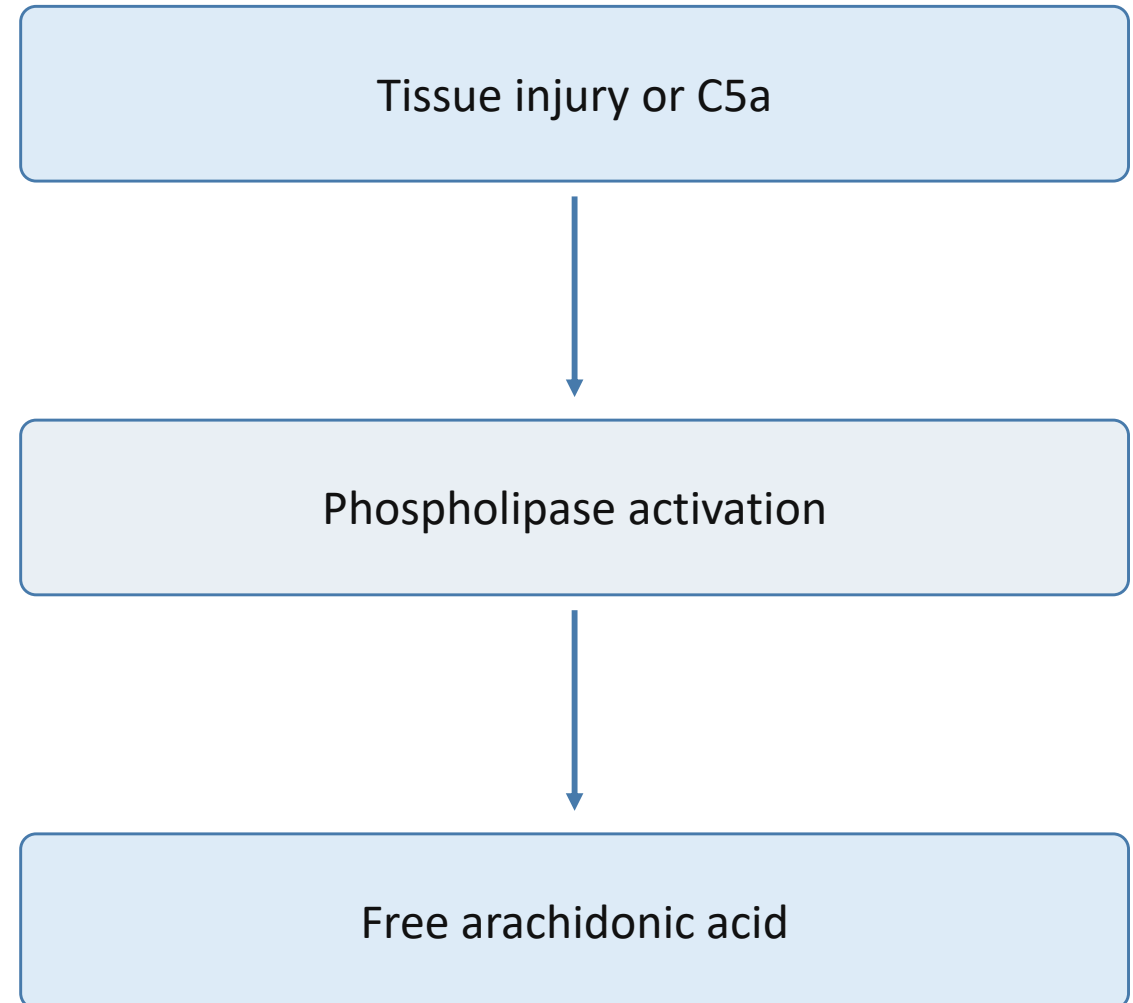
The nutritional precursor is linoleic acid

- AA may derive from dietary sources
- It can also be synthesized from essential linoleic acid
- The inflammatory pathways use liberated AA as substrate



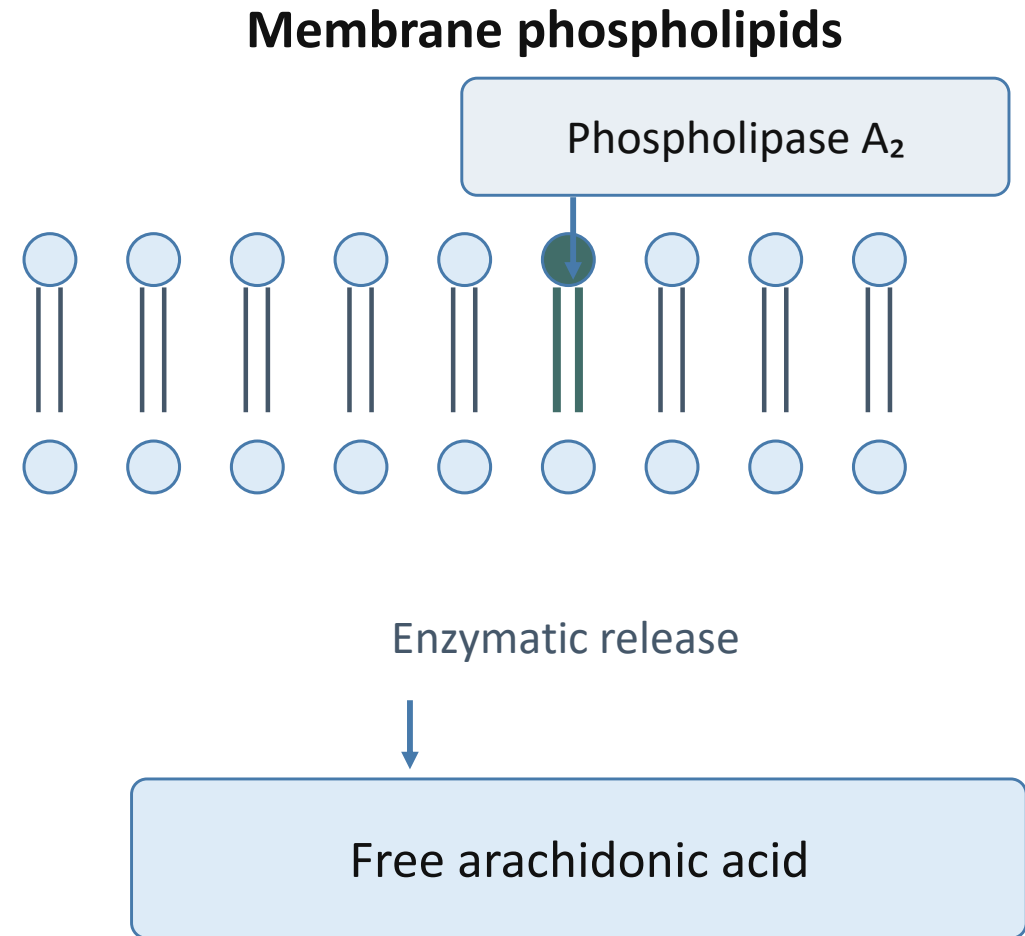
Inflammatory stimuli initiate lipid mobilization

- Mechanical, chemical, and physical stimuli can mobilize AA
- Other inflammatory mediators, including C5a, also induce release
- AA mobilization links upstream injury signals to lipid-mediator synthesis



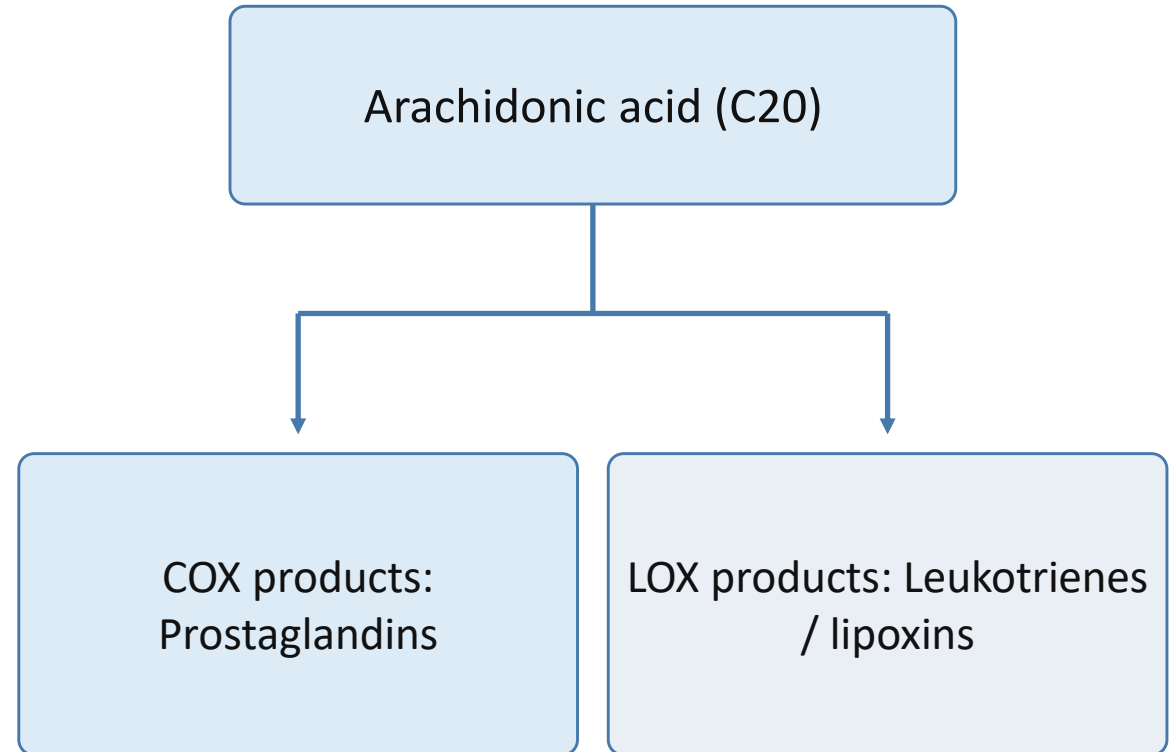
Phospholipase A₂ liberates arachidonic acid

- Cellular phospholipases release AA from membrane phospholipids
- Phospholipase A₂ is the principal enzyme emphasized
- Upstream enzyme inhibition can suppress multiple downstream branches



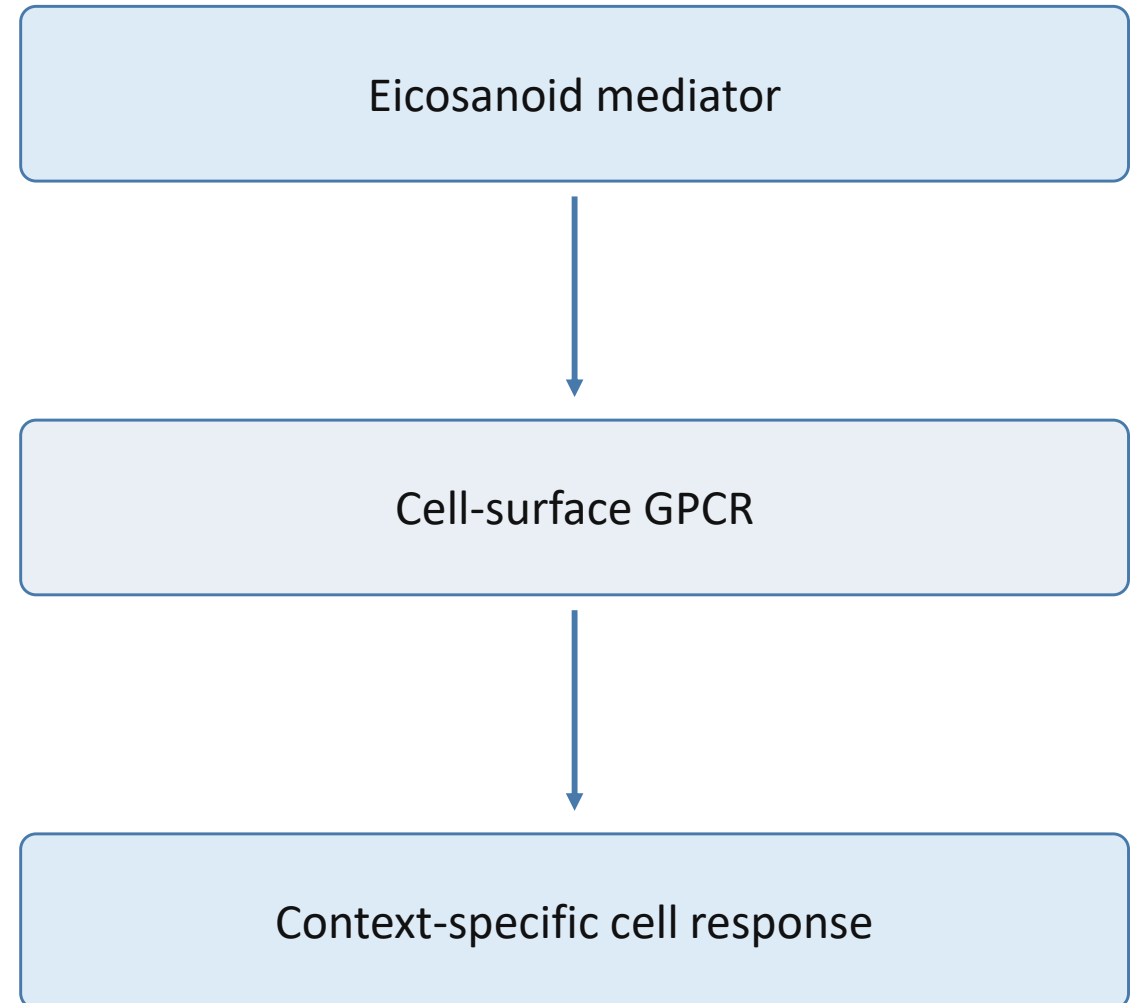
Eicosanoids are 20-carbon fatty-acid derivatives

- The term “eicosanoid” reflects a 20-carbon precursor
- Major inflammatory families include prostaglandins and leukotrienes
- Lipoxins are AA-derived lipoxygenase products with counter-regulatory activity



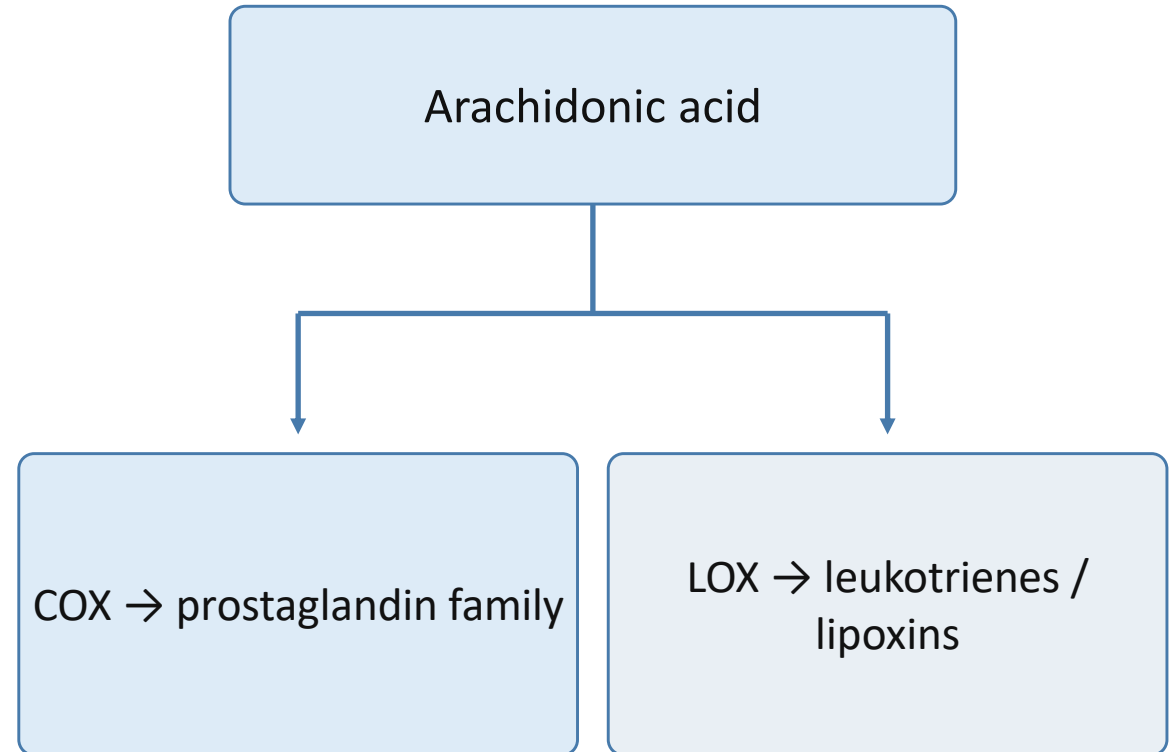
Most eicosanoid responses are receptor mediated

- Eicosanoids interact with G protein–coupled receptors
- Multiple cell types respond to their signals
- The outcome depends on the individual mediator and target cell



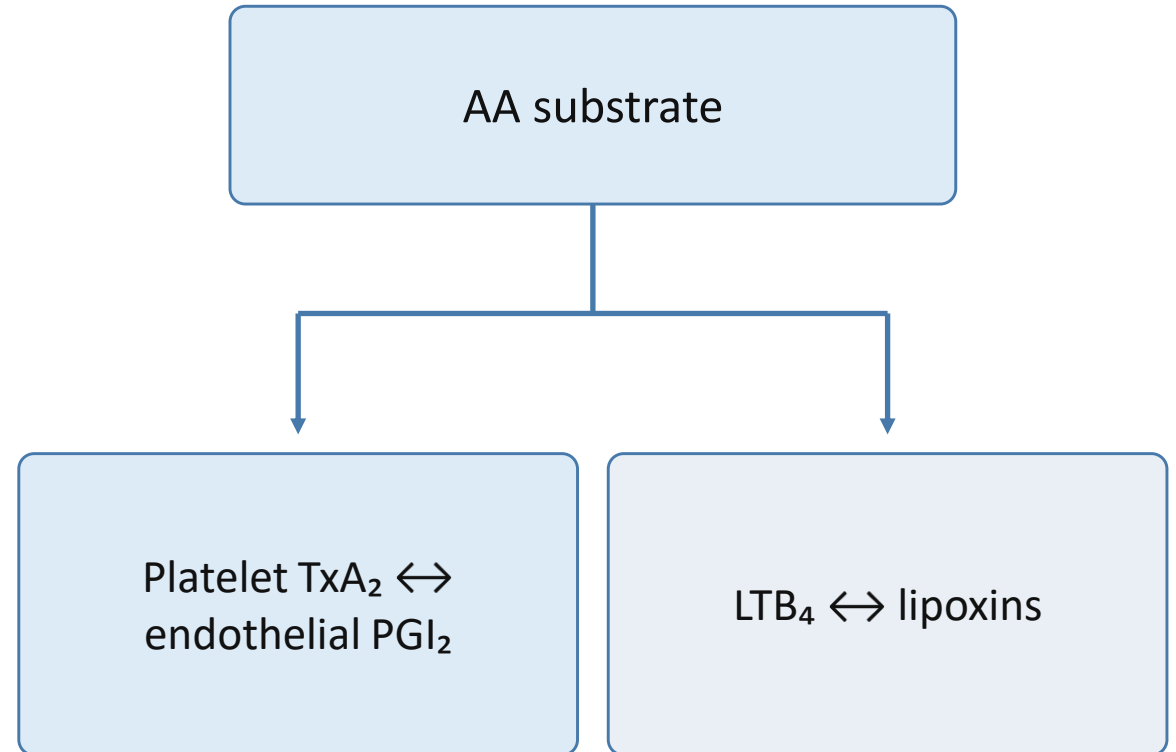
Two major enzyme branches govern AA metabolism

- Cyclooxygenases generate the prostaglandin family
- Lipoxygenases generate leukotrienes and lipoxins
- Different products may promote or restrain inflammatory responses



One substrate yields divergent biologic effects

- Eicosanoids are not functionally interchangeable
- Some increase leukocyte recruitment; Others oppose it
- Platelet and endothelial products also have opposing vascular actions



Cellular enzyme expression determines output

- Product formation depends on enzymes present in a cell
- Mast cells produce abundant PGD₂
- Platelets favor TxA₂; Endothelial cells favor PGI₂

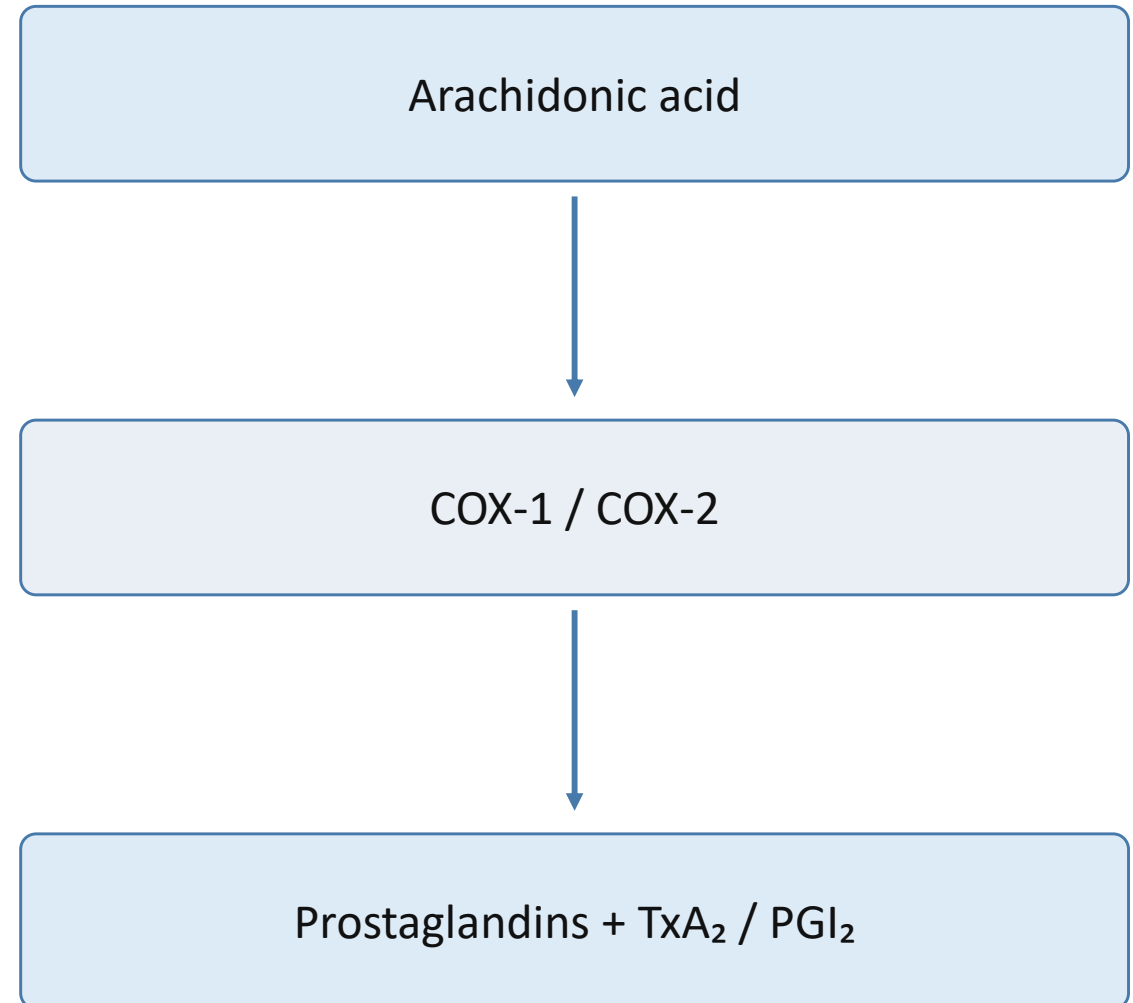
Mast cell → PGD₂

Platelet → TxA₂

Endothelium → PGI₂

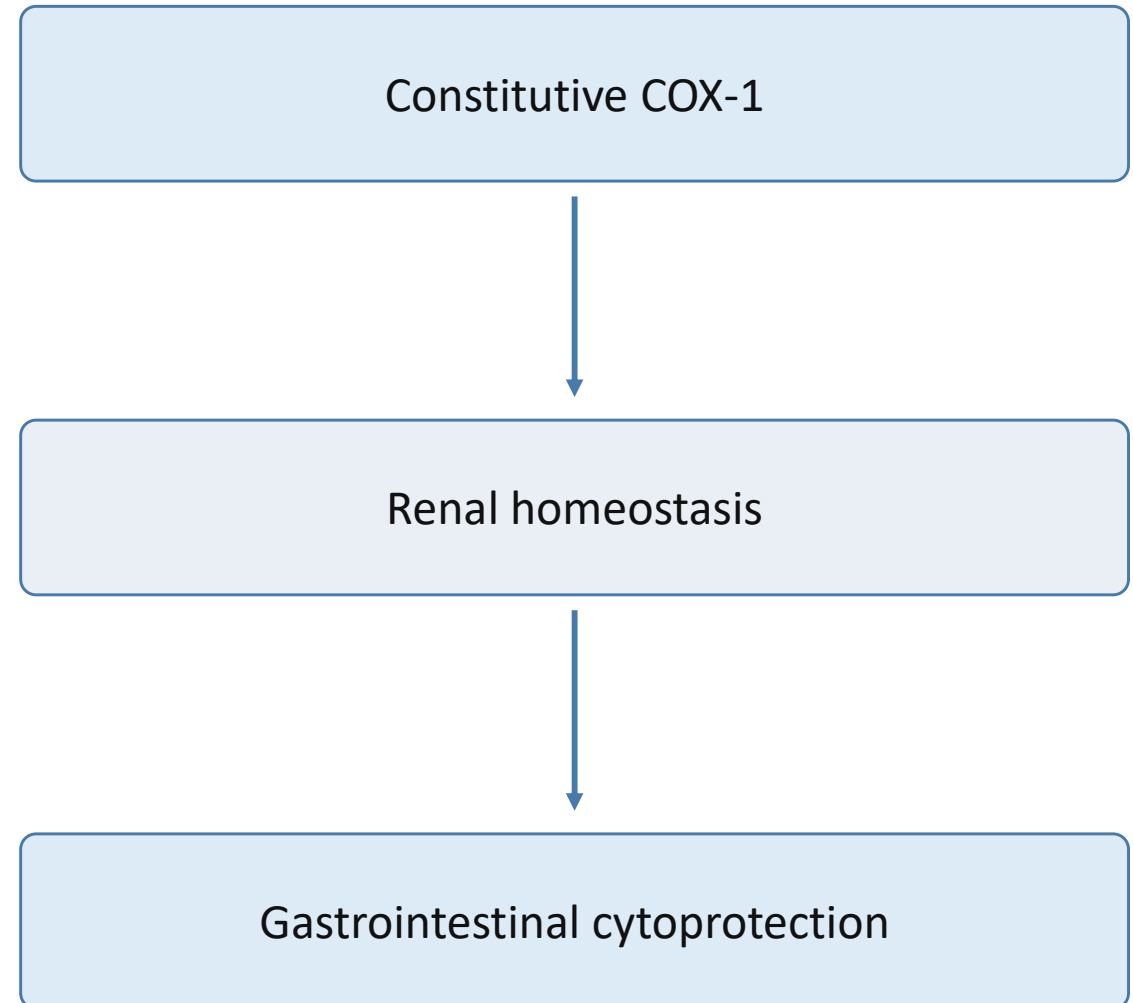
The cyclooxygenase pathway forms prostaglandins

- COX-1 and COX-2 convert AA along the prostaglandin pathway
- Downstream tissue-specific enzymes determine final products
- This branch mediates vascular responses, pain, and fever



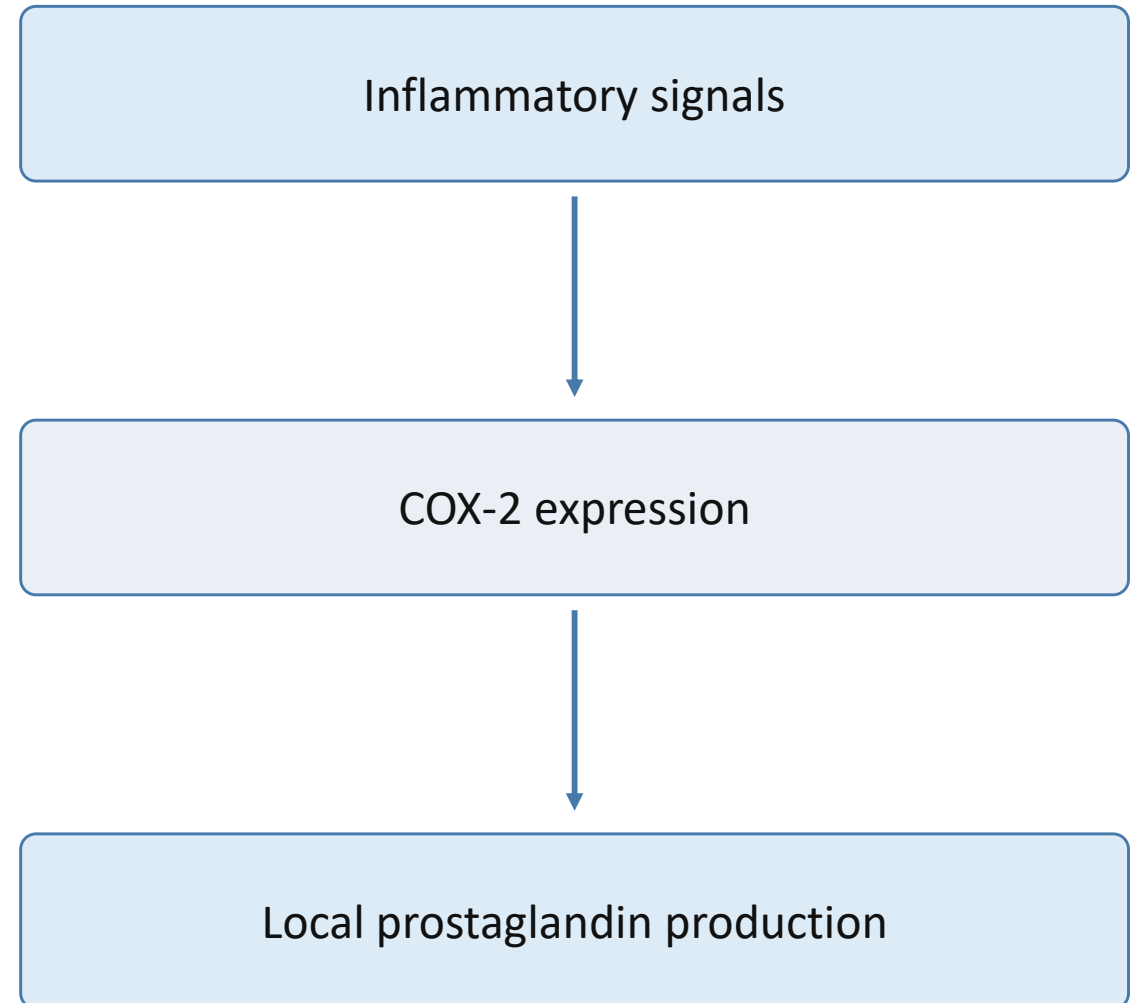
COX-1 has important constitutive functions

- COX-1 is present in many tissues under resting conditions
- Renal fluid/electrolyte balance
- Gastrointestinal cytoprotection is another important role



COX-2 is prominent in inflammatory reactions

- COX-2 expression is concentrated in participating inflammatory cells
- Its products contribute to inflammatory manifestations
- The distinction from COX-1 is useful but not absolute



COX-1 and COX-2: Qualified comparison

- COX-1 is widely constitutive; It may also be induced
- COX-2 is prominent during inflammatory responses
- Both can participate in physiologic or pathologic functions

COX-1	COX-2
Broad basal expression	Inflammatory expression
Homeostatic roles	Inflammatory PG formation

Prostaglandin names encode chemical structure

- The letter distinguishes structural families: PGD, PGE, PGF, etc.
- A subscript numeral indicates the number of double bonds
- Distinct prostaglandins may have different effects

PGD₂

PGE₂

PGF₂α

PGI₂

Inflammatory COX products are diverse

- Major products listed include PGD₂, PGE₂, PGF₂α, PGI₂, and TxA₂
- Different synthesis enzymes show tissue selectivity
- Do not infer identical effects from a shared biosynthetic branch

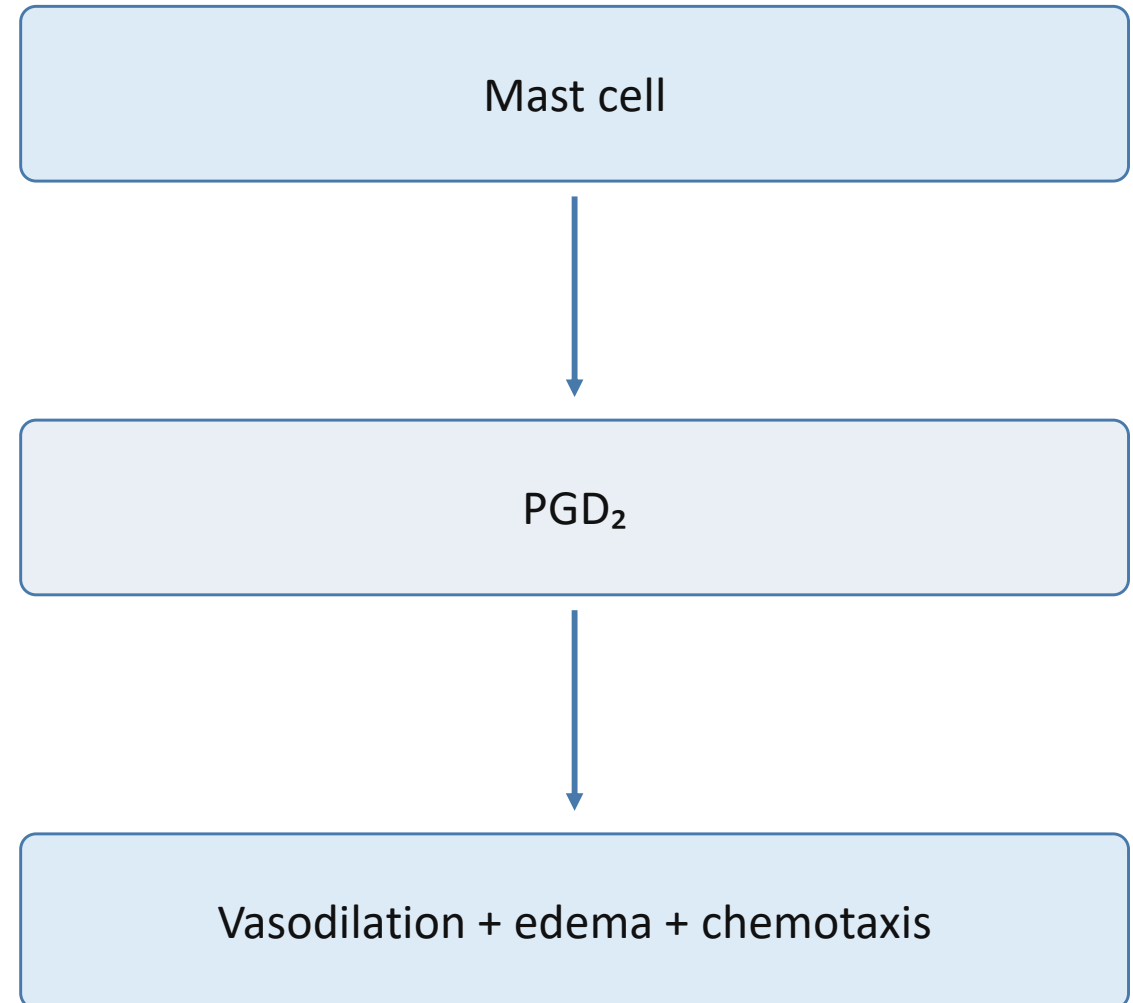
PGD₂ / PGE₂ / PGF₂α

PGI₂ (prostacyclin)

TxA₂ (thromboxane A₂)

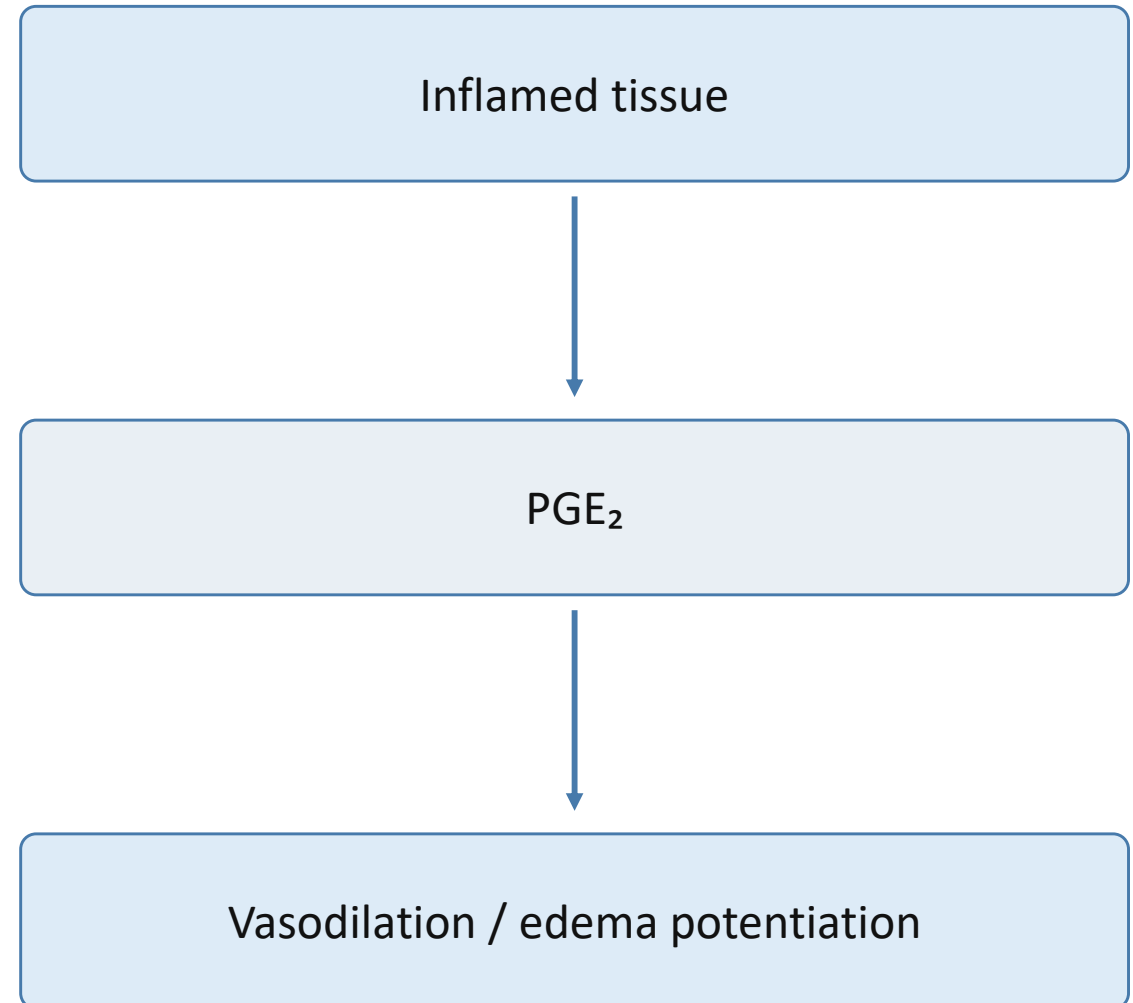
PGD₂ is prominent in mast cells

- Mast cells are the major source highlighted for PGD₂
- PGD₂ promotes vasodilation and increased venular permeability
- It also attracts neutrophils



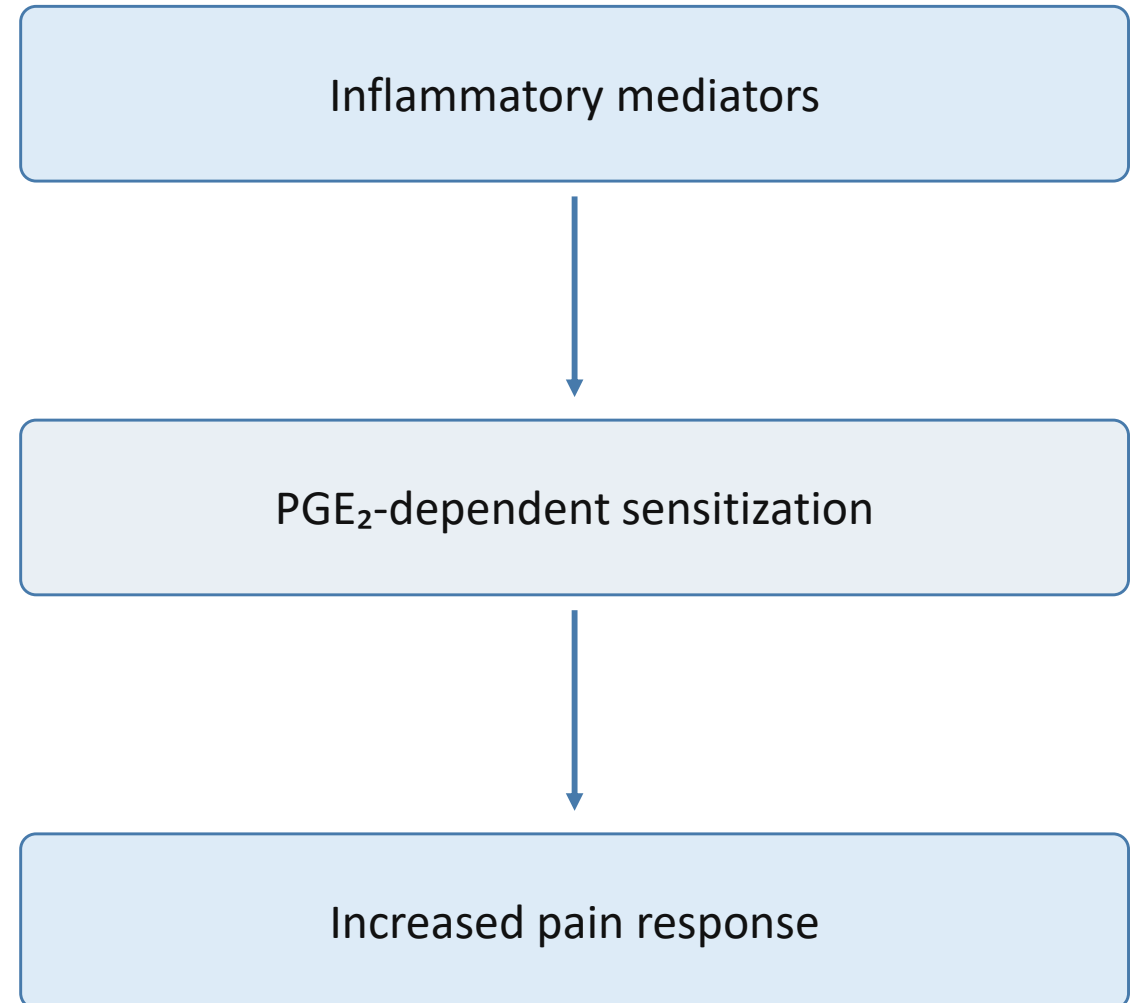
PGE₂ is broadly produced and vasoactive

- PGE₂ has a wider cellular distribution than PGD₂
- It contributes to dilation of blood vessels
- Together with other mediators, it can support edema formation



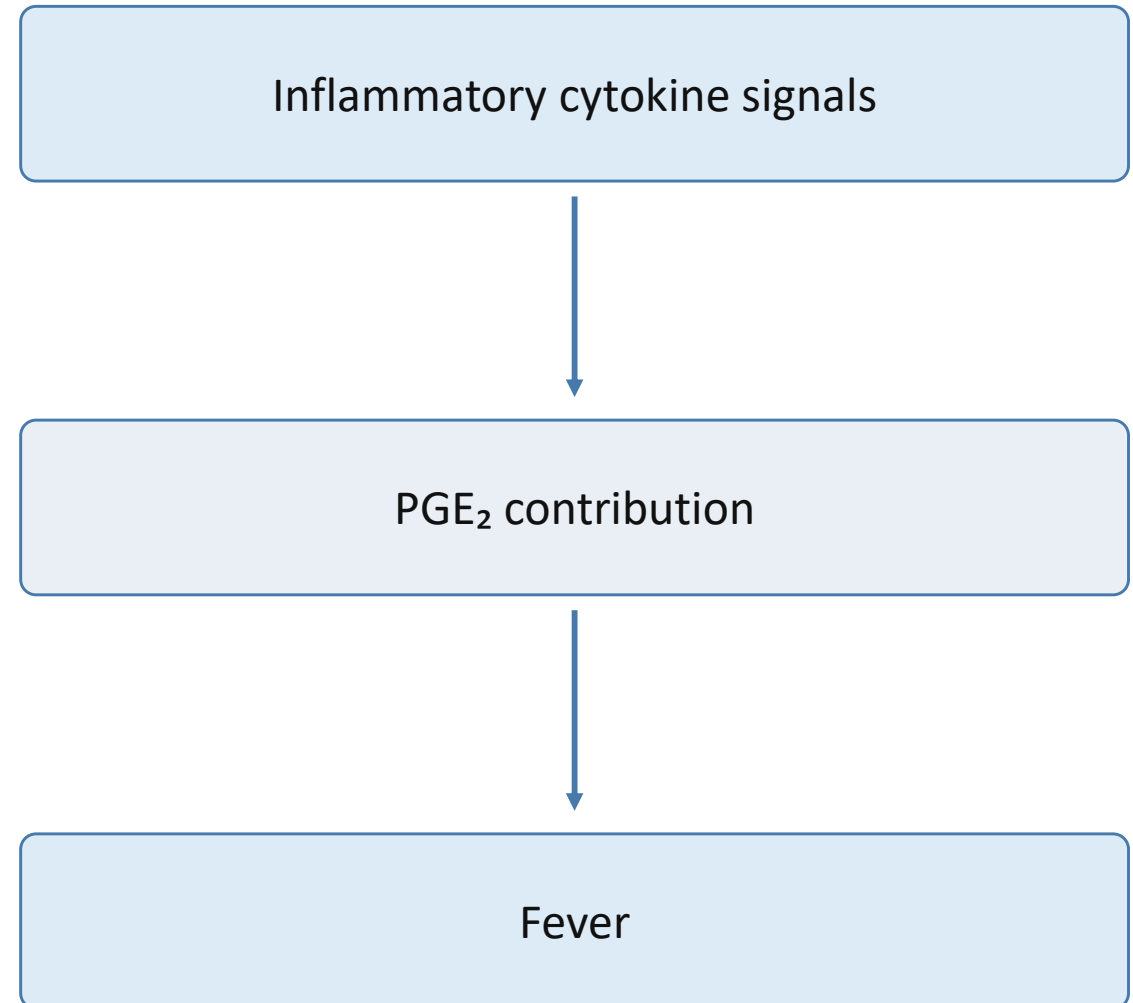
PGE₂ sensitizes tissues to painful stimuli

- PGE₂ is hyperalgesic rather than simply a stand-alone injurious stimulus
- It heightens responses to mediators such as histamine and bradykinin
- This provides a mechanism for inflammatory tenderness



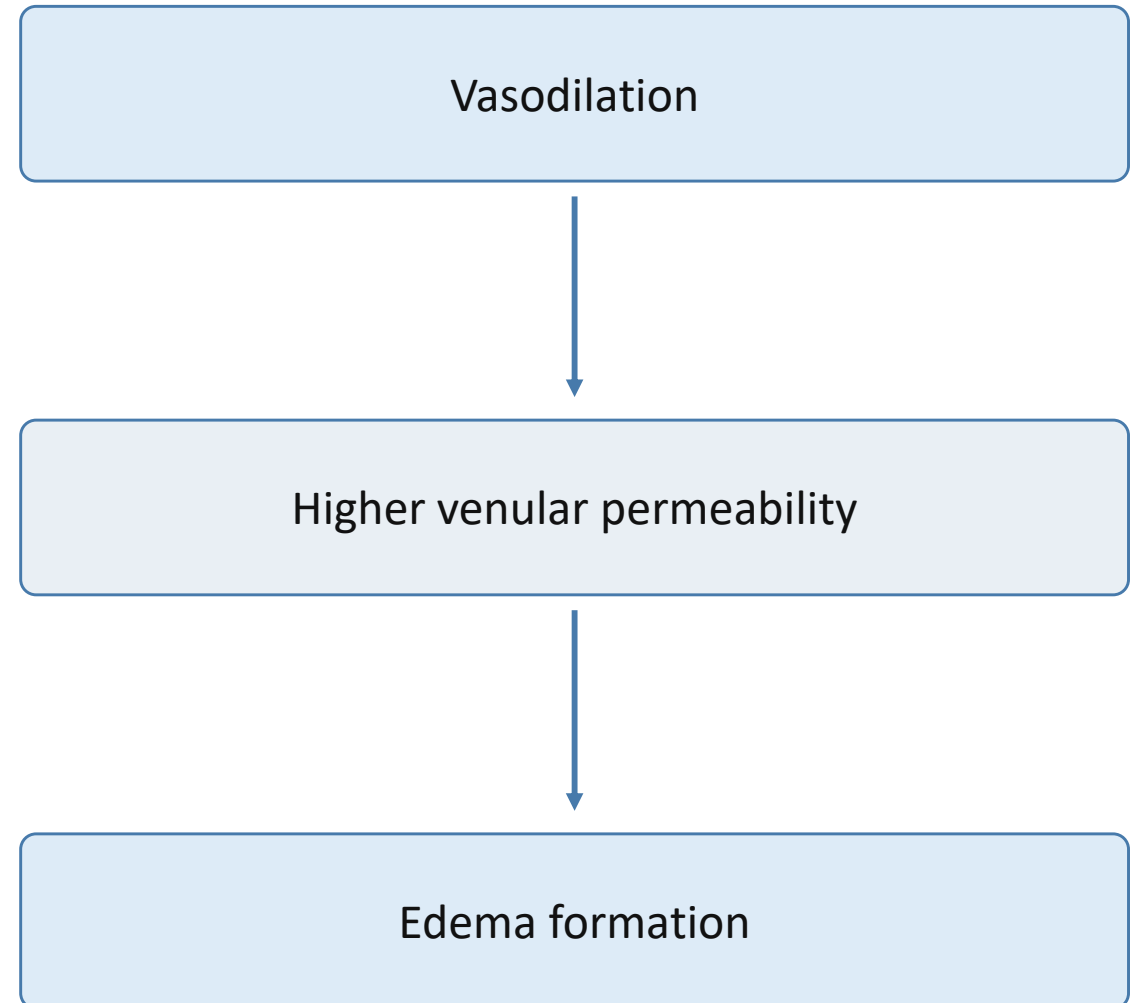
PGE₂ contributes to cytokine-induced fever

- PGE₂ participates in the febrile response during infection
- It links inflammatory cytokine signaling with systemic physiology
- Blocking prostaglandin synthesis can reduce fever



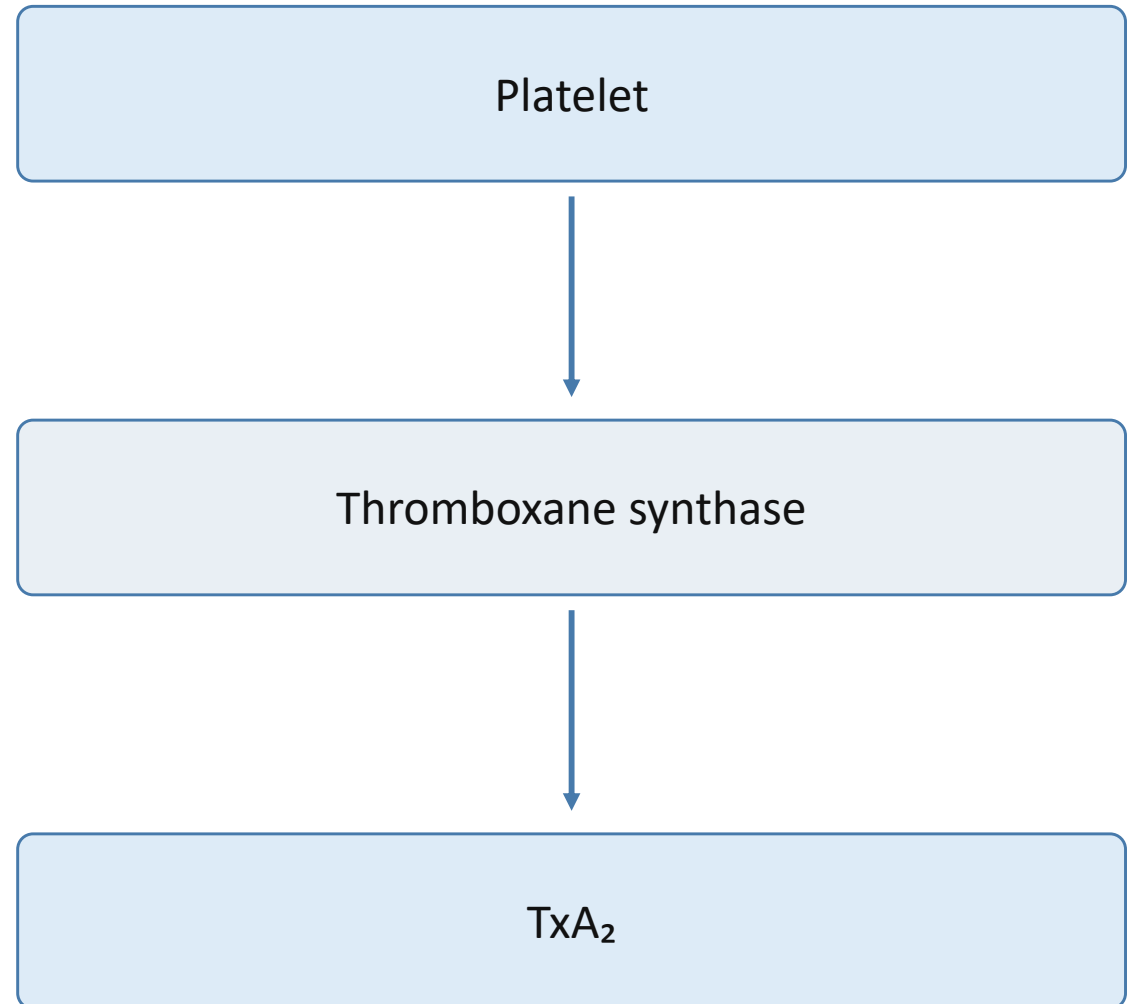
PGD₂ and PGE₂ connect inflammation to edema

- Both mediators cause vasodilation
- They support increased permeability of postcapillary venules
- Combined vascular effects promote fluid accumulation



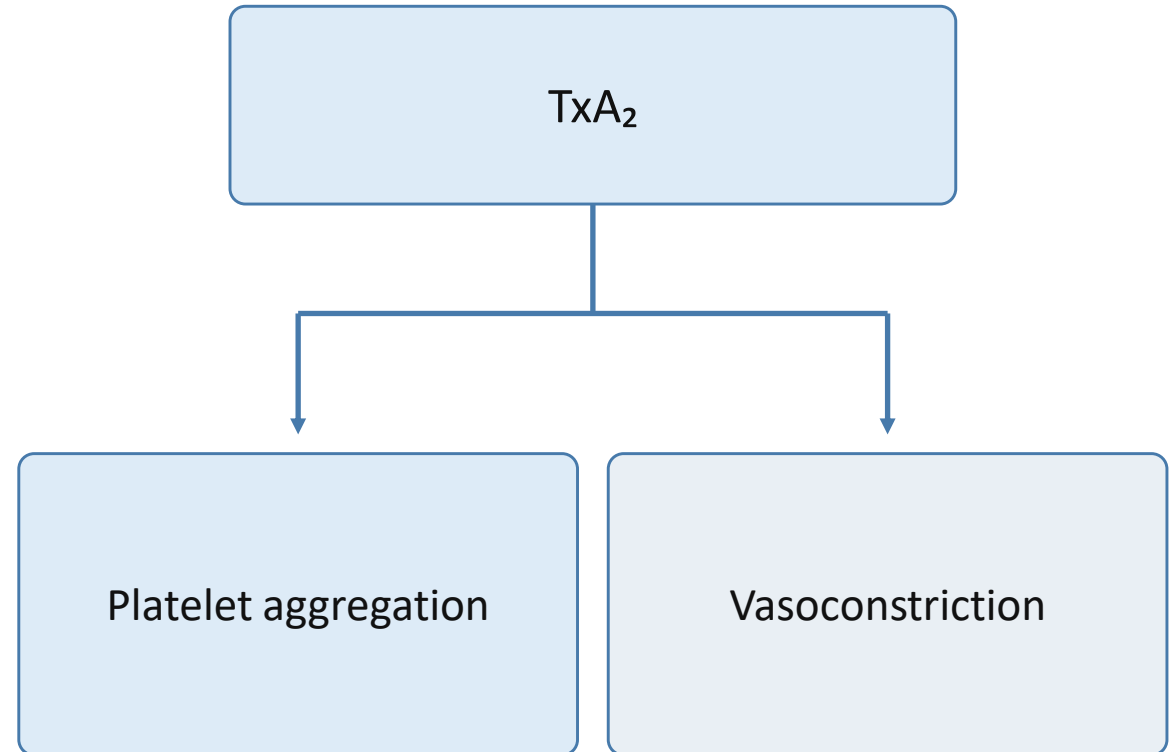
Platelet enzymes favor thromboxane A₂

- Platelets express thromboxane synthase
- TxA₂ is their major AA-derived mediator emphasized here
- Its production helps explain platelet-associated vascular responses



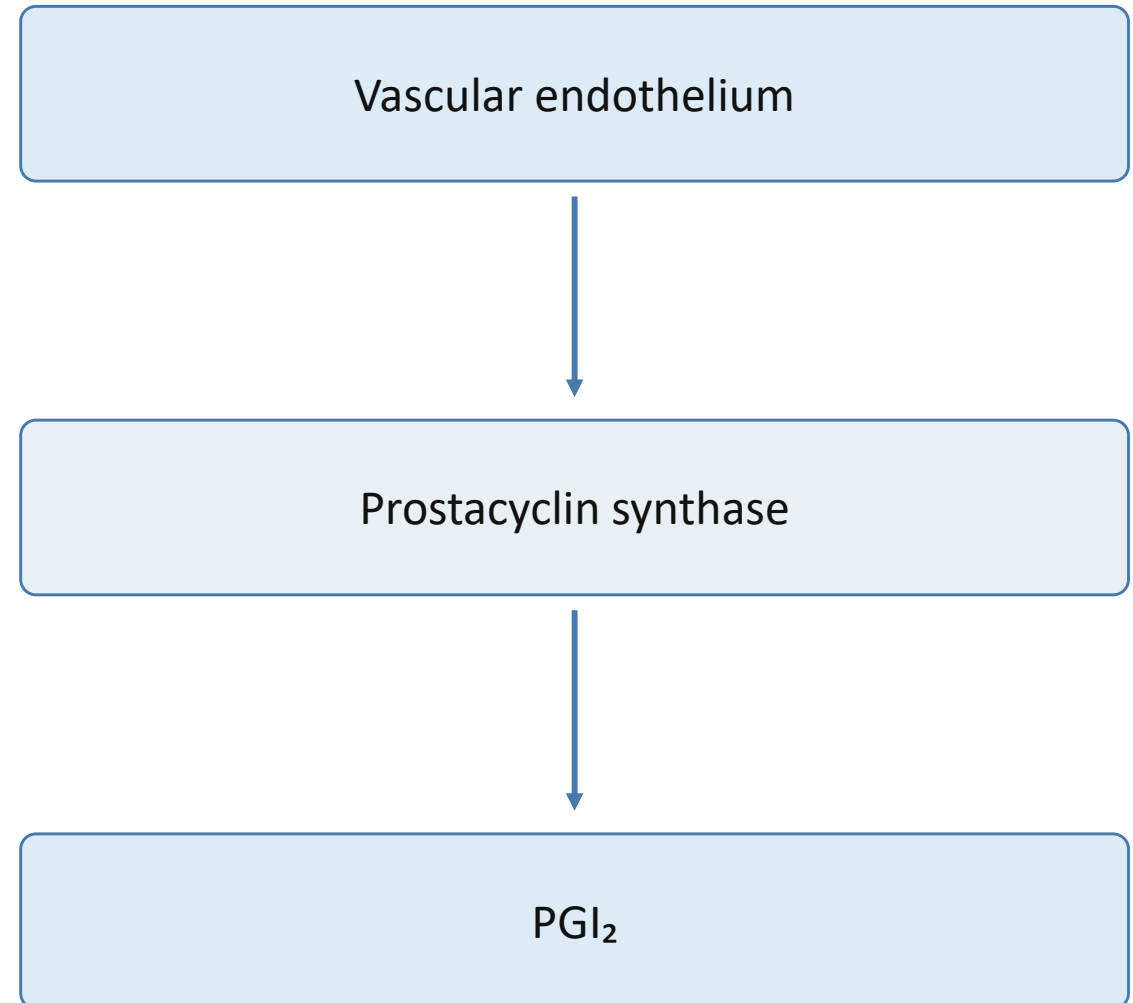
Thromboxane A₂ promotes clot-forming responses

- TxA₂ is a potent platelet-aggregating agent
- It is also a vasoconstrictor
- It is unstable and rapidly converted to inactive material



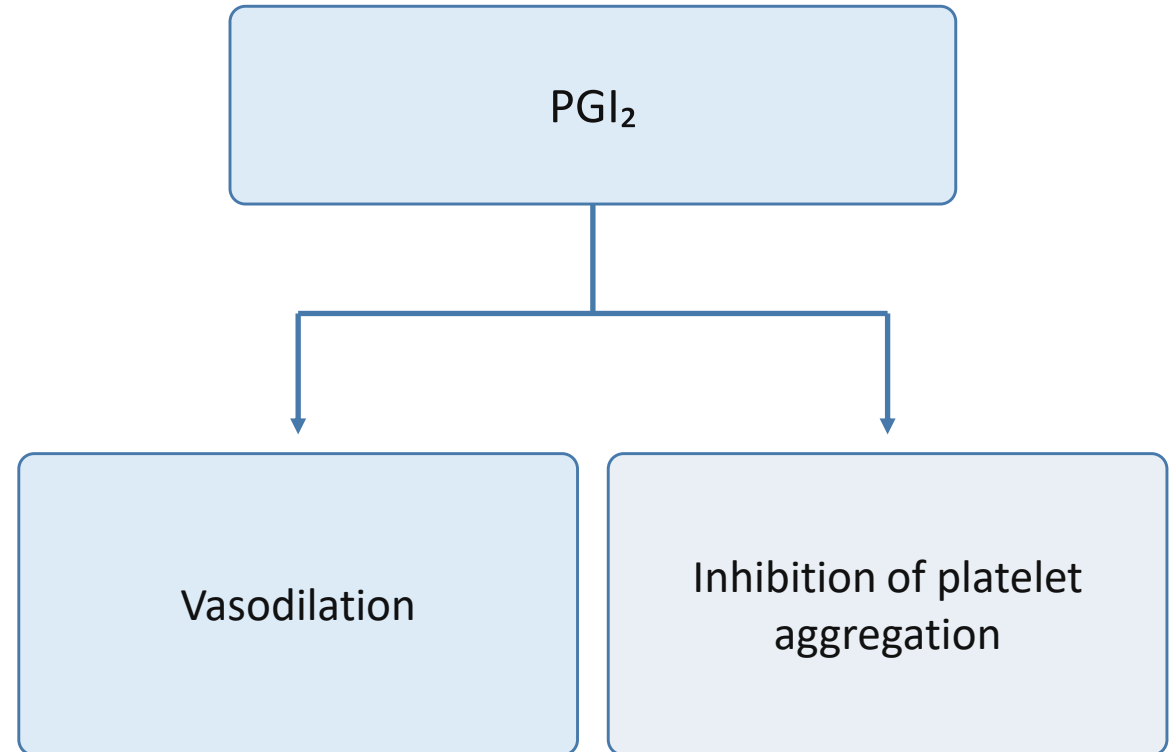
Endothelial cells favor prostacyclin

- Vascular endothelium expresses prostacyclin synthase
- It lacks platelet-type thromboxane synthase' description
- PGI₂ production helps oppose platelet-mediated thrombosis



Prostacyclin maintains an antithrombotic tendency

- PGI₂ produces vasodilation
- It strongly inhibits platelet aggregation
- It can potentiate selected permeability and chemotactic effects of other mediators



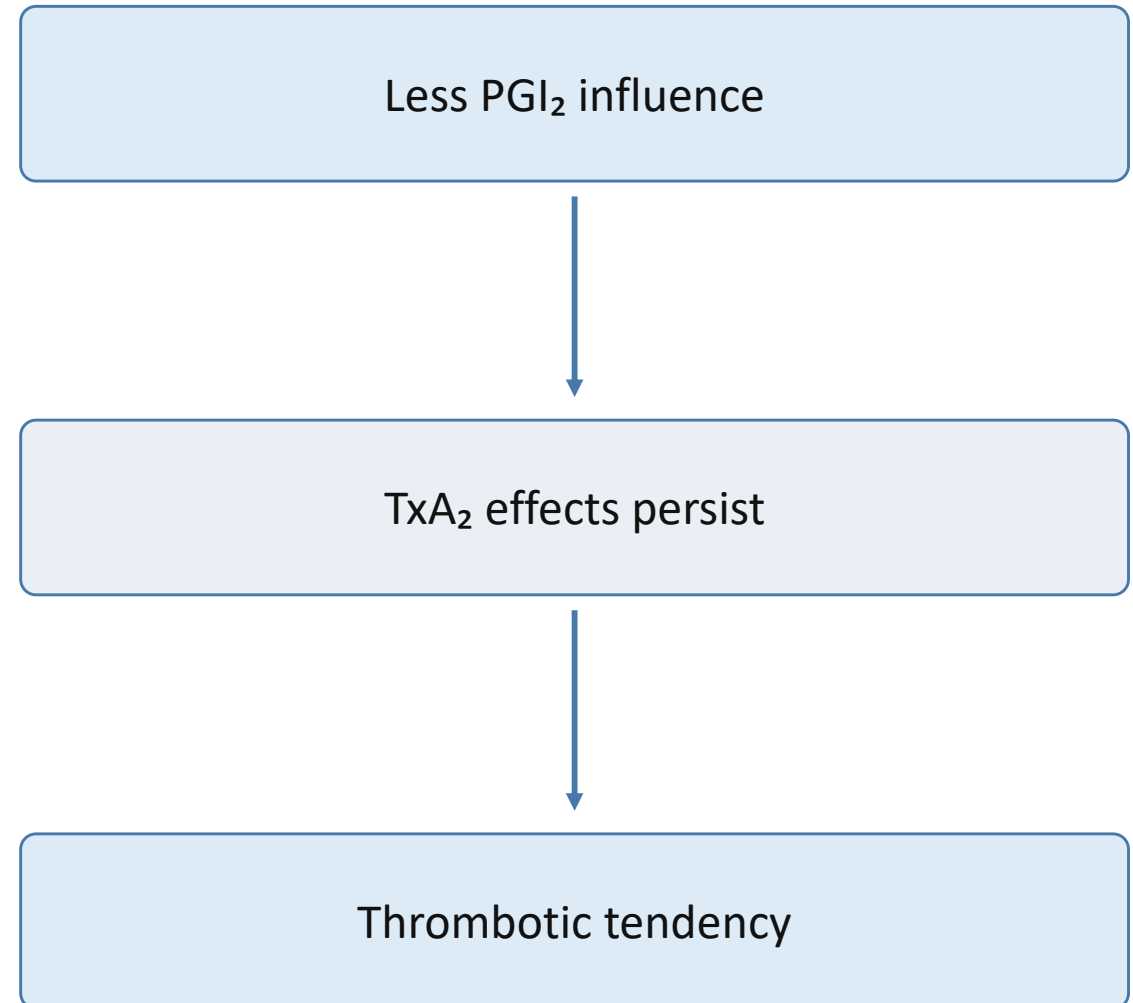
TxA₂ and PGI₂ oppose each other

- TxA₂ favors platelet aggregation and vasoconstriction
- PGI₂ favors inhibition of platelet aggregation and vasodilation
- Both products arise within the COX branch

TxA ₂	PGI ₂
Platelets	Endothelium
Aggregation + constriction	Antiaggregation + dilation

An eicosanoid imbalance can favor thrombosis

- A disturbance in the TxA_2 – PGI_2 balance is implicated in vascular thrombus formation
- Coronary and cerebral vessels
- Relative loss of PGI_2 protection may shift vascular behavior toward thrombosis



Cell origin predicts vascular mediator function

- Mast cell PGD_2 acts chiefly in inflammatory vascular responses
- Platelet TxA_2 promotes platelet aggregation
- Endothelial PGI_2 inhibits platelet aggregation

Mast cell: PGD_2

Platelet: TxA_2

Endothelium: PGI_2

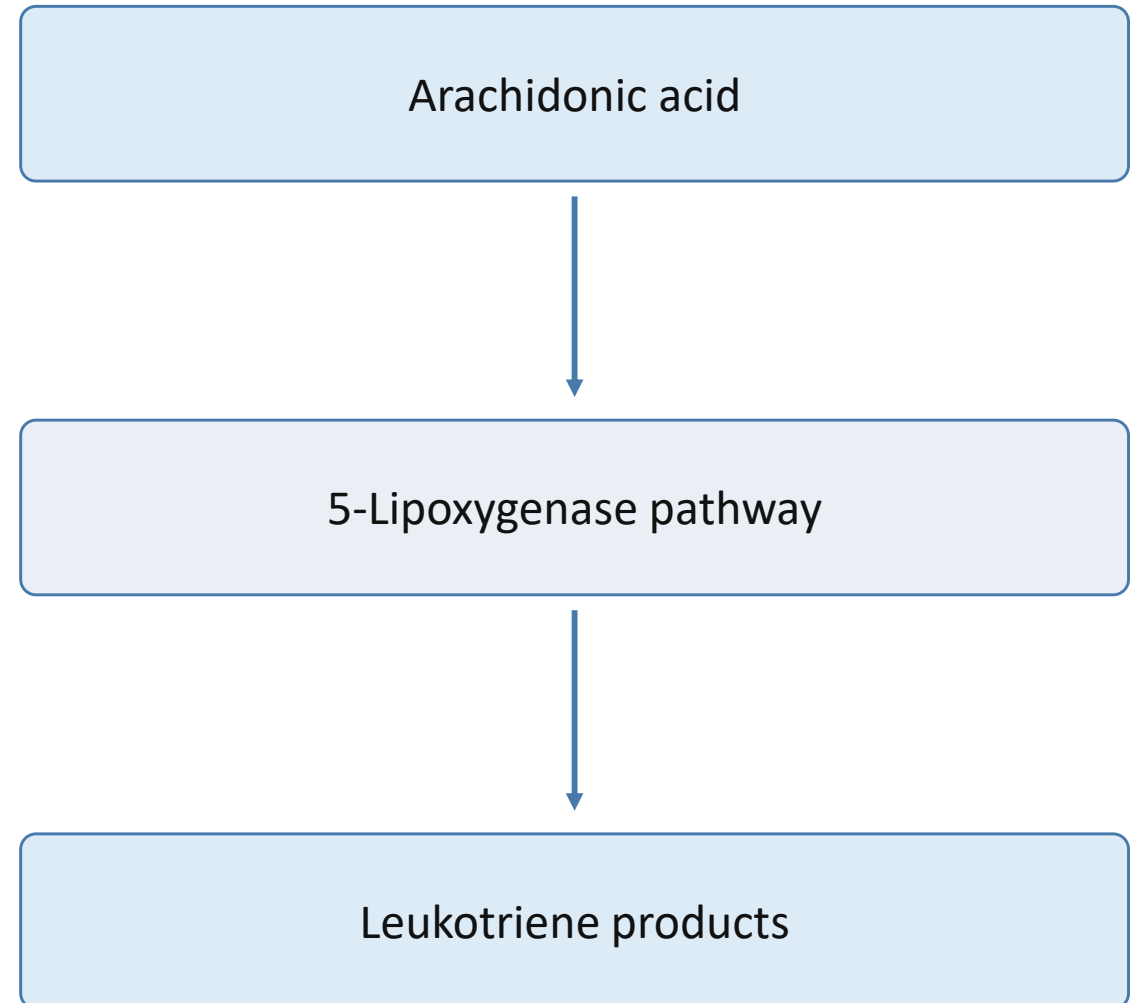
Prostaglandin functions: A targeted comparison

- Prostaglandins share a biosynthetic family but not one action
- PGD_2 / PGE_2 contribute to dilation and edema
- PGI_2 and TxA_2 exert opposing effects on platelet aggregation

PGD_2 / PGE_2	Vasodilation	Edema
PGI_2	Vasodilation	Inhibit platelets
TxA_2	Vasoconstriction	Aggregate platelets

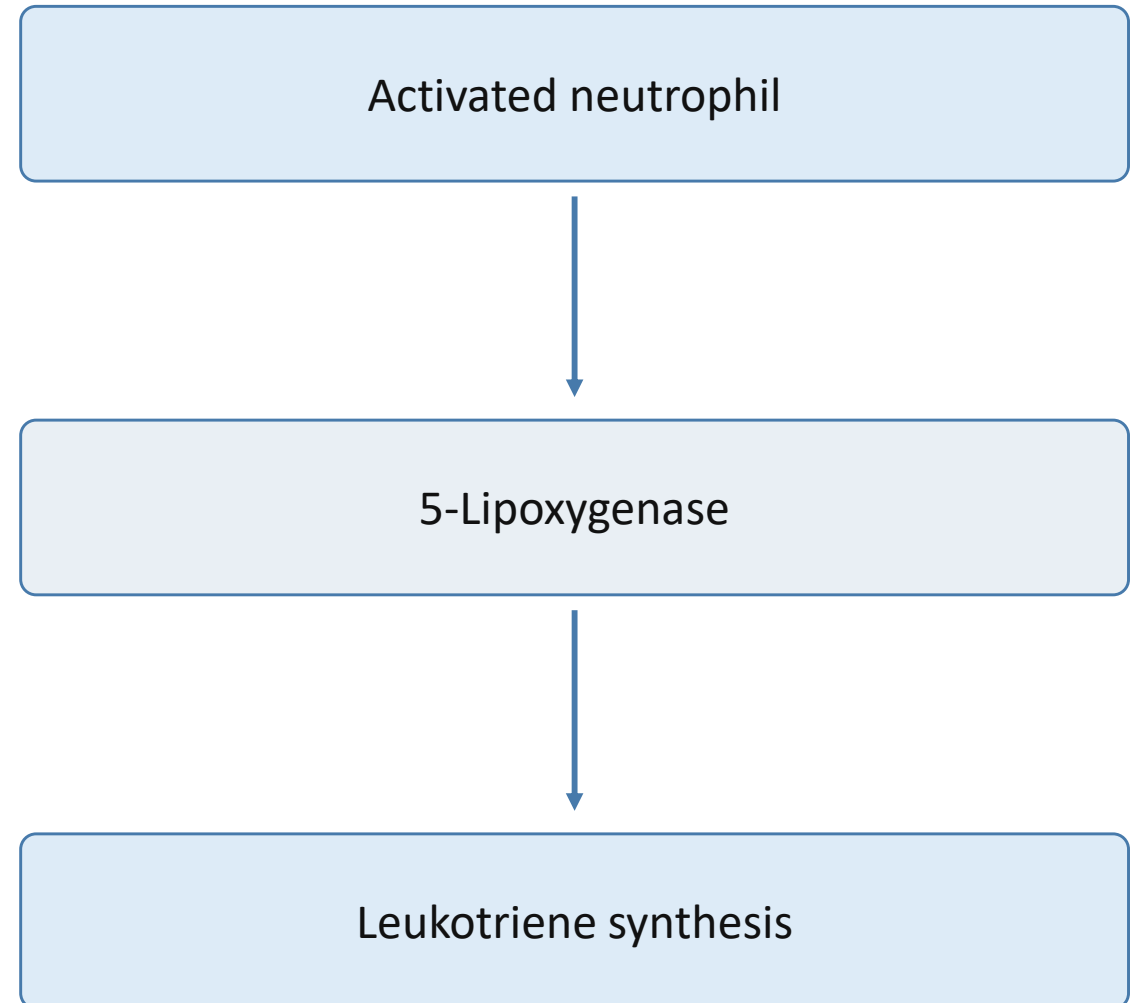
The lipoxygenase pathway generates leukotrienes

- Leukotrienes arise in leukocytes and mast cells
- Lipoxygenases convert AA to biologically active mediators
- These products affect leukocyte recruitment, smooth muscle, and vascular permeability



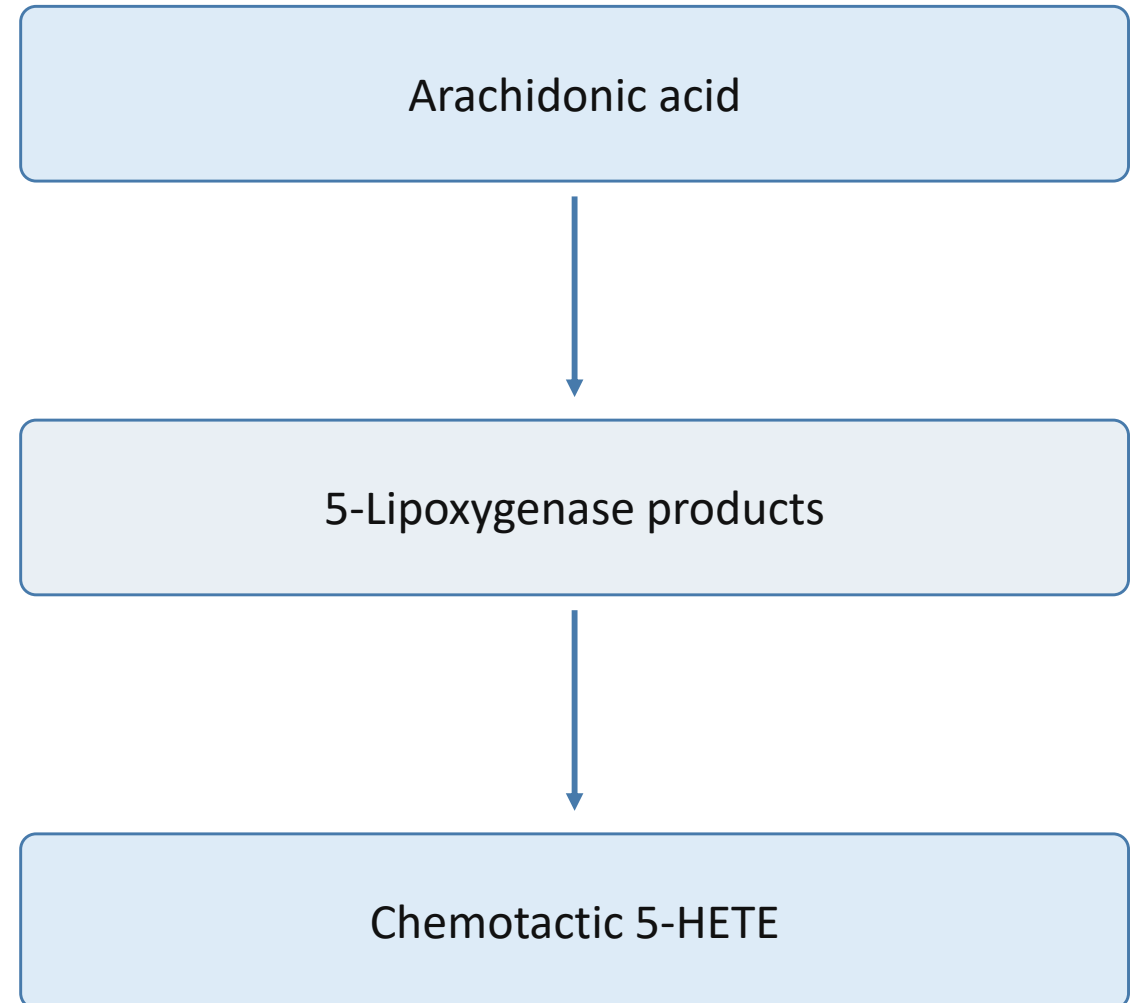
5-Lipoxygenase is important in neutrophils

- Three lipoxygenases are discussed
- 5-Lipoxygenase predominates in neutrophils
- The pathway connects AA metabolism to neutrophil functions



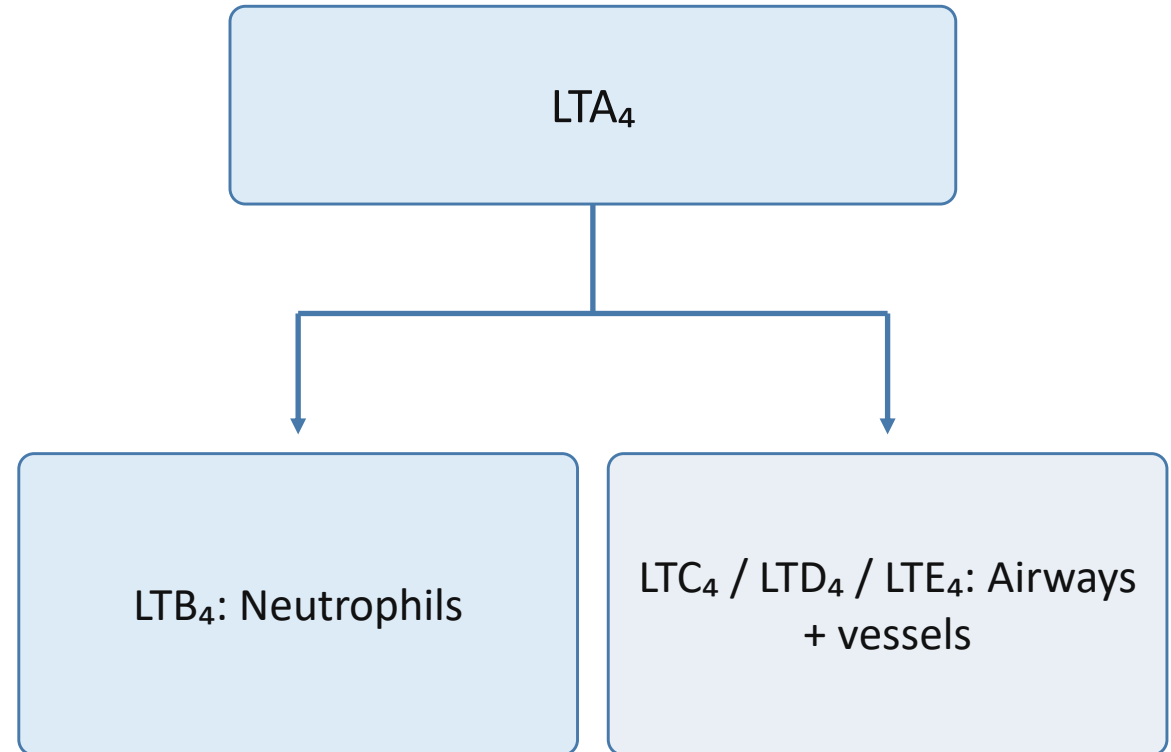
5-HETE is linked to neutrophil chemotaxis

- 5-Hydroxyeicosatetraenoic acid is discussed in the LOX pathway
- It has neutrophil-chemotactic activity
- The pathway also generates leukotriene intermediates



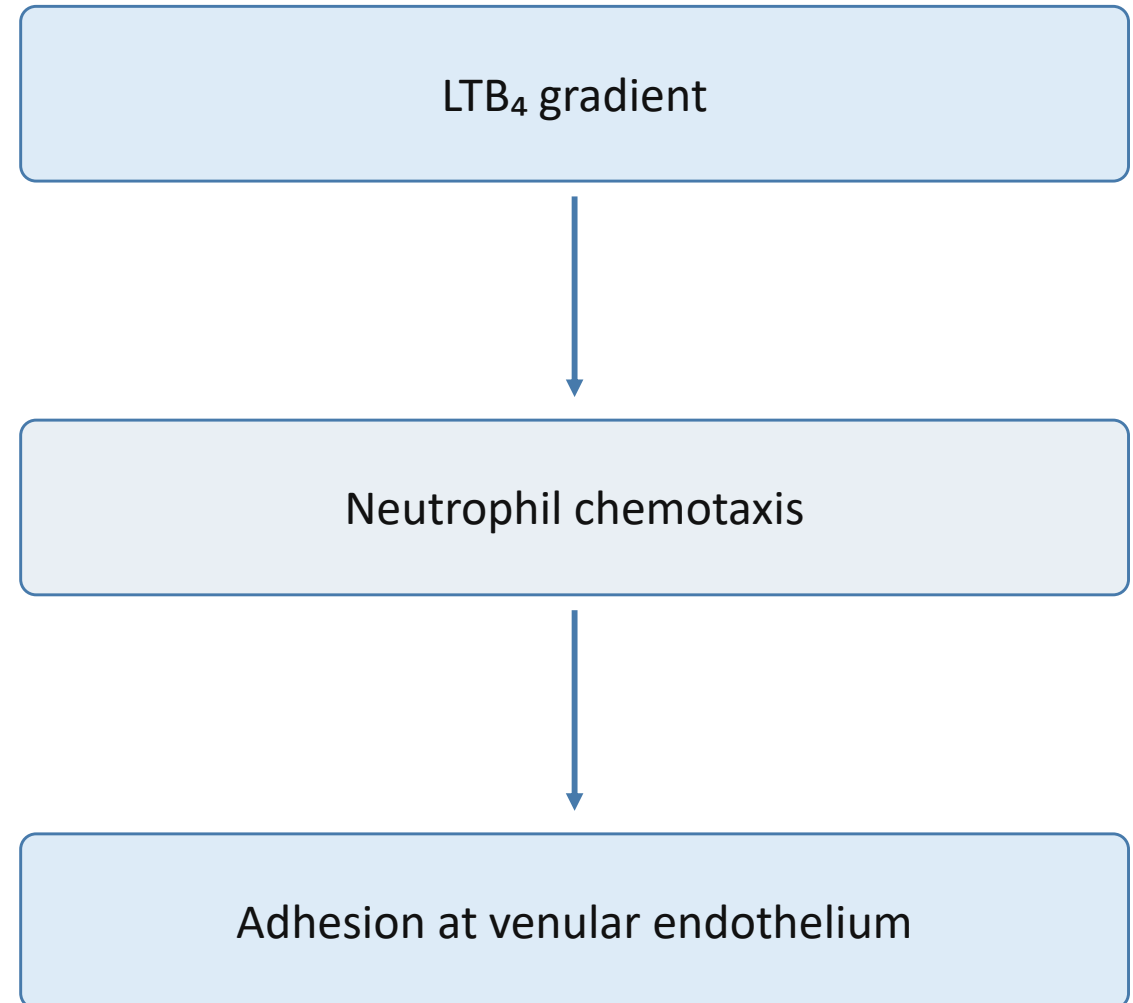
Leukotriene A₄ is a branch intermediate

- The textbook pathway diagram places LTA₄ upstream of leukotrienes
- Downstream products differ substantially in action
- LTB₄ emphasizes leukocytes; Cysteinyl leukotrienes emphasize vessels and airways



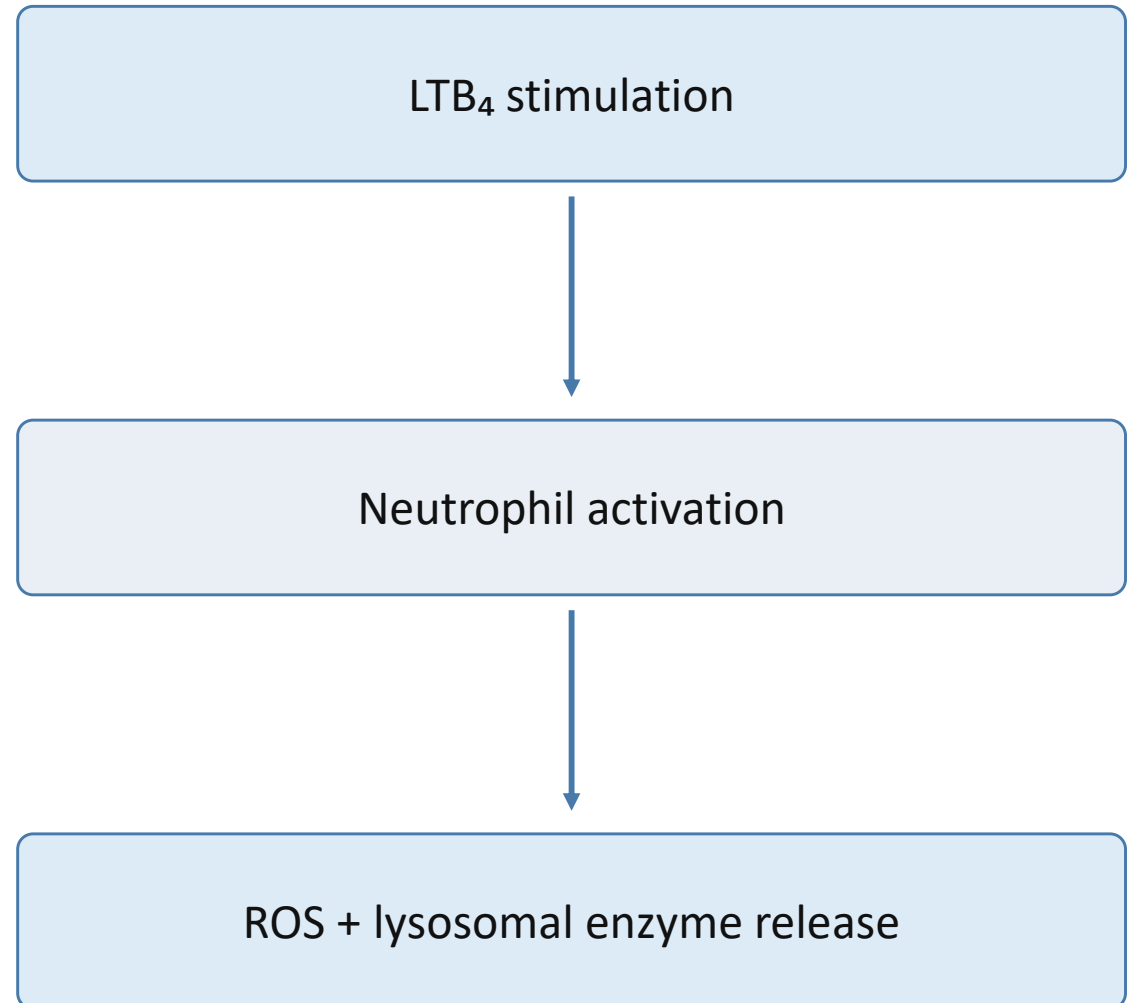
LTB₄ recruits neutrophils

- LTB₄ is a potent chemotactic agent
- It facilitates neutrophil movement toward an inflammatory site
- It also promotes neutrophil aggregation and adhesion



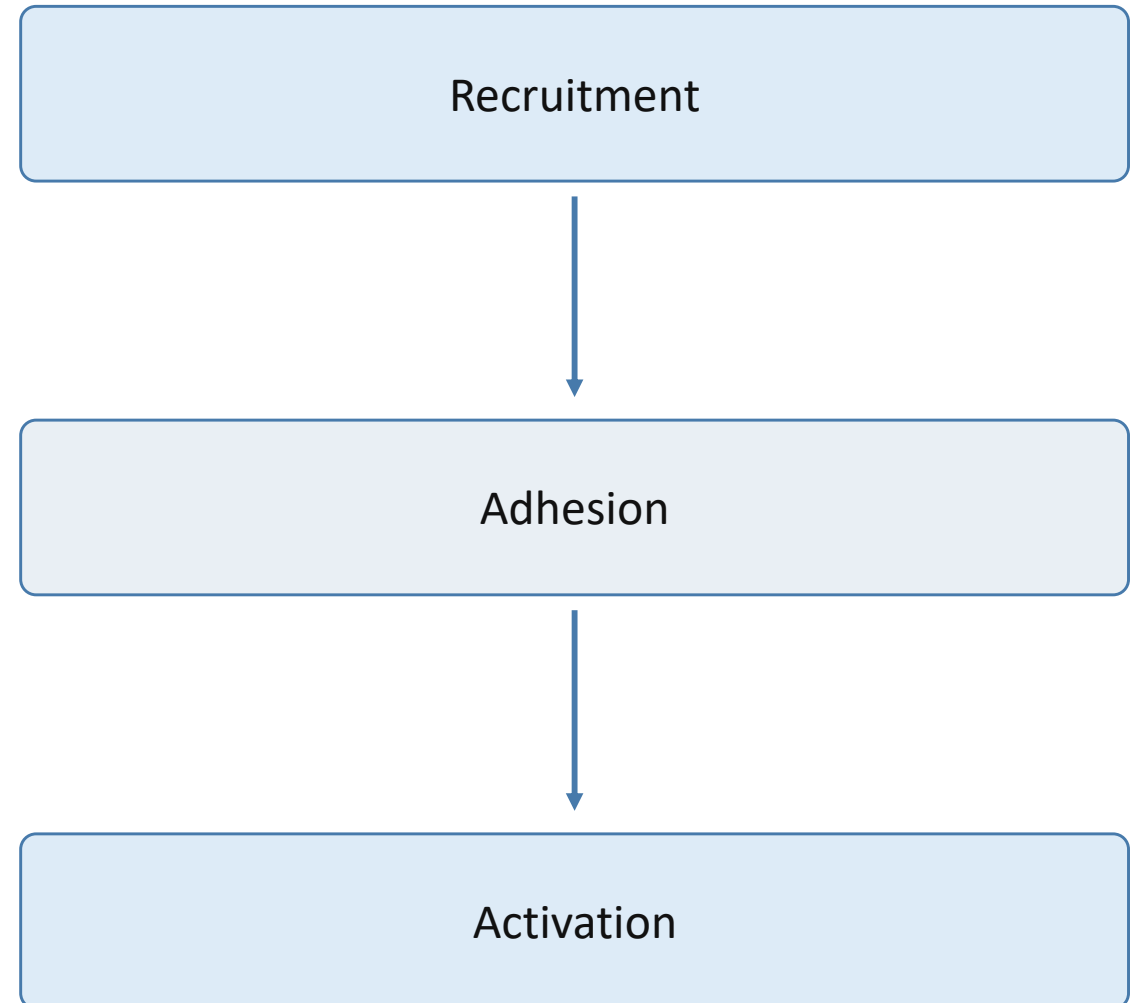
LTB₄ amplifies neutrophil effector functions

- LTB₄ activates neutrophils after recruitment
- It promotes production of reactive oxygen species
- It also promotes release of lysosomal enzymes



LTB₄ links recruitment and activation

- Chemotaxis directs neutrophils to the inflamed site
- Adhesion supports endothelial interactions
- Effector activation reinforces the acute inflammatory reaction



Cysteinyl leukotrienes form a distinct subgroup

- LTC₄, LTD₄, and LTE₄ contain cysteinyl moieties
- Their major actions differ from those of LTB₄
- The group has particular importance in asthma

LTC₄

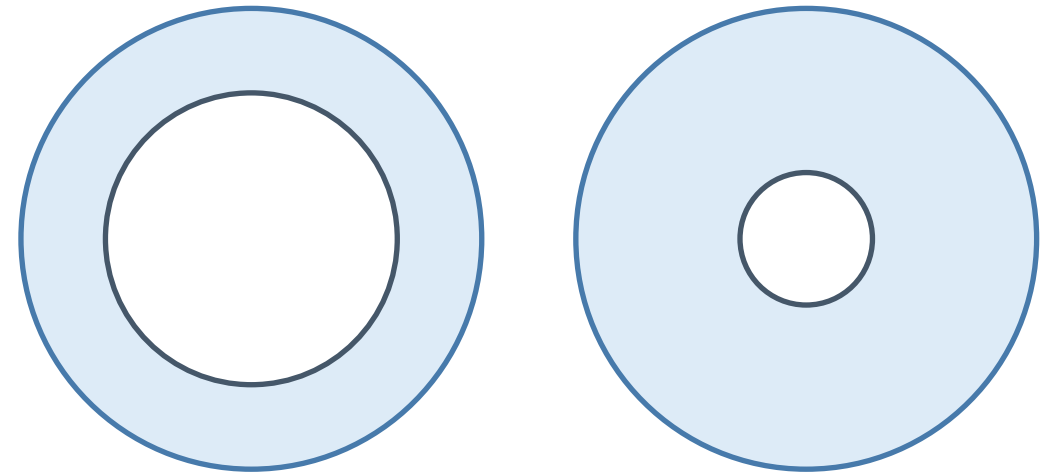
LTD₄

LTE₄

Cysteinyl leukotrienes cause bronchospasm

- LTC₄, LTD₄, and LTE₄ act on airway smooth muscle
- Their bronchoconstrictor effects are relevant in asthma
- This provides a target for leukotriene-directed treatment

Airway lumen — schematic



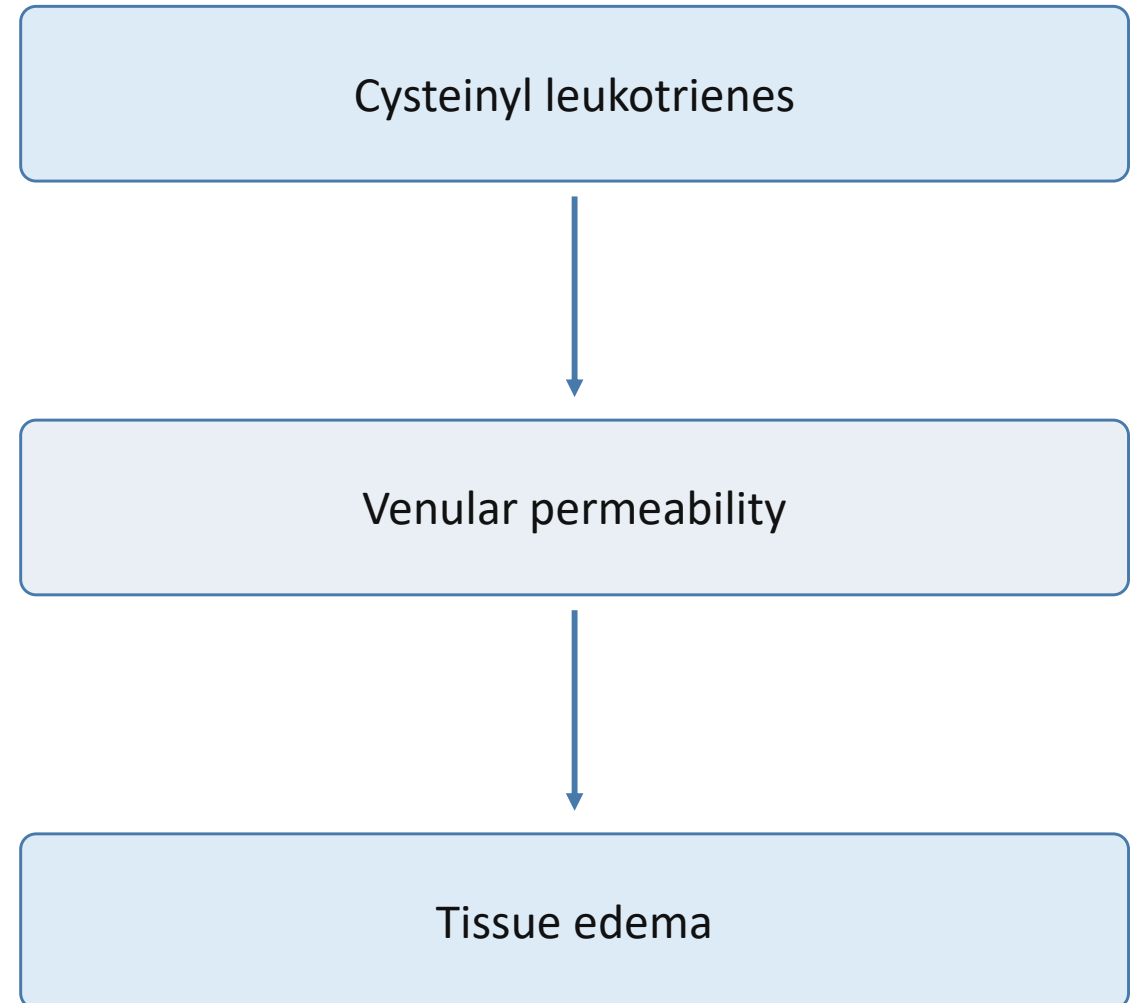
Relatively open lumen

Narrowed lumen

Cysteinyl leukotrienes → bronchospasm

Cysteinyl leukotrienes increase leakage

- LTC₄, LTD₄, and LTE₄ increase permeability of venules
- The resulting vascular leakage contributes to edema
- Their actions overlap with, but are not identical to, prostaglandin effects



Leukotrienes are functionally specialized

- LTB_4 is principally chemotactic and neutrophil activating
- LTC_4 / LTD_4 / LTE_4 act on airways and venules
- This distinction is essential for choosing receptor-directed therapy

LTB_4	$\text{LTC}_4/\text{D}_4/\text{E}_4$
Chemotaxis	Bronchospasm
Neutrophil activation	Venular leakage

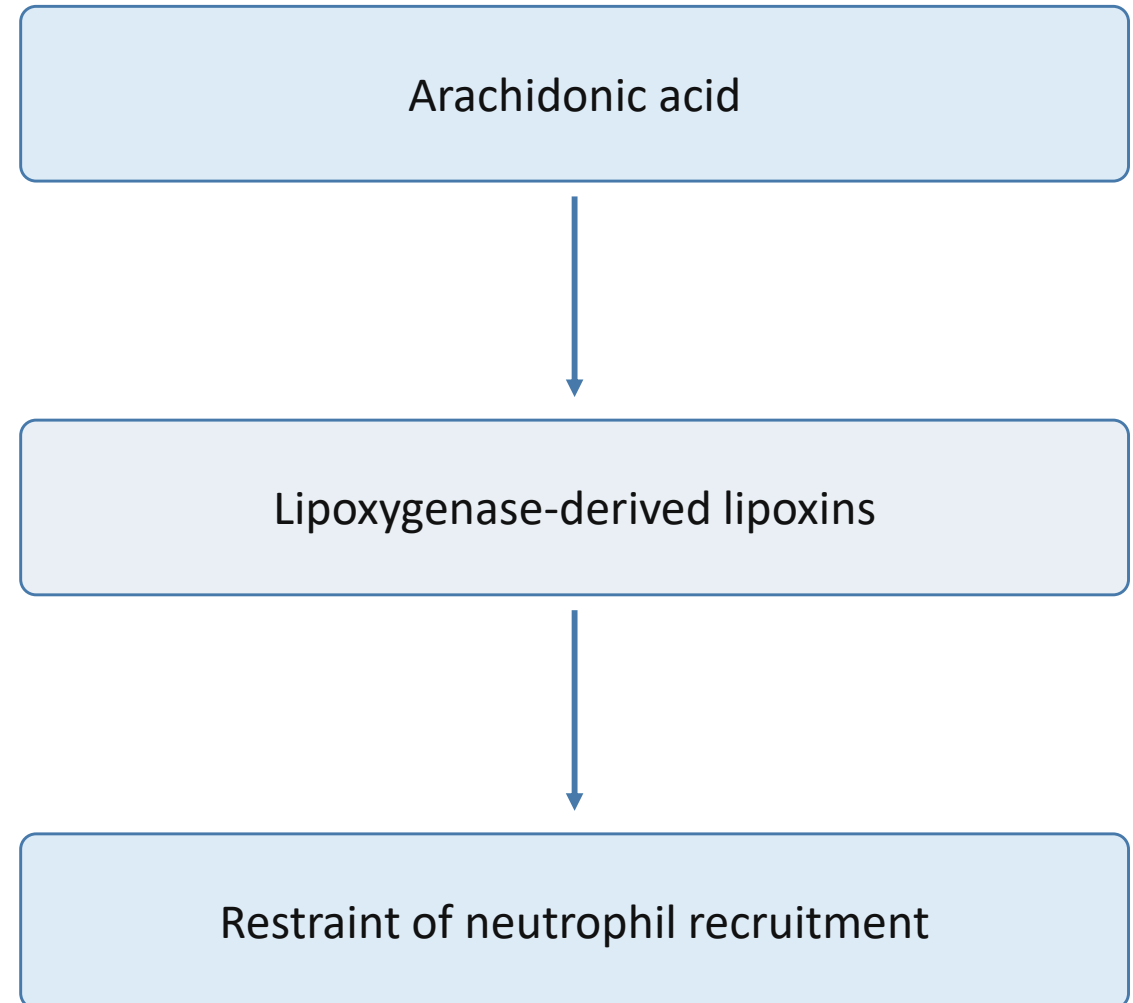
COX and LOX products act in different domains

- COX products include PGD₂, PGE₂, PGI₂, and TxA₂
- LOX products include LTB₄ and cysteinyl leukotrienes
- Pathway name alone does not predict anti- or proinflammatory action

COX	LOX
Vascular, pain, fever, platelets	Leukocytes, airways, permeability

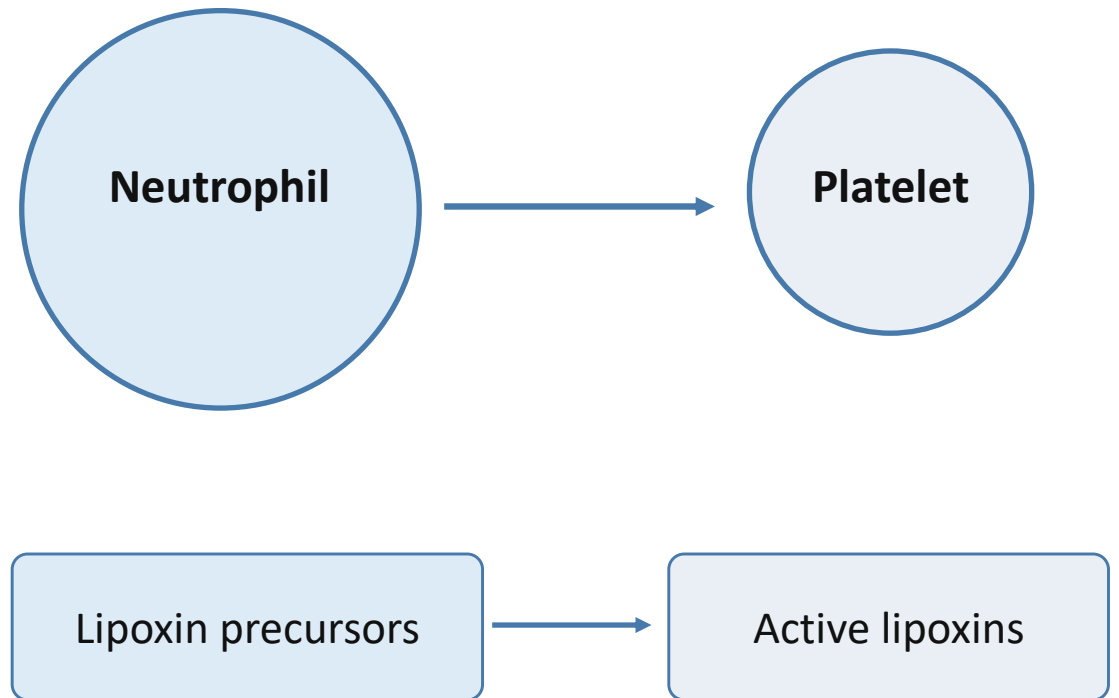
Lipoxins provide counter-regulatory signals

- Lipoxins are derived from AA through a lipoxygenase pathway
- In contrast to major leukotrienes, they suppress inflammation
- Their principal described targets are neutrophil behaviors



Lipoxin synthesis involves two cell populations

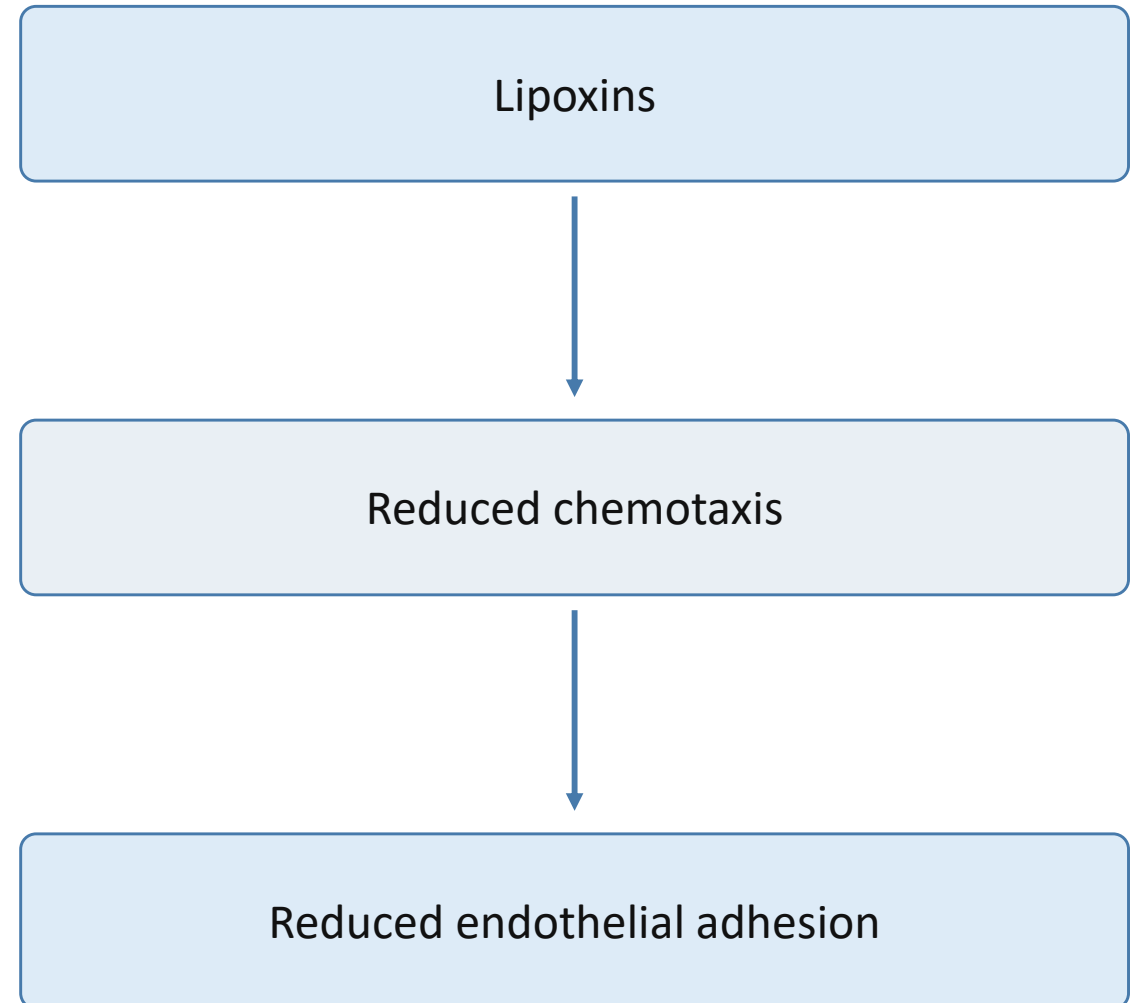
- Neutrophils generate precursors of active lipoxins
- Precursors pass to platelets
- Platelets then convert them into mature lipoxins



Transcellular biosynthesis

Lipoxins inhibit neutrophil recruitment

- Lipoxins inhibit neutrophil chemotaxis
- They reduce neutrophil adhesion to endothelium
- These effects counteract selected proinflammatory leukotriene actions



LTB₄ and lipoxins pull in opposite directions

- LTB₄ promotes neutrophil recruitment and activation
- Lipoxins inhibit chemotaxis and adhesion
- Their contrast illustrates the importance of product identity

LTB ₄	Lipoxins
Recruit + activate neutrophils	Restrain neutrophil recruitment

LXA₄ and LXB₄ are active lipoxins

- The AA pathway illustration identifies lipoxin A₄ and B₄
- Both are placed within the anti-inflammatory lipid branch
- Avoid equating lipoxins with the action of LTB₄

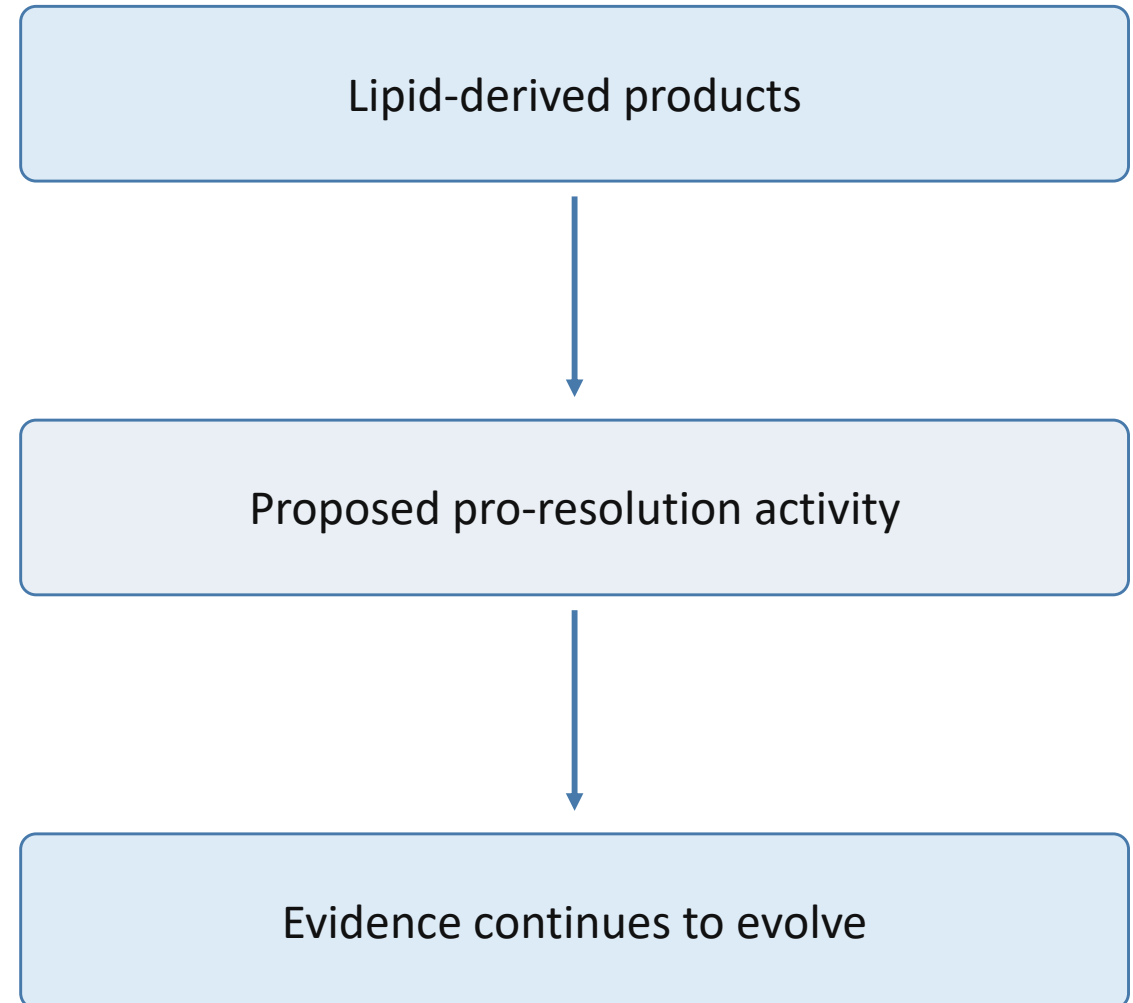
LXA₄

LXB₄

Inhibition of neutrophil recruitment

Resolvins: A developing area of investigation

- Robbins mentions additional anti-inflammatory lipid products
- Resolvins are proposed to aid resolution of acute inflammation
- Their precise contributions remain a topic of active study



A single pathway has both positive and negative outputs

- Proinflammatory eicosanoids can recruit leukocytes and promote edema
- Lipoxins inhibit selected neutrophil recruitment processes
- Inflammation therefore depends on the balance of multiple mediators

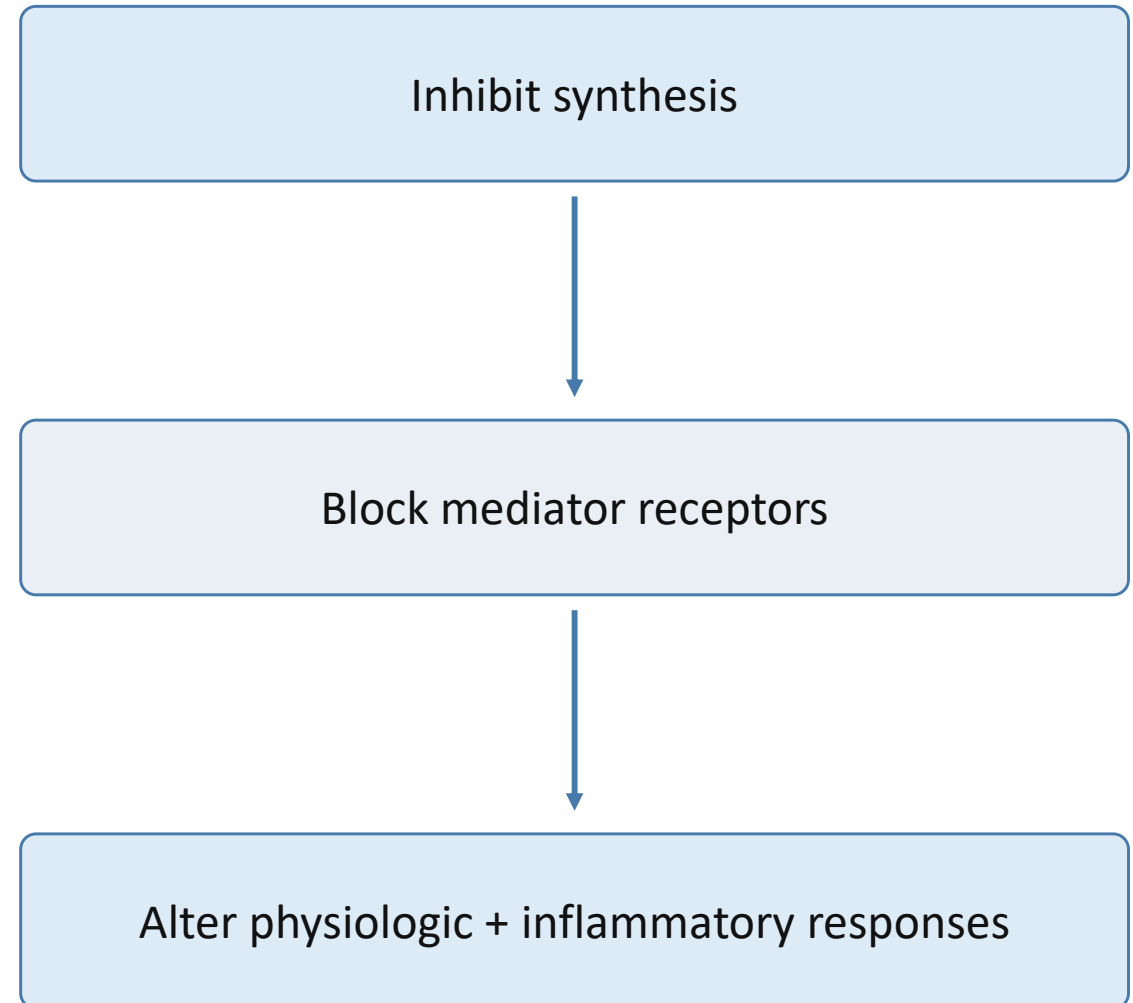
Recruitment: LTB₄

Vascular response: PGs + cysteinyl LTs

Restraint: Lipoxins

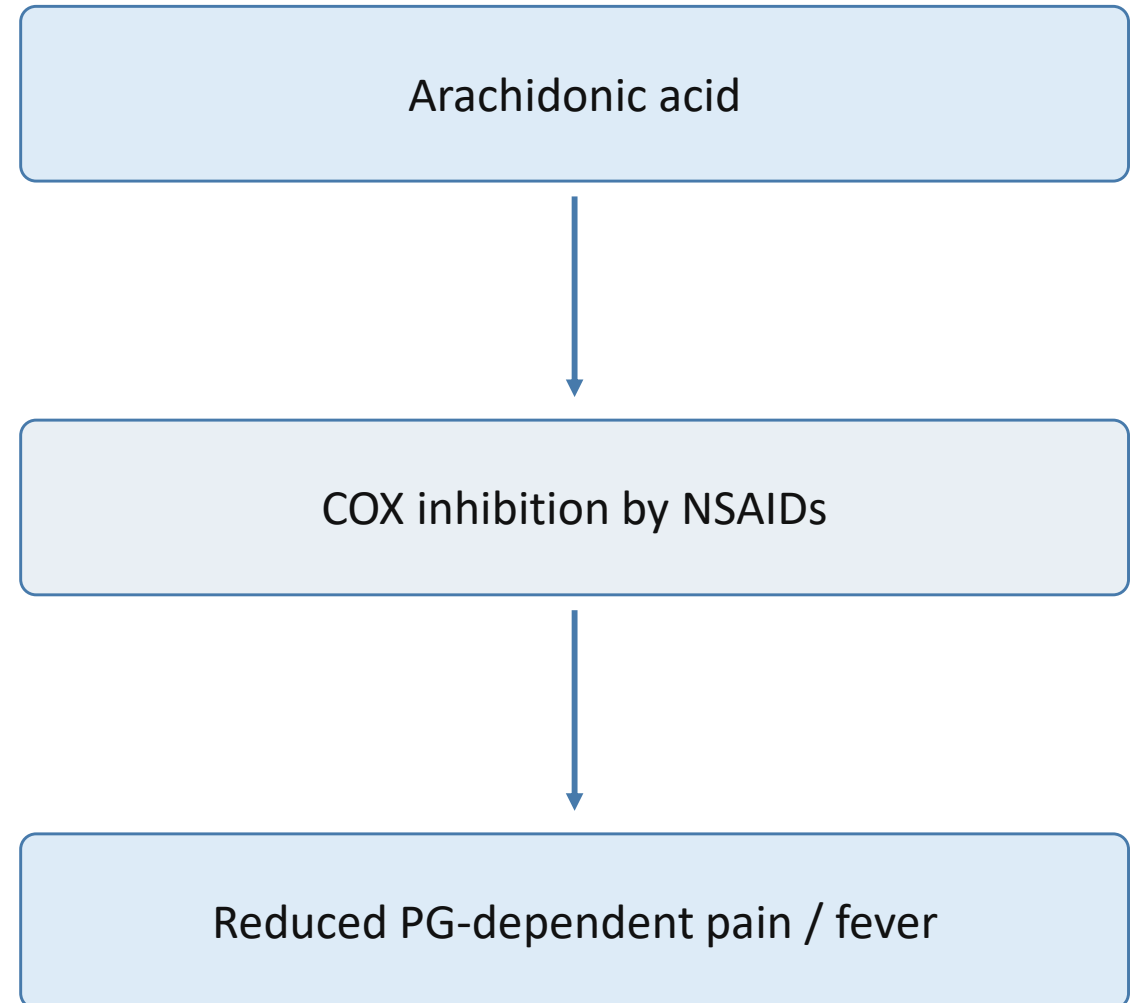
Drug therapy targets synthesis or receptor action

- An upstream block can reduce formation of mediator products
- Downstream receptor antagonism can block selected effector actions
- Drug breadth matters because eicosanoids have physiologic functions



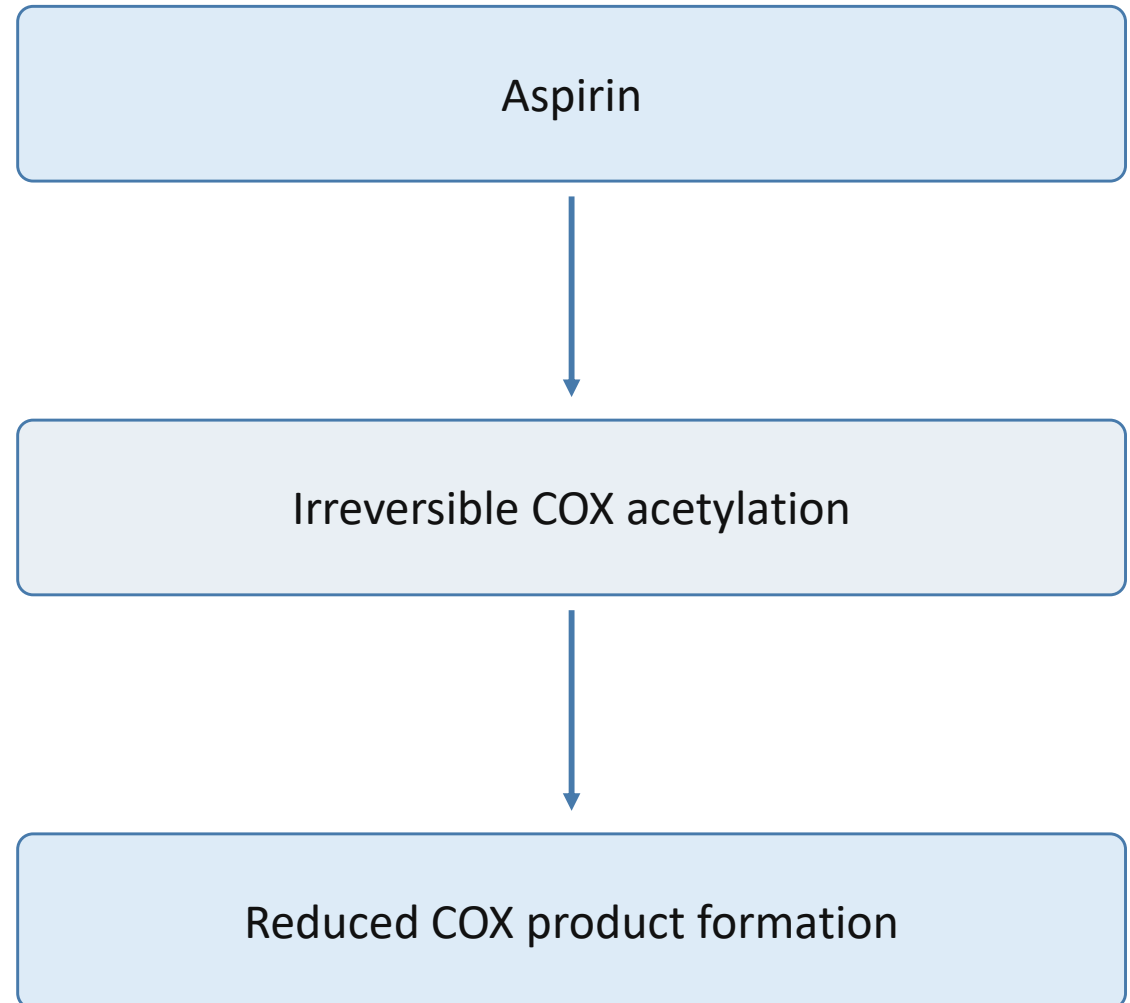
NSAIDs inhibit cyclooxygenase activity

- Aspirin and other NSAIDs suppress COX-mediated prostaglandin synthesis
- They generally inhibit the COX branch rather than the LOX branch
- This explains antipyretic and analgesic benefits



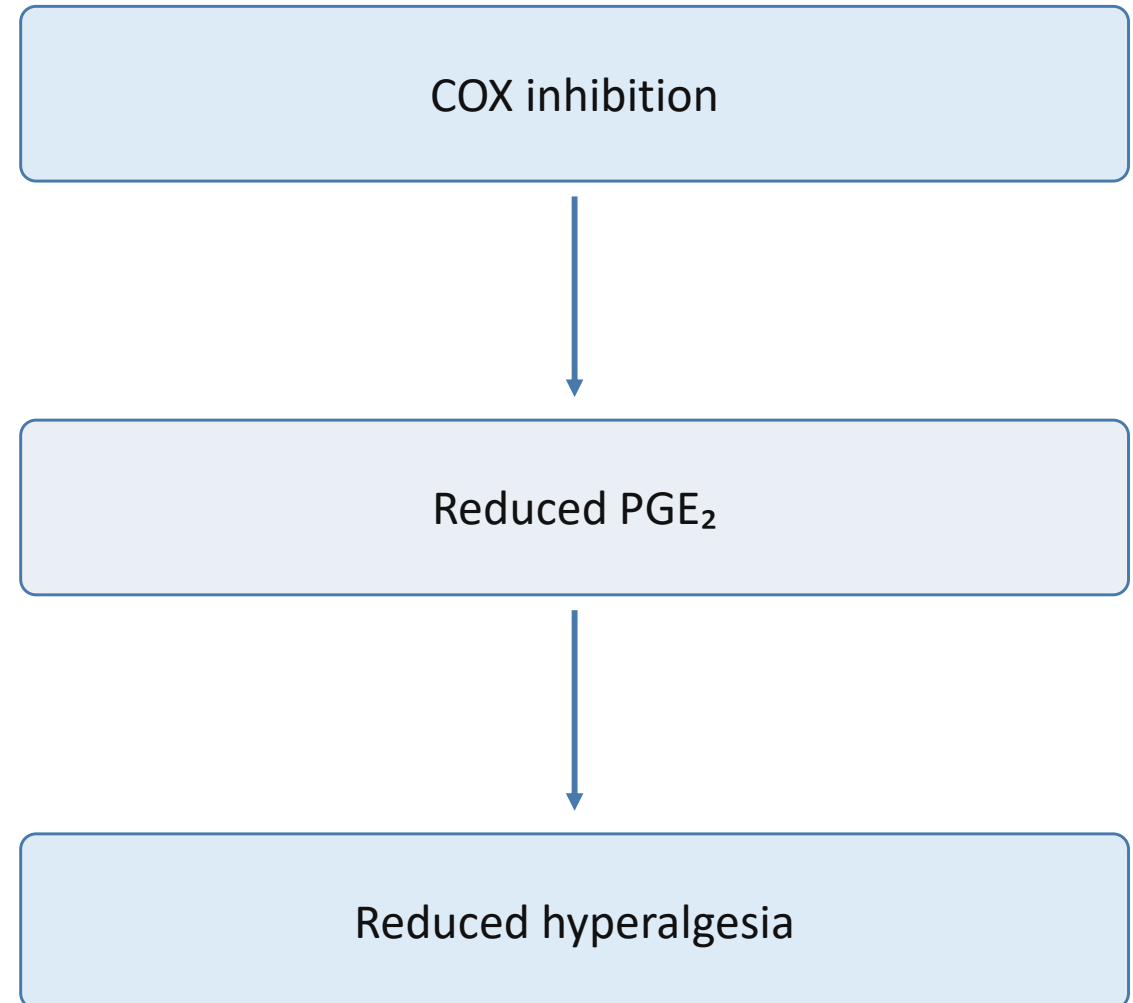
Aspirin irreversibly inhibits cyclooxygenase

- Aspirin-mediated irreversible acetylation
- Cyclooxygenase inactivation reduces downstream prostaglandin synthesis
- Irreversible inhibition is mechanistically distinct from transient enzyme blockade



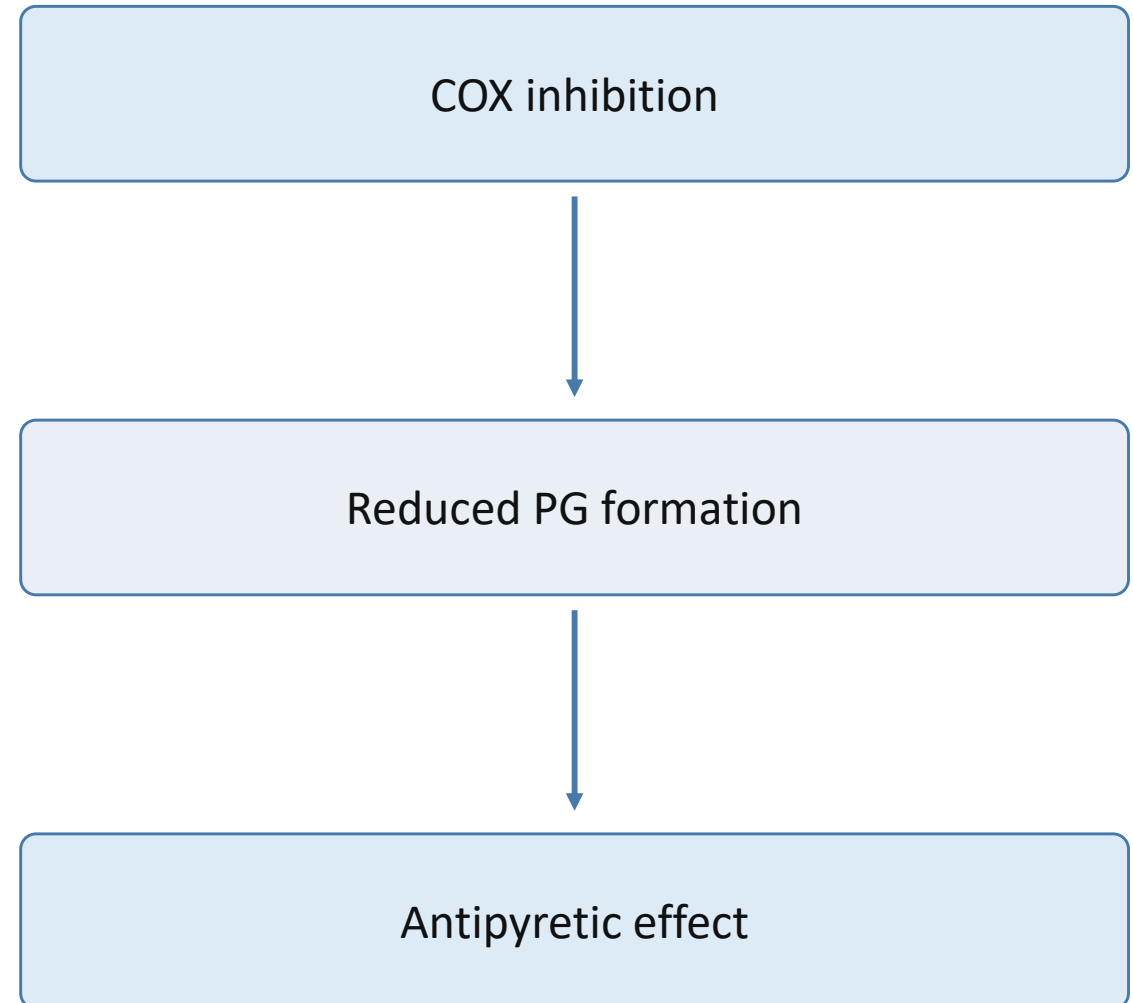
NSAID analgesia follows reduced PGE₂ signaling

- PGE₂ helps sensitize tissues to pain-producing stimuli
- COX inhibition limits its production
- Reduced sensitization contributes to analgesic action



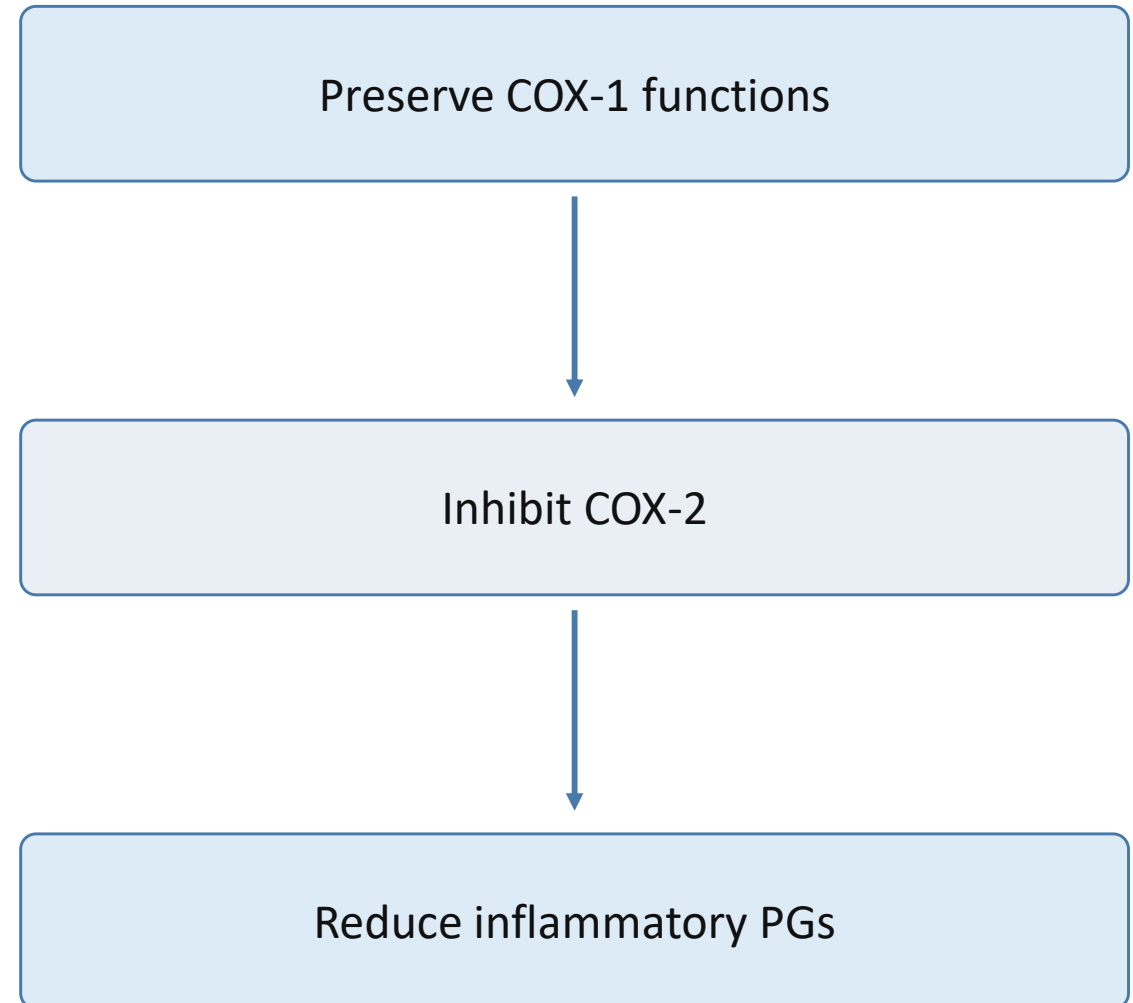
NSAID antipyresis follows reduced PG production

- PGE₂ contributes to inflammatory fever
- Reducing prostaglandin synthesis attenuates this component
- The mechanism differs from direct antimicrobial action



Selective COX-2 inhibition has a clear rationale

- COX-1 has important physiologic functions
- COX-2 is prominent in inflammatory reactions
- Selective inhibition aims to preserve more COX-1–dependent protection



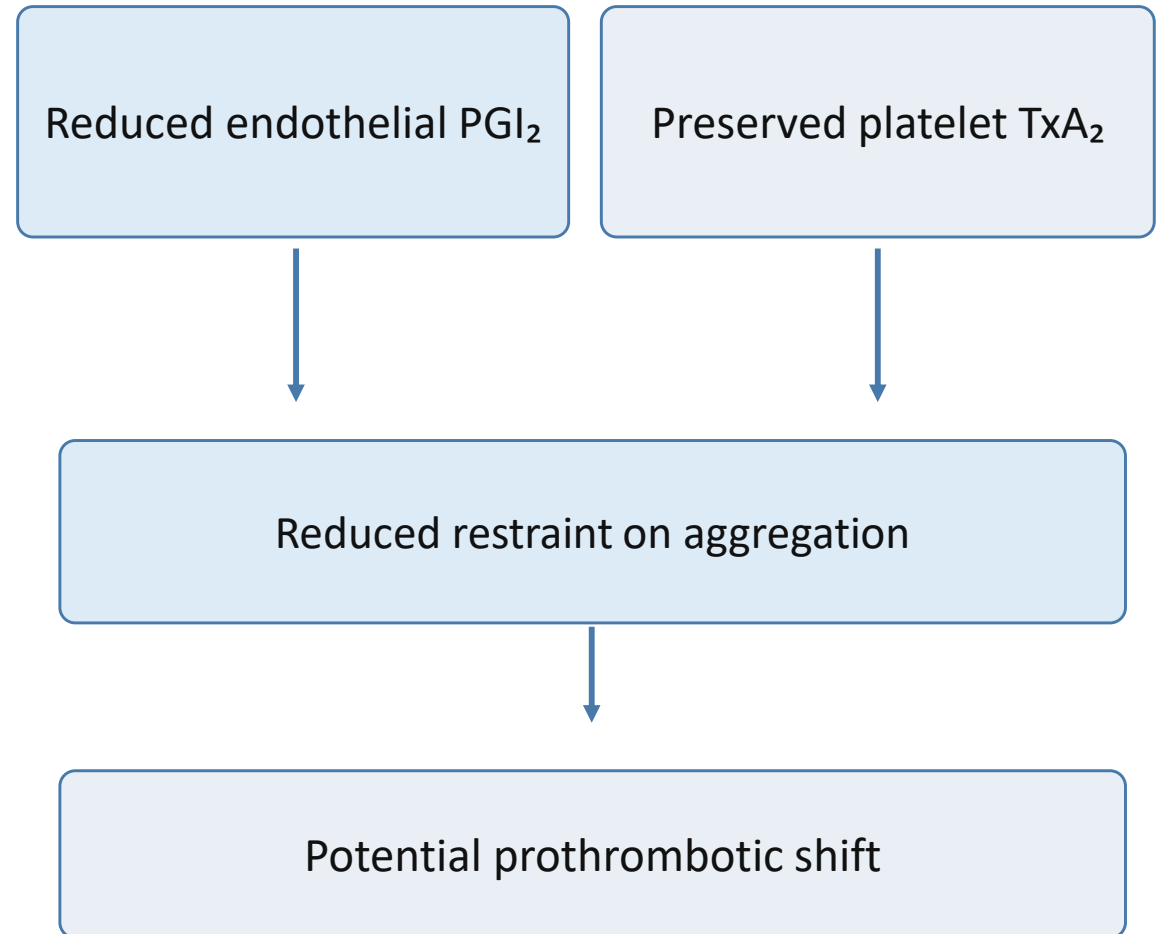
COX-1 versus COX-2 is not an absolute divide

- COX-1 can be induced during inflammation
- COX-2 also participates in cytoprotection
- A strict “good COX-1 / bad COX-2” model is oversimplified

COX-1	COX-2
Constitutive + inducible	Inflammation + protective roles

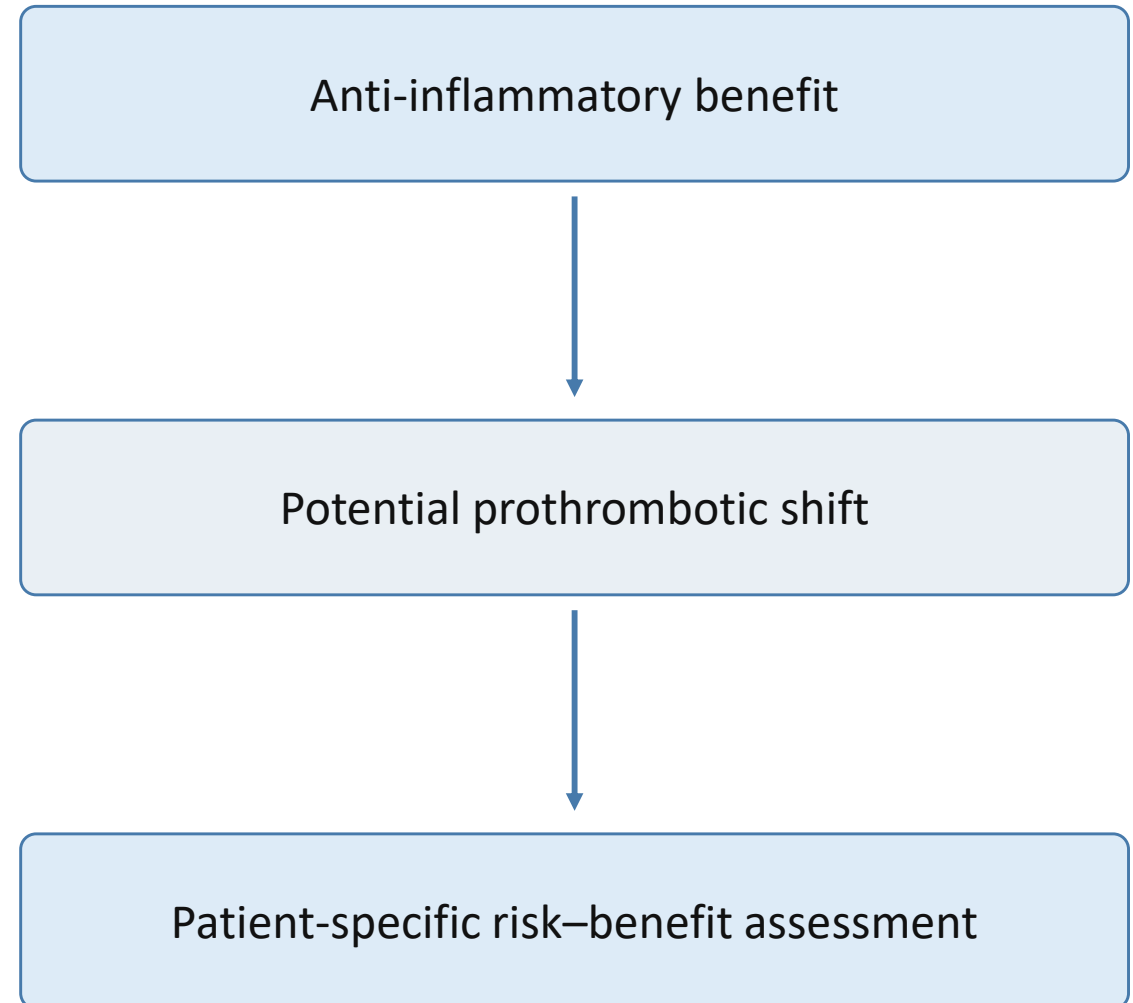
Selective COX-2 blockade can change thrombotic balance

- Endothelial PGI₂ production may be impaired
- Platelet COX-1–dependent TxA₂ production can persist
- The resulting imbalance may favor thrombotic vascular events



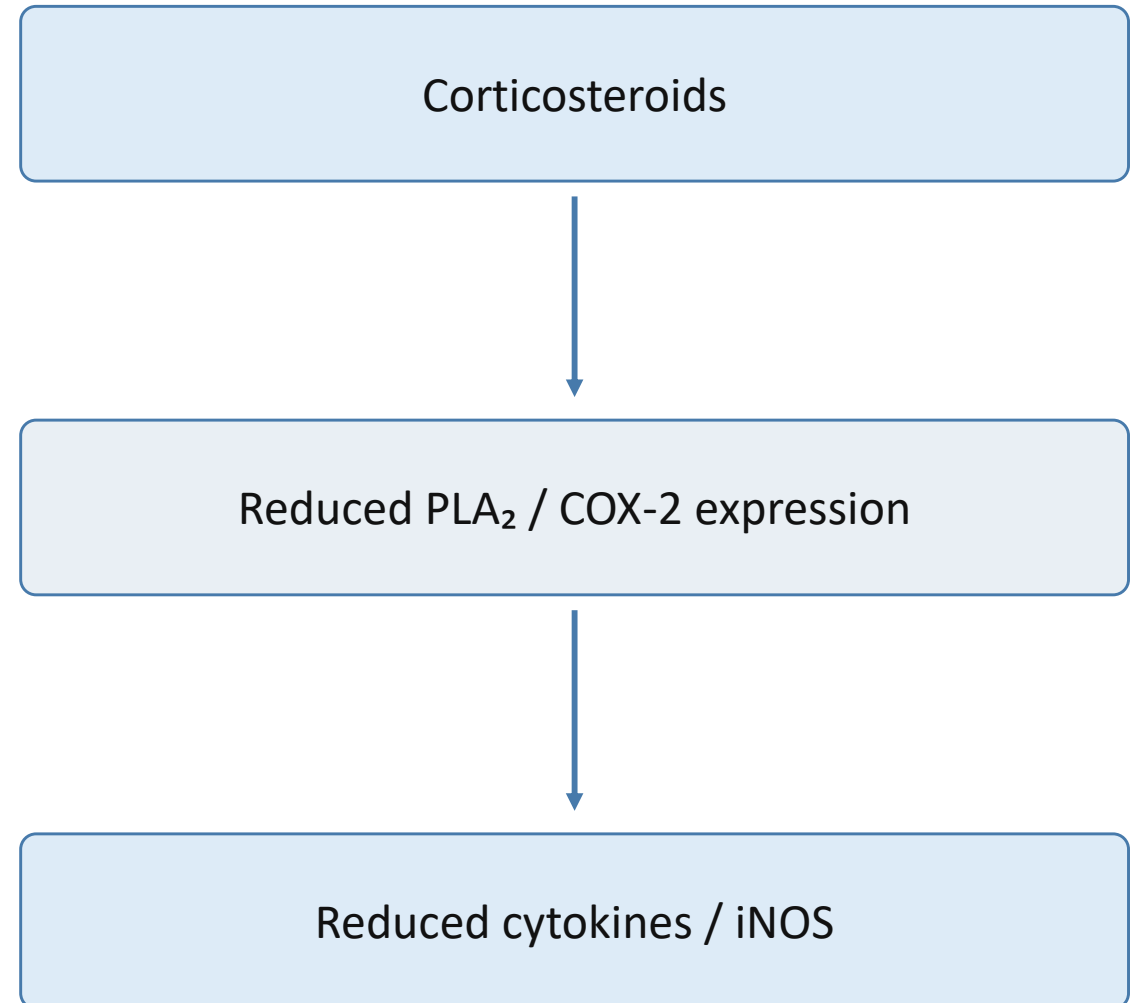
COX-2 inhibitors require vascular risk awareness

- Selective COX-2 inhibition to possible cardiovascular and cerebrovascular risks
- The proposed mechanism involves PGI₂–TxA₂ imbalance
- Clinical benefits must be weighed against patient risk factors



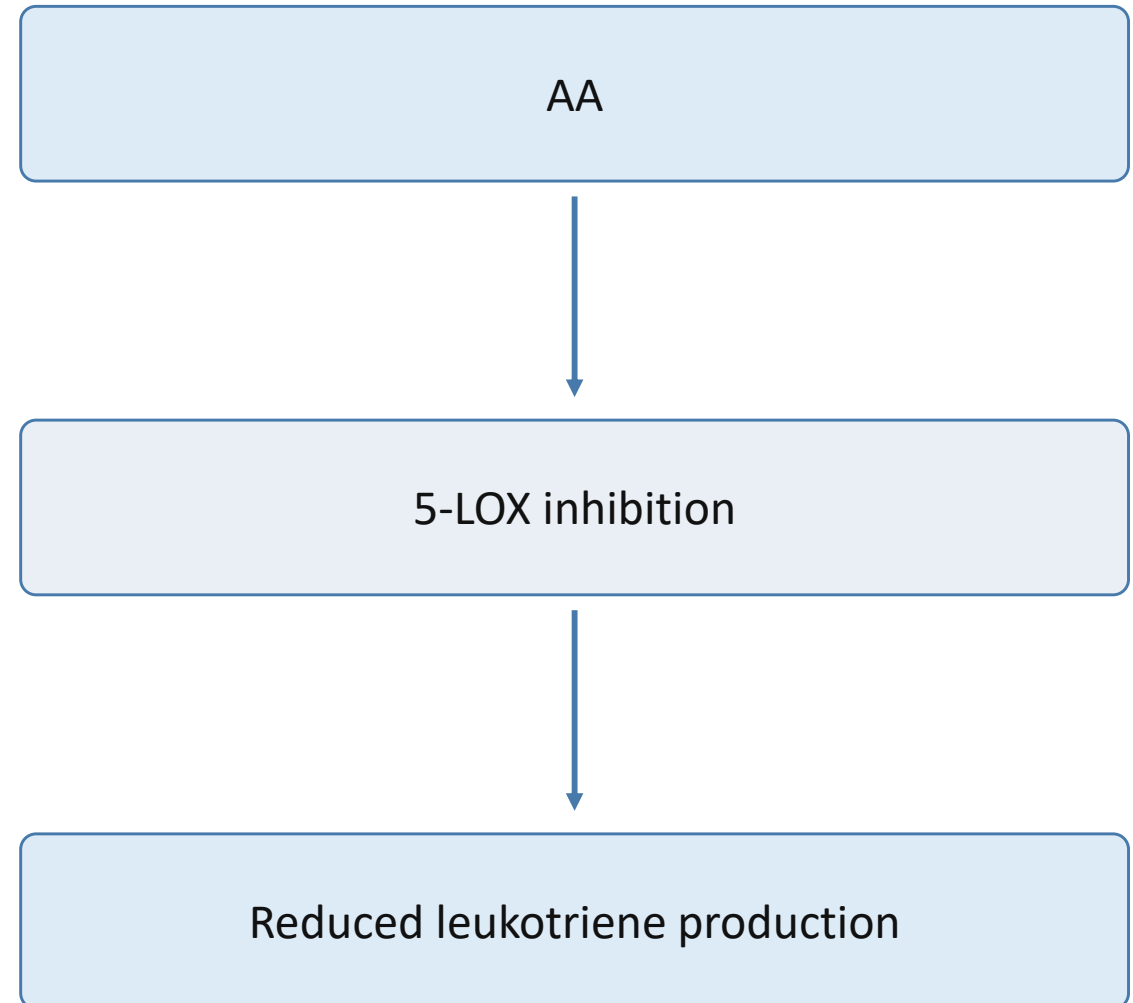
Corticosteroids suppress multiple inflammatory genes

- Reduced transcription of COX-2 and PLA₂-related genes
- They also suppress inflammatory cytokines and iNOS
- Their broader action differs from selective COX blockade



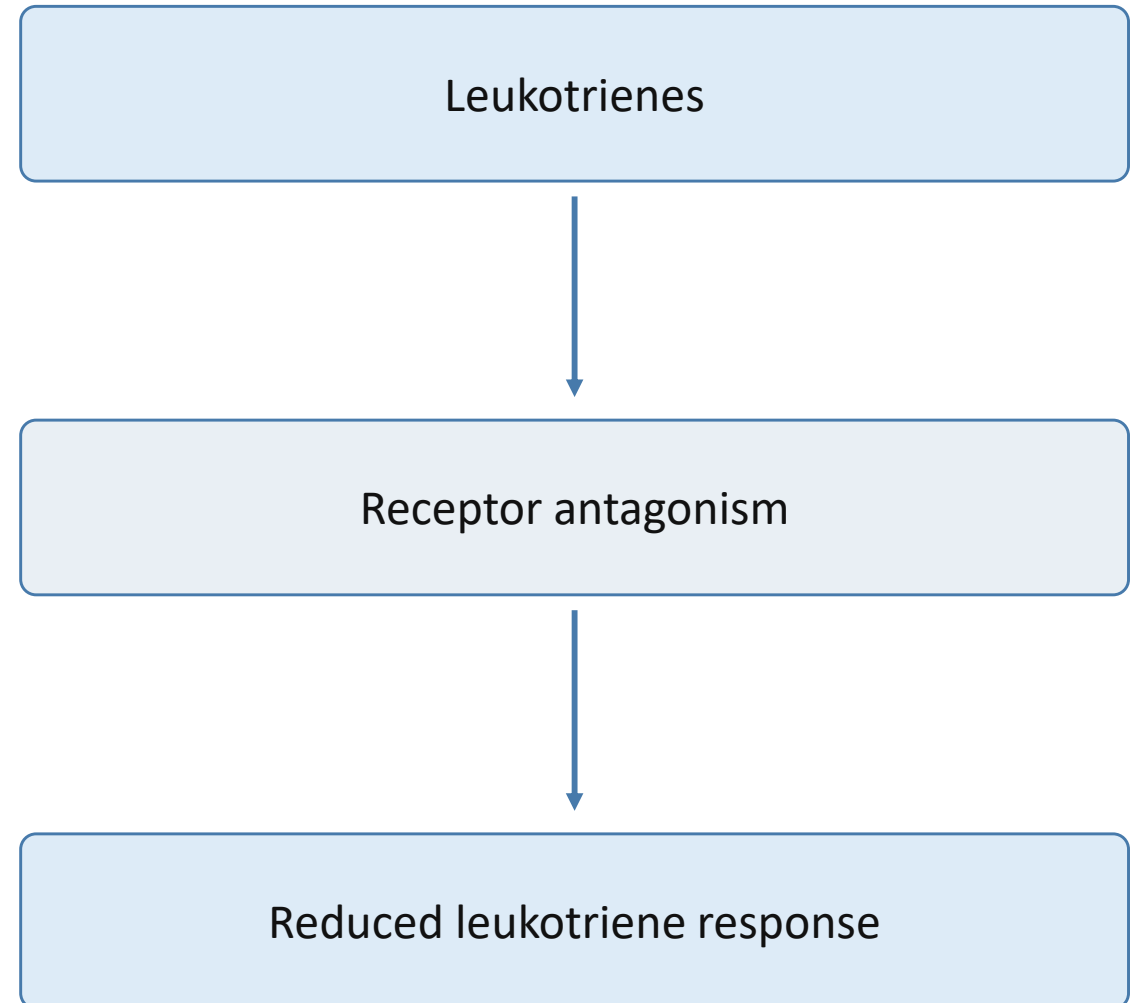
5-Lipoxygenase inhibitors target LT production

- The 5-LOX pathway is not blocked by standard NSAID COX inhibition
- Inhibiting it can reduce leukotriene formation
- Clinical usefulness in asthma



Leukotriene receptor antagonists block the response

- These drugs act downstream of mediator synthesis
- They inhibit leukotriene receptor-mediated effects
- They are used in asthma



Asthma treatment illustrates two distinct targets

- 5-LOX inhibition reduces leukotriene production
- Leukotriene receptor blockade reduces downstream signaling
- Both approaches address the leukotriene contribution to bronchospasm

5-LOX inhibitor

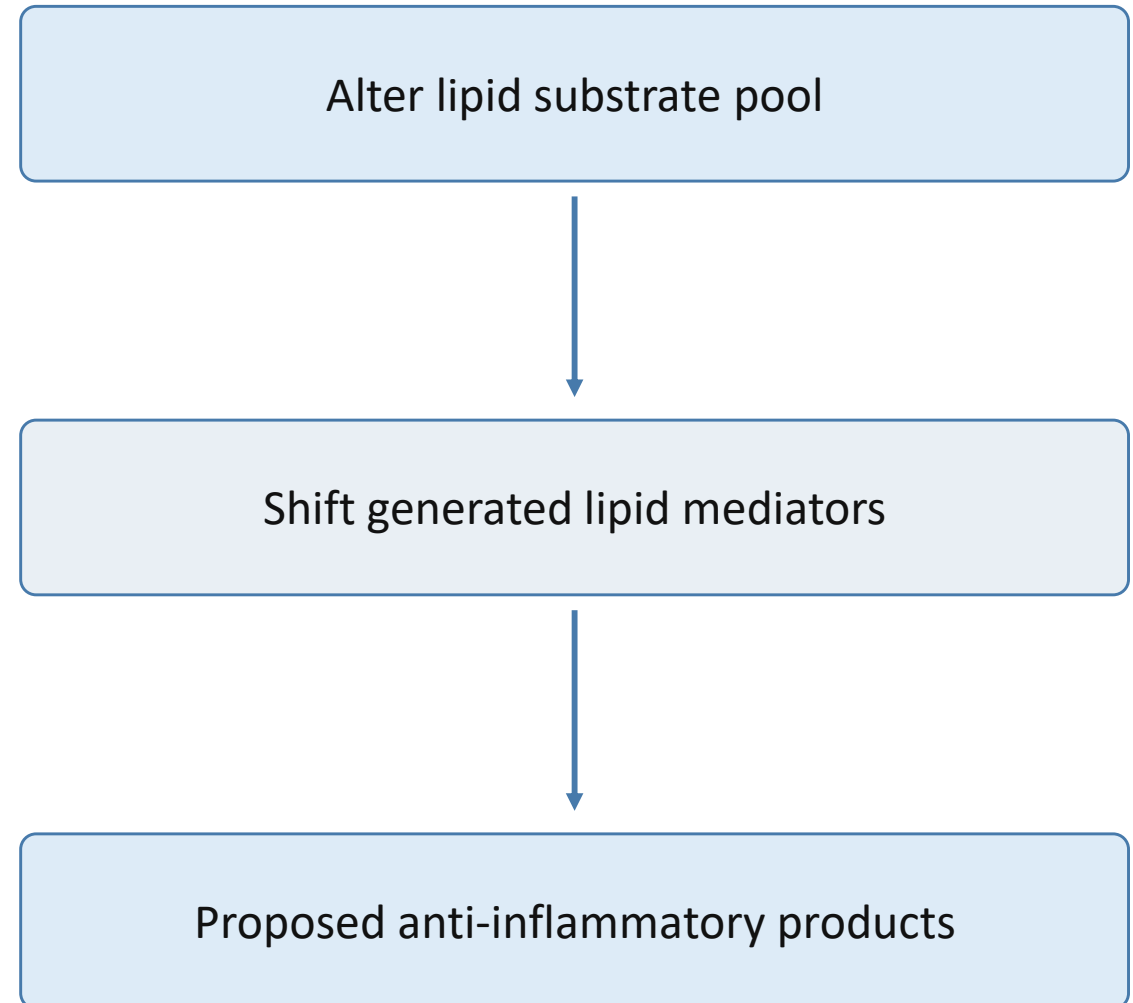
Reduce synthesis

LT receptor antagonist

Block signaling

Fish-oil-derived lipids: A proposed mechanism

- Manipulation of dietary lipid composition
- Fish-oil fatty acids are proposed to favor anti-inflammatory lipid products
- This mechanism is presented as a proposal, not established efficacy for a specific disease



Match mediator families to key vascular actions

- PGI₂, PGE₁, PGE₂, and PGD₂ are listed as vasodilators
- TxA₂ and cysteinyl leukotrienes are listed as vasoconstrictors
- Cysteinyl leukotrienes increase vascular permeability

Vasodilation

PGI₂ / PGE₁ / PGE₂ / PGD₂

Vasoconstriction

TxA₂ / LTC₄-E₄

Permeability

LTC₄-E₄

Match eicosanoids to leukocyte responses

- LTB₄ and HETE contribute to chemotaxis
- LTB₄ also promotes neutrophil adhesion and activation
- Lipoxins exert opposing effects on chemotaxis and adhesion

LTB₄ / HETE

Recruit leukocytes

Lipoxins

Limit chemotaxis /
adhesion

Application: Inflammatory edema and tenderness

- A focus of acute inflammation is edematous and tender
- Which AA product can account for pain sensitization?
- Which mediator group strongly increases venular leakage?

MECHANISM CHECK

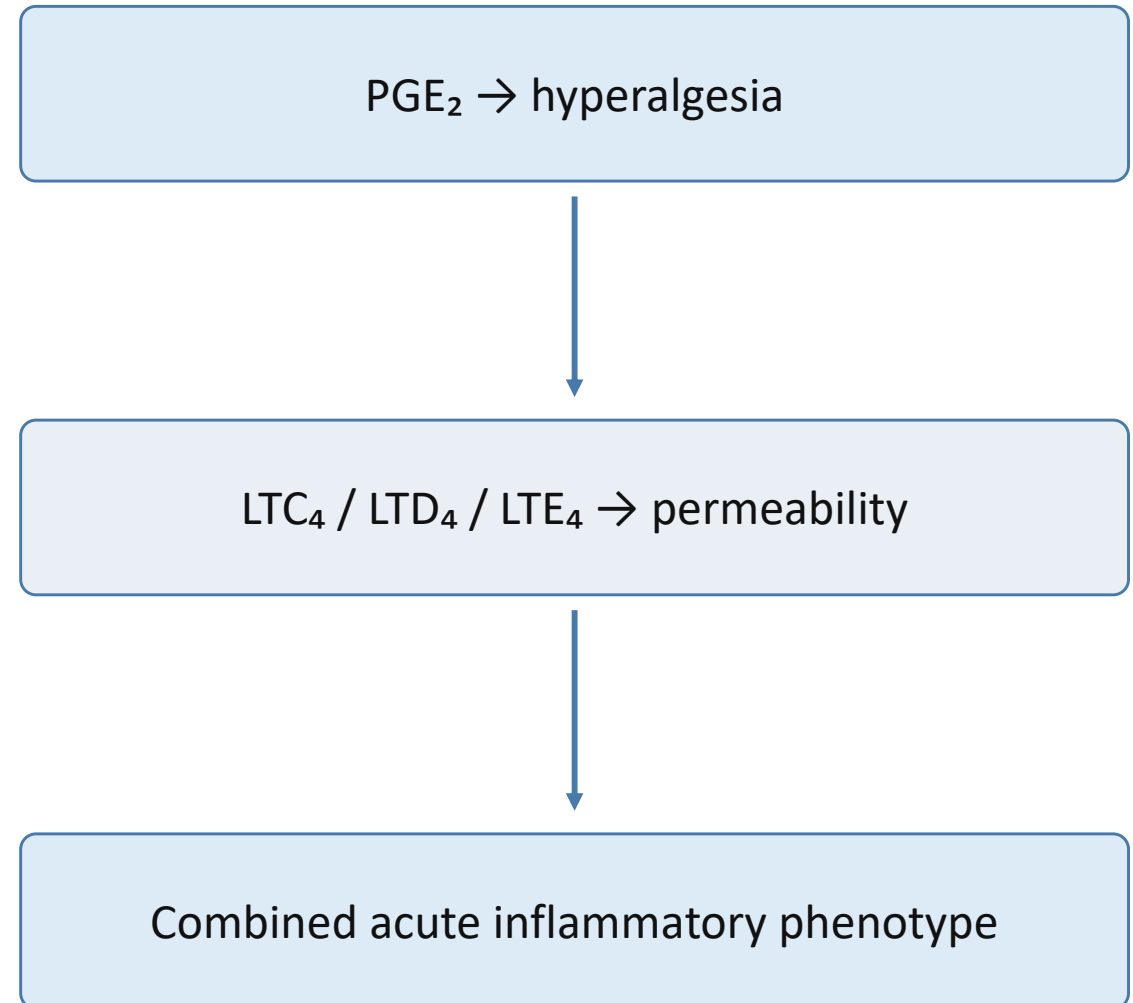
Tenderness ?

Venular leakage ?

Distinguish the mediators

Application explained: Different mediators, different actions

- PGE₂ provides a mechanism for heightened pain sensitivity
- Cysteinyl leukotrienes contribute to venular permeability
- Multiple mediators can cooperate in a single inflammatory lesion



Application: Selective enzyme inhibition

- Suppose endothelial PGI_2 is reduced while platelet TxA_2 persists
- Predict the direction of the platelet balance
- Identify the drug class that can produce this pattern

MECHANISM CHECK

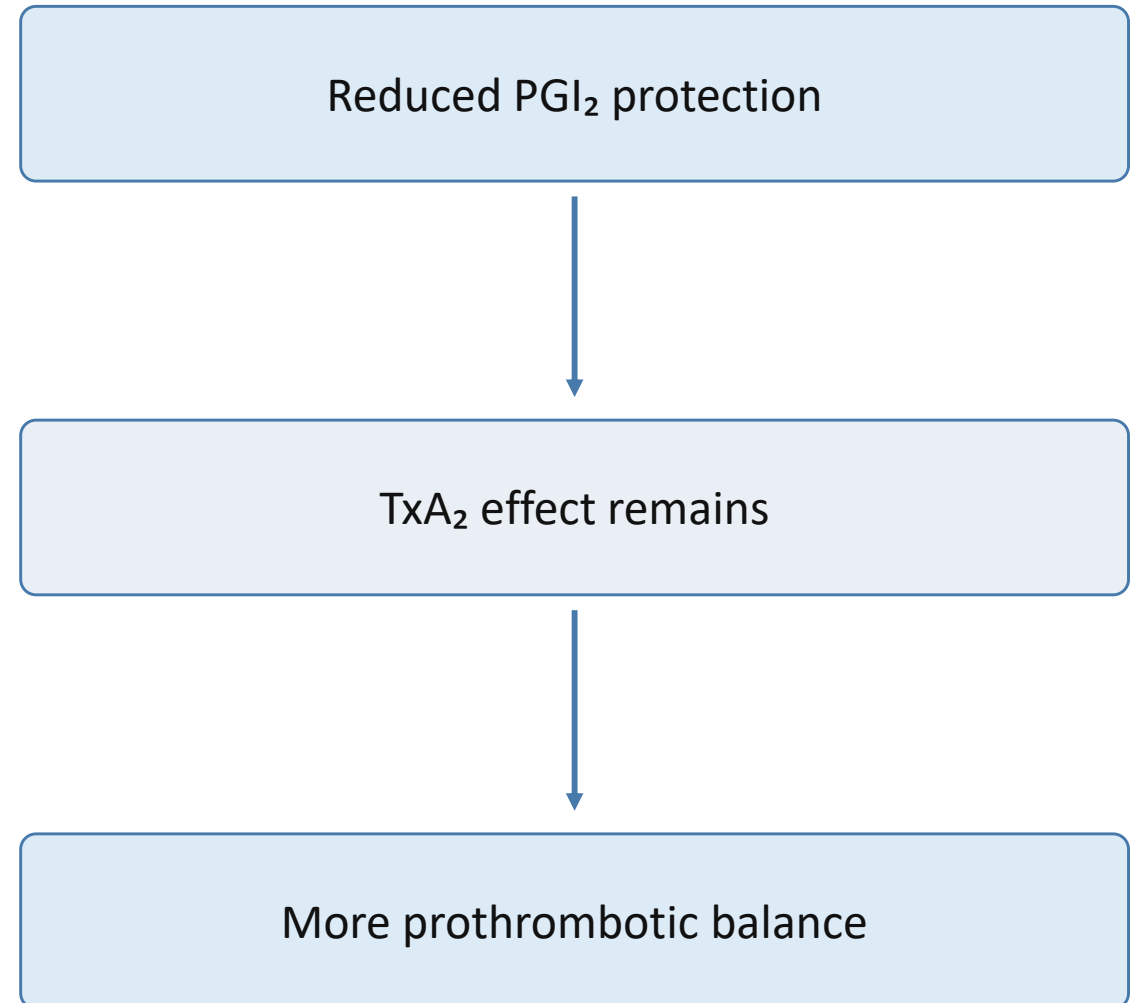
PGI_2 decreases

TxA_2 persists

Platelet balance ?

Application explained: The platelet balance shifts

- Loss of PGI₂ removes a restraint on platelet aggregation
- Persistent TxA₂ retains proaggregatory and vasoconstrictor effects
- Selective COX-2 inhibition is the mechanism highlighted by Robbins



Integrated enzyme-to-effect pathway

Membrane phospholipids

Phospholipase A₂



Arachidonic acid

Cyclooxygenase pathway

PGD₂: Vasodilation / edema; PGE₂: Pain / fever

PGI₂ ↔ TxA₂ → opposite platelet actions

Lipoxygenase pathway

LTB₄ → neutrophil recruitment and activation

LTC₄–E₄ → bronchospasm; Lipoxins → restraint

Five distinctions to retain

- PGE_2 : Hyperalgesia and fever; PGD_2 : Mast-cell vascular responses
- TxA_2 promotes aggregation; PGI_2 inhibits it
- LTB_4 activates neutrophils; $\text{LTC}_4\text{--E}_4$ constrict airways and increase permeability
- Lipoxins inhibit chemotaxis and adhesion; Drugs block synthesis or receptors

PGE_2 versus PGI_2

LTB_4 versus $\text{LTC}_4\text{--E}_4$

LTB_4 versus lipoxins

From inflammatory finding to mediator mechanism

- Pain sensitization and fever point toward prostaglandin E₂
- Platelet aggregation and vasoconstriction point toward thromboxane A₂
- Neutrophil recruitment and activation point toward leukotriene B₄
- Suppressed neutrophil chemotaxis and adhesion point toward lipoxins

PGE₂: pain / fever

TxA₂: aggregation

LTB₄: recruit / activate

Lipoxins: restrain recruitment