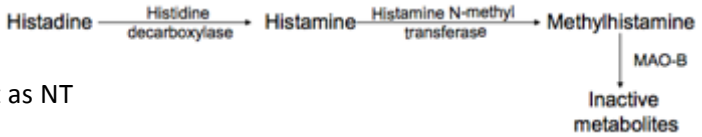
AUTOCOIDS: *Biologic factors that act like local hormones*

HISTAMINE:



- Stored in tissue **mast cells** (skin, lung, GI tract), CSF, & basophils
- Important mediator of immediate allergic & inflammatory reactions, gastric acid secretion, act as NT
- **Release:**
  - **INDUCED BY:** organic bases, **Tubocurarine**, Succinylcholine, Morphine, **Vancomycin**
  - **INHIBITED BY:**
    - **Physiologic Antagonists:** β agonists & **Epinephrine** – ↑cAMP & relax smooth muscle (*anaphylactic shock, acute allergic reaction)*
    - **Inhibition of Mast Cell Degranulation: Cromolyn sodium (specifically in *lung*)**, **Nedocromil (in *asthmatics*)** – inhibit IgE induced ↑Ca^{2+}

RECEPTORS	RESPONSE	PHYSIOLOGIC ACTION	DRUGS	ADVERSE
H1	**G_q:** ↑IP_3, DAG	**Smooth muscle, endothelium, brain** *Nitric Oxide* → ***Vasodilation*** *Contraction of endothelial cells* → ***Edema*** *Smooth muscle contraction* → ***↑GI motility, Bronchoconstriction, Abortion*** *Sensory nerve endings* → ***Pain + Itching***	Blocked by anti-histamines (**Pyrilamine**)	**"TRIPLE RESPONSE": Wheal & Flare** 1. Red spot (H_1) 2. Edematous wheal (H_1) 3. Red flare (H_1 + H_2) *Flushing, hypotension, tachycardia, HA, wheals, bronchoconstriction, GI upset* ***Contraindicated in asthmatics & ulcers***
H2	G_S: ↑cAMP	**Gastric mucosa, cardiac muscle, mast cells, brain** *Smooth muscle relaxation* *↑Heart rate* *Gastric parietal ells* → *↑cAMP* → *↑Ca^{2+}* → ***↑gastric acid secretion***	Antagonists ↓gastric acid secretion	
H3	G_i: ↓cAMP	**CNS: Presynaptic** *Feedback inhibition modulating release of NTs (hist, NE, serotonin, ACh)* **Myenteric plexus**		
H4	G_i: ↓cAMP	**WBCs & bone marrow** *Regulates neutrophil release BM, eosinophil shape, & mast cell chemotaxis*	Antagonists inhibit mast & eosinophil activity – ***treat asthma + allergies***	

ANTI-HISTAMINE: H1 Antagonists

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
1st Generation	*Reversible, competitive antagonist* Lipid Soluble: Rapidly absorbed (oral) Widely distributed: **CNS** Metabolized by LIVER	Allergic rhinitis, Urticaria Sleeping aids -- **SEDATIVE** Nausea & vomiting in pregnancy	– Sedation (excitation in children) – **Anti-muscarinic**: Urinary retention, rhinorrhea, blurry vision – α-Blocker: orthostatic hypotension, *associated mainly with phenothiazines* – **Torsades de pointes QT prolongation**
DIPHENHYDRAMINE (Benedryl)	ETHANOLAMINE	Cold medications Adjunct therapy in Parkinson's Motion sickness	
CHLORPHENIRAMINE	ALKALAMINE; *less sedating*		
2nd Generation	*Reversible, competitive antagonist* Do not penetrate CNS – *Lack sedative properties* Duration: **12-24 hours** Metabolized by LIVER	Seasonal allergies	
LORATADINE (Claritin)	PIPERIDINES		
CETIRIZINE (Zyrtec)	PIPERAZINE		
FEXOFENADINE (Allegra)	PIPERIDINES		

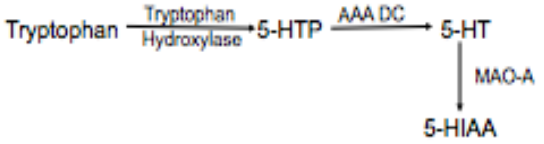
ANTI-HISTAMINE: H2 Antagonists

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
H2 Antagonists	*Reversible, competitive antagonist* **Block acid secretion induced by histamine**	PUD, Gastric Ulcers GERD Zollinger-Ellison Syndrome	Diarrhea, Dizziness, Rash, HA Granulocytopenia, thrombocytopenia, neutropenia, aplastic anemia Reversible hepatitis +/- jaundice
CIMETIDINE (Tagamet)	Oral absorption → **1st pass metabolism (liver)** Bioavailability only 50%* Secreted by kidneys – ↑*half life In renal failure*		**CNS (ELDERLY) –** somnolence, confusion, slurred speech, delirium **Anti-androgenic: GYNECOMASTIA, ↓sperm count, GALACTORRHEA** **INHIBITS CYP450 + ↓Hepatic blood flow** ** ↑ Warfarin, β-blockers, Ca^{2+} channel blockers, anti-arrhythmic agents*
RANITIDINE (Zantac)			*No drug interactions* ☺
FAMOTIDINE (Pepcid)			
NIZANTIDINE (Axid)	***Bioavailability of 90%**		

Green = Kaplan, Deja. First Aid, or Tulane

SEROTONIN (5-HT):

- Stored in **enterochromaffin cells** of GI tract, platelets, & CNS
- *Released via mechanical stretch + vagal stimulation + activation of platelets*
  - **INDUCED BY:** Chloroamphetamine
- Key role: regulation of BP, platelet aggregation, headache, & various CNS phenomena

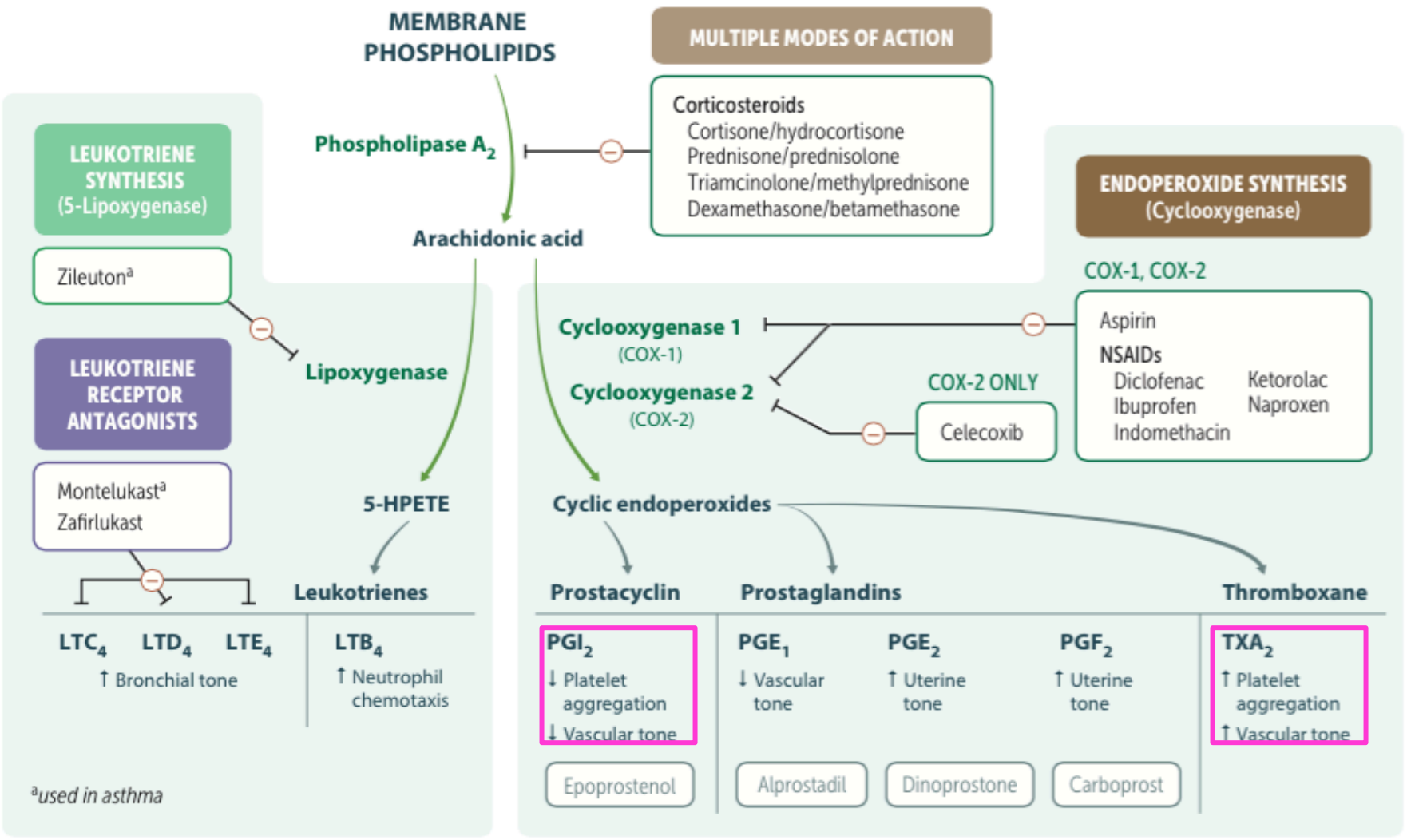


RECEPTORS	RESPONSE	PHYSIOLOGIC ACTION	DRUGS	ADVERSE
5-HT1	G_i: ↓cAMP	1B/1D: ***Vasoconstriction*** *in cranial vessels*	**Sumatriptan**: 5-HT1B/1D agonists	**SUBENDOCARDIAL FIBROPLASIA:** damaged valves + electrical conduction ***from chronic high levels***
5-HT2	G_q: ↑IP_3, DAG	2A: *platelet aggregation, contraction of smooth muscle, neuronal excitation, bronchoconstriction (in patients w/* ***Carcinoid Syndrome****)* 2B: ***vascular vasodilation via NO release*** – may stimulate migraine 2C: *modulates mood, feeding, repro, modulation of dopamine & NE release*		
5-HT3	**Na^+/K^+ ligand-gated channel**	In area postrema & on vagal afferents & enterochromaffin cells – *emesis*		
5-HT7	G_s: ↑cAMP	***Vasodilation of cranial vasculature*** → migraine		

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
SUMATRIPTAN (Imitrex)	**5HT1 (1B/1D/1F/1E) AGONIST** *Produces vasoconstriction in cranial vessels & prevents dural extravasation*	**ACUTE MIGRAINE HEADACHES**	Chest pain associated with coronary vasoconstriction ***Contraindicated in patients w/ coronary ischemia***
LORCASERIN	Direct acting **5HT2 (2C) AGONIST**	**WEIGHT LOSS**	
METHYSERGIDE (Sansert)	**5HT2 (2A/2B/2C) ANTAGONISIT**	**Prophylaxis: Migraraine**	GI, drowsiness, unsteadiness, confusion, hallucination, psychosis **INFLAMMATORY FIBROSIS** ***in chronic treatment*** – Retroperitoneal & pleuropulmonary fibrosis – Cardiac valvular damage
CYPROHEPTADINE (Periactin)	**5HT-2A ANTAGONISIT** H1 blocker, antimuscarinic, antidepressant	Post-gastrectomy dumping syndrome	
ONDANSETRON	**5-HT3 ANTAGONISTS**	Anti-emetic in chemotherapy	
FENFLURAMINE (MDMA*)	Halogenated amphetamine ***Directly stimulates 5-HT release***	***BANNED*** **APPETITE SUPPRESSANT**	Cardiotoxicity
FLUOXETINE (Prozac)	SSRI ***Inhibits 5-HT reuptake***	**Endogenous depression + OCD**	

Green = Kaplan, Deja. First Aid, or Tulane

Inflammatory mediators



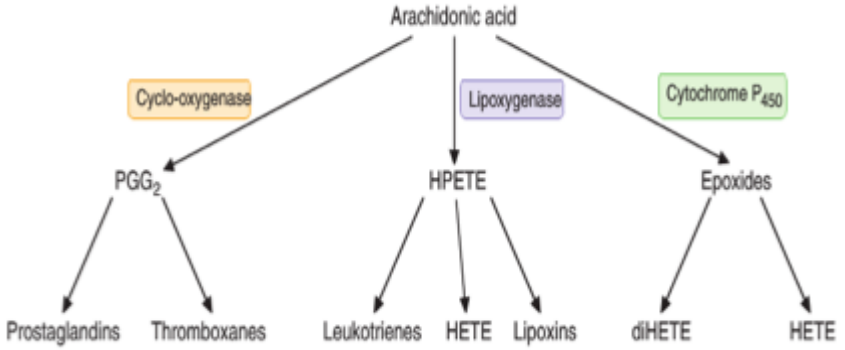
LTB_4 is a neutrophil chemotactic agent.
PGI_2 inhibits platelet aggregation and promotes vasodilation.

Neutrophils arrive "B4" others.
Platelet-Gathering Inhibitor.

Green = Kaplan, Deja. First Aid, or Tulane

EICOSANOIDS: Derivatives of Arachidonic Acid

- Not stored; synthesized & released as needed
- Half-lives of PGs are from 30 sec to a few minutes
- HETE = "**H**ydroxy-**E**icosa-**T**etra-**E**noic" acid



RECEPTOR	RESPONSE	CARDIO	BLOOD	RENAL	GI	LUNG	UTERUS	CNS
PGD	↑ cAMP							Induces natural sleep
PGE	↑/↓ cAMP	Vasodilator	↓Platelet aggreg	Diuresis Blocks ADH	↓Gastric acid ↑Mucus	Relax bronchial muscle	↑Uterine muscle tone	↑Temperature ↑Pain
$PGE_{2\alpha}$	↑ PLC, Ca^{2+}	Vasodilator	↓Platelet aggreg	↑Renin	↓Gastric acid	Relax bronchial muscle	↓Uterine muscle tone	↑Pain
PGI_2	↑ cAMP	Vasoconstrictor			Muscle contraction Diarrhea	Contract bronchial muscle	↑Uterine muscle tone	
TXA_2	↑ PLC, Ca^{2+}	Vasoconstrictor	↑Platelet aggreg			Contract bronchial muscle	↑Uterine muscle tone	
LTD_4	↑ PLC, Ca^{2+}	↓Blood volume	↑Leukocyte aggreg		Muscle contraction	Contract bronchial muscle + edema		↑Pain

EICOSANOIDS ANALOGS

DRUG	TYPE	INDICATION	ADVERSE EFFECTS
ALPROSTADIL	PGE1	Vasodilator, Inhibits platelet aggregation, Contracts uterine & intestinal smooth muscle, Patency of ductus arteriosis	Bradycardia, hypotension, fever
MISOPROSTOL	PGE1	Inhibits NSAID-induced gastric ulcers	
DINOPROSTONE	PGE2	Promotes uterine contractions & facilitates labor	Vomiting, diarrhea, fever, bronchoconstriction
LATANOPROST	PGF2α	Reduces intraocular pressure – useful in *glaucoma*	
EPOPROSTANOL	PGI2	Lowers BP – used in *pulmonary HTN*	Nausea, HA, hypotension, flushing

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
COX-1 & COX-2 Inhibitors	Potentiate anticoagulants because of their anti-platelet effects Reduce effects of diuretics & anti-HTN	**Anti-inflammatory, Anti-pyretic, Analgesic, Anti-platelet aggregation**	Excess PGE_2 + $PGF_{2\alpha}$ → Dysmenorrhea Gastric irritation + bleeding
ASPIRIN: **ACETYLSALICYCLIC ACID**	**IRREVERSIBLY** inhibits COX via *Acetylation*: – ↓Synthesis of TXA2 + PG – Converts Ω3 fatty acids EPA & DHA into resolvins (anti-inflammatory)	**Low Dose** ASA ↓risk of death due to thrombosis & MI	Gastric ulceration, Tinnitus (CN8) *Chronic use → renal failure* **REYE SYNDROME** in children treated w/ aspirin for a viral infection – *acidosis-alkylosis*
INDOMETHACIN (Indocin)	Reversibly inhibit COX1 & COX2 blocking PG synthesis	Closes PDA	Interstitial nephritis Gastric ulcer *(PGs protect gastric mucosa)* Renal ischemia *(PGs vasodilate afferent arteriole)*
IBUPROFEN (Advil)			
NAPROXEN (Aleve)			
Selective COX-2 Inhibitors		**Arthritis**	
CELECOXIB (Celebrex)	Reversibly inhibits COX2 in *inflammatory cells + vascular endothelium*	Rheumatoid Arthritis, Osteoarthritis	↓ Gastric irritation & ulceration (*spares COX1)* ↑Risk of thrombosis (spares TXA2)
ROFECOXIB (Vioxx)			↑Risk of MI
COX-3 Inhibitors			
ACETAMINOPHEN	Primary site of action: CNS *Reversibly inhibits COX*	Anti-pyretic & Analgesic (NOT anti-inflammatory) ***Used instead of Aspirin in Children w/ viral infection**	**OVERDOSE**: Hepatic necrosis – Metabolite (NAPQI) depletes glutathione & forms toxic byproducts
Anti-Leukotrienes			
ZILEUTON (Zyflo)	Inhibits 5'Lipoxygenase, blocking LT synthesis	**ASTHMA, Ulcerative colitis, Allergic rhinitis**	
ZAFIRLUCAST **MONTELUCAST**	Block LTD4 receptor	**Asthma**	

PLATELET ACTIVATING FACTOR (PAF) **A physiologic antagonist of PAF effects on platelets would be Prostacyclin*

BIOSYNTHESIS	DISTRIBUTION	MECHANISM OF ACTION	INDICATION	ADVERSE EFFECTS
Precursor: 1-O-alkyl-2-acyl-glycerophosphocholine	Restricted to blood cells, mast cells, renal medullary cells, vascular endothelial cells	Stimulates GPCRs, which activate phospholipase C, D, A_2	Vasodilation ↑Vascular permeability via contraction of **venular endothelial cells** Stimulates platelet aggregation Smooth muscle contraction	****MOST POTENT ULCEROGENIC SUBSTANCE KNOWN**