

Nervous system

• OVERVIEW •

Somatic \rightarrow ACh \rightarrow

Autonomic

- parasympathetic \rightarrow ACh \rightarrow

- sympathetic \rightarrow ACh \rightarrow

NA \rightarrow

Receptors

neuromuscular] cholinergic

muscarinic
adrenergic] noradrenergic

⊖ synthesis \leftarrow hemicholinium

⊖ storage \leftarrow vesamicol

⊖ release \leftarrow botulinum

⊖ synthesis \leftarrow metyrosine

⊖ storage \leftarrow reserpine

⊖ release \leftarrow guanethidine, amphetamine

⊖ reuptake \leftarrow cocaine, TCA

CHOLINOCEPTORS

(respond to ACh)

- (M₁) G_q-coupled
Nerves, gastric glands, brain
↳ MAIN EFFECT: secretion from salivary glands
- (M₂) G_i-coupled
Heart (atria, SA- and AV-node)
↳ MAIN EFFECT: decrease heart activity
- (M₃) G_q-coupled
Glands, smooth muscle, endothelium
↳ MAIN EFFECT: contracts smooth muscle + relaxes sphincters
- (M₄) G_i-coupled
CNS
- (M₅) G_q-coupled
CNS
- (N_N) } ANS ganglia, neuromuscular end plate
- (N_M) } ↳ MAIN EFFECT: Open Na⁺-K⁺ channels

ADRENOCEPTORS

(respond to NA)

- (α₁) G_q-coupled
Smooth muscle, glands
↳ MAIN EFFECT: contracts smooth muscle (& sphincters)
- (α₂) G_i-coupled
Nerve endings, some smooth muscle
↳ MAIN EFFECT: inhibits secretion, relaxes smooth muscle
- (β₁) G_s-coupled
Cardiac muscle, juxtaglomerular apparatus
↳ MAIN EFFECT: increase heart activity
- (β₂) G_s-coupled
Smooth muscle, liver, heart, uterus
↳ MAIN EFFECT: relaxes smooth muscle, increases heart activity
- (β₃) G_s-coupled
Adipose cells
↳ MAIN EFFECT: increases lipolysis

DOPAMINE RECEPTORS

(respond to D)

- (D₁) G_s-coupled
Smooth muscle
↳ MAIN EFFECT: ↑cAMP
- (D₂) G_i-coupled
Presynaptic nerve
↳ MAIN EFFECT: ↓cAMP

CHOLINERGICS

parasympathetic

AGONISTS

(↑ PSANS = parasympathomimetics)

DIRECT (ACh agonists)

- ACh
- Bethanechol ↑ bladder + intestinal motility
- Methacholine diagnose asthma
- Muscarine
- Pilocarpine] treat glaucoma + Sjögrens
- Cevimeline]
- Carbachol treat glaucoma

▼ **Toxicity**

- diarrhea
- urinary urgency
- vasodilation
- reflex tachycardia
- sweating
- bronchospasm
- miosis
- spasm of accommodation
- ↑ GI secretion → ulcers

INDIRECT (AChE inhibitors)

- Edrophonium diagnose myasthenia gravis
- Neostigmine] treat myasthenia gravis and reverse NM block
- Pyridostigmine] used in atropine overdose and acute glaucoma
- Physostigmine]
- Donepezil] used in Alzheimers
- Galantamine]
- Rivastigmine]
- Echothiophate] chronic glaucoma
- Parathion] insecticides and nerve gas
- Malathion]
- Sarin] course of death = respiratory failure

irreversible

▼ **Toxicity:**

- D - diarrhea
- U - urinary incontinence
- M - miosis
- B - bradycardia (+ reflex tachycardia)
- B - bronchoconstriction
- E - excitation of skeletal muscle
- L - lacrimation
- L - lethargy
- S - secretion (sweat, saliva...)

ANTIDOTE: Pralidoxime, Obdoxime (Atropine)

DIRECT

- Nicotine releases EPI from adrenals
- Varenicline] smoking cessation

Partial

▼ **Toxicity: (cholinergic crisis)**

- hypertension
- tachycardia
- nausea
- vomiting
- diarrhea
- sweating
- paralysis
- coma

DIRECT

- Succinylcholine used for muscle relaxation (depolarization block)

▼ **Toxicity:**

- muscle spasms
- hyperkalemia
- malignant hyperthermia

ANTAGONISTS

(↓ PSANS, TSANS)

M₁

(Gq-coupled)
GI-glands (↑ secretion)

MUSCARINIC

Pirenzepine] treat peptic ulcer
Telenzepine]

Atropine treats GI hypermotility + contractions ANTIDOTE: physostigmine
Scopolamine used in motion sickness
Benztropine used in Parkinson
Cyclopentolate treating eyedrop
Tropicamide diagnostic eyedrop
Ipratropium
Tiotropium
Acclidinium
Umeclidinum] used in asthma/COPD as bronchodilators

Darifenacine] used in urinary incontinence
Tolterodine]
Oxybutyni]

M₂

(Gq-coupled)
smooth muscle (bladder)
glands
lungs
eyes

▼ **Toxicity:**

- ↓ secretion: dry mouth
- hyperthermia in children (Belladonna alkalosis)
- mydriasis + cycloplegia: blurry vision
- tachycardia
- sedation
- urinary retention
- constipation

N_M

ganglions
adrenals
(blocks PSANS + SANS)

NICOTINIC

NOT USED CLINICALLY

- Hexamethonium treats hypertension
- Trimethaphan decreases blood pressure in surgery
- Mecamylamine used in smoking cessation

▼ **Toxicity:**

- block ANS
- postural hypotension
- dry mouth
- failure to ejaculate
- urinary retention

N_N

skeletal muscle

used prior to emergency surgery → flaccid paralysis

- Tubocurarine]
- Atracurium] izocholinic: histamine release
- Doxacurium]
- Mivacurium]
- Pancuronium]
- Vecuronium]
- Rocuronium]
- Pipecuronium]

steroid] ANTIDOTE: Sugammadex

ANTIDOTE: Neostigmine

▼ **Toxicity:**

- respiratory paralysis
- muscle pain in elderly and MG
- effects on → autonomic ganglia → histamine release → cardiac muscarinic receptors

ADRENERGICS

Sympathetic

AGONISTS

(↑SANS = sympathomimetics)

ANTAGONISTS

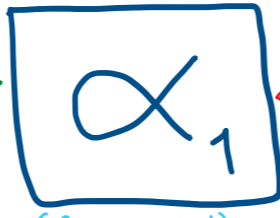
(↓SANS, ↑PSANS)

SELECTIVE α_1

Phenylephrine
Imidazoline
Naphazoline
Midodrine
Methoxamine

mydriasis
decongestant (nasal spray)

! Toxicity: [reflex bradycardia]



(Gq-coupled)
↑ contractility
vasoconstriction
↑ total peripheral resistance
↑ blood pressure
reflex bradycardia
↓ renin
urinary retention

SELECTIVE α_1

Prazosin Hypertension
Doxazosin Pheochromocytoma
Terazosin
Tamsulosin Benign prostatic hyperplasia

! Toxicity: [reflex tachycardia]

NON-SELECTIVE α

Phentolamine competitive
Phenoxybenzamine noncompetitive
Tolazoline

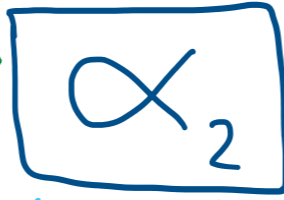
! Toxicity: [reflex tachycardia]

SELECTIVE α_2

α -Methyldopa
Clonidine ADHD
Guanabenz
Guanfacine
Methylnoradrenaline

Hypertension
Menopausal flushing
Migraine prophylaxis

! Toxicity: [platelet aggregation, ↓ insulin]



(Gi-coupled)
↓ norepinephrine
↓ insulin (don't give to diabetics!)
platelet aggregation
vasodilation
↓ blood pressure

SELECTIVE α_2

Yohimbine erectile dysfunction
Idazoxan

$\alpha_1 + \beta$ antagonists

Labetalol Hypertension
Carvedilol ↓ Mortality in heart failure

SELECTIVE β_1

Dobutamine
Xamoterol

congestive heart failure

! Cardiogenic shock



(Gs-coupled)
↑ heart rate
↑ stroke volume
↑ cardiac output
↑ renin
↑ pulse pressure

SELECTIVE β_1

Betaxolol
Esmolol
Metoprolol
Atenolol
Celiprolol
Nebivolol Vasodilator (NO-release)
Bisoprolol

NON-SELECTIVE ($\beta_1, \beta_2, \beta_3$)

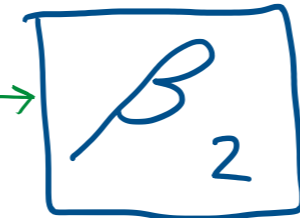
Isoproterenol

Heart block
Bronchospasms
Bradycarrhythmias

SELECTIVE β_2

Salmeterol
Albuterol
Terbutaline
Formoterol
Fenoterol

Asthma



(Gs-coupled)
vasodilation
↓ blood pressure
↓ total peripheral resistance
bronchodilation
↑ blood glucose
↑ insulin

SELECTIVE β_2

Butoxamine

NON-SELECTIVE (β_1, β_2)

Propranolol Sedative
Nadolol
Timolol Glaucoma
Sotalol

! Nephrotoxicity

SELECTIVE β_3

Solabergon
Mirabergon
Ambergron



(Gs-coupled)
↑ lipolysis

β -antagonists with partial agonist activity

Pindolol
Acebutolol β_1
Celiprolol
Penbutolol
Abetalol

! Less bradycardia/bronchoconstriction = safer in asthmatics!

INDIRECT AGONISTS

Amphetamine
Tyramine
Ephedrine
Cocaine
TCA

releasers
inhibits uptake

Norepinephrine

- works on all (β_1, β_2), so effects: \uparrow TPR, \uparrow TBP, \uparrow HR, \uparrow PP

Epinephrine:

- works on all, effects depend on dose:
- Low: $\beta_1 + \beta_2 \rightarrow \uparrow$ HR, \downarrow BP (vasodilation)
- Medium: $\beta_1 + \beta_2 + \alpha_1 \rightarrow \uparrow$ HR
- High: $\beta_1 + \beta_2 + \alpha_1 \rightarrow \uparrow$ BP (vasoconstriction)

Cardiac arrest
Hypotension
Anaphylaxis
Asthma

Dopamine vasodilation

- D₁ agonist - Fenoldopam Hypertensive crisis
- D₂ agonist - Bromocriptine ↓ Prolactin synthesis

! Toxicity - adrenomimetics:

- CNS \rightarrow restlessness, convulsions, tremor, cerebral hemorrhage, insomnia, anxiety
- Periphery \rightarrow hypertension, myocardial infarction, dysarrhythmias, heart failure, hyperglycemia

! Toxicity - Beta blockers:

- Bronchoconstriction (β_2)
- Heart failure
- Bradycardia (β_1)
- Hypoglycemia (β_2)
- Sedation
- Tremor
- Fatigue (β_1)
- Oculomucocutaneous syndrome

HISTAMINE

ANTAGONISTS

H₁

Gq-coupled

Allergy → ↓ blood pressure (vasodilation)
 ↑ edema
 ↑ bronchoconstriction
 bradycardia (↓ AV-node)
 ↑ mucus production
 pain
 itching



H₁ antagonists = antihistamines

- Uses → allergic reactions
 - motion sickness/nausea/vomiting
 - cold medication
 - Parkinson

- Non-competitive:
 - Ketotifen Conjunctivitis
 - Azelastine Nasal spray

- Competitive:
 - 1st generation
 - Hydroxyzine Anxiety
 - Cyclizine
 - Meclizine
 - Dimenhydrat
 - Diphenhydramine ↓ chemotherapy induced vomiting
 - Promethazine more sedative
 - Cyproheptadine Also 5HT-2 antagonist
 - Chlorpheniramine
 - Clemastine
 - Antazoline Nasal spray and eye drops

2nd generation Only used for allergy
 Cetirizine
 Fexofenadine
 Loratidine

- **Toxicity:**
 - Sedation
 - Antimuscarinic effects
 - Orthostatic hypotension
 - Arrhythmia (VERY RARE!)

H₂

Gs-coupled

↑ gastric acid secretion
 ↑ SA-node rate
 ↓ histamine release (negative feedback)
 (similar to β₁)

H₂ antagonists = ↓ gastric acid secretion

- uses → peptic ulcer disease (+ misoprostol (PGE₁))
 - GERD
 - Zollinger-Ellison syndrome

- Cimetidine [diarrhea, rash, dizziness, fatigue, constipation, myalgia]
- Ranitidine
- Famotidine
- Nizatidine

H₃

G_i-coupled

modulates peptide release in response to inflammation

H₄

G_i-coupled

chemotaxis - leukocytes + mast cells

SEROTONIN

5-HT = 5 Hydroxytryptamine

LOCATION

- Gastrointestinal tract
 - Enterochromaffin cells
 - Enteric neurons
- Platelets
- CNS neurons

Metabolite: 5-HIAA
 Metabolized by: MAO-A

SSRIs - selective serotonin reuptake inhibitors
 Antidepressants

ACTIONS

Physiological: peristalsis
 vomiting
 inflammatory mediators

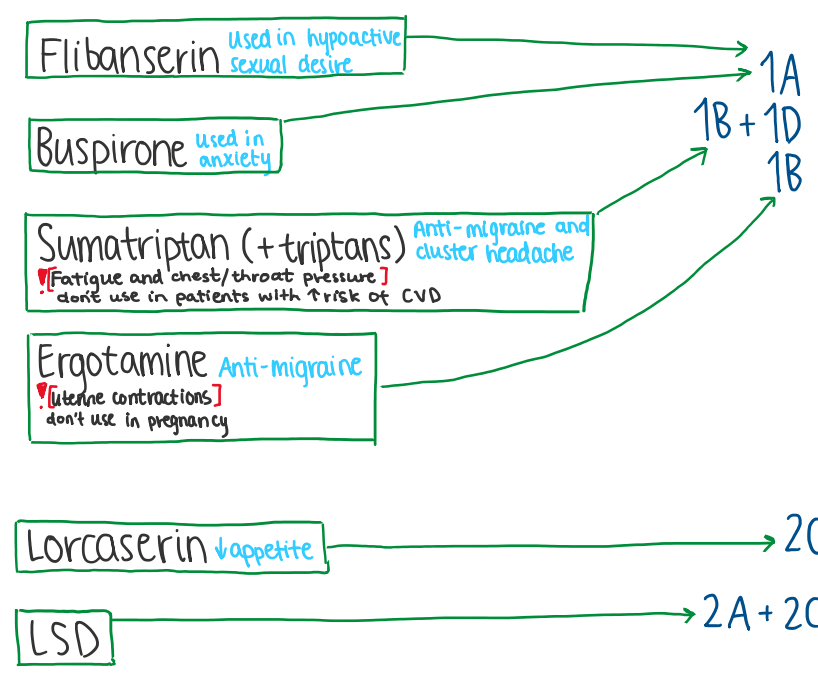
Pathophysiological: migraine
 carcinoid syndrome
 CNS disturbed function

Gastrointestinal tract → ↑motility
 ↑fluid secretion

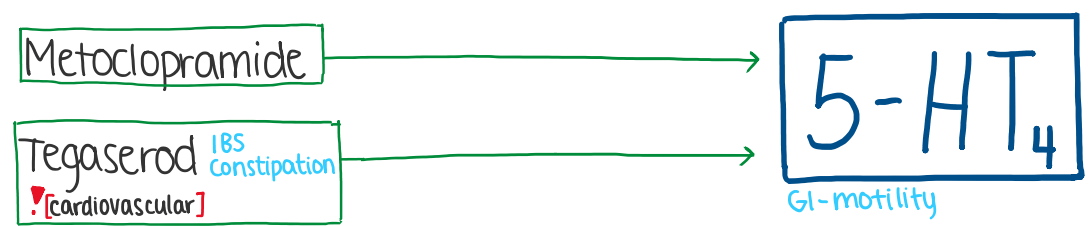
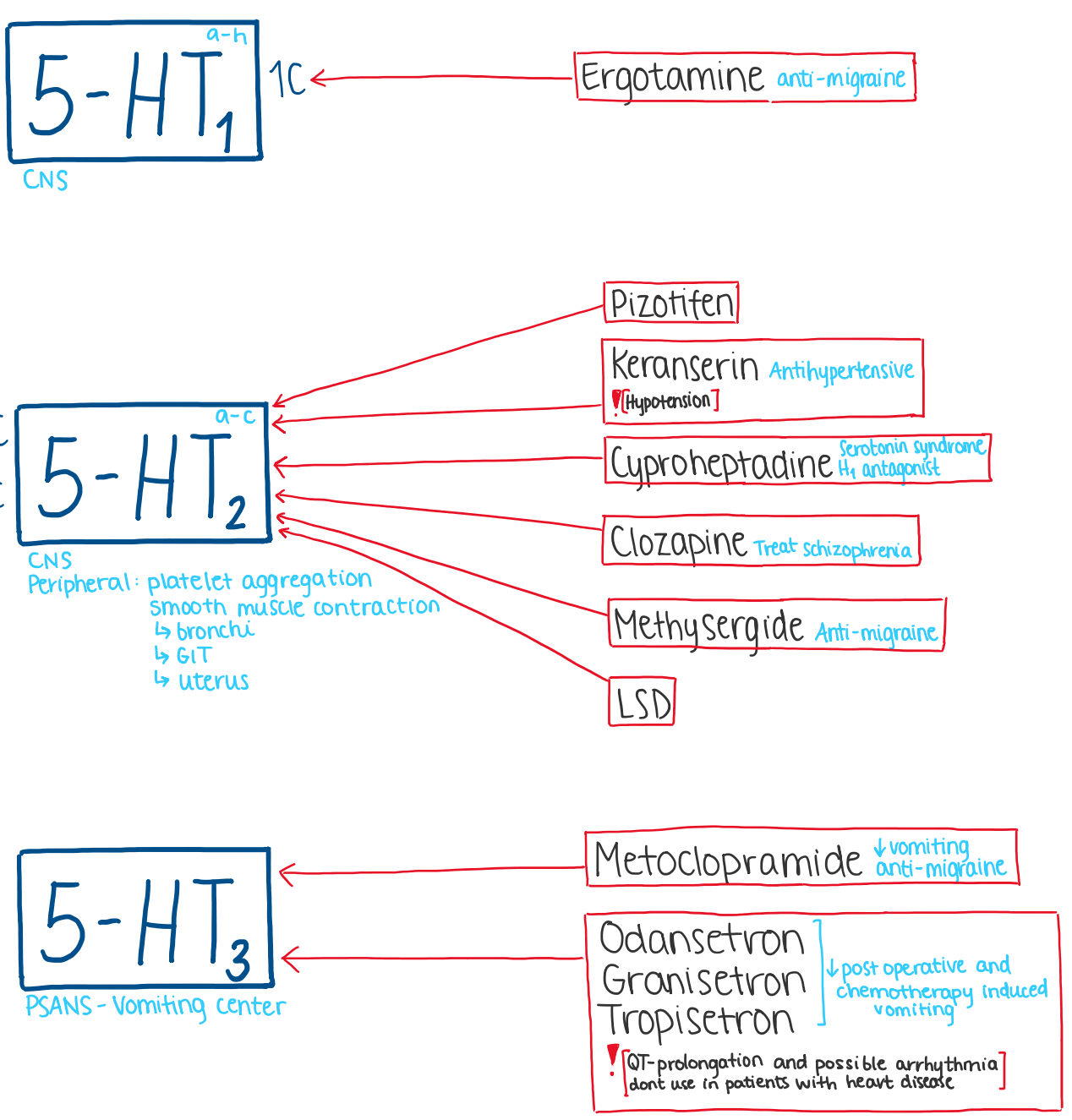
Smooth muscle → constriction

Platelets → aggregation

AGONISTS



ANTAGONISTS



• NITRIC OXIDE •

ENDOGENOUS

Synthesized by NOS
(Arginine → Citrulline + NO)

Types of NOS:

- Isoform 1 → bNOS, cNOS, nNOS
in epithelial and neuronal cells
- Isoform 2 → iNOS, mNOS
in macrophages and smooth muscle cells
- Isoform 3 → eNOS
in endothelial cells

⊖ Arginine analogs
⊕ Muscarinic agonists,
histamine, others.

EXOGENOUS

NO released from drugs
(NO donors)

EFFECTS

Smooth muscle → relaxation
→ vasodilation
→ physiologic: erectile tissue
→ pathophysiologic: hypotension in septic shock

Cell adhesion → ↓ platelet aggregation
↓ neutrophil adhesion

neurotransmitter

tissue injury = synthesis → ↑ inflammation
→ ↑ COX-2 → ↑ PG

apoptosis

parasite reactions

DRUGS

[NO gas] ⊕ guanylyl cyclase → ↑ cGMP → smooth muscle relaxation
used in pulmonary hypertension and neonatal hypoxic respiratory failure

[Nitroglycerin] NO donor
↓ arterial and venous tone
↓ preload and afterload
used to improve mismatch in oxygen demand and supply (e.g. ischemia)
and also to treat pulmonary edema
! [Methemoglobinemia]

[Sodium nitroprusside] NO donor
used in hypertensive emergencies to ↓ BP

[Molsidomine $\xrightarrow{\text{liver}}$ Linsidomine] Releases NO
used to treat angina pectoris

[Sildenafil] Viagra
Treats erectile dysfunction and pulmonary arterial hypertension

[Tadalafil] Like sildenafil - also treats benign prostatic hyperplasia (BPH)

VASOACTIVE PEPTIDES

ANGIOTENSIN

Renin inhibitor
 Aliskiren *Hypertension*
 ⚠️ [Angioedema and renal impairment]

ACE inhibitors
 Captopril *Hypertension, Heart failure, Diabetic kidney disease*
 Enalapril
 Fosinopril
 Quinopril
 Trandolapril
 Lisinopril
 Ramipril
 Perindopril
 ↑ MI survival
 ⚠️ [Cough, teratogenic, hyperkalemia]

Ang II AT₁ receptor inhibitors
 Losartan
 Valsartan
 Irbesartan
 Candesartan
 Telmisartan
 ⚠️ [Teratogenic, hyperkalemia (no cough!)]

BRADYKININ

Vasodilator produced by kallikreins
 Acts via β_1 and β_2 receptors → inflammation + asthma
 Degraded by ACE
 Causes edema and pain

Kallikrein inhibitor
 Ecallantide *Hereditary angioedema symptoms*

β_2 -receptor antagonist
 Icatibant *Acute attacks of hereditary angioedema*

VIP

Vasoactive Intestinal Protein
 Vasodilator + neurotransmitter

NPY

Neuropeptide Y
 Vasoconstrictor

ENDOTHELIN

Vasoconstrictor acting via ET_A and ET_B receptors
 More potent than NE
 Stimulate release of natriuretic peptide (ANP and BNP)
 + smooth muscle proliferation

ET_A and ET_B receptor antagonist
 Bosentan *Pulmonary hypertension*
 ⚠️ [Hepatic impairment, teratogenic]

SUBSTANCE P

Arteriolar vasodilator
 Stimulant of veins + intestinal/airway smooth muscle

Capsaicin *Topical use, Releases subst. P*

EICOSANOIDS

PROSTAGLANDINS

Type E: **PGE₁** Infusion to maintain ductus arteriosus open in infants before surgery
 Injected into penis to treat erectile dysfunction
 Protective effects on gastric mucosa - ↑HCO₃⁻ and mucus secretion
 ↳ used in peptic ulcer disease
 Vasodilation
 Uterine contractions → used as abortifacient

* Drugs: **Misoprostol and Alprostadil** *Used with NSAIDs*

PGE₂ Vasodilator, bronchodilator
 Released during menstruation, can cause dysmenorrhea
 Physiologic role in labor - softening of cervix at term
 Also cause uterine contractions → used as abortifacient
 Used to maintain ductus arteriosus

* Drug: **Dinoprostone**

PGE₃

Type F: **PGF_{1α}**

PGF_{2α} Released during menstruation, can cause dysmenorrhea
 Physiologic role in labor - causes uterine contractions → also used as abortifacient
 Reduces intraocular pressure, topical use in glaucoma
 Vasoconstrictor, bronchoconstrictor

* Drugs: **Latanoprost, Carboprost-Tromethamine**

PGF_{3α}

PROSTACYCLINS

PGI₂ vasodilation, bronchodilation
 used in pulmonary hypertension
 prevents platelet aggregation in dialysis machine

* Drugs: **Epoprostenol and Treprostinil**

THROMBOXANES

TXA₁

TXA₂ ↑platelet aggregation
 activation of new platelets
 vasoconstriction, bronchoconstriction

TXA₃

LEUKOTRIENES

LTA₄

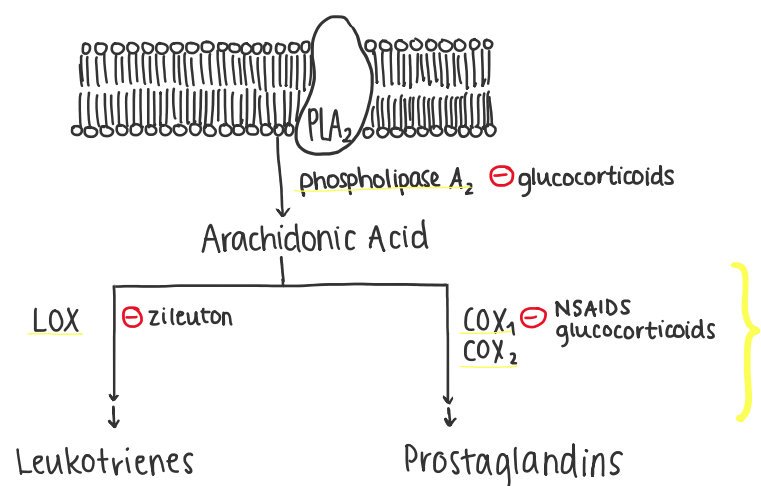
LTB₄ Chemotaxis in inflammation (neutrophils)
 Induce adhesion+activation of leukocytes on endothelium

LTC₄ Bronchoconstriction
 Slow Reacting Substance of Anaphylaxis (SRS-A)

LTD₄ Bronchoconstriction, vasoconstriction, smooth muscle contraction
 ↑vascular permeability
 SRS-A

LTE₄ Involved in inflammation
 Respiratory diseases → ↑LTE₄
 ↳ e.g. ↑urinary LTE₄ in severe asthma attacks

• NSAIDS •



COX₁: always expressed, functions as "housekeeper"
 TXA₂, PGE₁, gastric cytoprotective prostaglandins
 COX₂: expression induced by inflammation
 PGI₂, PGE₂, prostaglandins increasing vascular permeability and pain sensitivity
 Both: prostaglandins dilating afferent arteriole

Effects of NSAIDS:

- ↓ inflammation
- ↓ prostaglandin synthesis
- antipyrogenic
- analgesic
- non-selective → ↓ polyps, colon cancer risk
- ↓ cytoprotection in GIT

COX INHIBITORS

role is to inhibit COX-2, but some are non-selective

Aspirin effects:

- LOW DOSE → ↓ platelet aggregation used post MI
- INTERMED. → antipyretic + analgesic
- HIGH → anti-inflammatory

Non-selective

- Aspirin ! obs. children w/ viral inf. → ↑ risk of Reye's syndrome
- Salicylic acid] irreversible
- Diclofenac] Treat dysmenorrhea
- Diflunisal] Symptomatic treatment of RA
- Etodolac
- Fenoprofen] Less GI bleeding
- Flurbiprofen
- Ibuprofen
- Ketoprofen
- Indometacin] Treat acute gout, Ductus arteriosus closure
- ! Hematologic reactions
- Ketorolac] Use < 72h, systemic analgesic
- Metenamate
- Nabumetone] ↓ GI side effects
- Naproxen] Treat gout, dysmenorrhea, RA
- Piroxicam] Long duration
- Meloxicam

! Dose-dependent (worse with aspirin!)

| NORMAL | HIGH | VERY HIGH |
|-----------------------|-------------------------|----------------------|
| • GI upset + bleeding | • tinnitus | • metabolic acidosis |
| • gastric ulcers | • vertigo | • dehydration |
| • renal effects | • hyperventilation | • hyperthermia |
| • ↑ bleeding time | • respiratory alkalosis | • coma |
| • aspirin hypersens. | | • death |

Selective (COX₂ inhibitors)

- Celecoxib
- Valdecoxib
- Etoricoxib
- ! [Since no COX-1 effects → ↑ risk of ischemic CVD]

Acetaminophen

- Weak COX-inhibitor
- Effects → same as aspirin intermediate dose
- used in aspirin hypersensitivity and children with viral infection
- ! [Hepatotoxicity]

RHEUMATOID ARTHRITIS

DMARDs (disease modifying anti-rheumatic drugs) → slow down/reverse joint damage

* slow acting - 6 weeks → 6 months

* ALL can cause fatal toxicities, so monitoring is mandatory!

Cytotoxic drug

Methotrexate ↓ immune cells

! [Nausea, mucosal ulcer, teratogenic, hematotoxicity]

Interfering with macrophages

Auranofin oral } gold salts

Aurothioglucose parental

Penicillamine ↓ T-cells + IL-1 prevents collagen crossing

! [GI-upset, allergy symptoms, renal damage, hematologic effects in overdose]

Inhibitors of TNF α

Adalimumab

Infliximab

Golimumab

Etanercept

! [Same as for rituximab]

Interfering with T-cells

Hydroxychloroquine ! [CV collapse, convulsions]

Chloroquine Antimalaria 2nd line treatment of RA

Leflunomide Inhibits pyrimidine synthesis

Sulfasalazine Also used in IBD 2nd line

Abatacept Induces negative feedback → deactivation

! [Headache, GI disturbances, drowsiness, upper respiratory tract infection]

Interfering with B-cells

Rituximab Anti CD-20 Used with methotrexate

! [Carcinogenesis, mutagenesis, ↓ fertility]

Interleukin receptor antagonists

Anakinra ! [Injection site reaction, worsening of RA, upper resp. infection, headache, nausea, diarrhea, sinusitis]

Tocilizumab IL-6 antibody ! [upper resp. infection, headache, ↑ALT, hypertension, nasopharyngitis]

Glucocorticoid receptor agonist

Prednisone Inhibits leukocyte infiltration

Sophie H. 7.

• GOUT •

Pseudogout is also treated as gout!

Anti-inflammatory drugs
NSAIDs *Used in acute gout*
Colchicine *used in chronic gout and in Mediterranean fever*
↓ microtubule assembly
 ⚠️ [diarrhea, liver + kidney damage]

Uricosuric agents
Probenecid *Used in chronic gout*
Inhibits uptake
 ⚠️ *worsening of gout, hypersensitivity, inhibition of renal secretion of acid*
Aspirin *At very high dose*

Xanthine oxidase inhibitors
Allopurinol *Irreversible*
 ⚠️ [Steven Johnson syndrome, GI upset, rash, vasculitis, bone marrow dysfunction]
Febuxostat *Reversible, long term, used for chronic gout*
 ⚠️ [GI upset, headache, liver function abnormalities]

Converting uric acid → soluble allantoin
Rasburicase *often post-chemotherapy*
Pegloticase *Long term drug (2-4 weeks)*
i.v. drug
 ⚠️ *Anaphylaxis, infusion reaction, ↑gout flares, worsening of heart failure*

Inhibition of uric acid reuptake
Lesinurad *Inhibits URAT1 and OAT4*
Used together with XO inhibitor

Sofie H. 7.