

Steroids

Cell-membrane phospholipids:
(A.A is a part of phospho)

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activated by
chemical, mechanical
or physical stimuli
or by inflammation
(mediator (5a))

phospholip.
-ases

Arachidonic Acid (released from
phospholipid).

• edema
• phagocytosis
• mucus secretion

COX-1 & COX-2

inhibitors

(Aspirin &
indomethacin
inhibit)

COOxygenase - enzyme

PG₂

PGH₂

precursors for other
biolog. signif.
molecules

Endothelial
cells contain

Prostacyclin
synthetase

Prostacyclin
(PGI₂)

causes vasodilb;
inhibit platelets
aggregation

Thromboxane

A₂
(TXA₂)

[Platelets
contain
Thromboxane
synthetase]

cause vasoconstr;
promote platelets
aggregations broncho
constriction

major
metabolite
in
mast
cells

PGD₂

PGF_{2α}

PGE₂

vasodilation
increased vascular
permeability

Potentiate edema

augment
pain
sensitivity
and
inflammatory
cytokines to
cause
fever

Lipoxin
A₄
(LXA₄)

• inhibit Neutrophils adhesion
and chemotaxis

anti-inflamm
mediators

Lipoxin B₄
(LXB₄)

• endogenous antagonist of leukotenes

• responsible for physiologic produc.
of prostanoids (Tx and PGI₂, PA).

• It is constitutive enzyme that
regulate normal cellular process.
e.g gastric cytoprotective effect, vascular
homeostasis, platelet aggre & reproduc.
& kidney functions

∴ "Both're different binding site shape"

COX-II

• cause elevated production of prostanoids
that occur at site of inflamm.

• COX-II is constitutive enzyme
expressed in brain, kidney &
bone, expression at other
sites rises during state of
chronic inflamm.

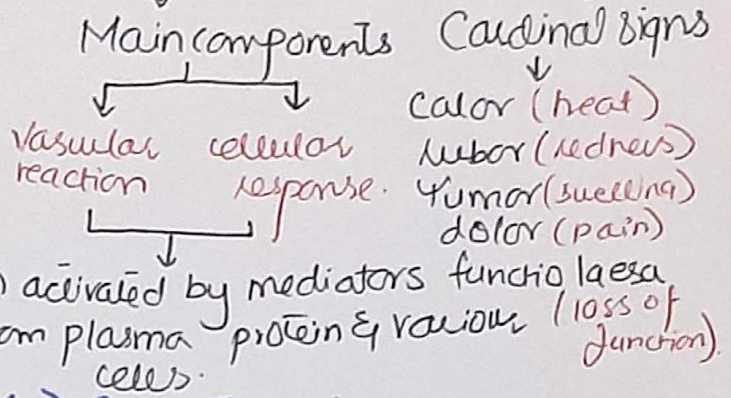
• Its expression is induced by
TNFα and IL-1.

• Inhibited by Glucocorticoids

INFLAMMATION → meaning burning.

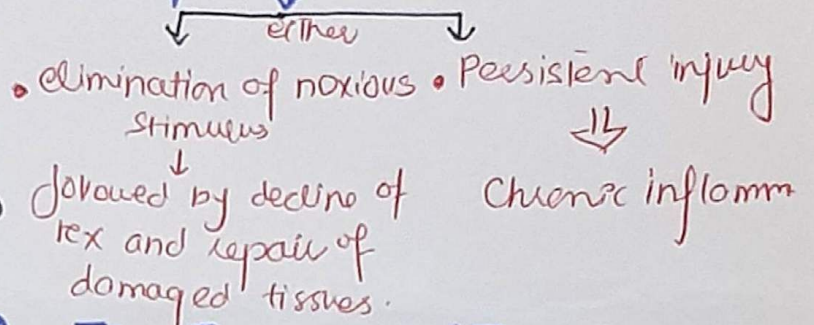
It is a defensive host response to foreign invaders and necrotic tissues
BUT, itself capable of causing tissue damage.

Youtube channel
PHARMACO-STUDY

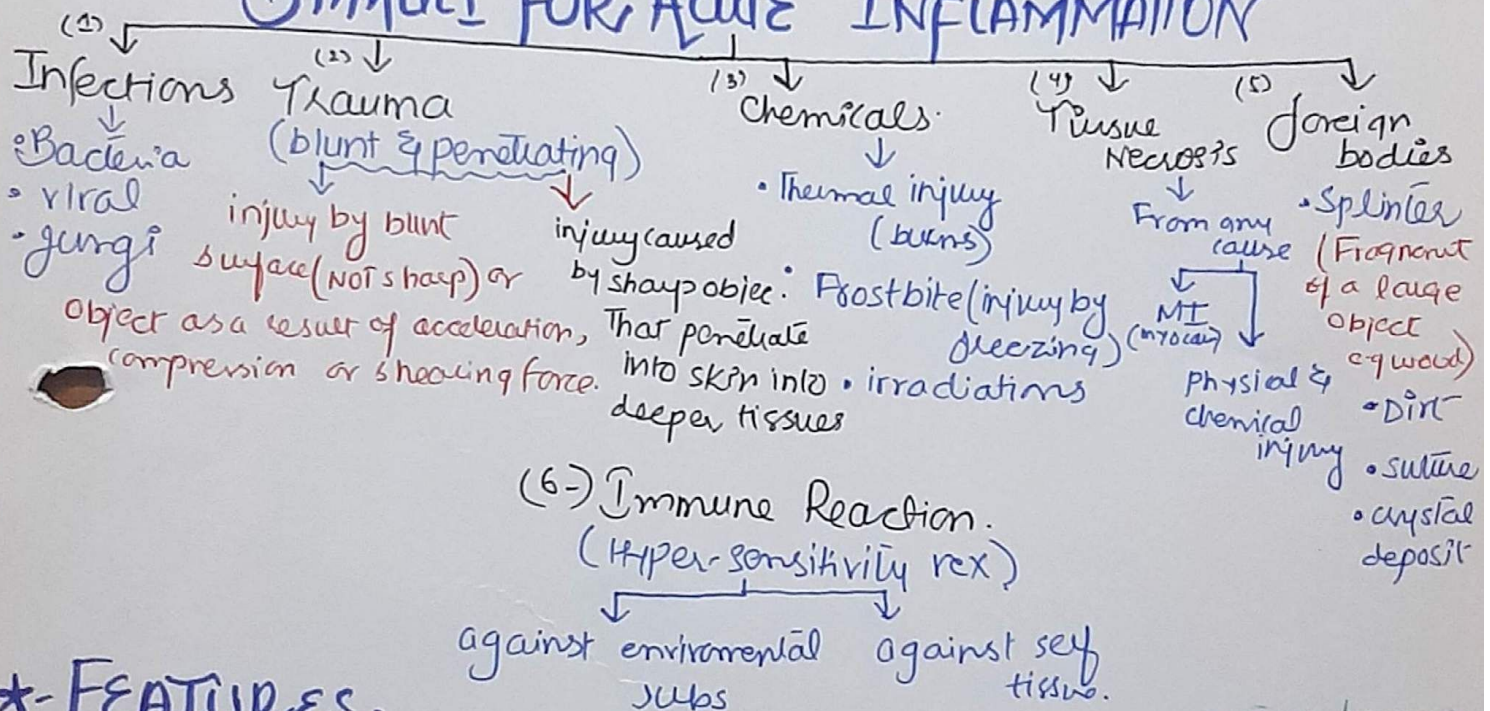


STEPS (5) & OUTCOMES

- 1- Recognition of injurious agent
- 2- Recruitment of leukocytes
- 3- Removal of agent
- 4- Regulation (control of response)
- 5- Resolution (Repair).



STIMULI FOR ACUTE INFLAMMATION



*- FEATURES:-

- 1) ONSET
- 2) cellular infiltrate
- 3) Tissue injury, fibrosis
- 4) Local & systemic signs

ACUTE

Fast (min → hrs)
mainly neutrophils
mild & self-limited

CHRONIC

slow - days.
monocytes / macro & lympho.
severe & progressive.

less: maybe subtle

*- Severe acute inflammation = dominant. AC

*- Acute Stage Sub acute Chronic

∴ neutrophils / macrophages are the phagocytes

Recognition of Microbes, Necrotic cells & foreign subs.

PATTERN-RECOGNITION RECEPTORS

Toll-like receptors

- Microbial sensors
- Name for founding member called Toll, discovered in *Drosophila*.
- The 10 mammalian TLRs, which recognise the products of bacteria (endotoxin & DNA), viruses (double strand RNA) and other pathogen

Are located in plasma membrane & endosomes
↓
collection of intracellular sorting organelles in eukaryotic cells

* RECOGNITION ⇒ Activate Transcription Factors

That stimulate production of membr. protein

These proteins include:

- mediator of inflamm. (cytokines)
- antiviral cytokines
- that stimulate lymphocyte activation

* - Natural Killer cell recognize virally infected cells

INFLAMMASOME

- multiprotein-cytoplasmic complex
- 1- recognizes the products of dead cells (e.g. uric acid, extracellular ATP, crystals and some microbial products)

2- Trigger the activation of enzyme CASPASE-1

↓
cleave precursor form of inflamm. cytokine Interleukin-1β (IL-1β) into active form (imp mediator of leukocyte recruit. in acute inflamm. response)

3- leukocyte phagocytose & destroy the dead cells.

* Gout: - Caused by deposition of urate crystals — which're ingested by phagocytes and activate inflammasome → IL-1β

↓
acute inflamma.
Thus - IL-1 antagonist → effective treatment in case of resistance to conventional anti-inflamm. therapy

* Atherosclerosis: - cholesterol crystals & free fatty acids also activate inflammasome — suggest that IL-1 play role in common diseases like atherosclerosis → Thus 'its antagonist' is effective in their treatment

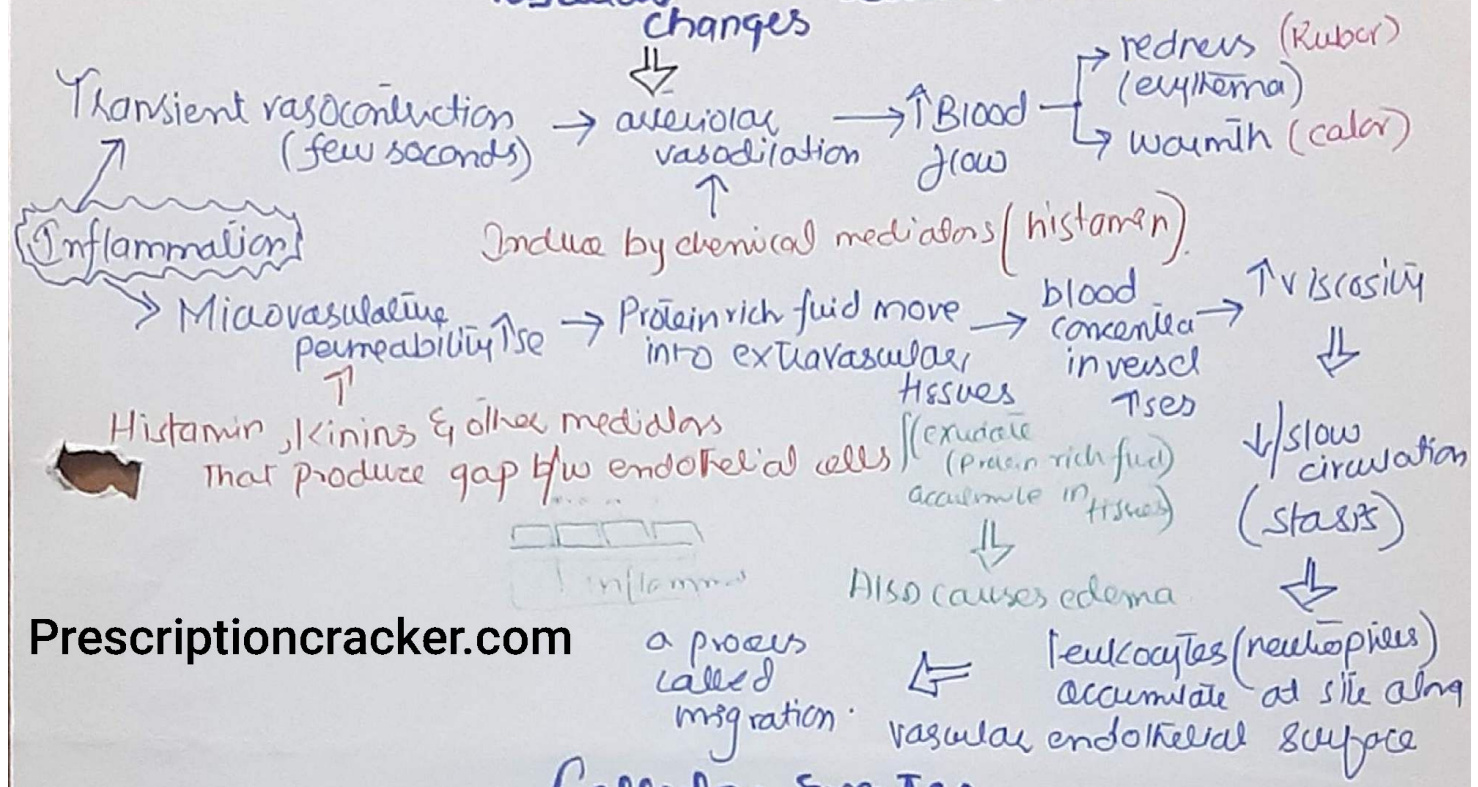
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es
and

Do watch lectures on Pharmaco-Study YouTube channel

EVENTS OF ACUTE INFLAMMATION

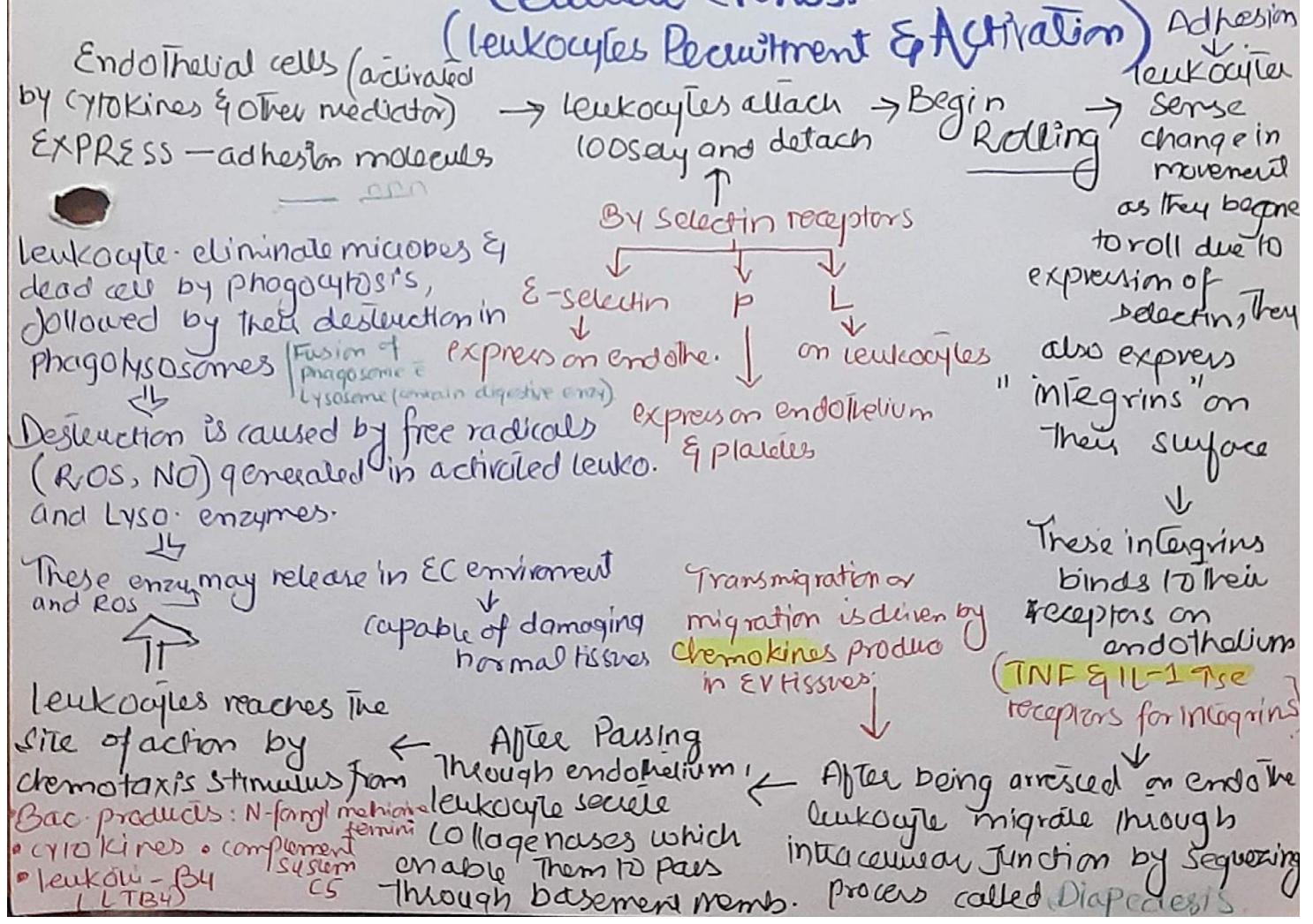
Rapidly deliver leukocytes & plasma proteins to site of injury

Vascular changes Cellular events



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Cellular Events: - (Leukocytes Recruitment & Activation)



CLINICAL EXAMPLES OF Leukocyte-INDUCED INJURY.

* DISORDER

CELL & MOL. INVOLVED IN INJURY

o Acute

- ARDS (acute respir. distress syndrome)

neutrophils

- Acute Transplant rejection

Lymphocytes antibodies & complement

- Asthma

Eosinophils; IgE antibodies

- Glomerulonephritis

Antibodies & complement; neutro. monocytes

- Septic shock

Cytokines.

Pharmaco- Study

o Chronic

- R. A

Lymphocytes, macroph. antibodies

- Asthma

Eosinophils; IgE antibodies

- Atherosclerosis

Macro and lympho.

- Chronic Transplant rejec.

Lympho, macro, cytokines.

- pulmonary fibrosis

Macro; fibroblasts.

CELL-DERIVED MEDIATORS

Vasodilatory Amine

Histamine, Serotonin

vasodilation & ↑ se
Vasculopermeab.

Arachidonic Acid
Metabolites

• Products from
arachidonic acid
metabo. affect variety of biolo.
processes including
INFLAMMATION AND
HEMOSTASIS

• AA. metab. also called eicosanoids becoz derived
from 20-C F.A; Greek eicosa = 20

• Their synthesis ↑ at site of inflamm. response, and agents that inhibit
their synthesis also diminish inflammation

• Leukocytes, M.C, endothelial cells and platelets → are major source of
A.A. metabo

Cytokines

usually act at
short range

• leukocyte recruit
• and migration
⇒ IL-1, IL-6
TNF and
chemokines.

ROS

• microbial killing
• tissue injury

NO

vasodilation
↑ lysosomal
enzym

ACTION

• vasodilation

• vasoconstriction

• ↑ se vascular permeab.

• chemotaxis, leukocyte adhesion

EICOSANOIDS

PGI₂, PG E₁, PG E₂, PG D₂
(Prostacyclin)

Thromboxane A₂, LTC₄, D₄, E₄

LTC₄, D₄ E₄

LTB₄, Hydroxyeicosatetraenoic acid (HETE)

* ACTIONS OF PRINCIPLE MEDIATORS OF INFLAMMATION

* Mediator

Source

Action

(cell-derived)

- 1) Histamine
 resident cell of connective tissue - contain histamine & heparin + in granules
 Mast cells, Basophil, platelet
 • vasodilation, ↑ se vascular permeability
 • endothelial activation
 • vasoconstriction
- 2) Serotonin
 Platelets
 vasoconstriction
- 3) Prostaglandin
 Mast cell, leuko.
 vasodilation, pain, fever
- 4) Leukotenes
 M.C, leukocytes
 ↑ se permeability, chemotaxis, leukocyte adhesion + activation
- 5) Platelet-Activating Factor
 Leukocyte, M.C
 vasodilation, ↑ permeability, chemotaxis, leukocyte (adhesion + activation), degranulation (platelet release inflammatory molecules)
- 6) Reactive-O₂-species
 Leukocytes
 oxidative burst
 killing of microbe & tissue damage
- 7) Nitric oxide
 Endothelium, macrophages
 vascular smooth muscle relaxation
 killing of microbes
- 8) Cytokines (TNF, IL-1, IL-6)
 macro, endothelial cells, mast cells
 Local: endothelial activation (express adhesion mol)
 Systemic: fever, metabolic aberr.
 Hypotension (shock)
- 9) Chemokines
 leukocyte, activated macroph.
 chemotaxis, leukocyte activation

PLASMA-PROTEIN-DERIVED

- Activated when microbe enters blood

1) complement

plasma (Produce in liver)

- leukocyte chemotaxis & activation
- Direct target killing (MAC)
- vasodilation

membrane attack complex or terminal complement complex

Complex of protein formed on surface of pathogen cell mem due to host complement activation

2) Kinins

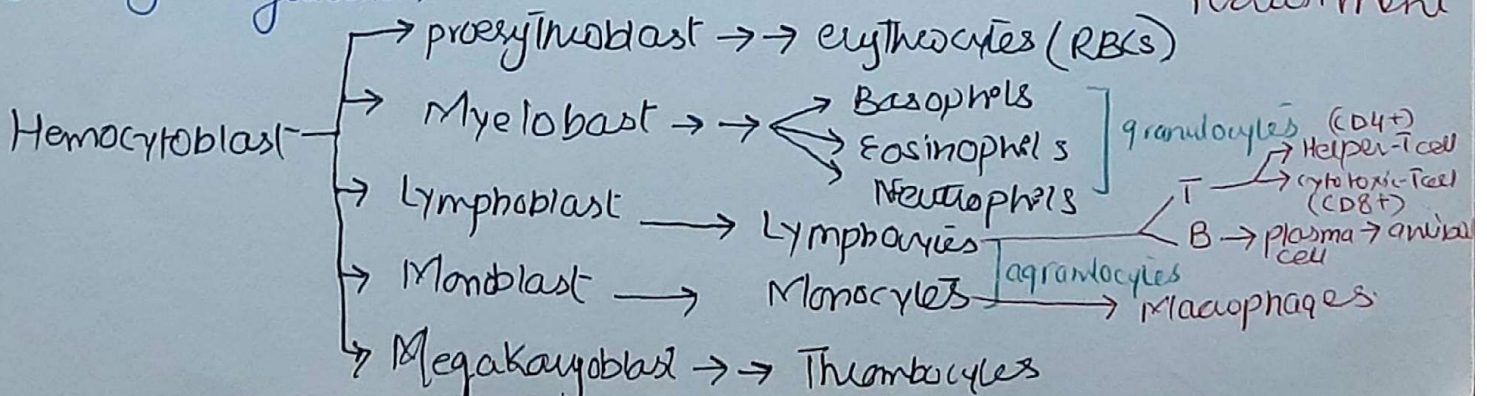
plasma (liver)

- ↑ se v. permeability, smooth muscle contraction
- vasodilation, pain

Endothelial activation, leukocyte recruitment

3) Proteases Activated during coagulation

"



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PROSTAGLANDINS

- modulating pain, inflamm. and fever
- role in acid secretion & mucous production in GI
- uterine contraction
- renal blood flow

* AL PROSTADIL: - it is PGI_1

that naturally produced in tissues such as seminal vesicles and cavernous tissues (refer to blood-filled spaces lined by endothel & surrounded by smooth muscle - present in erectile tissue of penis & clitoris (part of female genital)), in placenta and ductus arteriosus of fetus (artery that connect aorta & pulmonary artery)

The ductus arteriosus serve as a shunt b/w pulm. artery & aorta. In fetus the blood is oxygenated in placenta before being returned to body. The lungs are filled w/ amniotic fluid and therefore can't use to oxygenate the blood.

Alprostadil is use to treat erectile dysfunction & to keep the ductus arteriosus open in neonates w/ congenital heart conditions until surgery is possible.

* LUBIPROSTONE:

PGI_1 Derivative

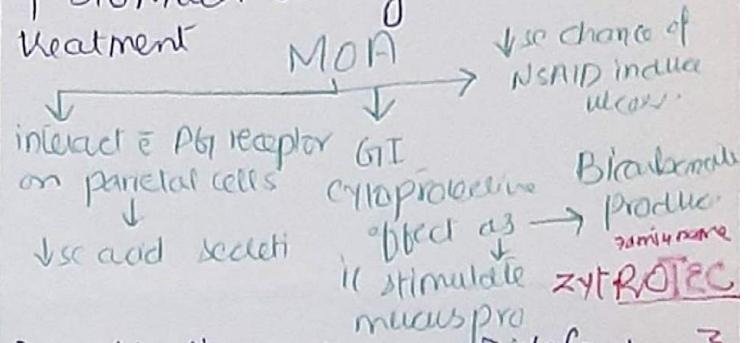
- use to treat constipation (chronic-idiopathic), opioid-induced constip. and IBS w/ constipation.
- N/D - S.E
- N ↓ if taken w/ food.

MOA: - Stimulate $5-HT_4$ receptor = ↑ action in intestinal lumen.

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* Misoprostol: - PGI_1 analog

use to protect the mucosal lining of stomach during chronic NSAID treatment



Combination product → Didofen + misoprostol

OFF-Label: For labor induction, as it interact w/ PG receptor on uterine

(PG) Diarr & abdo. pain

PG F $_{2\alpha}$ - Analogs:

Bimatoprost, latanoprost, Tafluprost and Travoprost - indicated for "open-angle glaucoma" (↓ IOP)

- Adm. as ophthalmic - OD. "being as effective as Timolol" Hypotensive
- Bimatoprost - ↑ eyelash prominence length and darkness

MOA: ↑ hair growth cycle

So approved for eye lash hypotrichosis

Inadeq. amount of eyelash - S.E = blurred vision, iris color change (↑ brown pigm), ocular irritation.

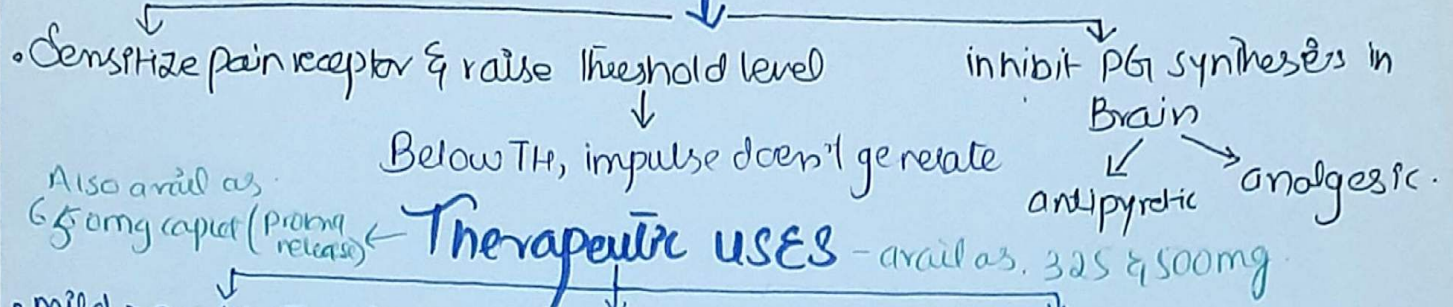
* PROSTACYCLIN (PGI_2) Analog

- Epoprostenol (ph-ceutical form of naturally occ)
- iloprost & Treprostinil - Synthetic
- indicated for treat. of pulmonary arterial HT
- All are short- $t_{1/2}$ agent
- Epo & trepr - continuous IV infus.
- Trepr - also as oral or IV or S/C.
- Ilo - Inhalation - can cause bronchospasm and cough.

Other S.E. of all of them → Dizziness, fainting, flushing, headache

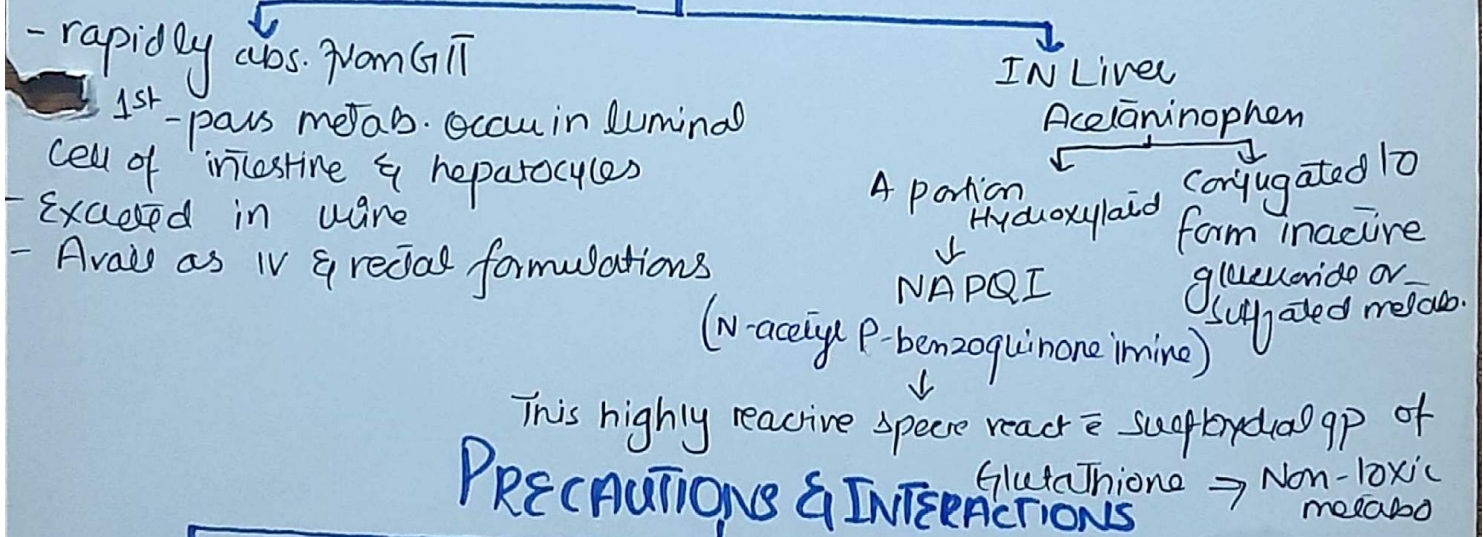
ACETAMINOPHEN

- NOT an NSAID - due to weak anti-inflam effect (due to peripheral inact)
- More action on COX-3 (blockade) → anti pyretic
- N-acetyl-p-aminophenol or (APAP) **MOA**



- mild → moderate pain
- Use fever
- post-immun pyrexia in infants
- Doc in children & viral infection or chickenpox (Due to Reye's synd. & Aspirin tox.)
- Acc. to American college of Rheumatology → It is 1st-line agent for osteoarthritis of knee & hip, NOT use for swelling and stiffness related to RA (as anti-inf is less).
- Acute migraine
- Adults (analgesic or antipyretic) → 500 - 1000mg TID - max 4000
- Osteoarthritis → 1000mg QID
- children 325mg q 4-6 hr as needed. - max 1600mg
- Now FDA has reduce this to 3250mg and even lower for alcoholics.
- NMT 10 days for pain
- NMT 3 days for fever
- (5 day pain) NMT → 2 day for Sore throat
- (3 day for fever)

KINETICS



PRECAUTIONS & INTERACTIONS

- e large dose, liver glutathione become depleted and NAPQI react & SH gp of liver proteins
 - ↓
 - Hepatic Necrosis - (N-AC, contain SH gp) is use as antidote.
- pt e active alcoholism, hepatic disease or viral hepatitis are at risk from chronic adm.
- Toxicity → 5g or more for mlt 2 month
- Acute dose of 10g or more
- Acetam inhibit metabo. of Zidovudine
 - ↓
 - ↑ use zidovu & Acetam. Toxicity

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

ASPIRIN & OTHER NSAIDS

- it is weak organic acid — that irreversibly acetylates COX.
- Other NSAIDS — REVERSIBLE INHIBITORS of COX.

MOA — NSAIDS include. Aspirin has 3 MOA

Anti-inflamm.

- cyclooxygenase inhibition

↓ (X)

prostaglandins.

They inhibit inflamm. in arthritis BUT neither arrest progression NOR induce remission.

Analgesic

- ↓ PGE₂ synthesis

↓ ⊖ →

Nerve ending doesn't get sensitized to the action of bradykinin, histamine & other mediator.

- COX-2 inhibition (which release during inflamm.).

"Rapid ↓ of body temp. of febrile pt. by ↑ing heat dissipation as a result of peripheral vasod. & sweating"

which elevate set point of Hypothalamic Thermoreg. centre

Antipyretic

infection, hypersensitivity, malignancy or inflammation

↓
WBCs activated

↓
Release fever producing agents pyrogens eg cytokines

↓
⊖ which stimulate PGE₂ synth

• NSAIDS have no effect on normal body temp.

Other MOA (Aspirin-only: NOT other salicylates)

Anti-platelet

Aspirin → Irreversibly inhibit COX in platelets

↓
which prevent formation of aggregating agent Thromboxane A₂.

PPB = 80-90%

Anti-Thrombotic

at high doses ↑ risk of CVS events

At low doses

Inhibit TXA₂

↓
blocking platelets aggreg. agent TXA₂

Small effect on prostacyclin

↓
so preserve the action of aggregation inhibitor (PGI₂)

Aspirin-THERAPEUTIC USES

Analgesic/Antinflamm

• relieve mild → moderate pain at low doses

• High doses — antiinflamm e.g

2 (325mg) QID — analgesia

12-20 (325) per day — inflam + analge.

Antipyretic

— Aspirin, Ibuprofen, Naproxen may be used to treat fever.

(Ar.) → in pt < 20 yrs viral infection (such as chickenpox or influenza) to prevent

Reye Syndrome (that cause hemorrhagic hepatitis & cerebral edema → often death).

CVS-Applic.

↓ use risks of stroke in women & MI in men

• men & women who has previous MI, Angina, coronary artery bypass surgery → candidates for Aspirin

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EXTERNAL APPLIC.

Salicylic acid

used Topically to treat acne, corns
(build up of hard skin near a bony area of
toe or b/w toes - caused by pressure from
shoe or friction) calluses (build up of hard-
skin - usually underside of foot) and warts
(is a small growth & rough texture - that can
appear anywhere on body - looks like
small cauliflower or hard blister)

Methyl Salicylates (oil of wintergreen)

As cutaneous counterirritant
in liniments such as
arthritis creams &
sports rubs.

Pharmaco-Study YouTube channel

Dose for analgesic or antipyresis = 325-650mg q 4hr OR 650-1000mg q 6hr.
max = 4g/day for NMT 10 day for pain or 3 day for fever.

KINETICS - Aspirin

After oral,

• Rapidly deacetylated by esterases in
body → produce salicylates.
unionized salicyl. absorb. from upper small
intestine (at higher pH)

• Anti-infl. doses (MT 4g/day) → Hepatic
metabo. pathway
salicylated
Zero-order elimi
 $t_{1/2}$ 15hr or more

• Being organic acid - affect wic acid
secretion.

(Ar.) → gout or pl. taking
Probenecid

• Cross - BBB and placenta except
(DFluorid)

• Convert to water soluble conjug. by liver
First order elimin $t_{1/2}$ 3.5hrs

• They inhibit PG synthesis BUT NOT LT system
So, should be use & caution in asthmatic
pt, as ↓ PG syn. may cause
↑ se shift toward leukotene synth.

PRECAUTIONS

Hypersensitivity

• occur in 0.5% population
• Cross-reactivity = >90% of
NSAID.
And 5% & Acetaminophen.

① → & bleeding disorder
or peptic ulcer.

• (pt < 20yr & viral infec)

PG

↓ RBF → edema
in some
AS

Caution require
& High doses
during last trimester

Becoz

Potential
bleeding risk

Prolonging or
complicating
delivery

• phytoin & valproic acid. Use

GI

disturbances

enteric coated dosages
and by taking salicyl.
& food or large doses
of antacids can
prevent GI
disturb.

CNS

disturb.

Salicyl.

↓

Tinnitus

Dizziness

Headache

Salicylate
toxicity
occur at
anti-inflam.
doses, in
addition to CNS
disturbances resp alkalosis,
Nausea, hyperthermia, confusion
& convulsions may occur.

Interactions

• Anticoagul. & Thrombolytic agents
• Use effect of hypoglycemics (anti-diab)

• ↓ Zidovudine
metabo.
• & caffeine, analgesic effect ↑.

NSAIDS

- Currently Ibuprofen & Naproxen are only NSAIDS - given over the counter
- NSAID → • mild-moderate pain and • Use inflammation
- Acetaminophen - initial treatment for osteoarthritis becoz of its safety profile - But NSAIDS - more effective for pain & inflamm.

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COMMON NSAIDS, USES

Diclofenac = Doc in joint pain

Naproxen

*- Ibuprofen

* Mefenamic Acid

* Diclofenac

Inhibit COX-1 & COX-II
may inhibit chemotaxis, alter Lymphocy. and cytokine activity (anti-inf. effect).

★ ONSET: 30 min

USES: Dental procedures, pain, R.A., O.A.,

- Ankylosing Spondylitis (longterm inflamm of joints & spine including paws)
- Dysmenorrhea
- Acute Gout (Take 2 food or 8-12 oz of H₂O to avoid GI effect)

★ (CI) = Ketorolac, Aspirin
ACEs Inhibi

ADR: Abdominal pain, Constip,

Nausea, edema, GI bleeding

For analgesia in adults: 220mg q 8-12hrs

R.A = 1100mg/day (Divide q 8-12hrs)

• MOA & onset Same as Naproxen

USES: pain, fever

• Dysmenorrhea

• O.A., R.A.

• Dental pain

• Acute migraine

• JIA in children

• Pain & Inflamm due to musculoskeletal disorders

• Headache

• Symp of cold & Influenza

• Pain & Inflamm due to soft-tissue injuries

• Post-immunization Pyrexia in infants

• Post-operative pain = 200-400mg q 4-6hrs

• Arth = 3200mg/day (divide)

• ONSET = rapid

USES:

• Pain

• Primary Dysmenor. (Adm. & onset of bleeding & pain)

• Musculo-skeletal disorders

• R.A., O.A.

• Migraine

• Toothache

• Menorrhagia (bleeding mtdays or heavy bleed)

• Pain & inflamm. in juvenile Idiopathic arthritis in child. intolerant to other

(autoimmune NSAIDS. disorder affect phs and other tissue <16yrs)

• For moderate to severe pain due to inflamm in rheumatic & m.s disord

• Acute gout

• Dysmenorhe

• K⁺ salt → rapid action than Nat salt

USES:

• PEI in m.s disorders

• Acute gout

• JIA in child post-oper. pain

• First 3 same as above

• Migraine

• Fever in ears nose or throat infection

• Dic-k⁺ use

★ - INDOMET - ACIN

↓

• For moderate to severe pain due to inflamm in rheumatic & m.s disord

• Acute gout

• Dysmenorhe

Precautions & Interactions

• CI = pt & bleeding disorder or peptic ulcer

• use & extreme caution in last trimester of Pg due to risk of premature closure of ducts of fetus

• cause GI distub, so take & food or large amount of antacid (Ibuprofen is prefer over Aspirin, as it cause fewer GI disturb)

• Renal toxicity (chronic adm) - may occur esp in

• Risk of CVS toxicity, Although risk is low, ibuprofen more risky than naproxen

• NSAID ↑ effect of anti-coag & thrombolytics

• Use effect of Anti-diabet (at antinf doses)

• Use adrs of GI reaction resulting from chemic alcohol or Salicylate use

• Caffein + Ibupro = ↑analgesia

• Hypertensiv to Aspirin can occur & NSAIDS

• Avoid NSAIDS in combination