Non-steroidal antiinflammatory drugs, Pharmacotherapy of gout, Pharmacotherapy of rheumatoid arthritis

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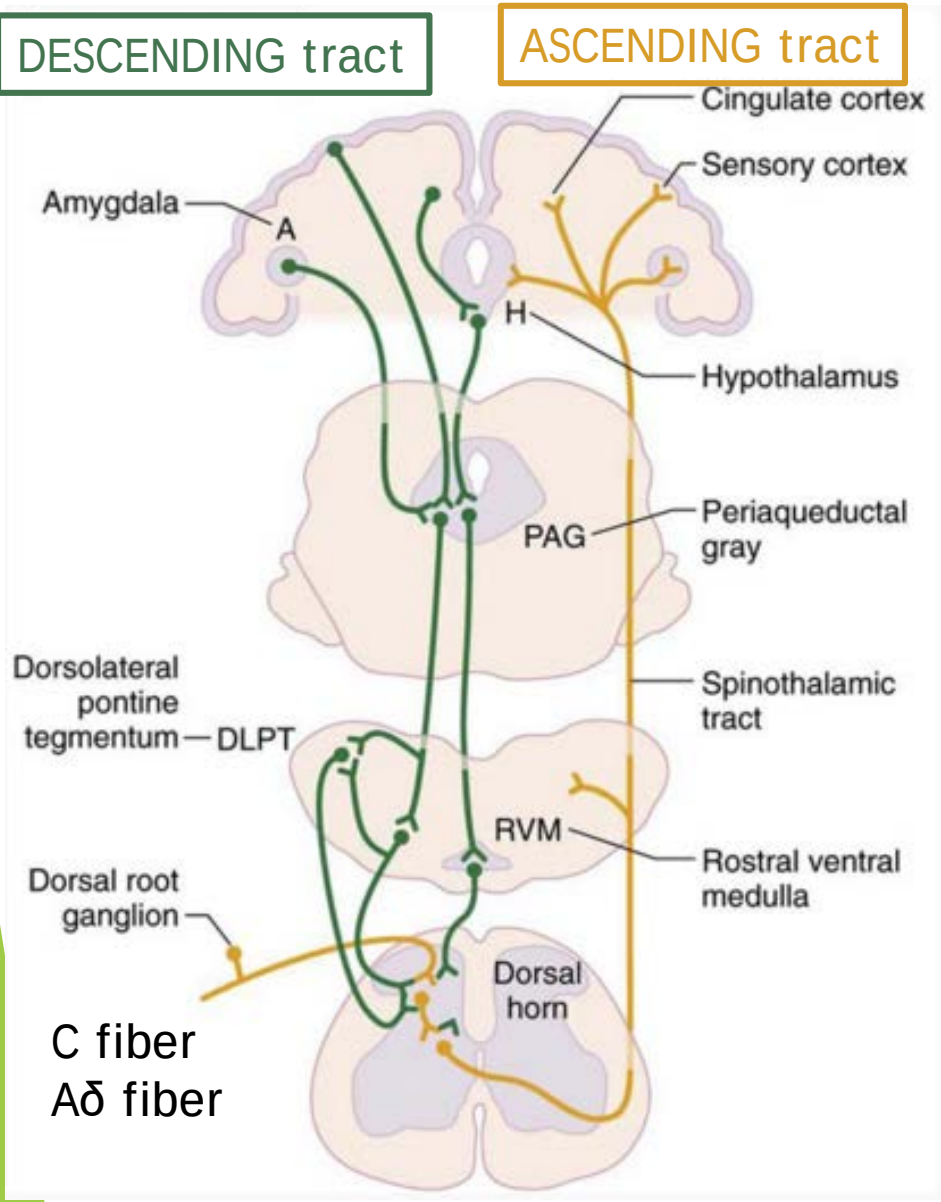
Nociceptive pathways



<u>ascending pathway:</u>

peripherial tissue
dorsal horn
spinothalamic tract
thalamus
cortex (area postcentralis)

<u>descending (modulatory) pathway:</u>

periaqueductal grey,
raphe nucleus
NTs: serotonine, endogene opioids

locus coruleus
NTs: NA, A, D, Ach

inhibited by GABAerg interneurons
(tonic inhibitory effect)

Nociceptor

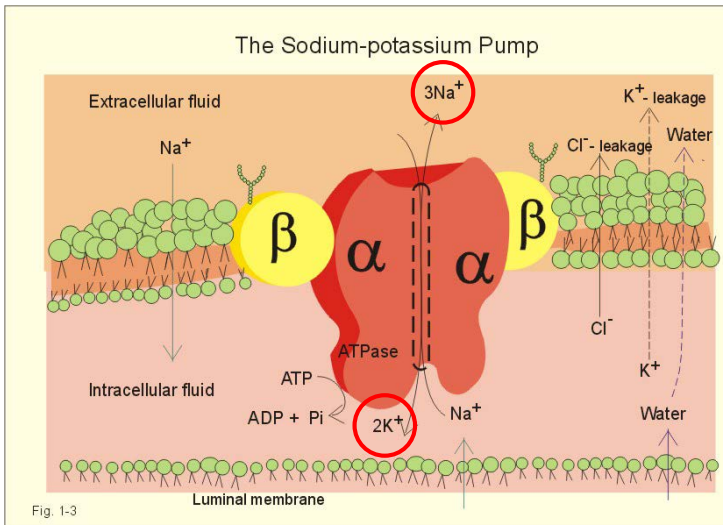
- A nociceptor is a **sensory neuron**.
- At the peripheral terminal of the nociceptor noxious stimuli are detected and transduced into electrical energy.
- environmental modalities they respond to = types of nociceptors:
  - Thermal
    - activated by heat or cold (through e.g. TRPV1 receptor = capsaicin receptor = vanilloid receptor activated by 42ºC or higher; TRPM8 rec. = menthol receptor = cold receptor activated by 20ºC or cooler)
  - Mechanical
    - respond to excess pressure or mechanical deformation
    - uses polymodal TRP receptors e.g. TRPA1 (TRP = transient receptor potential cation channels) (polymodal = responding to more than one of these modalities)
  - Chemical
    - respond to chemicals
    - uses polymodal TRP receptors e.g. TRPA1, TRPV1
  - Sleeping/silent
    - receptors of these nociceptors have high treshold, thus only activated in case of inflammation
  - Polymodal
    - nociceptor responding to more than one of these modalities

Neuronal pathways from nociceptors

- Nociceptors have two different types of axons.
  - Aδ fiber axons. They are myelinated and can allow an action potential to travel at a rate of about 20 meters/second towards the CNS.
  - C fiber axons. This type is lightly/non-myelinated and thus more slowly conducting (2 meters/second).
- As a result, pain comes in two phases.
  - Aδ fibers = initial extremely sharp pain
  - C fibers = somewhat later, more prolonged and slightly less intense feeling of pain

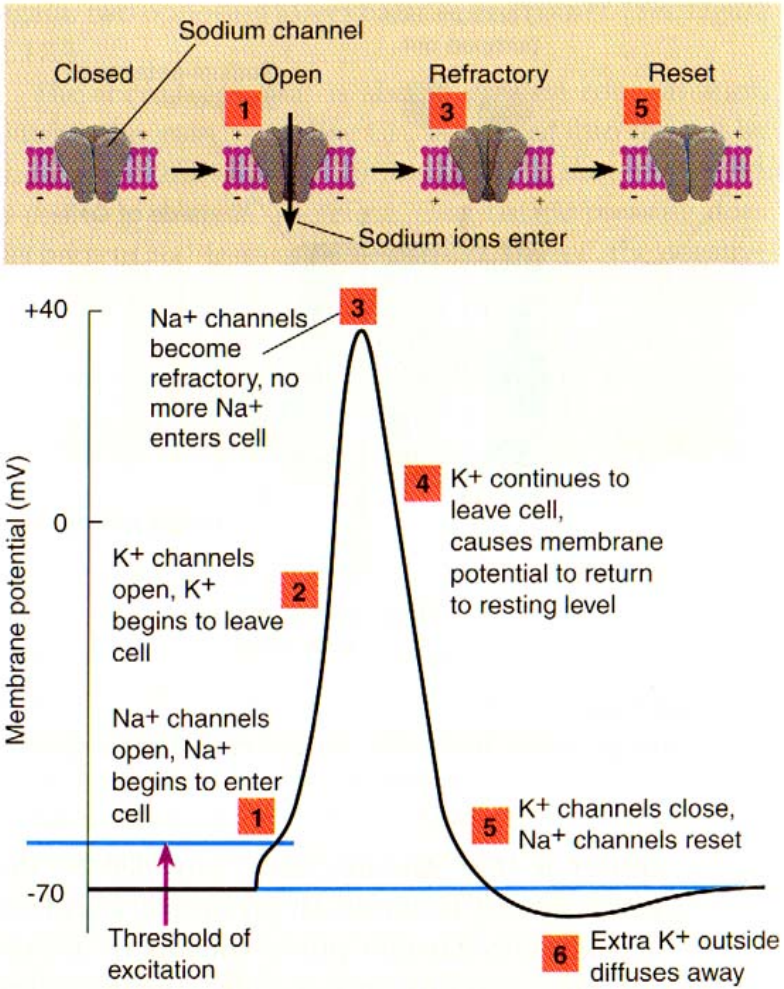
Nerve impulses – how they arise and travel

- At rest, intracellularly negative potential-difference exists: resting potential = -70mV
- Cause: diffusion potential, based on:
  - The fortyfold higher concentration of K+ in the axoplasm (as compared with the extracellular fluid)
  - The relatively high permeability of the resting axonal membrane to this ion.
  - (The Na+ and Cl- are present in higher concentrations in the extracellular fluid than in the axoplasm, but the axonal membrane at rest is considerably less permeable to these ions; hence their contribution to the resting potential is small.)
- These ionic gradients are maintained by an energy-dependent active transport or pump mechanism, namely the Na+/K+-ATPase



- The sodium-potassium pump uses up ATP to
  import 2 ions of K+ into the cell and
  to export 3 ions of Na+ out from the cell.

Action potential



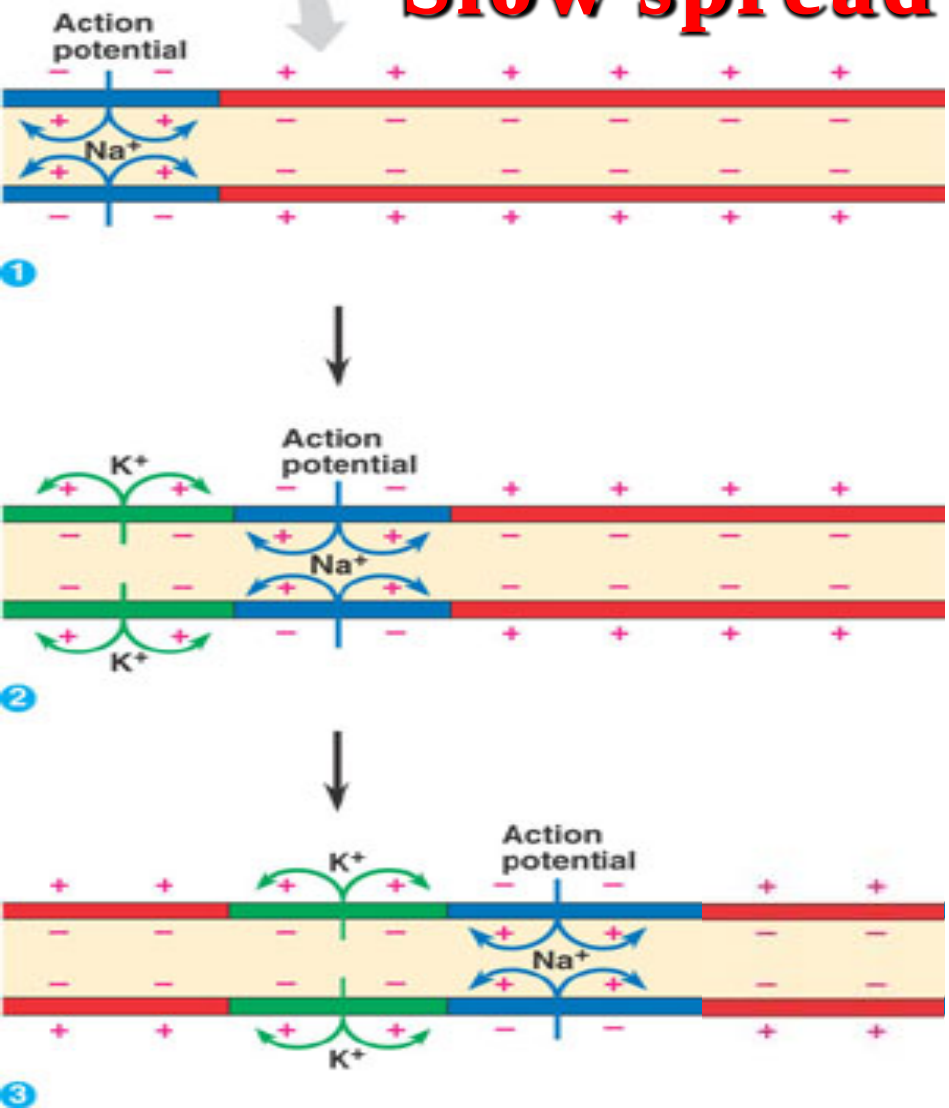
- In response to depolarization to a treshold level ➔
  an action potential or nerve impulse is initiated:

- voltage-sensitive Na+ channels open ➔
  Na+ inward = depolarization (from negative mV-s)
  + positive overshoot (above 0mV)

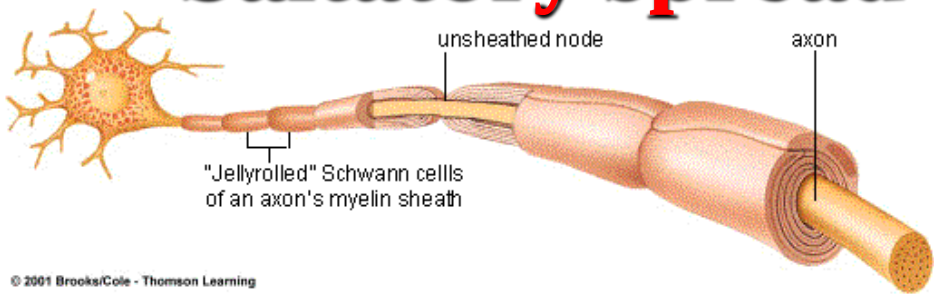
- rapid inactivation of the Na+-channel and the delayed opening of a K+ channel ➔
  K+ outward = repolarization to resting potential

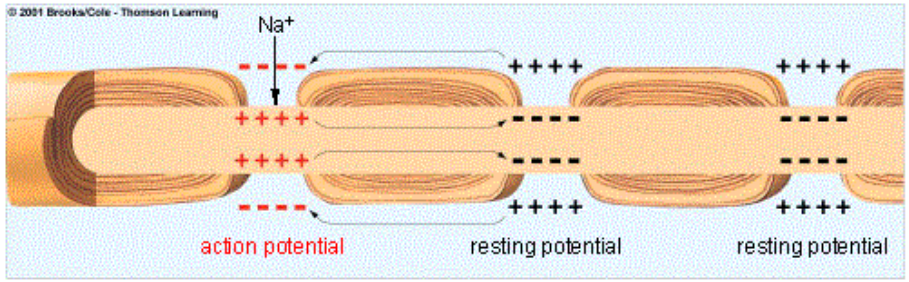
Action potential rides along the axon

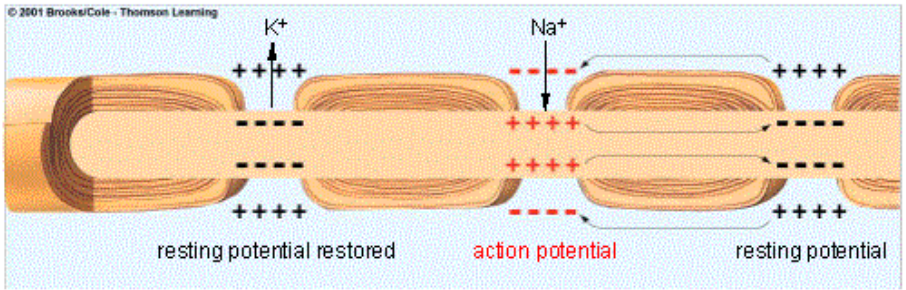
Slow spread



Saltatory spread







A series of Schwann cells' myelin sheaths block ion movements ➔Action potential must „jump" from node to node

Why does the impulse travel faster on a myelinated axon?

- Because voltage-sensitive Na-channels exists almost solely at the node of Ranvier and
- Because the myelin sheath is a good insulator
  (=does not conduct current)
  - thus it prevents the point-to-point conduction of impluses, and
  - the action potential generated at the node of Ranvier depolarises the next myelinated axon-membrane simultaneously, at once

Endogenous Noxious/pain-causing mediators

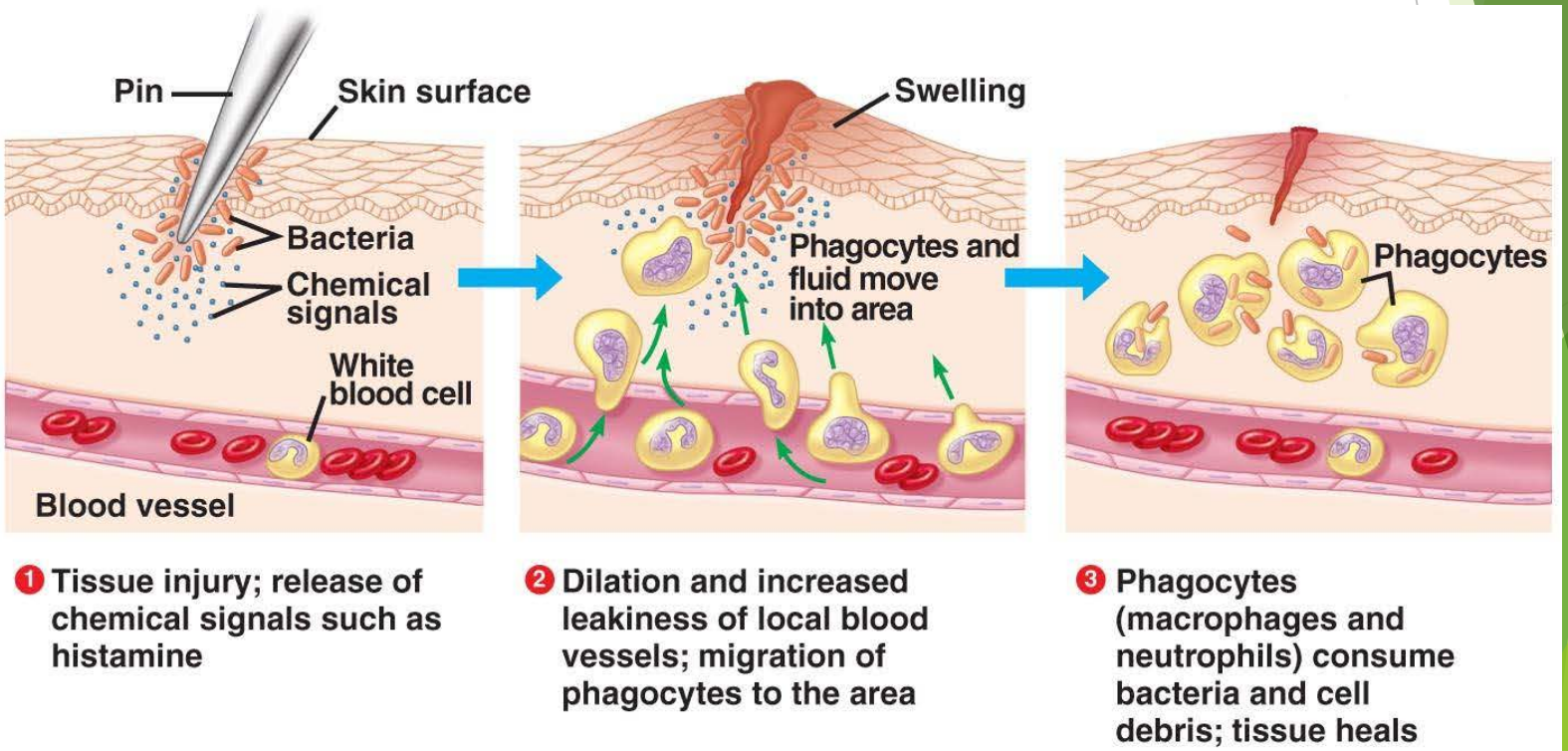
Due to injury to tissues endogenous substances are released, that increase sensitivity of primer sensory neurons and cause pain. Such noxious mediators include:

- ***Substance-P*** acting on neurokinine receptors,
- ***Prostaglandines*** *including:* PGE_1 and prostacyclin (PGI_2) are direct stimulators of nociceptors, PGE_2 causes release of substance-P,
- *adenosin* causes analgesia on A_1 receptors, while causes nociception on A_2 receptors,
- *glutamate* acting on AMPA receptors is responsible for fast synaptic transmission in the first synapsis of the spinal cord
- ***bradykinin*** causes release of prostaglandines,
- *Serotonin, histamin,* ***cytokines*** (released by cells of immune system) and *NO* (synthetised by sensory neurons) are involved in inflammatory pain

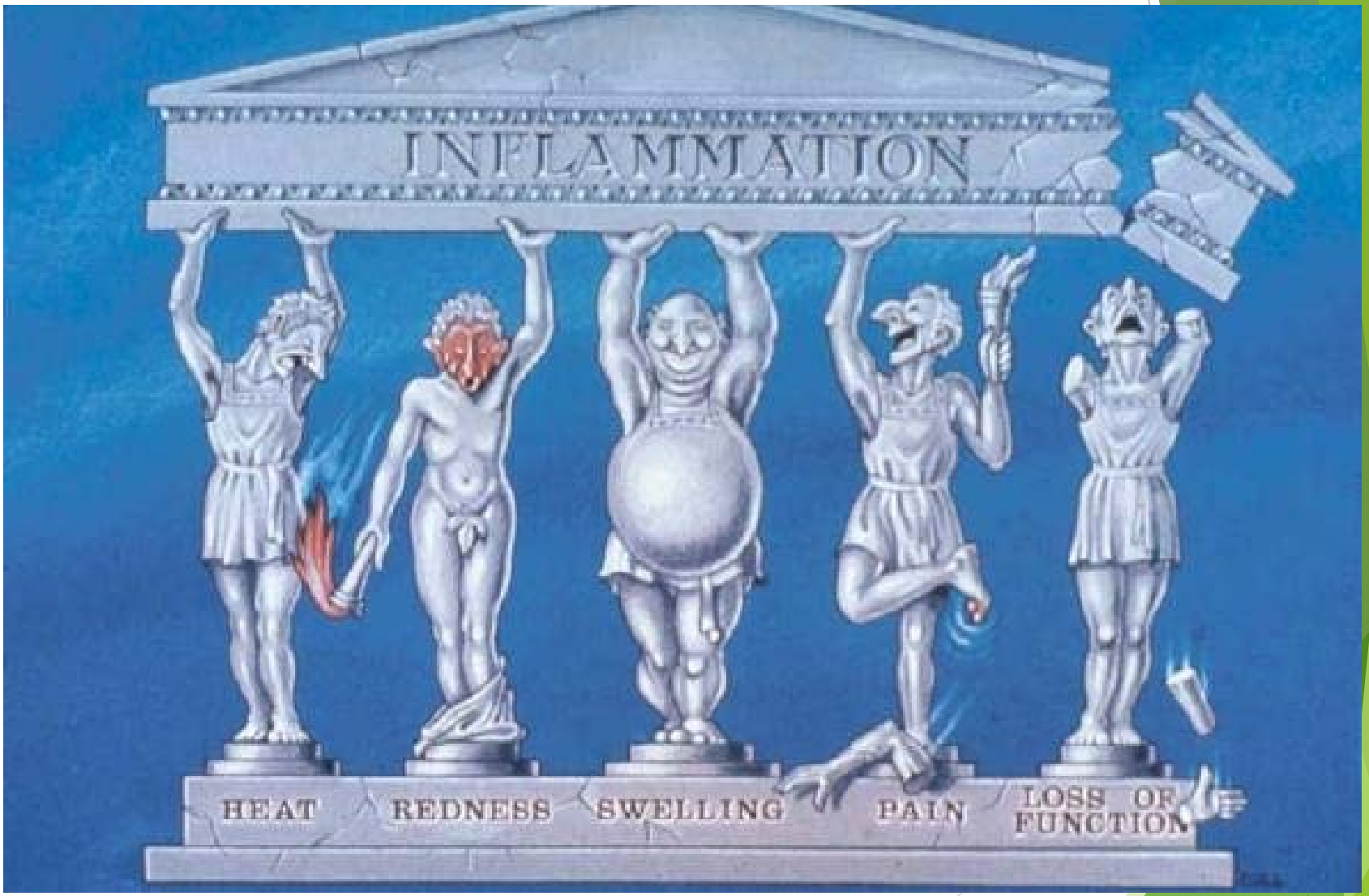
The inflammatory response

- **The inflammatory process** is the response to an injurious stimulus evoked by a wide variety of noxious agents (*infections, antibodies, or physical injuries)*

- (1) an acute phase characterized by transient local vasodilation and increased capillary permeability;
- (2) a delayed, subacute phase characterized by infiltration of leukocytes and phagocytic cells;
- (3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur.

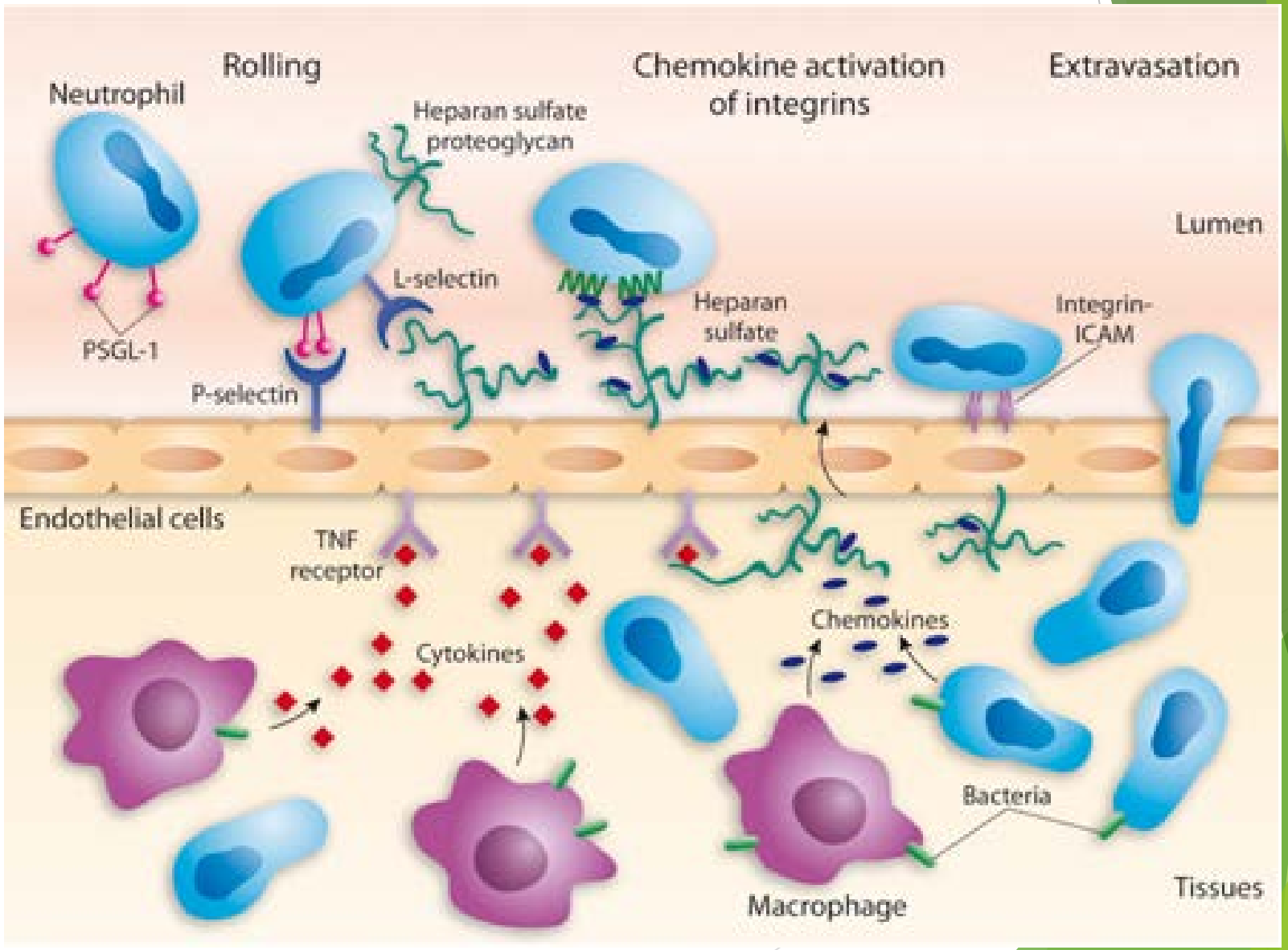


Signs of inflammation

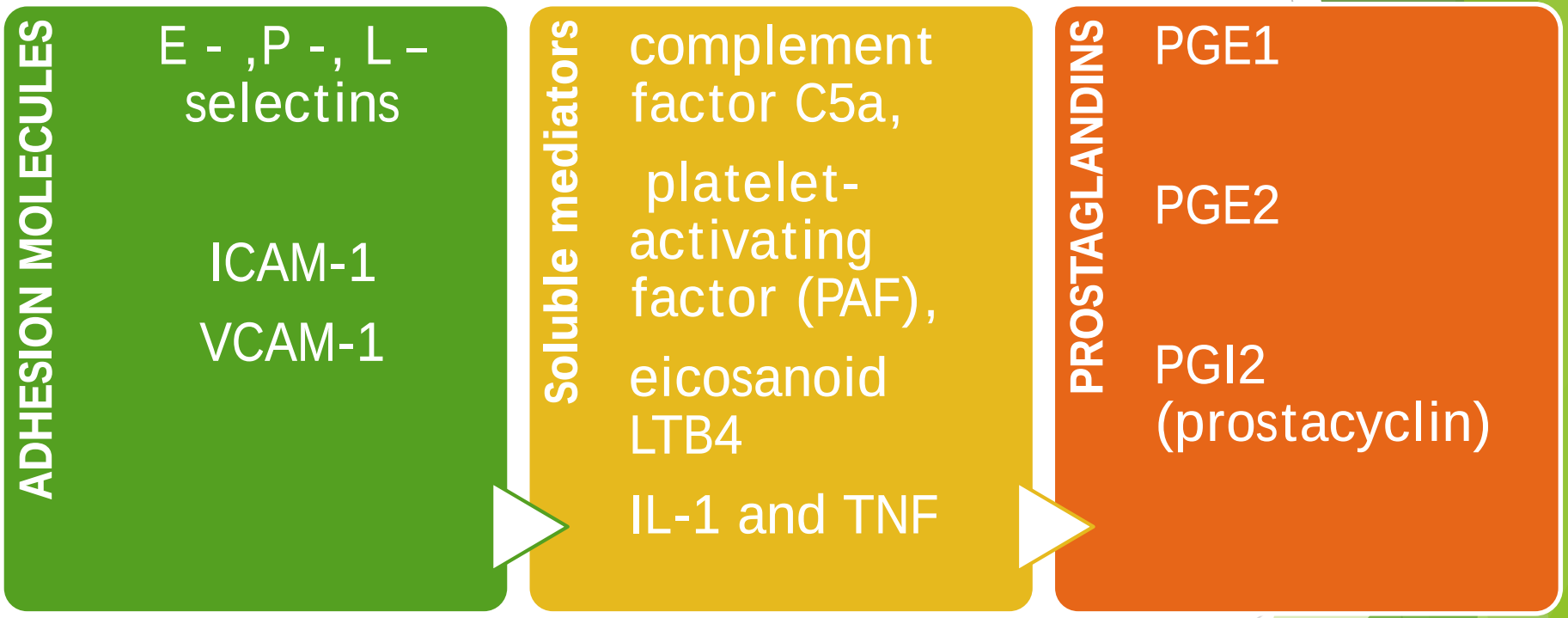


calor rubor tumor dolor functio-laesa

Molecular mechanisms of extravasation

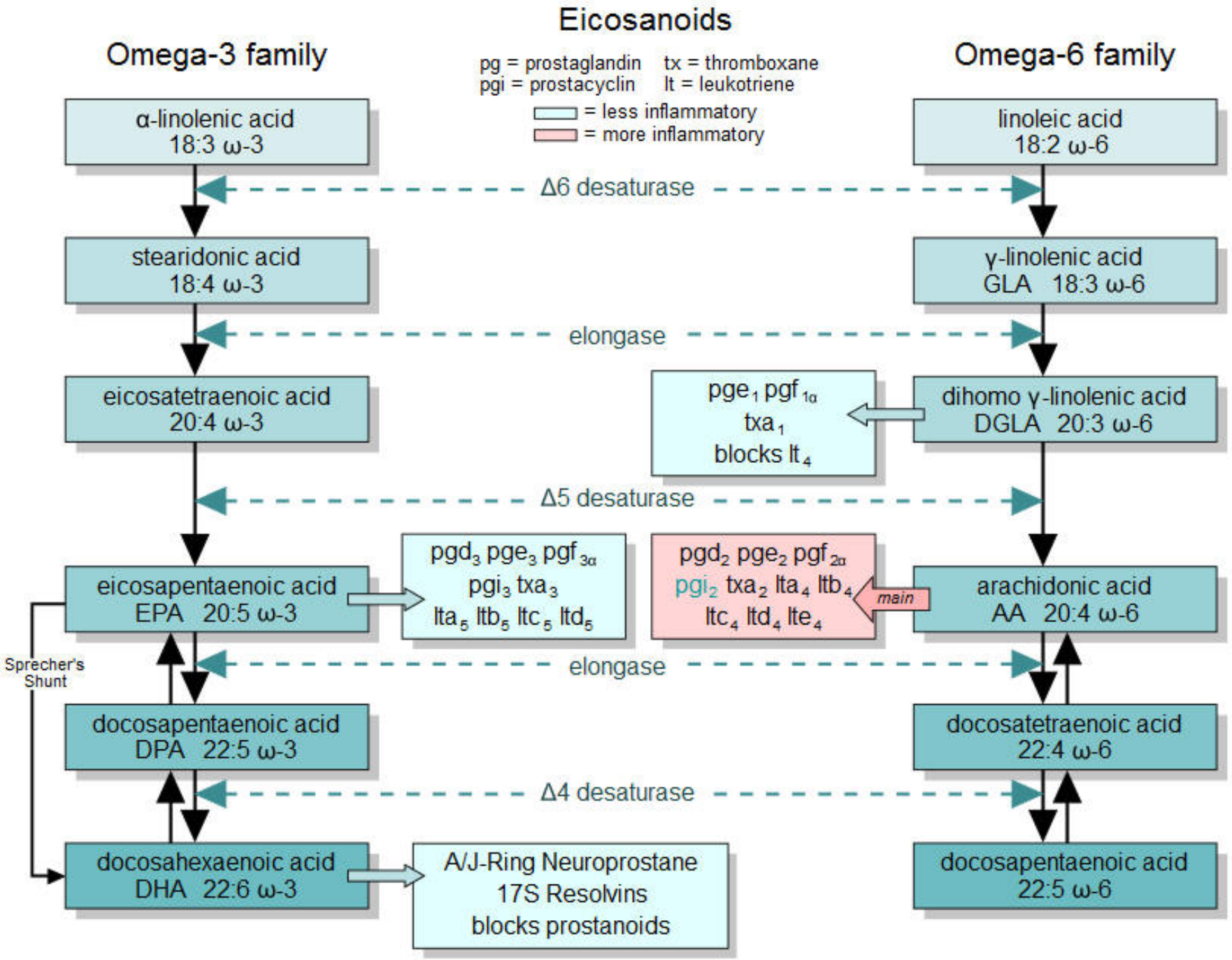


Mediators and molecules involved



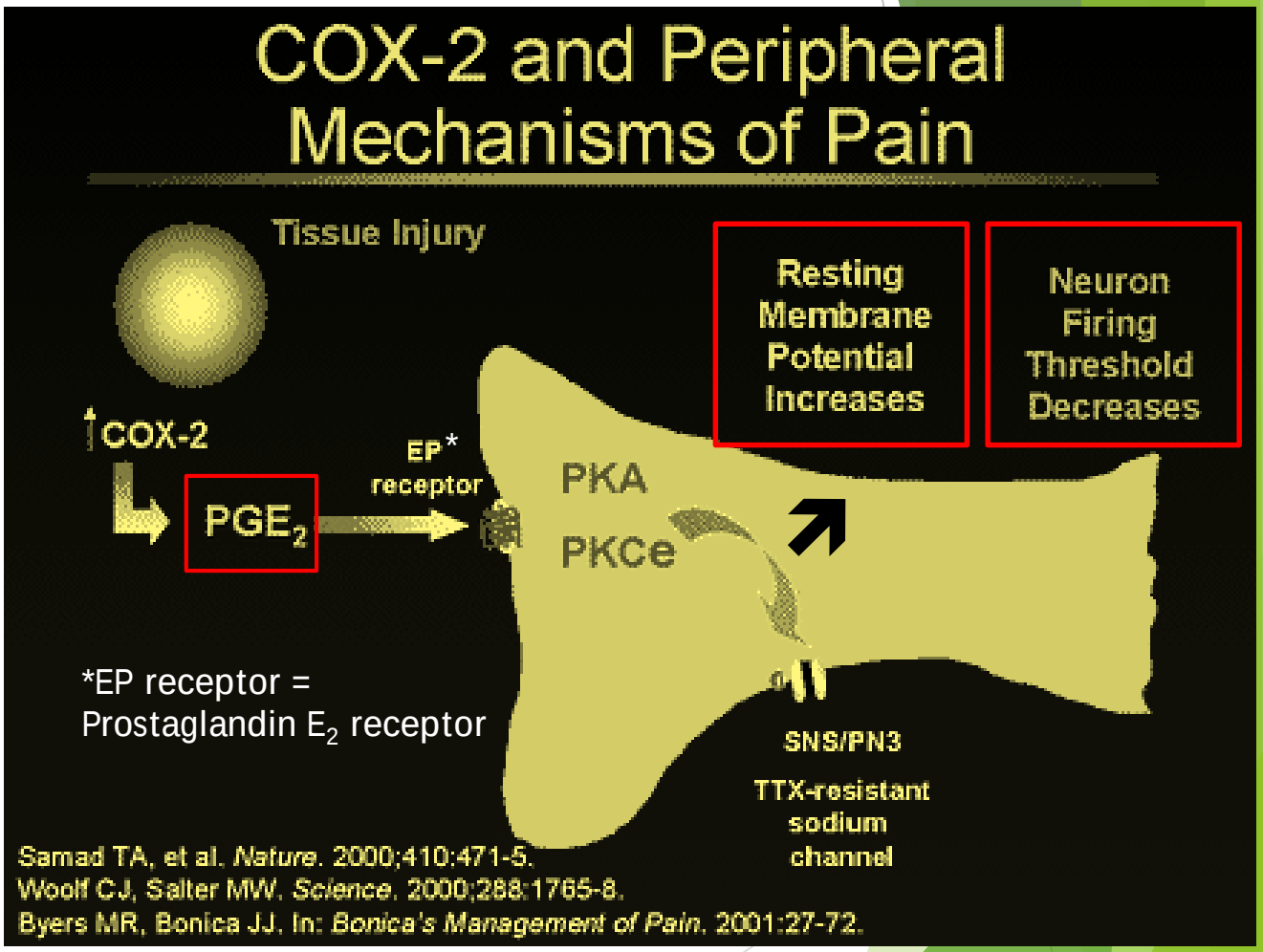
What is what?

- cytokines:
  - small proteins (~5–20 kDa) that are important in cell signaling
  - released by cells and affect the behavior of other cells
  - Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells
  - Cytokines include interferons (IFN), interleukins (IL), tumour necrosis factor (TNF) etc.
- eicosanoids:
  - signaling molecules made by oxidation of 20-carbon fatty acids
  - Eicosanoids are derived from either omega-3 (ω-3) or omega-6 (ω-6) fatty acids. In general, the ω-6 eicosanoids are pro-inflammatory; ω-3s are much less so
    - Eicosapentaenoic acid (EPA) (ω-3), Arachidonic acid (AA) (ω-6), etc
  - eicosanoids include the prostaglandins (PG), prostacyclines (PGI) thromboxanes (TX), and leukotrienes (LT) etc.
  - eicosanoids are named with a letter (which indicates the type of ring structure) followed by a number (which indicates the number of double bonds in the hydrocarbon structure)
  - receptors include: DP=PGD_2-rec., EP=PGE_2-rec., FP=$PGF_{2\alpha}$-rec., IP=PGI_2-rec; TP=TX_{A2}-rec., BLT=LT_{B4}-rec


Eicosanoids
Omega-3 family
Omega-6 family
pg = prostaglandin
pgi = prostacyclin
tx = thromboxane
lt = leukotriene
= less inflammatory
= more inflammatory
α-linolenic acid
18:3 ω-3
linoleic acid
18:2 ω-6
Δ6 desaturase
stearidonic acid
18:4 ω-3
γ-linolenic acid
GLA 18:3 ω-6
elongase
eicosatetraenoic acid
20:4 ω-3
pge1 pgf1α
txa1
blocks lt4
dihomo γ-linolenic acid
DGLA 20:3 ω-6
Δ5 desaturase
eicosapentaenoic acid
EPA 20:5 ω-3
pgd3 pge3 pgf3α
pgi3 txa3
lta5 ltb5 ltc5 ltd5
pgd2 pge2 pgf2α
pgi2 txa2 lta4 ltb4
ltc4 ltd4 lte4
main
arachidonic acid
AA 20:4 ω-6
Sprecher's Shunt
elongase
docosapentaenoic acid
DPA 22:5 ω-3
docosatetraenoic acid
22:4 ω-6
Δ4 desaturase
docosahexaenoic acid
DHA 22:6 ω-3
A/J-Ring Neuroprostane
17S Resolvins
blocks prostanoids
docosapentaenoic acid
22:5 ω-6

Prostaglandins sensitize pain perception

- Prostaglandin-evoked (inflammatory) pain probably results from:
  - local/direct stimulation of pain fibers and
  - enhanced pain sensitivity (hyperalgesia),
- Hyperalgesia=
  - increased excitability of nociceptors



Biosysnthesis of prostaglandins

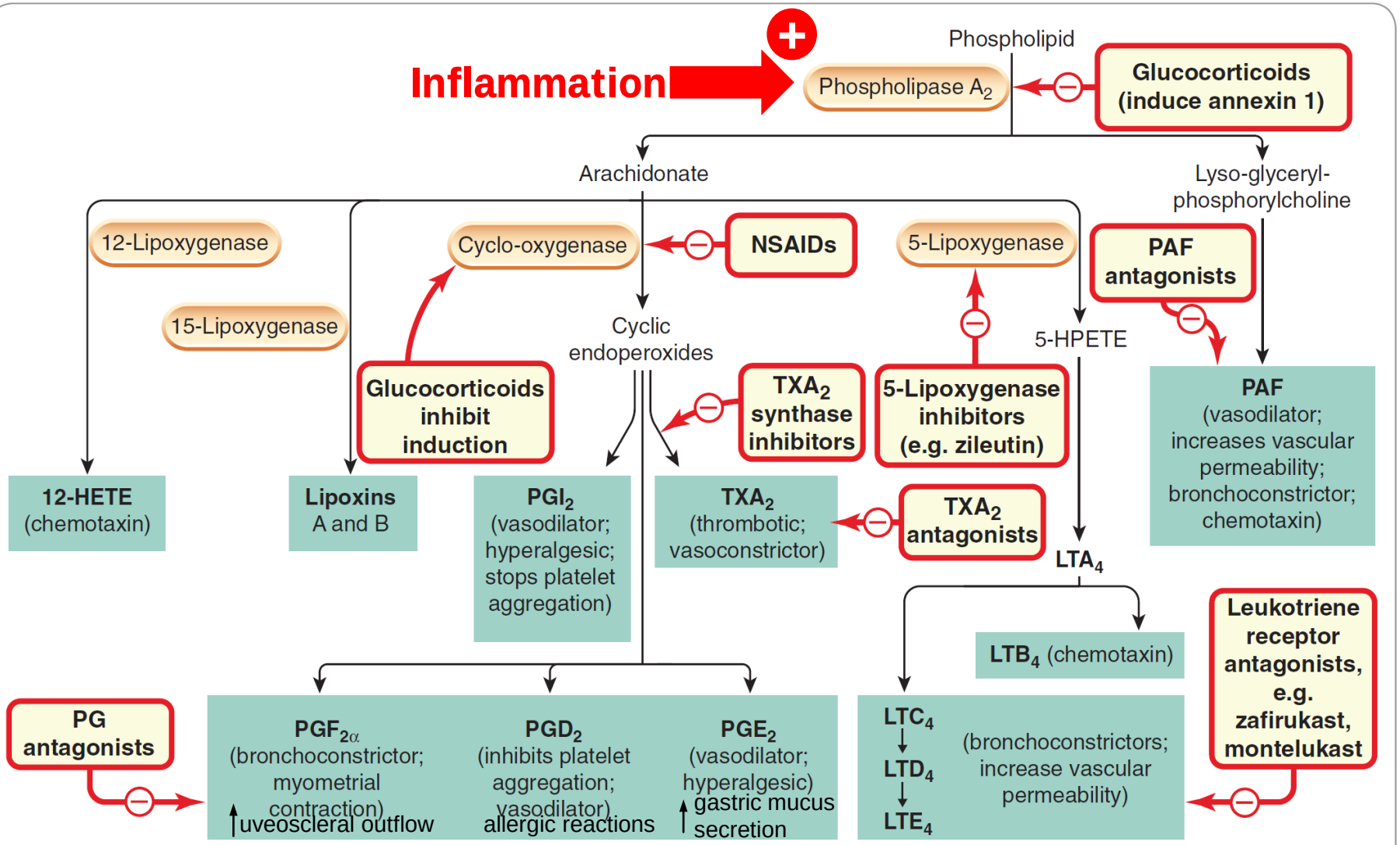
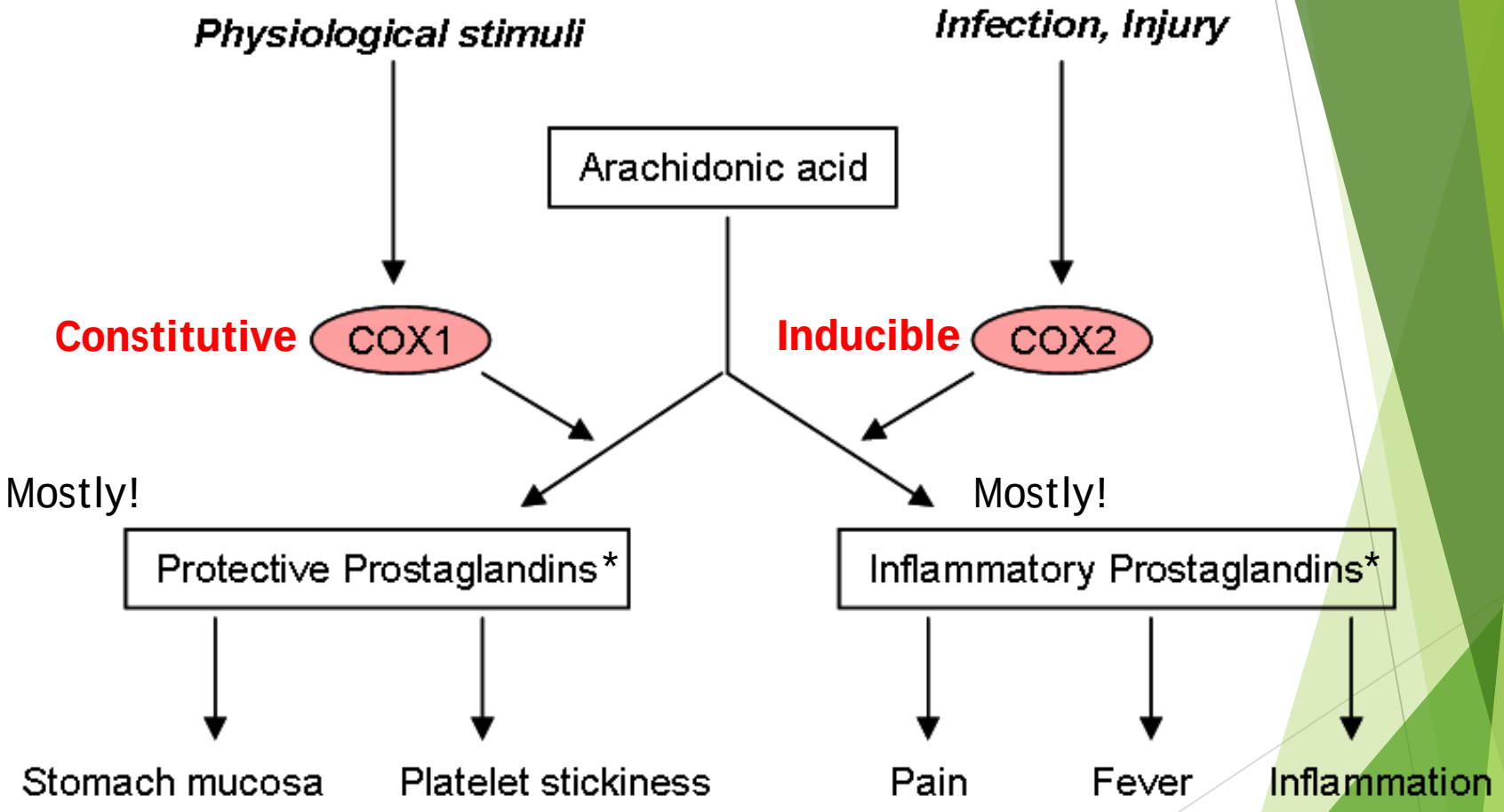


Fig. 17.1 **Summary diagram of the inflammatory mediators derived from phospholipids, with an outline of their actions and the sites of action of anti-inflammatory drugs.** The arachidonate metabolites are eicosanoids. The glucocorticoids inhibit transcription of the gene for cyclo-oxygenase-2, induced in inflammatory cells by inflammatory mediators. The effects of prostaglandin (PG)E_2 depend on which of the three receptors for this prostanoid are activated. HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LT, leukotriene; NSAID, non-steroidal anti-inflammatory drug; PAF, platelet-activating factor; PGI_2, prostacyclin; TX, thromboxane.

Cyclooxygenase (COX) isoforms



*same prostaglandins, but synthetised/acting in different tissues and/or in different doses
Constitutive = basal PG levels continuously, inducible = high PG levels in inflammation
COX1 = physiologic sites, COX2 = inflammed tissue

Non-steroidal anti-inflammatory drugs

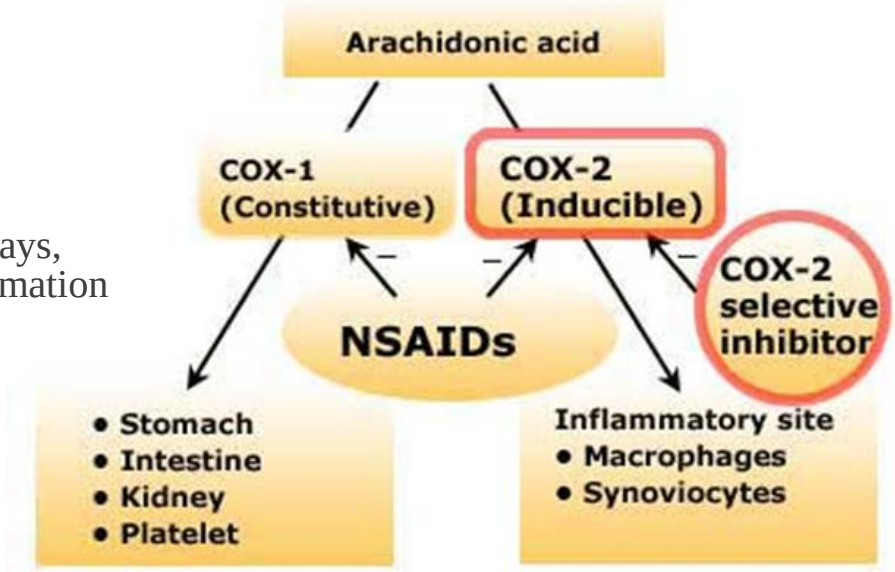
NSAIDs

or minor analgesics

NSAIDs

- **NSAIDs** are **a chemically heterogeneous group** of organic acids that share certain therapeutic actions and adverse effects
- All classic and newer NSAIDs are **anti-inflammatory, analgesic, and antipyretic** medications
- Often OTCs!
- 2 special molecules often distinguished:
  - Aspirin (irreversible COX 1, + other effects)
  - Paracetamol (Acetaminophen) – antipyretic and analgesic, but lack of anti-inflammatory action (central COX3 inhibition??)

- Mechanism of action:
  - Inhibition of prostaglandin (PG) biosynthesis by blocking COX
  - they <u>do not inhibit</u> the lipoxygenase pathways, hence do not suppress leukotriene (LT) formation



Therapeutic effects – 1. PAIN

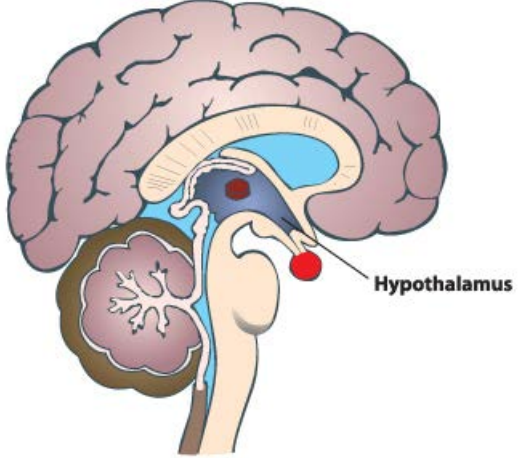
- NSAIDs usually are classified as **mild analgesics**
- NSAIDs are **particularly effective when inflammation has caused sensitization of pain receptors** to normally painless mechanical or chemical stimuli.

Pain types NSAID effectively decrease

- Pain of low-to moderate intensity, such as
  - dental pain
  - musculoskeletal disorders, Rheumatoid pain
  - Headache, migraine
  - Chronic postoperative pain
  - pain arising from any inflammation
  - menstrual pain

- Pain arising from the hollow viscera (gall bladder, GIT) is usually not relieved! (≈ spastic pain due to smooth muscle spasms)
  - An exception to this is menstrual pain. (because it is related to prostaglandins)

Therapeutic effects – 2. FEVER



- **The hypothalamus regulates the set point at which body temperature is maintained**
- This set point is elevated in fever (from infection, tissue damage, inflammation, graft rejection etc..)
- **IL-1b, IL-6, interferons, and TNF-*a* increase synthesis of PGE2**,
- PGE2, in turn, increases cAMP ➔ triggers the hypothalamus to elevate body temperature
- NSAIDs suppress this response by inhibiting PGE2 synthesis
- but do not influence body temperature when it is elevated by factors such as exercise

Therapeutic effects – 3. INFLAMMATION

- inhibition of immune response (antiinflammatory-antiphlogistic effect)
  - inhibition of chemotaxis
  - ↓sensitivity of vessels to histamine
  - down regulation of IL-1 production
  - decreased production of free radicals and superoxide

Therapeutic effects – 4. INHIBITION OF PLATELET AGGREGATION

- Low dose aspirin (100mg/day)
  - **Cardioprotection** by the inhibition of platelets' COX-1–dependent TXA2 formation
  - Aspirin covalently modifies COX-1 and COX-2, **irreversibly** inhibiting COX activity
  - in platelets, which, being anucleate, have a markedly limited capacity for protein synthesis.
  - Thus, the consequences of inhibition of platelet COX (COX-1) last for the lifetime of the platelet

Common adverse effects

System	Manifestations
GI (adverse effects decreased with COX-2–selective drugs)	Abdominal pain Nausea Anorexia Gastric erosions/ulcers (inhib. of PG synthesis – protective factor) Anemia GI hemorrhage Perforation Diarrhea
Renal	Salt and water retention Edema, worsening of renal function in renal/cardiac and cirrhotic patients Decreased effectiveness of antihypertensive medications Decreased effectiveness of diuretic medications Decreased urate excretion (especially with aspirin) Hyperkalemia
CNS	Headache Vertigo Dizziness Confusion Depression Lowering of seizure threshold Hyperventilation (salicylates)
Platelets (adverse effects decreased with COX-2–selective drugs)	Inhibited platelet activation Propensity for bruising Increased risk of hemorrhage
Uterus	Prolongation of gestation Possible prolongation of labor
Hypersensitivity	Vasomotor rhinitis Angioedema Asthma (LT↑) Aspirin asthma Urticaria Flushing Hypotension Shock
Vascular	Closure of ductus arteriosus

Possible drug interactions!!

Avoid in pregnancy!!!!

COX-2 inhibitors are not better. Why?

COX-1 inhibition ➔ inhibition of antiulcer PGs (PGI2 and PGE2) ➔ ulceration

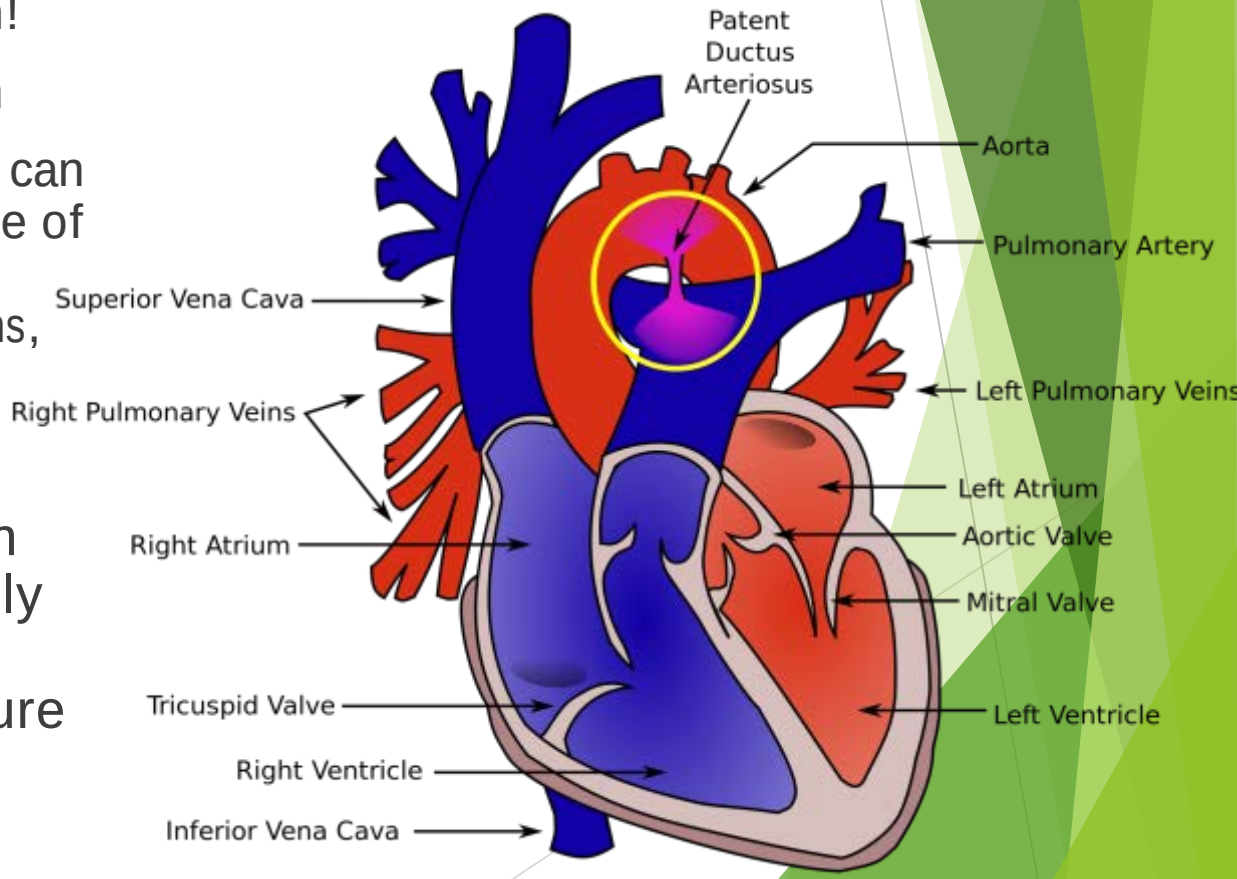
COX-2 found in inflammed tissues ➔ COX-2 inhibition ➔ less GI side effects

BUT increased cardiovascular events !?!

- While low-dose aspirin protects against heart attacks and strokes by blocking COX-1 from forming thromboxane A2 (TXA2) in platelets.
  - TXA2 = thrombotic = platelet aggregation ➔ inhibition = protective/antithrombotic
- selective COX-2 inhibitors inhibit high-level PGI2 formation in endothel!
  - PGI2 = anti-thrombotic ➔ inhibition = promotes clotting (thrombotic) = increased cardiovascular risk
  - Plus as they are selective to COX-2 they don’t inhibit TXA2 synthesis ➔ also thrombotic

Ductus arteriosus Botalli

- A vessel in the fetal heart, between aorta and pulmonary artery, bypassing the lungs, needed for fetal blood circulation. Prostglandines keep it open!
- Normally closing after birth
- NSAIDs in the 3rd trimester can cause the premature closure of Ductus arteriosus, causing circulation problems, elevated BP in the fetus
- NSAID cause prolongation of labour, but this possibly beneficial effect is counteracted by DA closure



Reye's syndrome

- **Reye's syndrome** is characterized by the acute onset of encephalopathy, liver dysfunction, and fatty infiltration of the liver and other viscera after viral illnesses
- The etiology and pathophysiology are not clear.
- However, there is epidemiologic evidence for an **association** between **aspirin use in children and Reye's syndrome**
- Due to the association with Reye's syndrome, aspirin and other salicylates are **contraindicated in children** and young adults <20 years old with fever associated with viral illness
- DRUG of CHOICE in case of antipyresis in child: ACETAMINOPHEN (paracetamol)

General pharmacokinetic features of NSAIDs

- weak organic acids → pKa≈3.0 → rapid absorption from stomach
- metabolized in the liver (CYP3A, CYP2C)
- high cc. in synovial fluid (repeated exposure)
- highly protein bound (≈98%)
- renal excretion

Drug interactions

- NSAIDs may increase the frequency or severity of GI ulceration when combined with ***glucocorticoids***
- augment the risk of bleeding in patients receiving ***warfarin***
- that NSAIDs might attenuate the effectiveness of **ACE inhibitors** by blocking the production of vasodilator and natriuretic prostaglandins
- Many NSAIDs are ***highly bound to plasma proteins*** and thus may displace other drugs from their binding sites
  - with warfarin, sulfonylurea hypoglycemic agents, or *methotrexate;*

Classification

- according to selectivity
  - selective (=mainly) COX-1 inhibitors
    - aspirin, tolmetin
  - COX-1 inhibitors (low selectivity)
    - ibuprofen, indometacin, piroxicam
  - COX-1, COX-2 inhibitors
    - diclofenac
  - selective COX-2 inhibitors
    - meloxicam, celecoxib, etodolac, rofecoxib

- according to mechanism of action
  - irreversible
    - aspirin
  - reversible
    - indometacin, ibuprofen

Groups of NSAIDs

Salicylates

- Aspirin
  - Main side effects: ulcus, hypersensitivity reaction, inreased bleeding time
  - Avoid in children with acute febrile illness
  - *Salicylate poisoning or serious intoxication often occurs in children and sometimes is fatal*

Para-aminophenol derivative

- Acetaminophen = Paracetamol
  - Drug of choice in children **(and during pregnancy, warfarin use)**
  - Overdose (up than 4g/day) leads to toxic metabolite (NAPQI) and liver necrosis (cannot conjugate with glutation, because cystein storage is limited – toxic metabolite forming.
  - Antidote and prevention: acetyl-cysteine (ACC) administration)

Groups of NSAIDs

Acetic acid derivatives

- Indomethacin
  - 10-40 times more potent
  - Side effects: *headache, neutropenia,* thrombocytopenia;

Fenamates

- Mefenamic acid
- Diclofenac
  - Protein binding 99%
  - Available in topical gel, ophtalmic solution

Groups of NSAIDs

Propionic acid derivatives

- Ketoprofen
- Flurbiprofen
- Naproxen
- Ibuprofen
  - Protein binding 99%
  - Suitable for children as well
  - For dental and muscoskeletal pain

Groups of NSAIDs

Enolic acid derivatives

- Piroxicam
- Meloxicam
  - smaller doses (7-15 mg/day)
  - these agents show **some COX-2 selectivity**! COX2 > COX1

COX-2 selective inhibitors (COXIBs)

(developed to decrease GI side effect due to COX-1 inhibition – succesful, but elevated risk of cardiovascular mortality (stroke, AMI), some are withdrawn from market)*

mainly COX-2 is responsible for the synthesis of the vasodilator prostacycline formed in the endothel

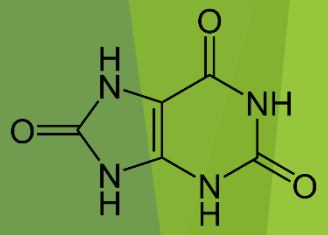
- ***Celecoxib, etoricoxib, parecoxib, valdecoxib*, rofecoxib*, lumiracoxib****

Agents for the treatment of gout

Gout

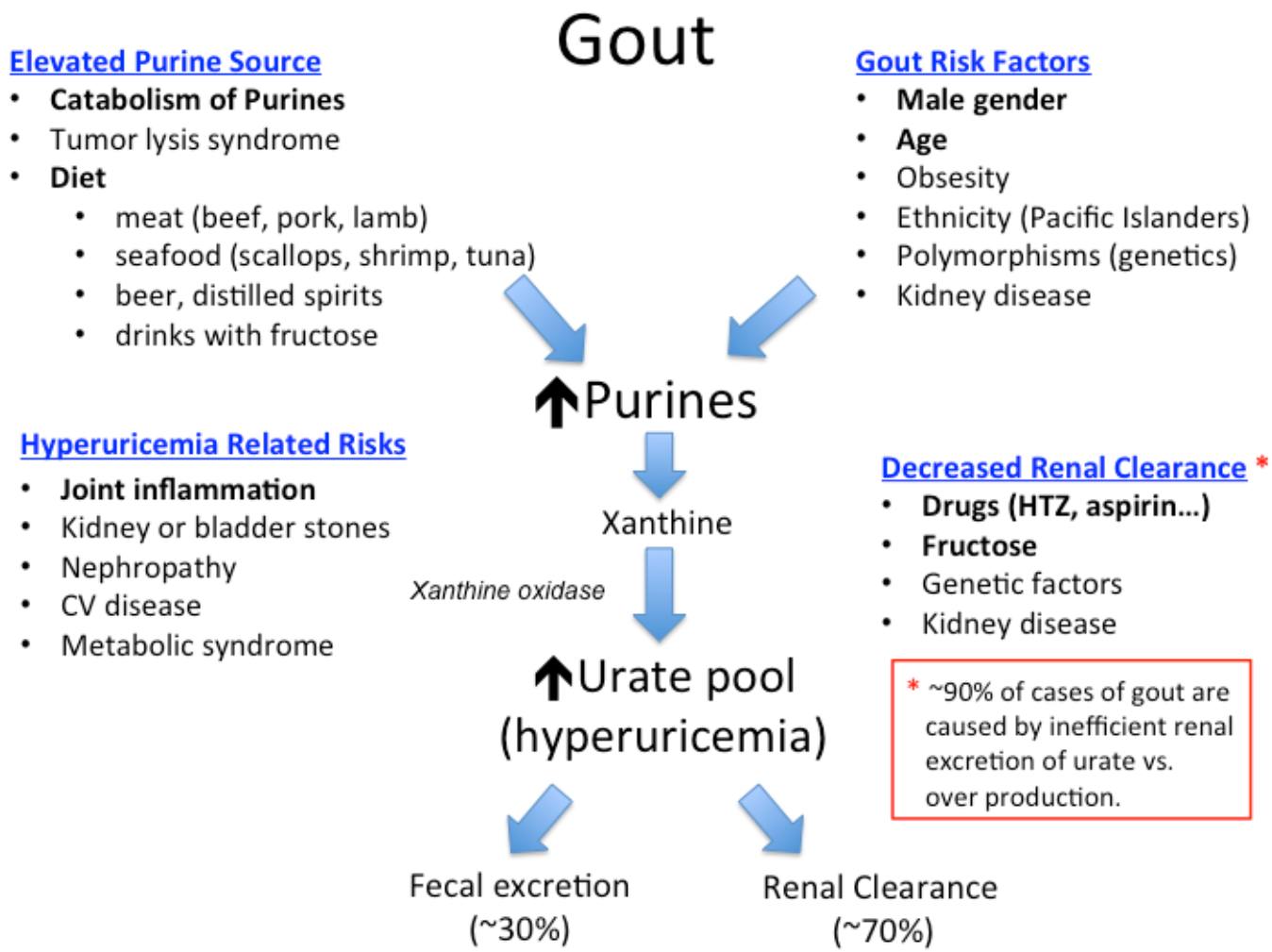
- **Gout** affects ~0.5–1% of the population of Western countries.
- Gout results from the **precipitation of urate crystals** in the tissues and the subsequent **inflammatory response**
- Acute gout usually causes an exquisitely painful **distal monoarthritis**, but it also can cause
  - joint destruction,
  - subcutaneous deposits (tophi),
  - and renal calculi (stones) and damage
- Hyperuricaemia = pre-gout stage
  - plasma urate > male 420 umol/l, female 360 umol/l

Pathophysiology of gout



- Gout is a metabolic disease („disease of the kings")
  - Uric acid is the end product of purine metabolism (e.g. ATP),
  - Uric acid is relatively insoluble compared to its hypoxanthine and xanthine precursors, and normal serum urate levels approach the limit of solubility.
  - hyperuricaemia - uric acid↑ (serum level)
    - increased production (tumors, diet, haemolysis)
    - decreased excretion (most cases: 90%) (Chronic Renal Failure, drugs- low dose aspirin)
  - deposition of monosodium urate (joints, cartilage)
    - recurrent acute arthritis (e.g. toe)
    - interstitial nephritis, nephrolith
    - tophus
- Pathogenesis
  - Urate tends to crystallize in colder or more acidic conditions.
  - Neutrophils ingesting urate crystals
  - secrete inflammatory mediators that lower the local pH and lead to further urate precipitation.
  - monosodium urate phagocytosed by synoviocytes
  - release of chemotactic factors (PGs, ILs)
  - chemotaxis – inflammation - destruction

Pathophysiology of gout

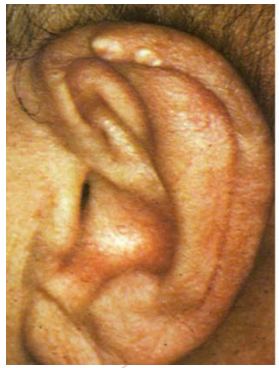


Stages of gout

- 0. hyperuricaemia without symptoms
- 1. First acute gout flare (gouty attack)
- 2. Repeated attacks
- 3. Chronic gout with visceral complications and tophi (tophus = „stone”)

Diagnosis

- Absolute criteria:
  - Urate crystals in synovial fluid
- Relative criteria:
  - **Acute gouty attacks (typical localization! Monoarthritis)**
  - **React quickly to colchicine (fast remission)**
  - **Tophi**
  - **Urate nephrolithiasis**
  - **Hyperuricaemia**

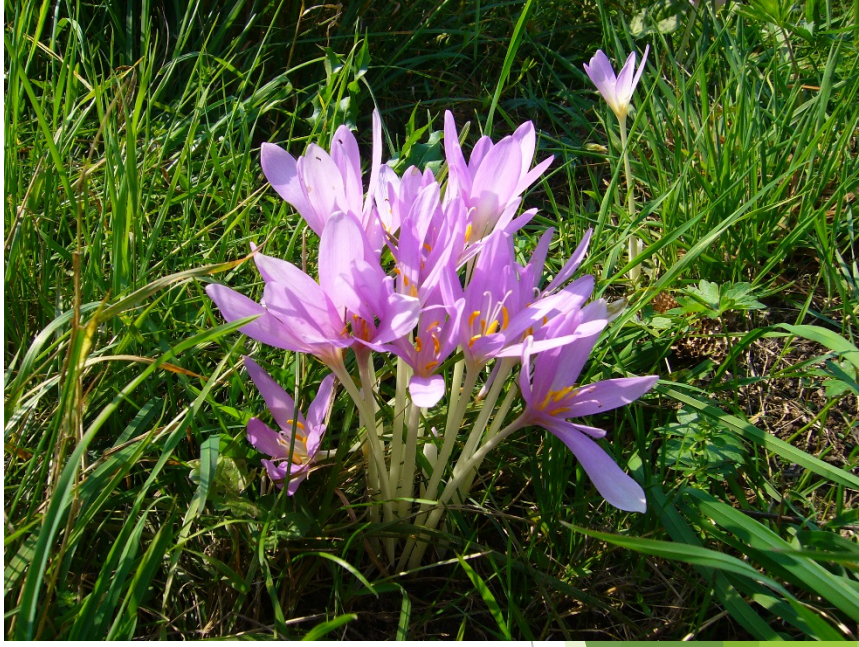


Drugs used in gout

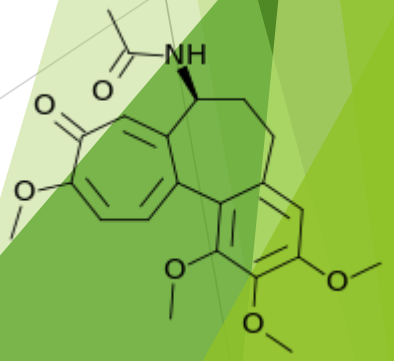
- NSAIDs
  - therapy
    - inhibits chemotaxis, urate crystal phagocytosis
    - pain relieving effect in acute episode
  - aspirin is not used (due to increased risk of renal calculi = kidney stone)
  - NSAIDs should be given at relatively high doses for 3–4 days and then gradually reduced for a total of 7–10 days.
  - Indomethacin, naproxen, sulindac, etoricoxib (a selective COX2 inhibitor) are approved

naproxen

Drugs used in gout

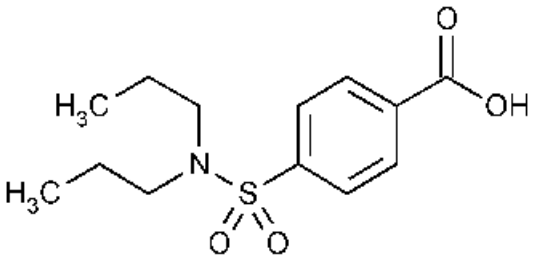


- colchicine
  - primary treatment
  - alkaloid (Colchicum autumnale)
  - inhibits leukocyte migration and phagocytosis
    - binds to ic. tubulin → prevents microtubule polymerization (cytoskeloton destruction)
    - antimitotic effect: arresting cell division in G1 by interfering with microtubule and spindle formation
  - inhibits the LTB4 secretion
  - used <u>for attack</u> and <u>for prevention</u> (3 x 0.6mg-1.2mg p.o.)
  - a.e.: **narrow therapeutic window ➔ toxicity**
    - diarrhea
    - nausea, vomitus
    - bone marrow suppression
    - shock, haematemesis, heamaturia (iv. adm.)

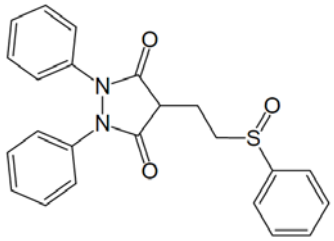


Drugs used in gout

- probenecid, sulfinpyrazone (uricosuric agents)
  - acting on proximal tubules
  - inhibit uric acid reabsorption (and other organic acid transport)
  - interference with other drugs secreted in the proximal tubules (penicillin, furosemide)
  - Adverse effects:
    - urolithiasis (renal stones)
    - GIT irritation
    - aplastic anaemia



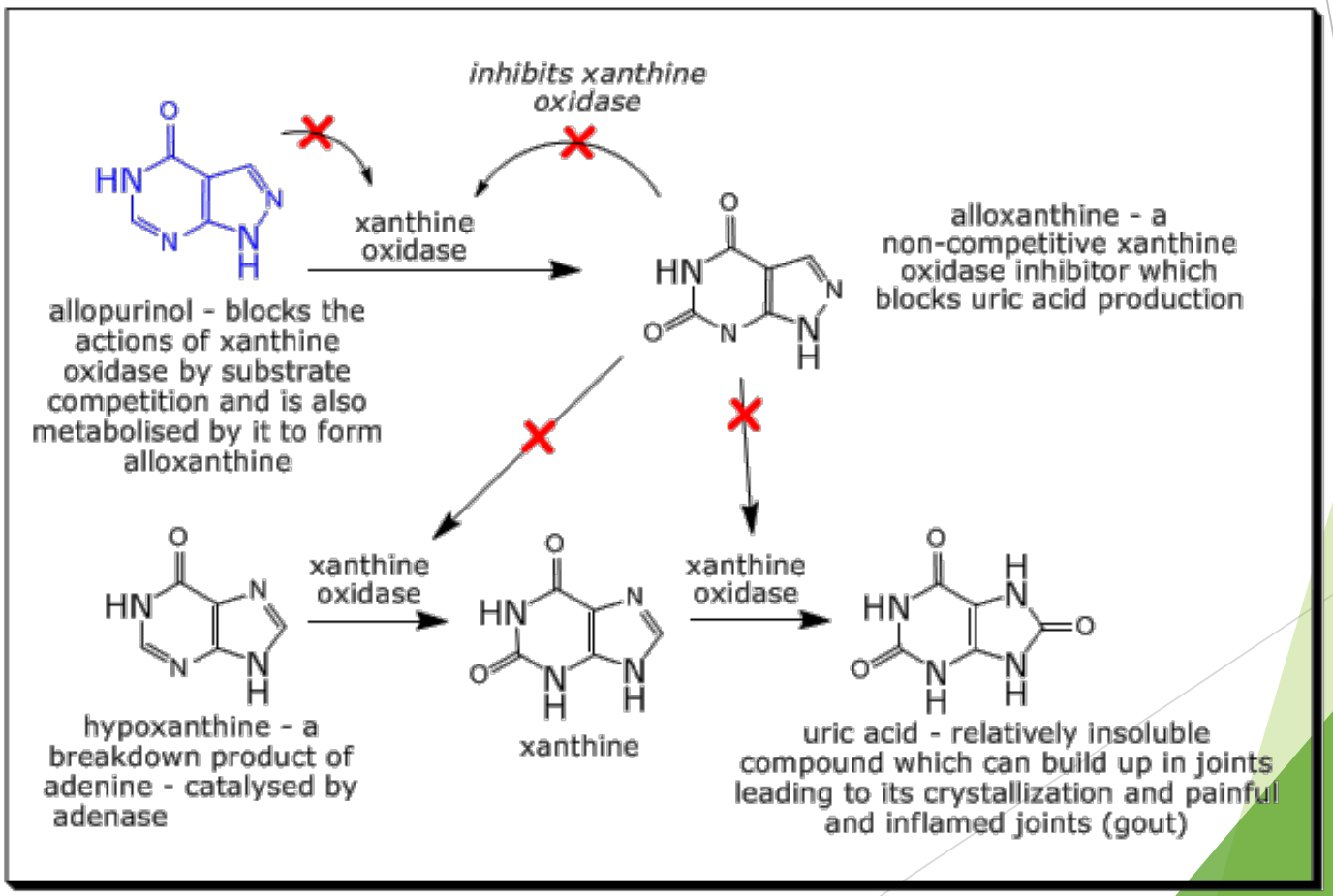
probenicid



supfinpyrazone

Drugs used in gout

- allopurinol
  - „urate lowering drug” = decreases urate pool
  - facilitates the dissolution of tophi
  - treatment in the intercritical periods
  - th.dose: 100-900mg/day
  - Mechanism of action:



Introduction to Rheumatoid arthritis

Rheumatoid arthritis

- RA is a chronic, progressive polyarthritis with unknown etiology and with underlying autoimmune processes.

- Prevalence: 0,5% of population
- (Hungary: ~50 thousand patient affected)
- female/male ratio = 2-3 : 1
- Starts between 30 and 50 years

Rheumatoid arthritis

- Wear-of = arthrosis! ⇔ rheumatoid arthritis

Differential diagnosis:

- Usually one joint is affected (or starts with 1) = gout
- less than 4 joints = post infectious arthritis
- 5 or more = polyarthritis: RA

Distribution:

- Asymmetric: gout
- Symmetric: RA

Characteristic joints affected:

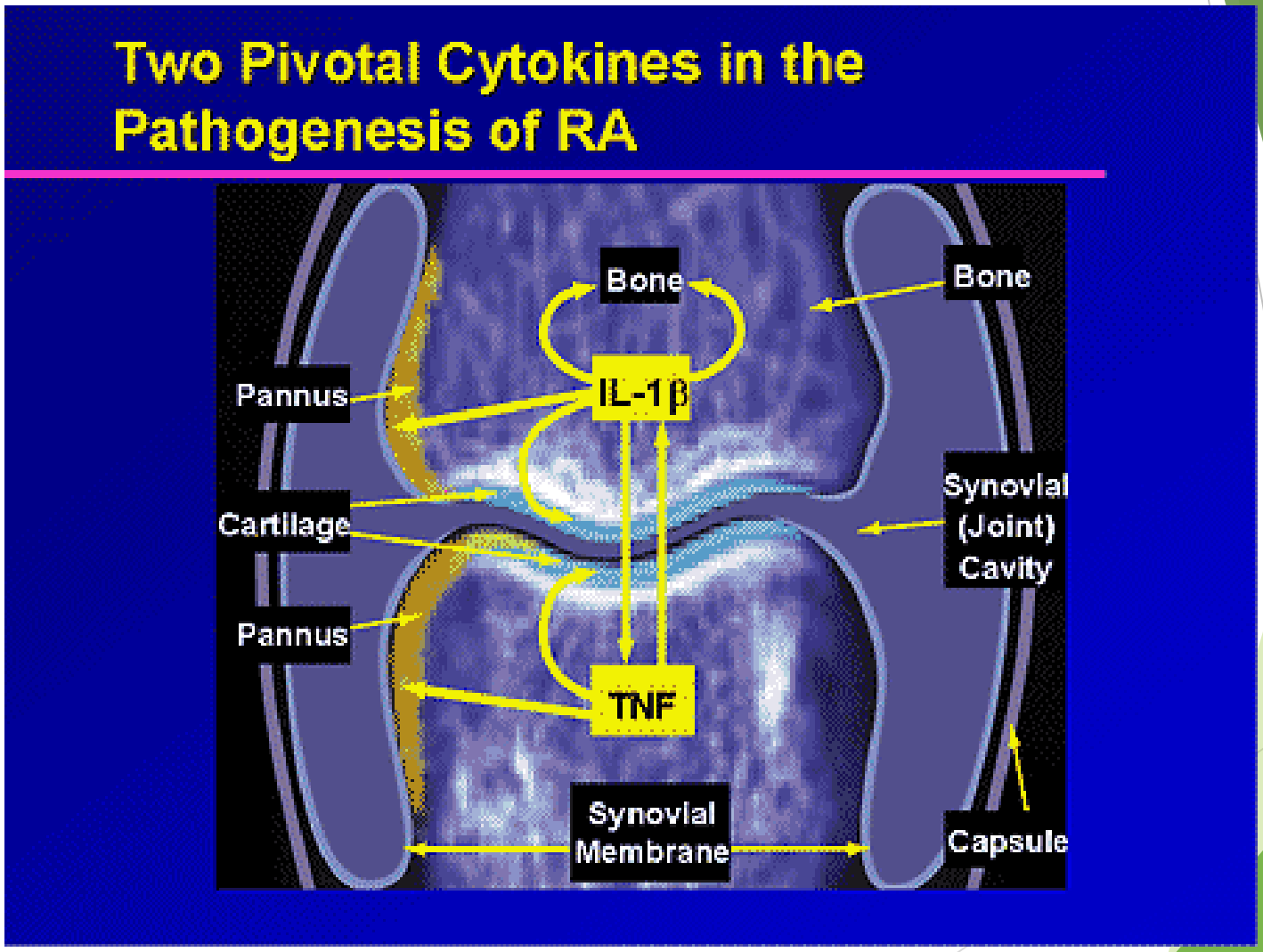
- Small joints of hands and feet
- wrists, knees and shoulders

Diagnosis

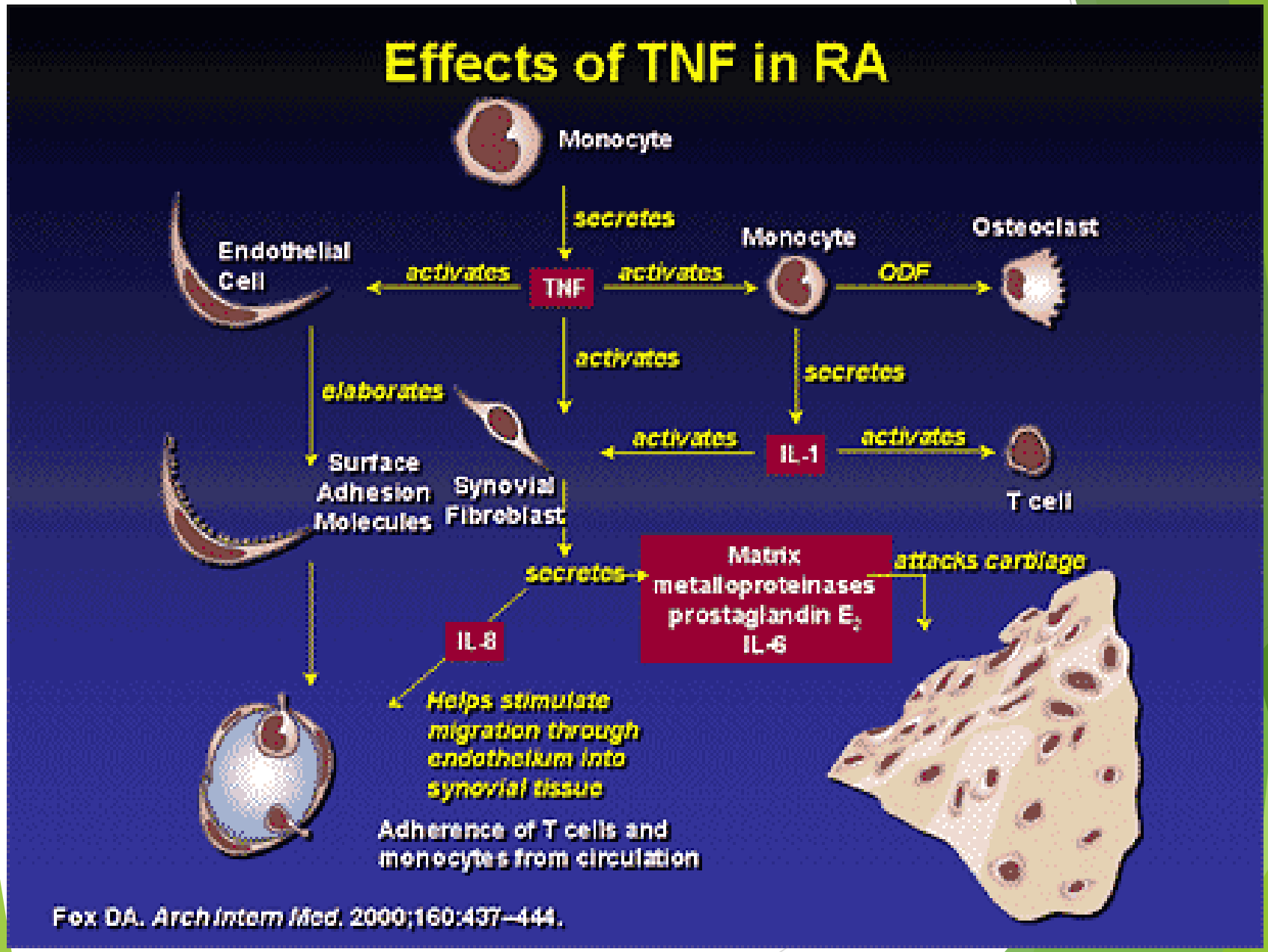
- At least 4 is true of the followings:
  - **Morning stiffness in joints (> 1 hour)**
  - **3 or more regions are inflammated**
  - **Inflammated joint at least in 1 region of the hand**
  - **Symmetric inflammation of joints**
  - **Rheumatoid nodes (even extra-articularly as well)**
  - **Radiologycal changes (erosions, decalcification)**
  - **Rheumatoid factor is presented in the serum**

„Swan neck”
Terminal phase

Pathogenesis

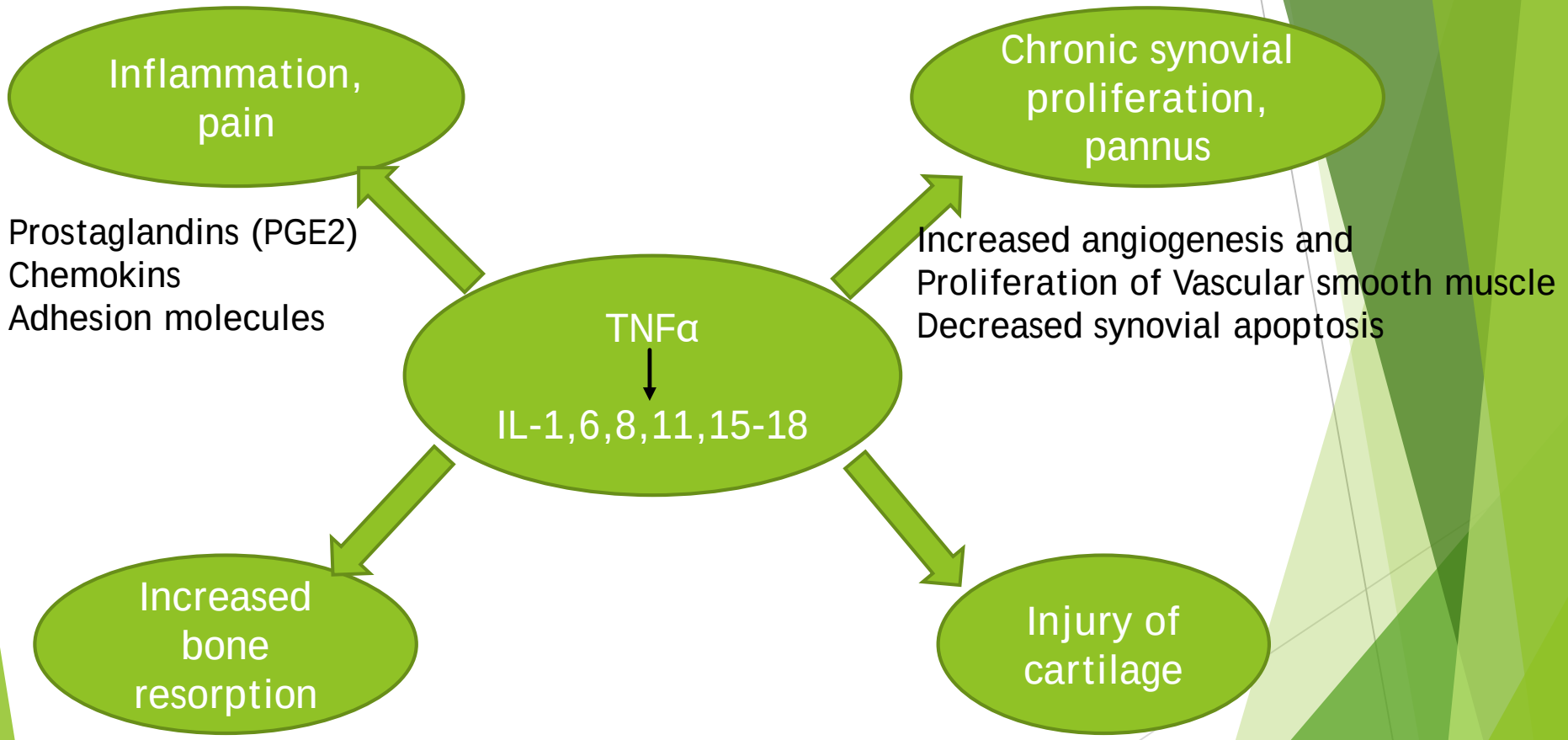


Pathogenesis

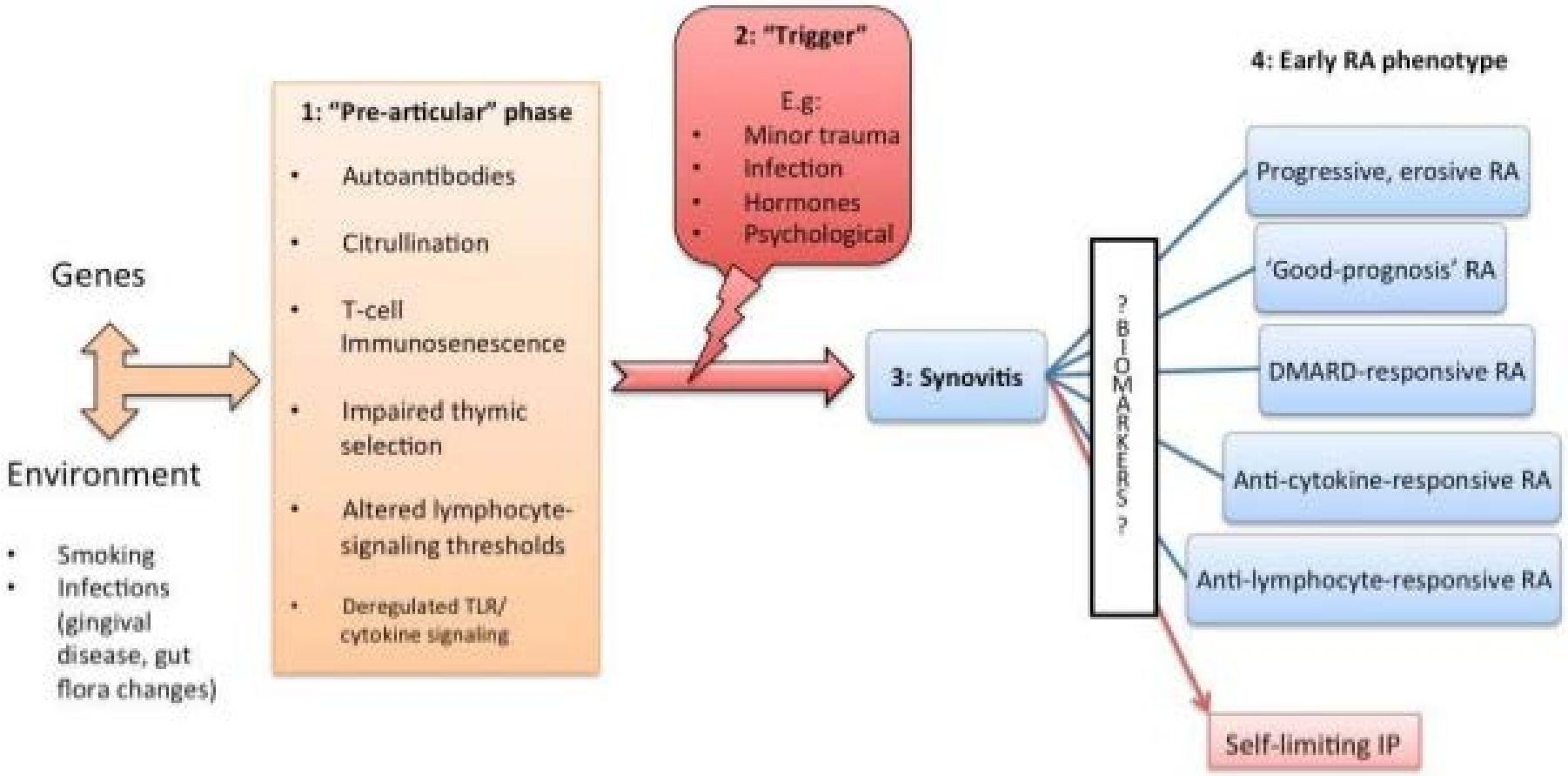


ODF = osteoclast differentiation factor

Pathogenesis



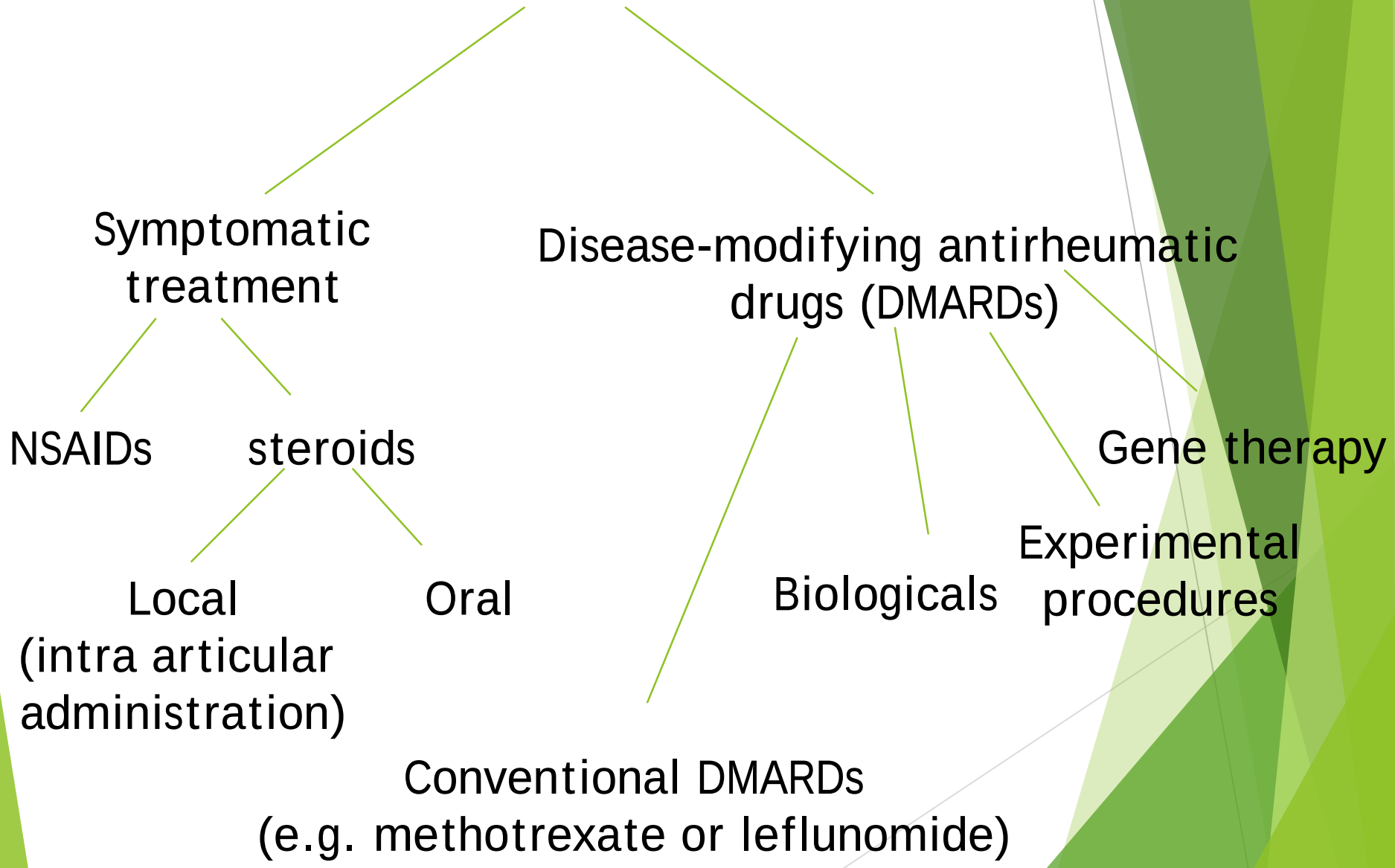
Pathogenesis of RA



Legend:
TLR: Toll like receptor; **DMARD**: Disease-modifying anti-rheumatic drug; **IP**: Inflammatory polyarthritis

Adapted from Best Pract Res Clin Rheumatol. 2009 February; 23(1): 37–48.

Pharmacologic treatment



Pharmacotherapy

- **NSAIDs**

- Basic therapy
- these drugs alone do not change the course of the disease of rheumatoid arthritis or prevent joint destruction.
- Mostly COX-2 selectives
- DO NOT combine with others or steroids

- celecoxib, Celebrex®
- etoricoxib, Arcoxia®
- lumiracoxib, Prexige®

Pharmacotherapy

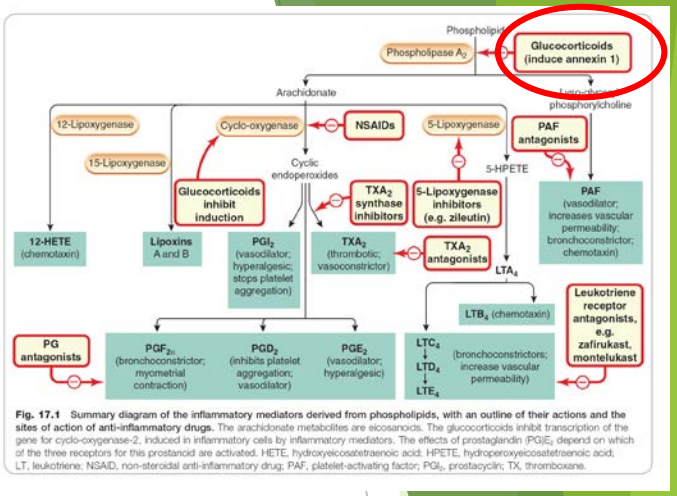


Fig. 17.1 Summary diagram of the inflammatory mediators derived from phospholipids, with an outline of their actions and the sites of action of anti-inflammatory drugs. The arachidonate metabolites are eicosanoids. The glucocorticoids inhibit transcription of the gene for cyclo-oxygenase-2, induced in inflammatory cells by inflammatory mediators. The effects of prostaglandin ($PGIE_2$ depend on which of the three receptors for this prostanoid are activated. HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LT, leukotriene; NSAID, non-steroidal anti-inflammatory drug; PAF, platelet-activating factor; PGI_2, prostacyclin; TX, thromboxane.

- **Corticosteroids**
- E.g. prednisone; methylprenisolone, Medrol®
- have both anti-inflammatory and immunoregulatory activity

Complex effect (decrease number of inflammatory cell, inhibits cytokine-synthesis, inhibits formation of arachidonic acid)

- Give locally if possible, not systemically
- Systemic application only in case of exacerbations for short time
- continuous dose < 5 - 7.5 mg/day
- Most frequent adverse effects:

ulcus duodeni, hypertonia, diabetes mellitus, osteoporosis, increased risk of infection, cataracta, myopathy, psychic disorders

Classification of Corticosteroids (CS)

Drug	ROA	Duration of action	Mineralo-C potency	Gluco-C potency
Short-acting drugs				
Hydrocortisone (cortisol)	Oral, parenteral, topical	8-12 hr	1	1
Cortisone	Oral, parenteral, topical	8-12 hr	0.8	0.8
Fludrocortisone	Oral	8-12 hr	200	10
Intermediate-acting drugs				
Methyl-prednisolone	Oral, parenteral, topical	12-36 hr	0.5	5
Prednisolone	Oral	12-36 hr	0.7	3.5
Triamcinolone	Oral, parenteral, topical	12-36 hr	0	5
Long-acting drugs				
Betamethasone	Oral, parenteral, topical	24-72 hr	0	30
Dexamethasone	Oral, parenteral, topical	24-72 hr	0	30

Conventional DMARDs – disease modifying antirheumatic drugs

- only DMARD agents have been shown to alter the disease course and improve radiographic outcomes

Mechanism of action:

- Immunosuppressants,
- inhibition of cell proliferation
- Inhibition of cytokine production
- antimetabolites

Conventional DMARDs

Conventional DMARDs include:

- **Azathioprine (Imuran)**
- **Cyclophosphamide (Cytoxan)**
- **Cyclosporine (Neoral)**
- **Hydroxychloroquine (Plaquenil)**
- **Leflunomide (Arava)**
- **Methotrexate (Rheumatrex, Trexall)**
- **Sulfasalazine (Azulfidine)**
- **Tofacitinib (Xeljanz)** Janus kinase (JAK1,3) inhibitor

Conventional DMARDs

- Azathioprine (AZT)
  - metabolite: 6-MP (purine-analoge)
    - suppresses inosinic acid synthesis (purine synthesis)
    - ↓T-cell, B-cell function
    - ↓IG production
    - ↓IL-2 secretion
  - clinical use
    - 2mg/kg/day
    - RA
    - (cancer chemotherapy)
  - a.e.:
    - bone marrow supression
    - GIT disturbances
    - infection!

Conventional DMARDs

- cyclophosphamide
  - active-metabolite: phosphoramide mustard
  - Cross-links DNA!
    - ↓ T-and B-cell function
  - active metabolites
    - akrolein: cystitis (heamorrhagic)
    - aldophosphamide: (bonemarrow suppression)
  - clinical use:
    - 2 mg/kg p.o.
    - RA, SLE
    - lymphoma, leukaemia
- cyclosporine
  - Immunosupressant ➔ regulation of gene transcription
    - ↓ IL-1, IL-2 R production
    - ↓ T-cell, macrophage responsiveness
  - clinical use
    - 3-5 mg/kg/day
  - nephrotoxicity!!!

Conventional DMARDs

- chloroquine, hydroxichloroquine

  - antimalaric agents
  - effect:
    - suppression of T-lympocytes
    - decreased leukocyte chemotaxis
    - inhibition of DNA and RNA synthesis
    - trapping free radicals
  - tissue selectivity – melanin containing tissues
  - clinical use (apart from RA)
    - SLE, Sjögren syndrome
    - chloroquin: 200 mg/day
  - a.e:
    - ocular toxicity

Conventional DMARDs

- Leflunomide
  - Prodrug = active metabolite: teriflunomide
    - Immunomodulatory = ↓ leukocyte reproduction
    - (antiviral = Inhibits virion asembly)
  - Mechanism of action:
    - inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) = *de novo* synthesis of uridine monophosphate (UMP) ➔ inhibition of DNA/RNA synthesis
  - Clinical use
    - RA
    - Active arthritis psoriatica
    - 10-20mg daily (oral)
  - Adverse effects
    - Hepatotoxicity
    - Due to immunosupression ➔ infections

Conventional DMARDs

- Methotrexate (MTX)
  - effects:
    - inhibition of dihydrofolate reductase (DHFR) → ↓FH4 → TS ↓ (= ↓ dUMP → dTMP) → ↓DNA synthesis
  - clinical use
    - RA (first choice!)
    - cancer chemotherapy (AML)
  - Adverse effects:
    - mucosal ulcers
    - hepatotoxicity
    - bone marrow suppression
    - Antidote: leucovorin!

Conventional DMARDs

- sulfasalazine
  - intestinal bacteria metabolise it into: sulfapyridine + 5-ASA
    - ↓ T-cell function
    - ↓ release inflammatory citokines (IL-1, IL-6, IL-12)
  - Mechanism of action:
    - 5-ASA: COX-inhibitor, inhibits synthesis of leukotrienes, and trapping free radicals
  - clinical use
    - 2-3g/day
    - RA
    - 5-ASA – IBD!
  - Adverse effects (mainly due to sulfapyridine)
    - agranulocytosis
    - hypospermia

Drug	Onset of action	Major toxicities	Dosing	Monitoring	Comments
Methotrexate	1 - 2 months	Hepatotoxicity, myelosuppression, teratogenicity, stomatitis, interstitial lung disease	PO or SC, IM dosing (opt for SC, IM administration if mucositis/GI adverse effects with PO or if lack of response to PO); start at 10 - 15 mg/wk, increase 5 mg/mo to 20 - 25 mg/wk	Check baseline CBC count, CMP, hepatitis B and C serologies; monitor CBC count, CMP every 2 months	Give daily folic acid; contraindicated in hepatitis B and in hepatic failure; adjust dose for renal insufficiency; counsel patients to avoid alcohol use and about contraception
Hydroxychlor-oquine	2 - 3 months	Retinopathy	200 - 600 mg/d PO, < 6.5 mg/kg; can be divided into bid dosing	Annual eye examination	Exercise caution in hepatic failure; adjust dose for renal insufficiency
Sulfasalazine	4 - 6 weeks	GI upset, allergic reaction to sulfa moiety, rash, anemia, hemolysis, agranulocytosis and, rarely, drug-induced lupus	500 mg/d PO for 1 week, then 500 mg PO bid for 1 week, then 500 mg PO tid for 1 week, then 1 g PO bid	Check for G6PD deficiency before starting; check baseline CBC count, CMP; monitor CBC count at least monthly for the first 3 months, then every 3 months	Contraindicated in hepatic failure; adjust dose for renal insufficiency
Leflunomide	4 weeks	Hepatotoxicity, myelosuppression, teratogenicity, rash	100 mg/d for first 3 days, then 20 mg/d PO	Check baseline CBC count, CMP, hepatitis B and C serologies; monitor CBC count, CMP every 2 months	Contraindicated in hepatitis B and in hepatic failure; adjust dose for renal insufficiency; counsel patients to avoid alcohol use and about contraception

DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; CBC, complete blood cell; CMP, comprehensive metabolic panel; G6PD, glucose-6-phosphate dehydrogenase.

Most important DMARDs

Agent	Pharmacology	Usual dosage	Adverse effects and risks
Methotrexate	Anti-metabolite	10–25 mg weekly (oral or subcutaneous)	Hepatotoxicity, myelotoxicity, fibrosing alveolitis
Sulfasalazine	Anti-inflammatory and antimicrobial	1,000–1,500 mg twice daily (oral)	Hepatotoxicity, myelotoxicity, hypersensitivity reactions
Antimalarial drugs	Interference with antigen-processing?	Hydroxychloroquine 200–400 mg daily (oral)	Retinopathy
Leflunomide	Anti-metabolite	10–20 mg daily (oral)	Hepatotoxicity, myelotoxicity, hypertension
Gold salts (parenteral)	Unknown	50 mg weekly (intramuscular)	Hypersensitivity reactions, nephritis, fibrosing alveolitis
Auranofin (oral gold salt)	Unknown	3–6 mg daily (oral)	Diarrhoea, hypersensitivity reactions
Ciclosporin A	T-cell activation inhibitor	2.5–5.0 mg/kg per day (oral)	Nephrotoxicity, hypertension
Azathioprine	Cytostatic	50–200 mg daily (oral)	Hepatotoxicity, myelotoxicity, gastrointestinal

Medscape

Pharmacotherapy - biologicals

- **Cytokine inhibitors**
  - **TNFα** blockers
    - **mAb**
      - **infliximab/Remicade**
      - **adalimumab/Humira**
      - **golimumab/Simponi**
    - PEGylated **mAb** — **certulizumab pegol/Cimzia**
    - Soluble **TNFα receptor** — **etanercept/Enbrel**
  - **IL-6 R** blocker — **tocilizumab/Roactemra**
  - IL-1 antagonist — anakinra
- **Agents acting on cell surface**
  - **T-** cells — **abatacept/Orencia**
  - **B-** cells — **rituximab/Mabthera**

TNF=tumor necrosis factor, IL=interleukin, mAb=monoclonal antibody

Biological DMARDs

- TNF-α blocking agents

  - adalimumab
    - IgG like anti-TNF monoclonal antibody
    - binding soluble TNF-α
    - ↓ T-cell, macrophage function
    - clinical use
      - sc.
      - RA, Crohn's disease
    - a.e.:
      - infection (upper respiratory tract)

  - infliximab
    - IgG like monoclonal antibody
    - binding soluble and membrane bound TNF-α
    - inhibition of macrophage and T-cell function
    - clinical use
      - RA, psoriasis, Wegener granulomatosis,
      - 3-5mg/kg, i.v.
      - coapplication: methotrexate
    - a.e.:
      - infection (upper respiratory tract)

  - Golimumab
    - clinical use
      - RA, ulcerative colitis, psoriatic arthritis and ankylosing spondylitis
      - Together with: methotrexate

Similar:
Afelimomab
Certolizumab pegol (PEGylated)
Nerelimomab

Biological DMARDs

- TNF-α inhibitor agents (cont.)
  - etanercept
    - Soluble TNF-α receptor
    - Fusion protein: TNF-receptor's binding site + IgG fc part
    - PEGylated version = Pegsunercept
    - Clinical use
      - sc.
      - RA, psoriasisos arthritis etc
    - Adverse Effects:
      - Infections (upper respiratory tract)

Biological DMARDs

- IL-6 receptor blocker
  - Tocilizumab
    - Humanized monoclonal antibody against IL-6 receptor
    - Clinical application
      - i.v. or sc.
      - RA, juvenile idiopathic systemic arthritis etc
    - Adverse effects:
      - Infections (upper respiratory tract)
- IL-1 receptor antagonist
  - Anakinra
    - NOT antibody; recombinant version of the physiological so-called interleukin 1 receptor antagonist (protein)
    - Clinical application
      - sc.
      - RA
    - Adverse effects:
      - Infections (upper respiratory tract)

Biological DMARDs

T-cell inhibitor

- Abatacept
  - Fusion protein: CTLA4 (=CD152) receptor-domain + IgG fc region
    - CTLA4 (and thus abatacept also) binds B7 protein ➔ T-lymphocyte activation will not be established
    - Things needed for T-lymphocyte activation:
      - APC must present an antigen bound to MHC for the T-cell receptor
      - AND the APC also must present a B7 protein for T-cells' CD28 (~B7-receptor)
  - Clinical application:
    - i.v.
    - RA

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)

Biological DMARDs

B-cell inibitor

- rituximab
  - monoclonal antibody (targeting CD20+ B-lympocytes)
    - Targets the cell for NK-cell mediated destruction ➔ B-lymphocyte depletion
  - clinical use:
    - Refractory RA
    - Against many immunological diseases (lymphomas, leukemias, transplant rejection, and autoimmune disorders)
    - iv. infusion 1000mg

Biologicals MA

Agent	Structure	Pharmacology	Usual dosage	Specific side effects and risks	Regulatory status
Abatacept	Recombinant CTLA4 molecule dimerized on Ig frame	T-cell co-stimulation blocker	500–1,000 mg monthly (intravenous)	Infusional reactions, infections	Approved in Europe and US
Adalimumab	Human monoclonal	TNF blockade	40 mg biweekly (subcutaneous)	Injection site reactions, infections (including tuberculosis)	Approved in Europe and US
Anakinra	Recombinant IL-1 receptor antagonist	IL-1 receptor blockade	100 mg daily (subcutaneous)	Injection site reactions, infections, neutropenia	Approved in Europe and US
Certolizumab pegol	Pegylated Fab' fragment from humanized monoclonal antibody	TNF blockade	200 mg biweekly or 400 mg monthly (subcutaneous)	Injection site reactions, infections (including tuberculosis)	Approved in US
Etanercept	Recombinant TNF receptor (p75) dimerized on Ig frame	TNF blockade	50 mg weekly (subcutaneous)	Injection site reactions, infections (including tuberculosis)	Approved in Europe and US
Golimumab	Human monoclonal	TNF blockade	100 mg every 4 weeks (subcutaneous)	Injection site reactions, infections (including tuberculosis)	Approved in US
Infliximab	Chimeric monoclonal	TNF blockade	3–10 mg/kg every 4–8 weeks (intravenous)	Infusional reactions, infections (including tuberculosis)	Approved in Europe and US
Rituximab	Chimeric monoclonal	B-cell depletion	1,000 mg, 2 intravenous infusions 2 weeks apart	Infusional reactions, infections	Approved in Europe and US
Tocilizumab	Humanized monoclonal	IL-6-receptor blockade	8 mg/kg every 4 weeks (intravenous)	Infusional reactions, infections, cytopenias, elevated cholesterol	Approved in Europe

Abbreviations: CTLA4, cytotoxic T-lymphocyte antigen 4; IL, interleukin; TNF, tumor necrosis factor.