NSAIDs, DMARDs,
Drugs applied in gout,
Drugs applied in Alzheimer's disease,

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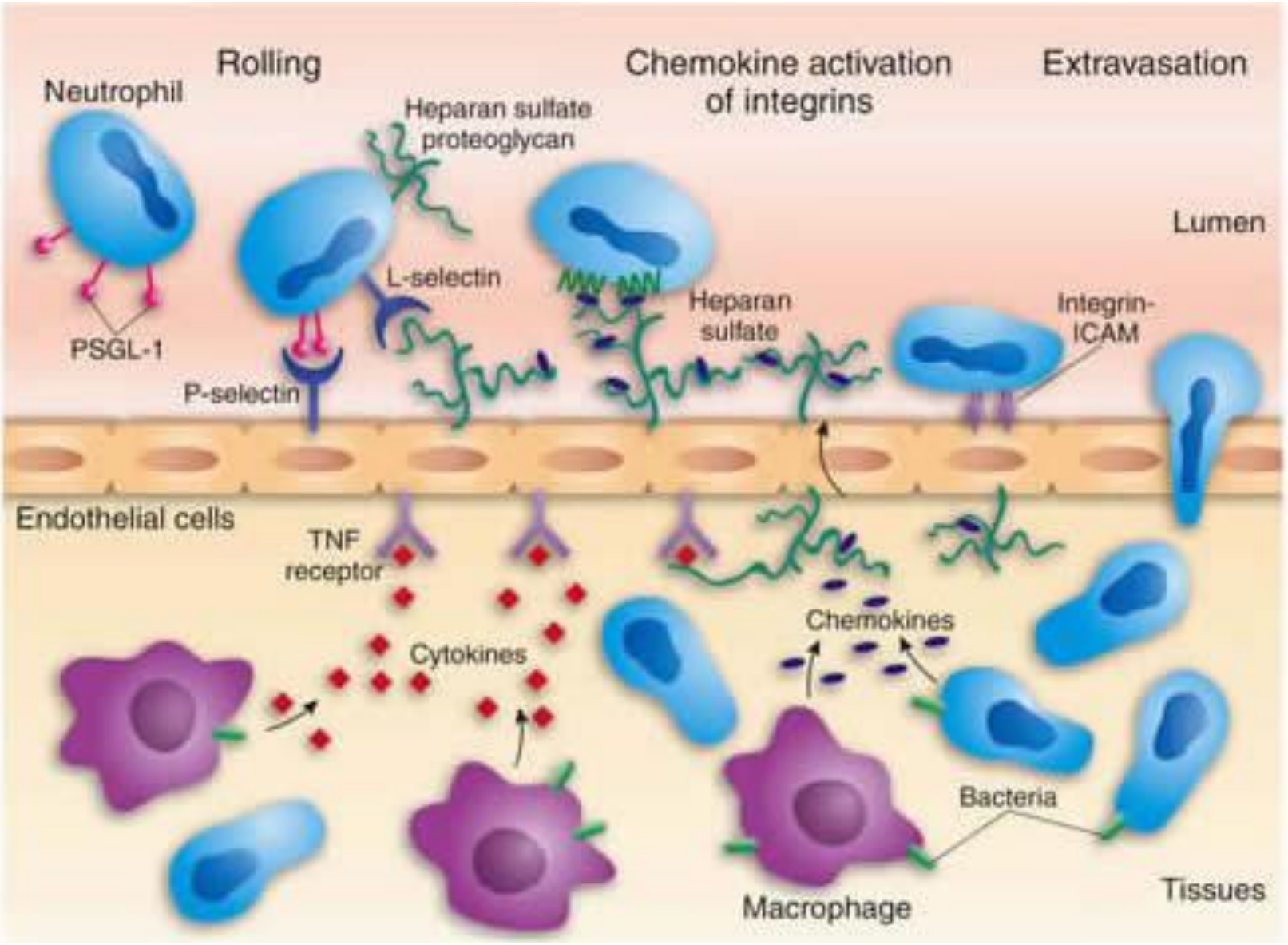
Immune response / Inflammation

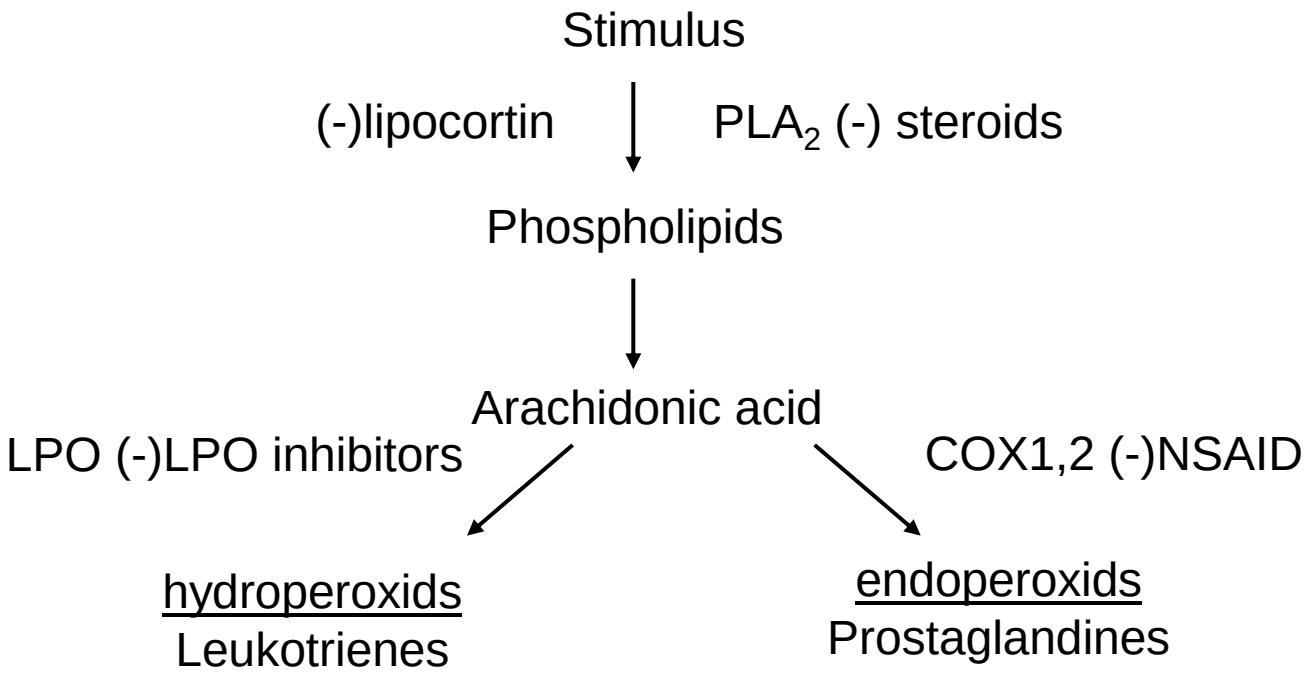
- endogenous/exogenous antigen/stimuli induced complex response reaction of the vascularized connective tissue!!!
  - protective effect
  - elimination of necrotic tissue
  - but! „autoimmune”
  - 3 main types
    - acute
    - subacute
    - chronic


Neutrophil
Rolling
Heparan sulfate proteoglycan
Chemokine activation of integrins
Extravasation
Lumen
L-selectin
PSGL-1
P-selectin
Heparan sulfate
Integrin-ICAM
Endothelial cells
TNF receptor
Cytokines
Chemokines
Bacteria
Macrophage
Tissues

Therapeutic strategies

- Autoimmune disease
  - RA, spondyloarthritis, Bechterew's disease,
  - Sjögren syndrome, SLE, PM/DM
- NSAIDs
  - symptomatic relief for pain and inflammation
  - „long time" treatment periods
  - no influence on disease progression
  - rapid effect
- DMARDs
  - „slow acting" drugs
  - modify the disease
  - block disease progression
- COX-1- gastric mucosa, thrombocytes, endothel, kidney
- COX-2 induced by immune response

Immune response



LTB_4: phagocyte attraction, act.
LTC_4: bronchoconstr., ↑secr.
LTD_4: chemotaxis, vasodilation

PGI_2: vasodilation, inhib. of thromb.aggr.
PGE_2: fever, inflammation, pain
$PGF_{2\alpha}$: uterus contraction
TXA_2: vasoconstriction, facil. of thromb. aggr.

LTR antagonists

Classification

- according to selectivity
  - selective 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

NSAIDs

- Pharmacokinetic features
  - weak organic acids → pKa≈3.0 → rapid absorption
  - metabolized in the liver (CYP3A, CYP2C)
  - high cc. in synovial fluid (repeated exposure)
  - highly protein bound (≈98%)
  - renal excretion
- Pharmacodynamic features/effects
  - inhibition of immune response (antiinflammatory-antiflogistic effect)
    - inhib. of chemotaxis
    - ↓sensitivity of vessels to histamine
    - down regulation of IL-1 production
    - decreased production of free radicals and superoxide
  - antipyretic effect
    - cAMP↓ in hypothalamic thermoregulation centr.
  - analgesia
    - peripherial inhib. of nociception (PGs facilitate effects of bradykinine)
  - antithrombotic effect
    - TXA_2 ↓, platelet aggregation↓

NSAIDs

- adverse effect profile
  - CNS:
    - headache, tinnitus, dizziness
  - Cardiovascular:
    - fluid retention, hypertension, edema
  - GIT (inhib. of PG synthesis – protective factor)
    - ulcers, bleeding, nausea, vomiting, pancreatitis
  - Hematologic (bone marrow suppr.)
    - thrombocytopenia, neutropenia, aplastic anaemia
  - Hepatic (metamizol, aspirin)
    - Hepatitis, (Reye's syndrome)
  - Pulmonary (LT↑)
    - Aspirin asthma!!!
  - Renal
    - RBF(autoregulation)↓, renal insufficiency, renal failure, hyperkalaemia

NSAIDs

- acetyl-salicylic acid, ASA (Aspirin®)
  - irreversible inhibitor of COX-1
  - isolated from willow (bark)
  - rapid absorpion of stomach and small intestine
  - antipyretic, analgesic, antiflogistic effect
  - antithrombotic effect (platelet aggregation↓)
  - clinical use:
    - TIA, AMI - 300mg – reduce platelet aggregation -secundary prevention of AMI, stroke
    - 0,5-2,5g/day – antipyretic, analgesic effect
    - 2,5-4g/day – antiflogistic
    - 5g/day – uricosuric effect
  - pills (intestinosolvent)
  - aspirin intoxication! (metabolic acidosis)
  - a.e.:
    - gastric ulcer, gastric intolerance
    - aspirin-asthma
    - hepatotoxicity
    - CI:haemophilia

NSAIDs

- non selective COX inhibitors
  - diclofenac
    - phenylacetic acid derivative
    - inhibition of COX-1, COX-2
    - potent analgesic effect
    - selectiv. for muscle-joint inflammation
    - ulceration of GIT
      - coappl.! omeprazole or famotidine or misoprostole
    - 150 mg/day
    - adm. form.
      - topical gel. 1-3%
      - i.m. injection
      - ophtalmic preparation – prevention of p.o. ophthalmic inflamm.
  - ibuprofen
    - phenylpropionic acid derivative
    - analgesic effect
    - antiinflammatoric effect (>2400mg) = 4000mg ASA
    - closure of ductus arteriosus (preterm infants)
    - adm. routes
      - i.m.
      - p.o.
      - topical cream
    - effective in headache, dental pain, premenstrual pain
    - combined with spasmolytics

NSAIDs

- indometacin
  - one of the first explored NSAIDs (1963)
  - indol derivative
  - effects:
    - non-selective COX inhibition
    - inhibition of phospholipase A and C
    - ↓neutrophil migration
    - ↓T-,B-cell proliferation
  - closure of ductus arteriosus
  - broad a.e. profile
    - GIT effects+pancreatitis!
    - dizziness, confusion, hallucinations
    - thrombocytopenia, aplastic anaemia
    - renal papillary necrosis
- ketoprofen
  - propionic acid derivative
  - inhibit. of COX and LPO
  - 100-300 mg/day
- ketorolac
  - analgesic, no anti-inflammatory effect
  - i.v. /i.m. administration
  - coapplication with morphine→postoperative analgesia
- naproxen
  - naphtylpropionic acid derivative
  - rheumatologic indications
  - slow-release formulation

NSAIDs

- phenylbutazon
  - analgetic, antipyretic, antiflogistic
  - obsolete
  - inhibits uric acid reabsorption (applied in gout)
  - a.e.:
    - ulcerative!!!
    - aplastic anaemia!!
    - oedema – fluid retention
  - clinical use:
    - gout
    - RA
  - coapplication: prednisolon
- phenazon, noraminophenazon
  - antipyretic effect
  - potent analgetic effect
  - a.e.:
    - agranulocytosis
    - pro-convulsive effect

NSAIDs

- selective COX-2 inhibitors
  - COX-1 vs. COX-2
  - no antithrombotic effect
  - reduced side effect profile
  - prevention of Alzheimer's disease
    - reducing neural immune response
  - prevention of colorectal cc.
    - elevated level and act. of COX-2 in neoplas. tissue
    - PGE_2↑, proliferation↑, immune response↓
    - th. use: HNPCC, FAP
  - COX-2 mediated PG synthesis in vascular endothel!
    - ↑incidence of thrombotic attacks
    - RR↑
    - withdrawal of the market! (rofecoxib-Vioxx – celecoxib - Celcox)
  - celecoxib, meloxicam
  - clinical use: rheumatic indications!

NSAIDs

- paracetamol (acetaminophen)
  - analgesic, antipyretic effect
  - no anti-inflammation
  - „aspirin alternative”!
    - aspirin asthma, haemophilia, gastric ulcer
  - clinical use:
    - hyperpyrexia - children
    - headache, myalgia, postpartum pain
  - >4g/day – hepatotoxicity
    - n-acetyl-benzokinone – toxic metabolite!
    - A.D.! SH donor – N-acetyl-Cys

DMARDs

- Azathioprine (AZT)
  - metabolite: 6-TG (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!

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
    - SLE, Sjögren syndrome
    - chloroquin: 200 mg/day
  - a.e:
    - ocular toxicity

DMARDs

- methotrexate
  - effects:
    - inhibition of dihydrofolate reductase (AICAR transformylase) → ↓FH4 → TS ↓→ ↓DNA synthesis (dUMP → dTMP)
  - clinical use
    - RA (first choice!)
    - cancer chemotherapy (AML)
  - a.e.:
    - mucosal ulcers
    - hepatotoxicity
    - bone marrow suppression
    - A.D.: leucovorin!

DMARDs

- cyclophosphamide
  - active-metabolite: phosphoramide mustard
  - cross linked DNA!
    - ↓ T-and B-cell function
  - active metabolites
    - akrolein: cystitis (heamorrhagic)
    - aldophosphamide: (b.m. supp.)
  - clinical use:
    - 2 mg/kg p.o.
    - RA, SLE
    - lymphoma, leukaemia
- cyclosporine
  - regulation of gene transcription
    - ↓ IL-1, IL-2 R production
    - ↓ T-cell, macrophage responsiveness
  - clinical use
    - 3-5 mg/kg/day
  - neprotoxicity!!!

DMARDs

- mycophenolate mofetil
  - active metabolite: mycophenolic acid
  - effects:
    - inhibits CMP dehydrogenase
      - ↓ T-cell proliferation
  - clinical use
    - 2g/day
    - SLE, vasculitis, Wegener granulomatosis
- rituximab
  - monoclonal antibody (targeting CD20+ B-lympocytes)
    - B-lymphocyte depletion
  - clinical use:
    - alternative route!
    - iv. infusion 1000mg

DMARDs

- sulfasalazine
  - sulfapyridine + 5-ASA (intestinal bacteria)
    - ↓ T-cell function
    - ↓ release inflammatory citokines (IL-1, IL-6, IL-12)
  - clinical use
    - 2-3g/day
    - RA
    - 5-ASA – IBD!

DMARDs

- TNF-α blocking agents
  - adalimumab
    - IGG like anti-TNF monoclonal antibody
    - binding soluble TNF-α
    - ↓ T-cell, macrophag 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, Wgener granulomatosis,
      - 3-5mg/kg, i.v.
      - coapplication: methotrexate
    - a.e.:
      - infection (upper respiratory tract)
  - etanercept
    - soluble TNF-α receptor

Drugs used in gout

- Gout as disease
  - metabolic disease („disease of the kings”)
  - „Metabolic syndrome”
  - hyperuricaemia - uric acid↑ (serum level)
    - increased production (tumors, diet, haemolysis)
    - decreased excretion (90%) (CRF, drugs- low dose aspirin)
  - deposition of monosodium urate (MNU) (joints, cartilage)
    - recurrent acute arthritis (toe)
    - interstitial nephritis (tophus), nephrolith.

- pathogenesis
  - monosodium urate phagocytosed by synoviocytes
  - release of chemotactic factors (PGs, ILs)
  - chemotaxis – inflammation - destruction

- therapeutical strategies:
  - relieve acute gouty attacks
  - prevent gouty episodes

Drugs used in gout

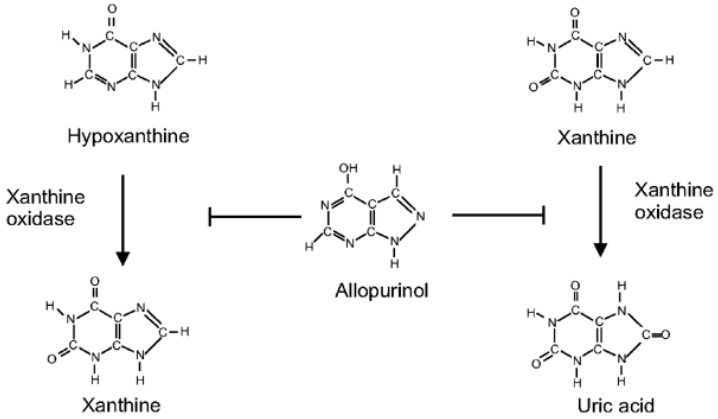
- NSAIDs
  - therapy
    - inhibits chemotaxis, urate crystal phagocytosis
    - pain relieving effect in acute episode
  - aspirin is not used (<2,6g/d uric acid retention) – (>5g/d uricosuric-adv.eff.!)
  - indomethacin – replacement of aspirin

- colchicine
  - primary treatment
  - alkaloid (Colchicinum autumnale)
  - inhibits leukocyte migration and phagocytosis
    - binds to ic. tubulin → prevents mictotubule polymerization (cytoskeloton destr.)
  - inhibits the LTB4 secretion
  - used for attack and for prevention(3 x 0,6mg-1,2mg p.o.)
  - a.e.:
    - diarrhea
    - low TI
    - nausea, vomitus
    - bone marrow suppression
    - shock, haematemesis, heamaturia (iv. adm.)

Drugs used in gout

- probenicid, sulfinpyrazone (uricosuric agents)
  - acting on proximal tubules
  - inhibit uric acid reabsorption (↓)
  - interference with other drugs secreted in the prox.tub. (penicillin, furosemide)
  - a.e.:
    - urolithiasis (renal stones)→hyperhidration, alkalic pH
    - GIT irritation
    - aplastic anaemia

- allopurinol
  - „urate lowering drug”
  - metabolized by xanthin oxidase→alloxanthine
  - inhibits xanthin oxidase
  - decreases urate pool
  - treatment in the intercritical periods
  - antiprotozoal indications
  - increase the effect of AZT, cyclophosphamide
  - th.dose: 300mg/day



Pharmacotherapy of Alzheimer's disease

- progressive impairment of memory and cognitive functions
- elderly(>85ys≈20%)
- inherited and environmental factors
- deposits of amiloid β in cerebral cortex
  - loss of cholinergic neurons
  - cerebral atrophia

- molecular processes (pharmacologic targets)
  - mitochondrial dysfunction
  - synthesis and aggregation of tau protein
  - synthesis and aggregation of amiloid β
  - impaired glucose utilization
  - accumulation of abnormal proteins

Pharmacotherapy of Alzheimer's disease

- Cholinesterase inhibitors
  - galantamine, tacrine, rivastigmine
  - rapid penetration to CNS
  - cholinomimetic adverse effects
  - oral application
- NMDA antagonists
  - memantine
  - competitive blockade
- MAO-B inhibitors
  - selegiline
  - beneficial effects
- Modifiers of glucose utilization
  - rosiglitazone
  - PPARγR agonism
- Antilipid drugs
  - statins
- Anti amyloid antibodies
  - bapineuzumab
- Antioxydants
  - tocoferol, ascorbinic acid