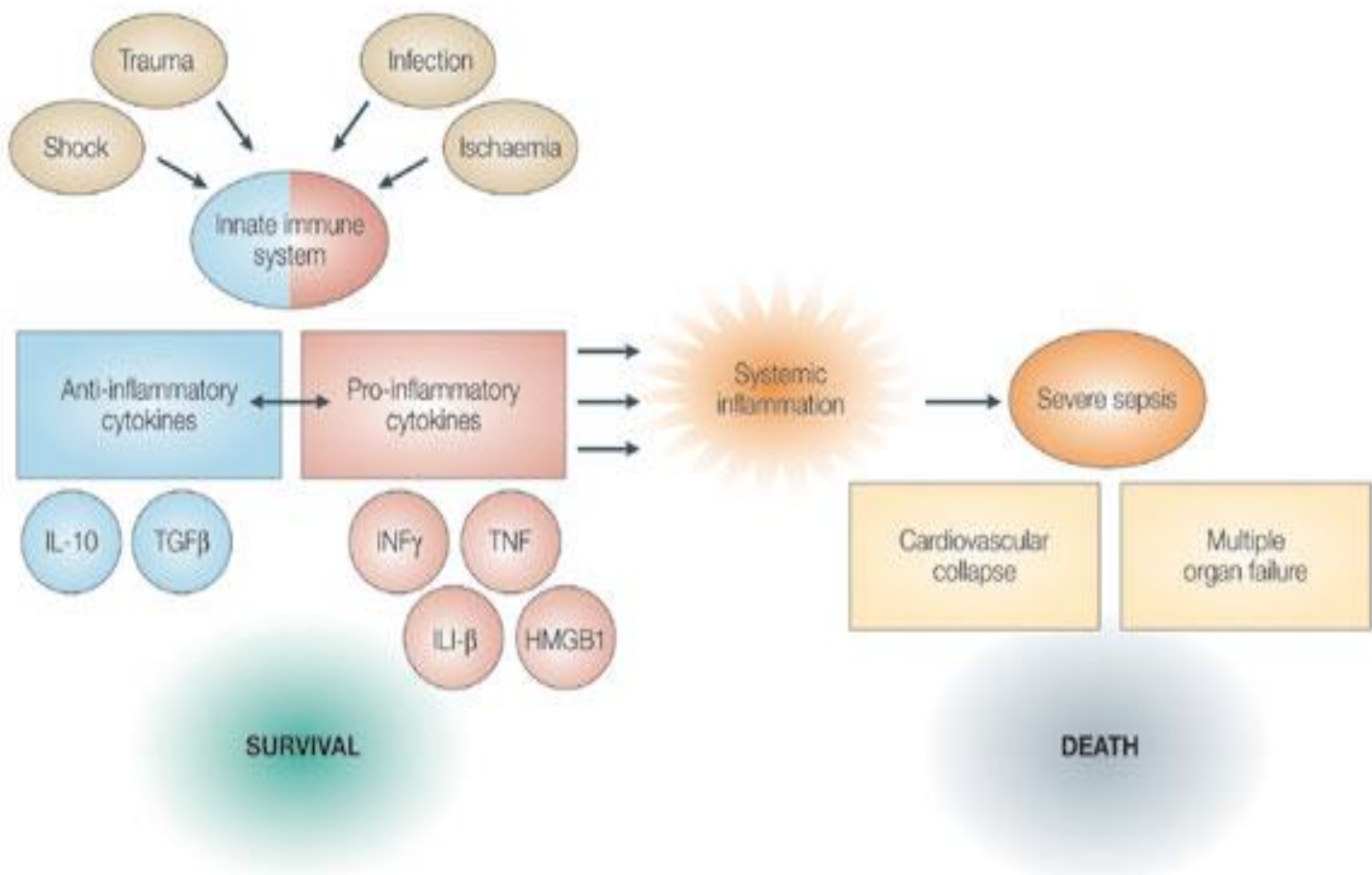


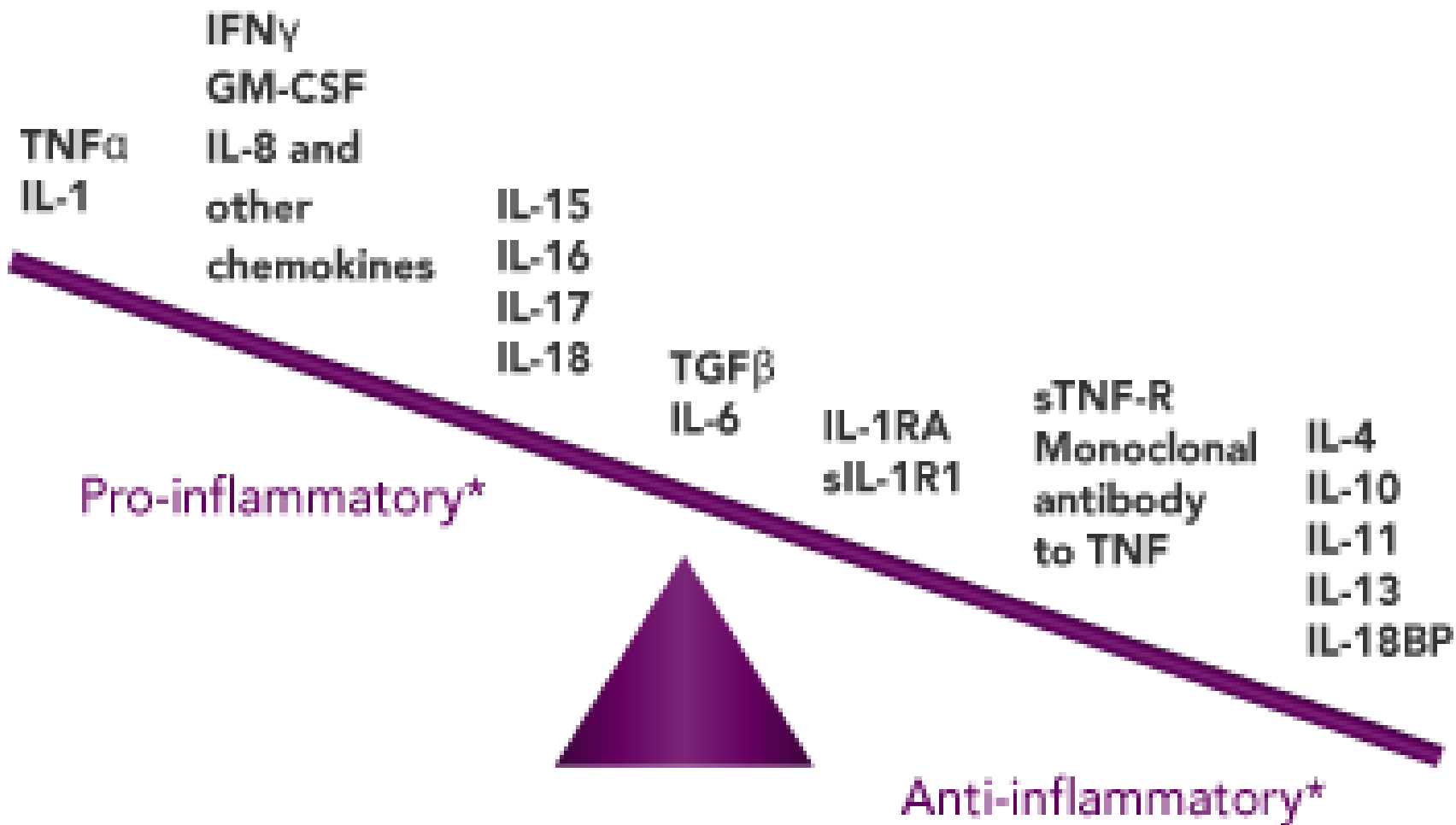
OVERVIEW OF ANTI INFLAMMATORY DRUGS

DR SHAMS SULEMAN

LEARNING OBJECTIVES

- Classify anti inflammatory drugs
- Describe the role of DMARDs and glucocorticoids as anti inflammatory agents





Cytokines drive the inflammatory response⁵

Signs of Inflammation

5

Four cardinal signs

1. **Callor (heat)**
2. **Rubor (Redness)**
3. **Tumor (Swelling)**
4. **Dolor (Pain)**

May also observe:

5. **Loss of function**





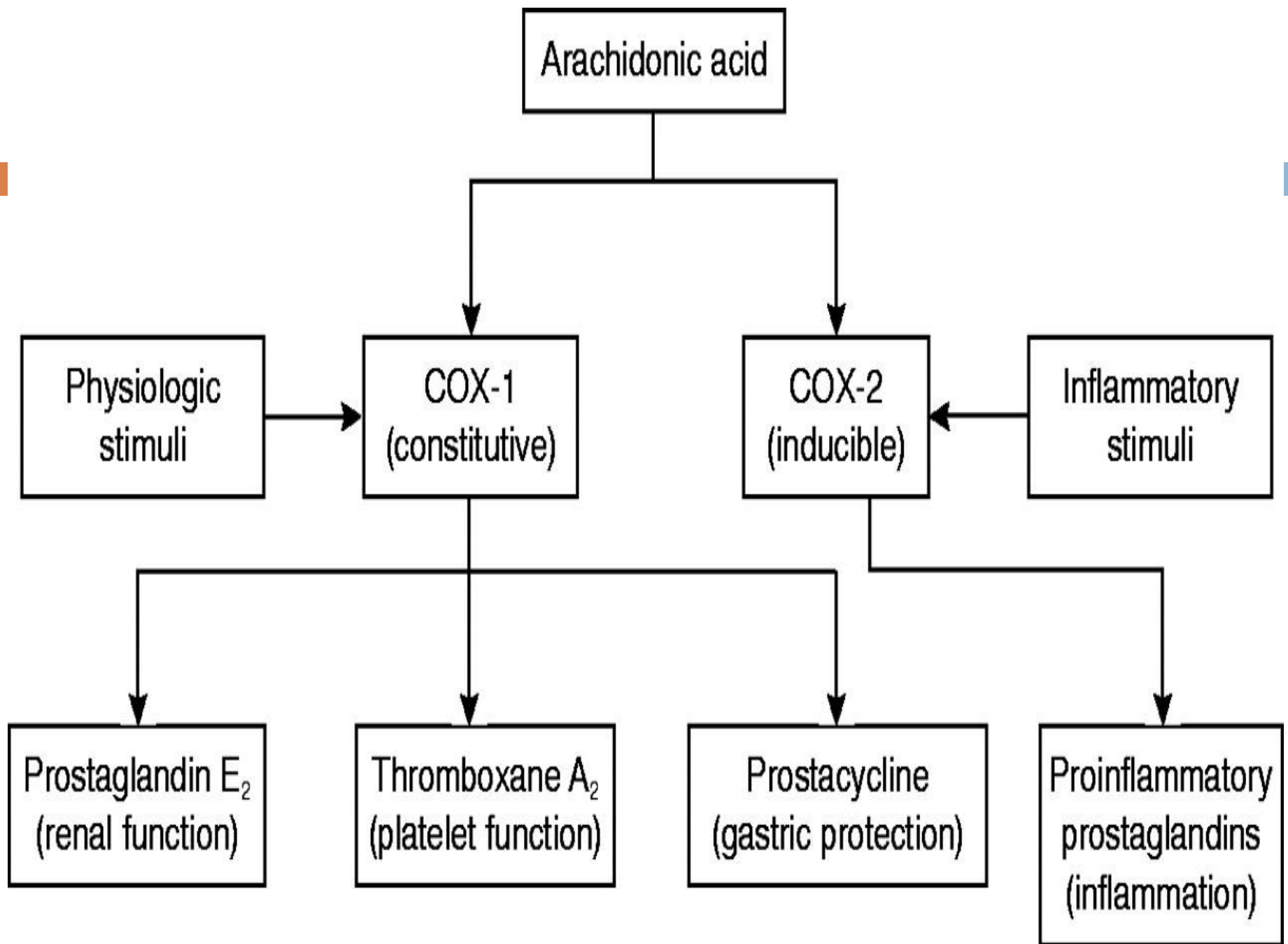


Swollen and
inflamed joint

Masses of uric
acid (tophi)



Uric acid
crystals



Phospholipid

Phospholipase A2

Arachidonic acid

Lipoxygenase

Cyclooxygenase

Leukotrienes

Thromboxane

Prostaglandins

**"Physiological
prostaglandin"
(constitutive COX 1)**

**"Pathological
prostaglandin"
(inducible COX 2)**

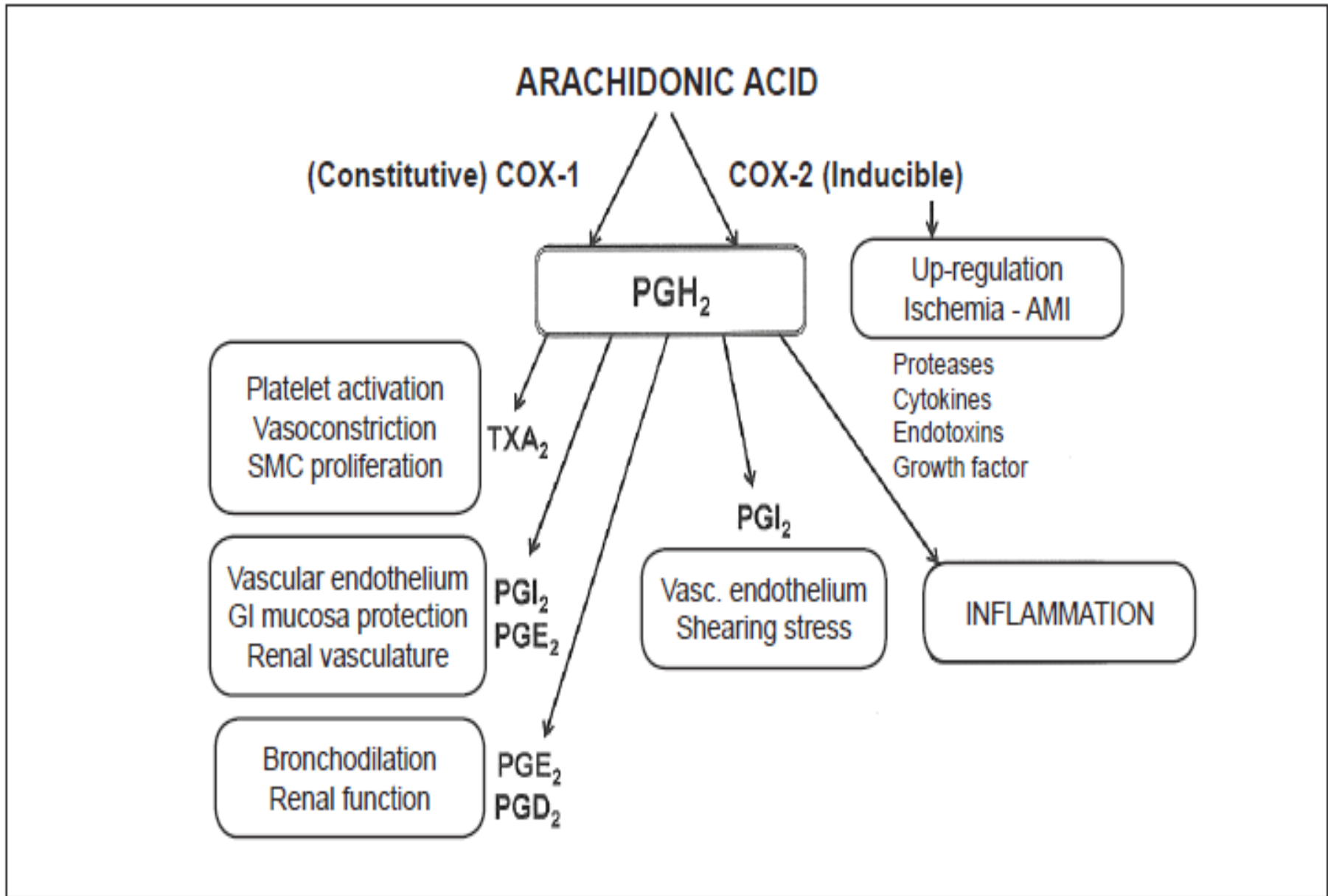


Figure 1 - Schematic representation of the effects related to the COX-1 and COX-2 activation. COX - cyclooxygenase; PG - prostaglandin; TX - thromboxane; AMI - acute myocardial infarction.

5 FOODS THAT REDUCE INFLAMMATION



BROCCOLI



SALMON



TURMERIC



BLUEBERRIES



OLIVE OIL

CLASSIFICATION

- **ANTI INFLAMMATORY AGENTS**
 - **STEROIDAL**
 - **NONSTREOIDAL**



NONSTREOIDAL ANTI INFLAMMATORY AGENTS

ANTI-INFLAMMATORY DRUGS

NSAIDs

- *Aspirin*
- *Diflunisal*
- *Diclofenac*
- *Etodolac*
- *Fenamates*
- *Fenoprofen*
- *Flurbiprofen*
- *Ibuprofen*
- *Indomethacin*
- *Ketorolac*
- *Ketoprofen*
- *Meloxicam*
- *Methyl salicylate*
- *Nabumetone*
- *Naproxen*
- *Oxaprozin*
- *Piroxicam*
- *Sulindac*
- *Tolmetin*

COX-2 INHIBITORS

- *Celecoxib*

OTHER ANALGESICS

- *Acetaminophen*

DRUGS FOR ARTHRITIS

- *Abatacept*
- *Adalimumab*
- *Anakinra*
- *Chloroquine*
- *Etanercept*
- *Gold salts*
- *Infliximab*
- *Leflunomide*
- *Methotrexate*
- *D-Penicillamine*
- *Rituximab*

DRUGS FOR GOUT

- *Allopurinol*
- *Colchicine*
- *Probenecid*
- *Sulfinpyrazone*

ANTI INFLAMMATORY DRUGS

PHARMACOKINETICS

- All= weak acids except Nebutomone (ketone)
- Racemic, single (naproxen), non (diclofenac)
- Biotransformation= phase 1 & 2 reactions
- CYT P₄₅₀ 2C, CYT P₄₅₀ 3A
- Enterohepatic circulation
- Excretion = renal

ANTI INFLAMMATORY DRUGS

PHARMACODYNAMICS

Inhibition of prostaglandins = cyclooxygenase

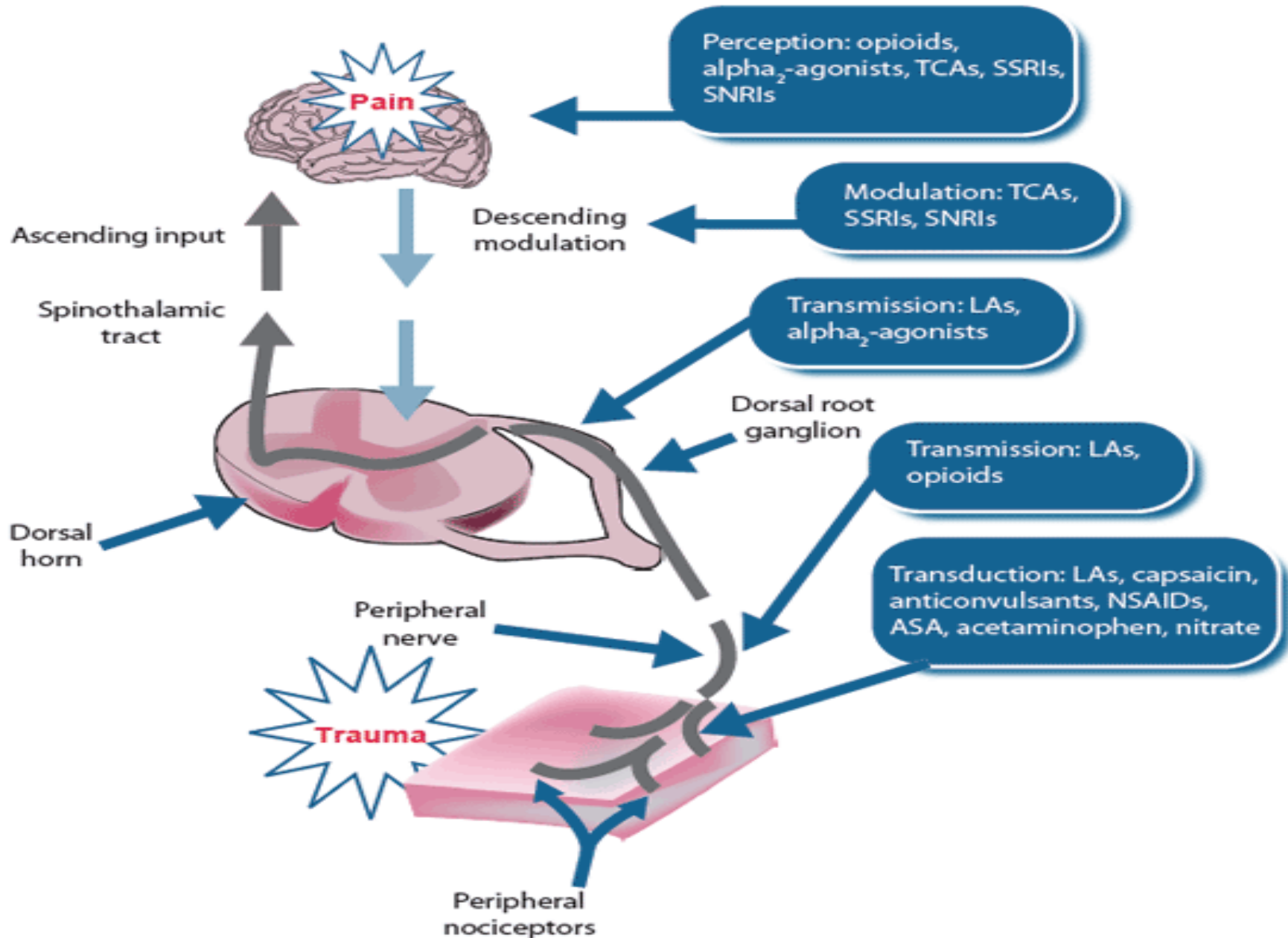
Reversible acetylation (aspirin= irreversible)

Minor mechanisms

- Inhibition of chemotaxis
- IL 1 down regulation
- Decreased free radicals & superoxides
- Interference with intracellular calcium

PHARMACODYNAMICS.....

- ✓ **NOT** Disease Modifying
- ✓ Non selective inhibition = most
- ✓ Aspirin, indomethacin, piroxicam and sulindac = mostly COX 1
- ✓ Ibuprofen, meclofenamate = both equally
- ✓ Celecoxib, Refocoxib, Valdecoxib, melocoxib and etoricoxib = selective COX 2 inhibitors
same efficacy, gastroprotection , more edema

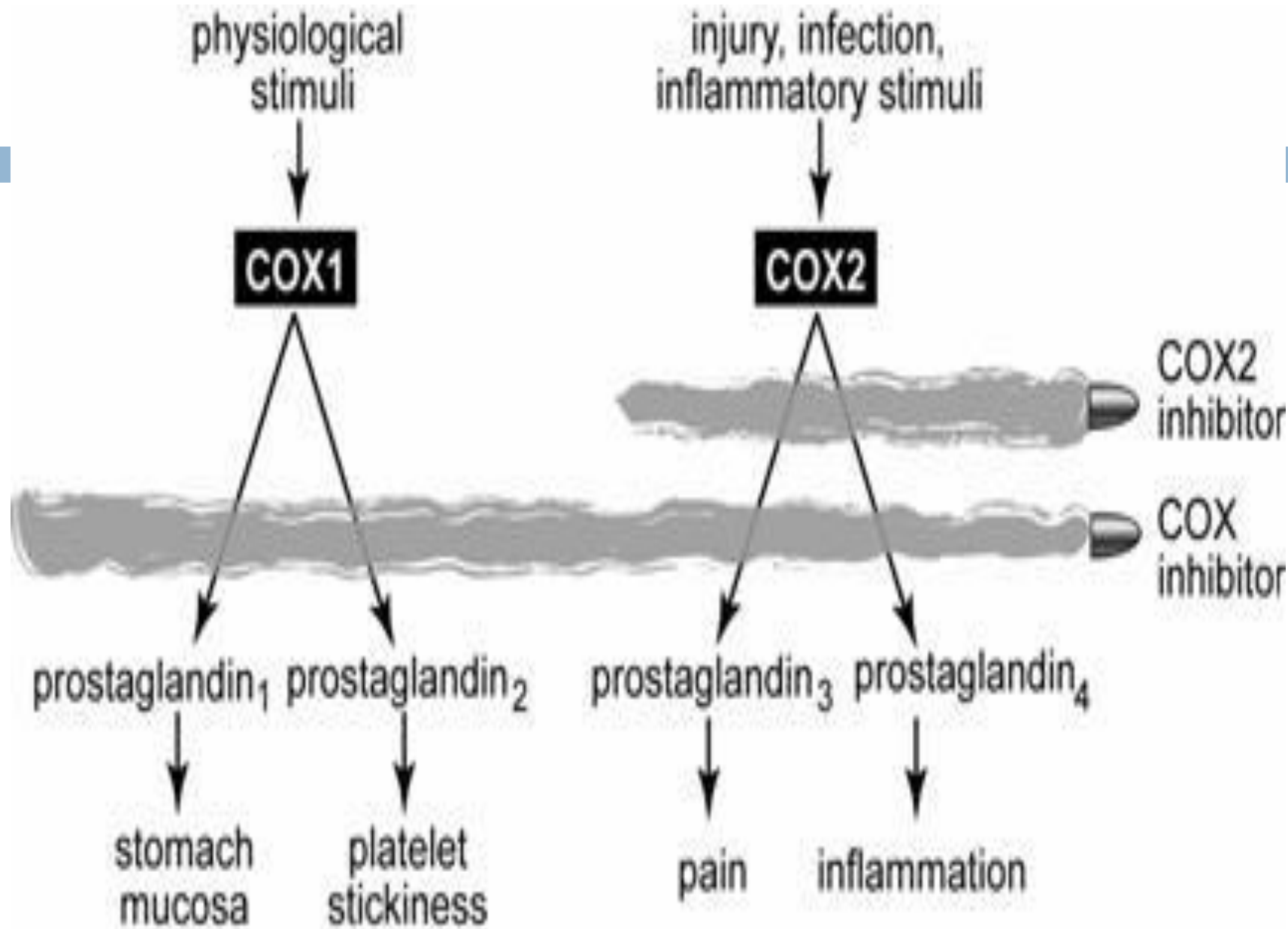


ANTI INFLAMMATORY DRUGS

USES

most NSAIDS are effective in

- ❖ Rheumatoid arthritis/Rheumatic heart disease
- ❖ Ischemic heart disease
- ❖ Inflammatory bowel disease/reactive arthritis
- ❖ Ankylosing spondylitis, Psoriatic arthritis, Gout
- ❖ Trauma, post operative, dental diseases
- ❖ Menstrual disorders/ dysmenorrhoea
- ❖ Patent ductus arteriosus, carcinoma colon



ANTI INFLAMMATORY DRUGS

ADVERSE EFFECTS

- CNS= headache, tinnitus, dizziness
- CVS= edema, hypertension, CCF
- GIT= Dyspepsia, bleeding, nausea, vomiting
- Hematological= thrombocytopenia, aplastic anemia(rare), neutropenia
- Renal= Hyperkalemia, proteinuria, azotemia
- Hepatitis, asthma, rashes, SJ syndrome

ASPIRIN (ASA)

- ASA = Pka, 3.5 vs 3.0 (salicylic acid)
- Esterases = 15 minutes ---acetic acid and salicylates--- stomach, upper GIT
- Avoid = concomitant ibuprofen, probenecid
- Can use acetaminophen
- Albumin bound, Elimination $t_{1/2}$ = 3-5 hours
- Salicylism, respiratory alkalosis, metabolic acidosis--- urinary alkalization, dialysis

INDOMETHACIN & OTHERS....

- **MEFANAMIC ACID**
- Inhibits both cyclooxygenase and phospholipase A
- **DICLOFENAC SODIUM**
- Avoid with Aspirin
- Hepatotoxic : like Sulindac

INDOMETHACIN & OTHERS....

KETOPROFEN

- Both lipooxygenase and cyclooxygenase enzymes are inhibited
- Intravenous and oral

KETOROLAC

- Analgesic without much anti-inflammatory properties
- May obviate the need for opioids

IMMUNOMODULATORS

DISEASE MODIFYING DRUGS

- Immunosuppressant
- Immunostimulant





Skin Lichenification

IMMUNOSUPPRESSANTS

CLASSIFICATION

- Corticosteroids
 - Methylprednisolone
 - Prednisolone
 - Prednisone
- Immunophilin ligands ; antibiotics
 - Cyclosporin A (CsA)
 - Tacrolimus (TAC)/Sirolimus(SIR)

IMMUNOSUPPRESSANTS CONTD....

□ ENZYME INHIBITORS

Mycophenolate Mofetil (MMF)

Mycophenolate sodium(MMS)

Leflunamide

Pentostatin (ADA inhibitor)

IMMUNOSUPPRESSANTS CONTD....

□ CYTOTOXIC AGENTS

Azathioprine (AZT)

6 Mercaptopurine (6 MP)

Cyclophosphamide

Hydroxychloroquine

Methotrexate

Thalidomide

IMMUNOSUPPRESSANTS CONTD....

□ ANTI INFLAMMATORY / IMMUNE MAB

Anti TNF α

Adalimumab

Etanercept

Infliximab

Anti CTLA-4

Iplimumab

IMMUNOSUPPRESSANTS CONTD....

ANTI CD28

Abatacept ; CD80/86

ANTI LFA 3

Alefacept ; CD2

IL2 ANTAGONIST

Basiliximab

Daclizumab

IMMUNOSUPPRESSANTS CONTD....

IL 1 ANTAGONISTS

Anakinra

ANTI LFA-1

Efalizumab ; ICAM 1

ANTI IGE ANTIBODIES

Omalizumab

MISCELLANEOUS

Abciximab

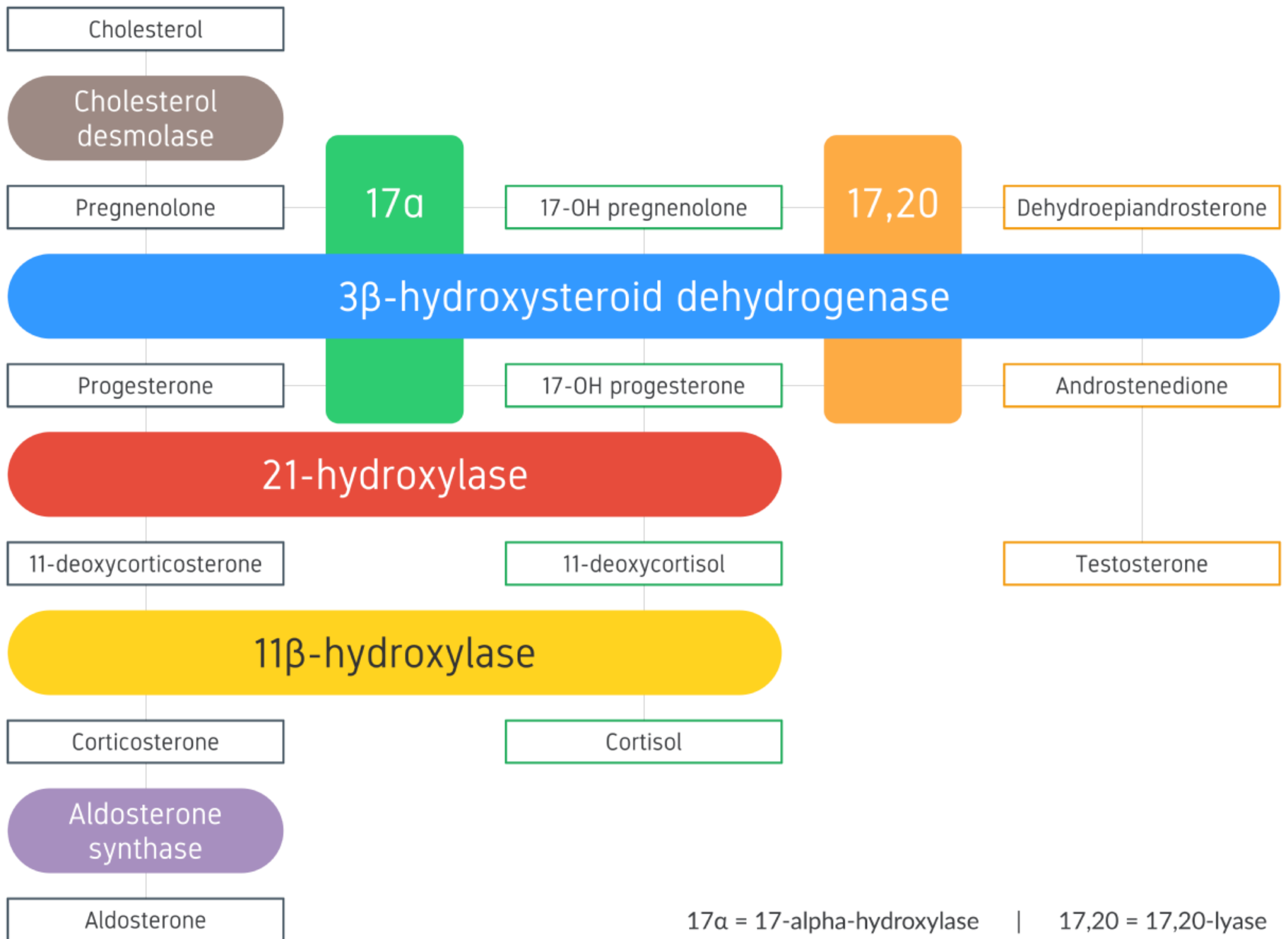
Palivizumab



CORTICOSTEROI DS

ANTIINFLAMMATORY & IMMUNOSUPPRESSIVE ACTION

- Reduce manifestations of inflammation
- ↓ release of vasoactive & chemoattractive factors
- ↓ secretion of lipolytic & proteolytic enzymes
- ↓ extravasation of leukocytes (increased neutrophils in blood, decreased lymphocytes)
- ↓ fibrosis
- ↓ expression of pro-inflammatory cytokines, COX



CORTICOSTEROIDS

- Corticosteroids are involved in a wide range of physiologic systems such as:
- Stress response,
- Immune response & regulation of inflammation,
- Carbohydrate metabolism,
- Protein catabolism,
- Blood electrolyte levels & behavior.

CORTICOSTEROIDS

- Glucocorticoids such as cortisol control carbohydrate, fat & protein metabolism & are anti-inflammatory.
- Mineralocorticoids such as aldosterone control electrolyte & water levels, mainly by promoting sodium retention in the

CLASSIFICATION

1. Short acting
2. Intermediate acting
3. Long acting
4. Inhalational

Classification (contd.)

Short acting (8-12 hours)

- Hydrocortisone (cortisol)
- Cortisone

Classification (contd.)

Intermediate acting (12-36 hours)

- Prednisone
- Prednisolone
- Methylprednisolone
- Fluprednisolone
- Paramethasone
- Triamcinolone

Classification (contd.)

Long acting (36-72 hours)

- Betamethasone
- Dexamethasone
- Beclomethasone
- Budesonide
- Fluticasone

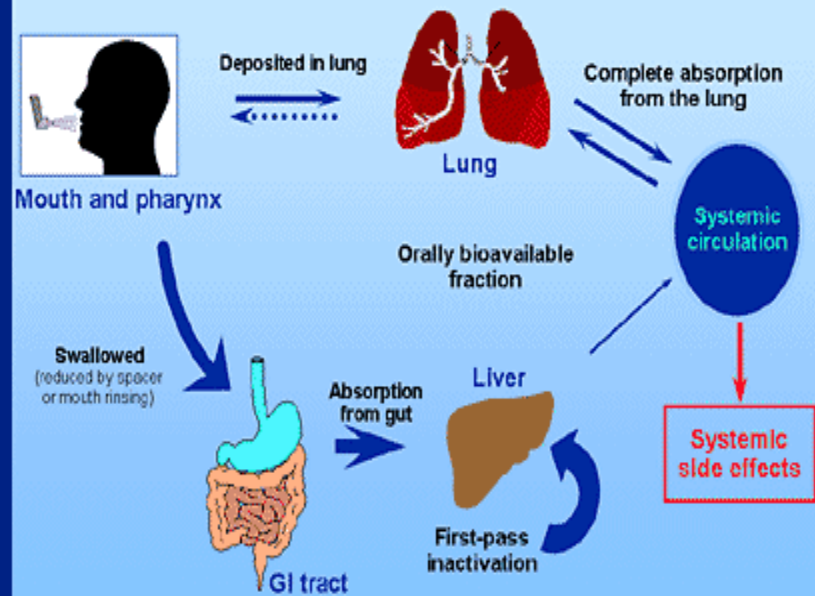


Classification (contd.)

Inhalational

- Triamcinolone
- Beclomethasone
- Budesonide
- Fluticasone
- Ciclesonide
- Flunisolide
- Mometasone

Fate of Inhaled Corticosteroids



PHARMACOLOGICAL EFFECTS

(Extensions of physiological effects)

1. PHYSIOLOGIC EFFECTS

- direct effects
- permissive effects
 - Response of vascular & bronchial smooth muscle to catecholamines
 - Lipolytic response of fat cells to ACTH, catecholamines, growth hormones

PHARMACOLOGIC EFFECTS

2. METABOLIC EFFECTS

- Carbohydrate – gluconeogenesis, glycogen, decrease glucose utilization, increase blood glucose levels
- Protein (catabolic & anti-anabolic effects) – in lymphoid tissue, muscle, fat, skin
- Lipid – lipolysis, redistribution of body fat (different tissue sensitivity)

PHARMACOLOGIC EFFECTS

3. ANTI-INFLAMMATORY EFFECTS
4. IMMUNOSUPPRESSIVE EFFECTS
5. CNS – sense of well being, insomnia, restlessness, depression, psychosis
6. Skeletal muscle: required for normal function
7. CVS: mineralcorticosteroid –induced changes, enhance vascular reactivity to other vasoactive substances

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