PHARMACOLOGY

Lecture 2: NSAIDs

OBJECTIVES:

- Define NSAIDs
- Specify the general mechanism of actions
- Classify this group of drugs
- Describe the general pharmacological actions
- Enumerate the therapeutic uses
- Describe the general adverse effects
- Describe the general contraindications
- Know the difference between the selective & non-selective NSAIDs

Terminology:

Important to be understood before studying this lecture:

- **Clinical uses:** diseases or conditions for which a drug is used.
- **Adverse Drug Reactions (ADRS):** an injury caused by taking a medication.
- **Contraindications:** a specific situation in which a drug, procedure, or surgery should not be used, because it may be harmful to the person.

- Important.
- Extra notes.

Pharmacology lecture 2: NSAIDs

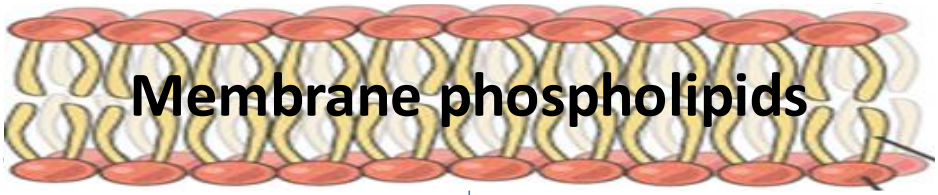
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are group of drugs that share in common the capacity to induce the following effects:

NSAID's effects:

- analgesic
- antipyretic
- anti-inflammatory

Explained more later…

Mechanism of action of NSAIDs:



"Corticosteroids" act on phospholipase enzyme and prevent the formation of arachidonic acid

phospholipase

NSAIDs and paracetamol (acetaminophen) inhibit **cyclooxygenase (COX) enzymes** responsible for the production of prostaglandins (PGs) which promote **inflammation** necessary for healing, **pain** and **fever. As a consequence, ongoing inflammation, pain and fever are reduced.**

Arachidonic acid

Lipoxygenase

Cyclooxygenase

Leukotrienes
" mediate allergic reactions"

Prostanoids

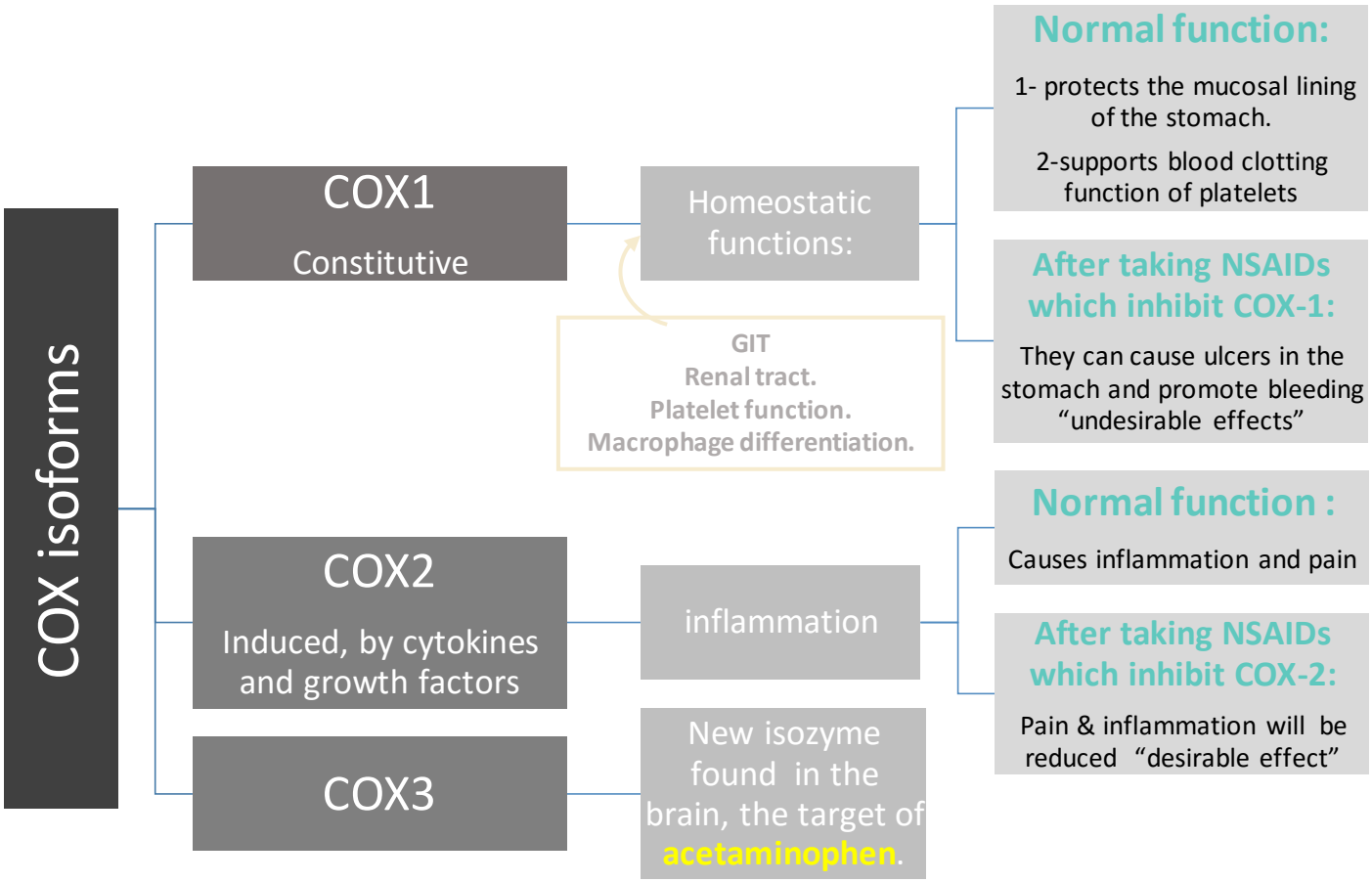
Prostaglandins

thromboxane

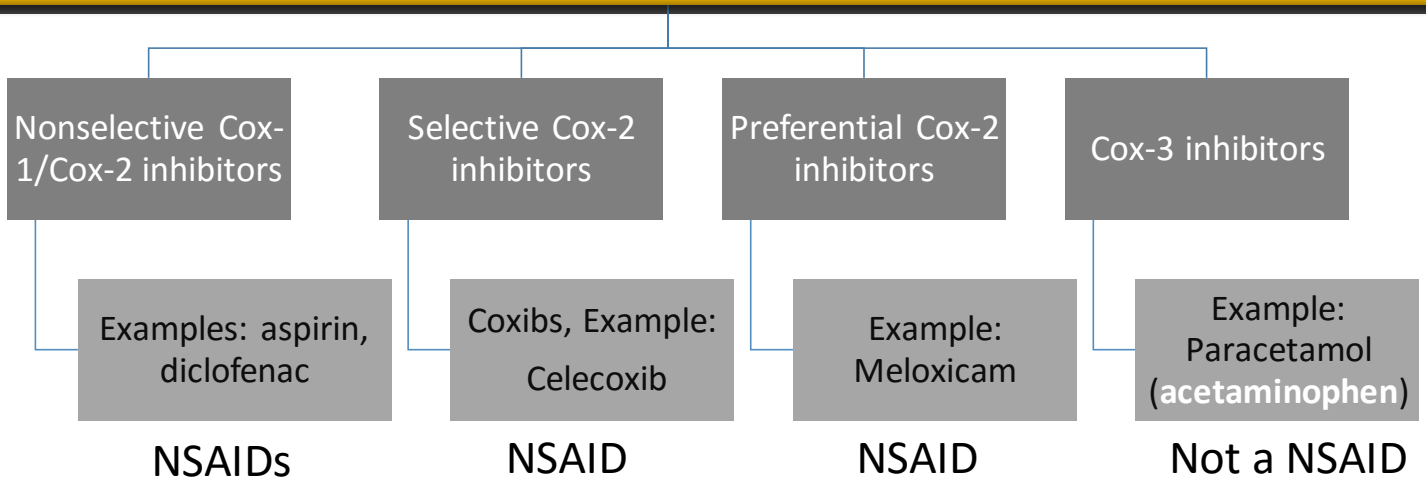
Prostacyclin

YouTube NSAID Pharmacology: An Introduction

COX isoforms(isozymes) and inhibition



Classification of COX inhibitors



NSAIDs & Acetaminophen - Learn with Visual Mnemonics

NSAIDs effects

Analgesic (painkiller)

Prostaglandins (PGE2, PGF2) + bradykinin and histamine at the site of the injury normally sensitize pain sensors at nerve ends to produce PAIN.

NSAIDs analgesics mechanism: block PGs production.
Site of action: peripheral tissue
Clinical uses:

- Headache, Migraine* (headache that affects one side of the head)
- Dysmenorrhea* (painful menstruation and abdominal cramps)
- Dental pain (moderate pain).

Antipyretic (reduce fever)

Pyrogens (substances typically produced by bacteria) stimulate formation of Prostaglandins (PGE2), which then increase the set point of the thermoregulatory center in the brain.
This leads to ↑ heat production and ↓ heat dissipation (breaking up), resulting in FEVER.

NSAIDs antipyretics mechanism: block PGs production
Site of action: CNS
Clinical uses:

- Reducing fever back to normal body temperature.

Anti-inflammatory

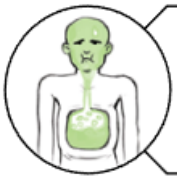
When there is an inflammation, Prostaglandins (PGE2 PGF2) + bradykinin and histamine and 5HT "serotonin" initiate the symptoms of INFLAMMATION: (Redness, swelling, heat, pain, and sometimes loss of function).

NSAIDs anti-inflammatory mechanism: block PGs production
Site of action: peripheral tissues
Clinical uses:

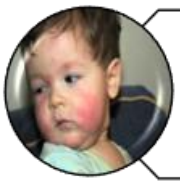
- Rheumatoid arthritis
- Myositis* (inflammation and degeneration of muscle tissue).
- Common cold* (a viral infectious disease of the upper respiratory tract, causing pharyngitis, sinusitis, and conjunctivitis).

YouTube How Do Pain Relievers Work? - George Zaidan

Adverse Drug Reactions (ADRs)

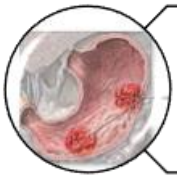


GIT upsets (nausea, vomiting) thus shouldn't be consumed on empty stomach



Hypersensitivity reactions

Inhibition of PGs leads to inducing leukotrienes



GIT bleeding & ulceration

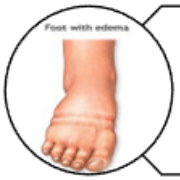
By inhibiting Cox1 which protect the lining of the stomach from the damaging acids

Inhibition of uterine contraction

By inhibiting Prostaglandins, which induce labor.

Bleeding

NSAIDs act as Anti-platelet, causing platelet dysfunction

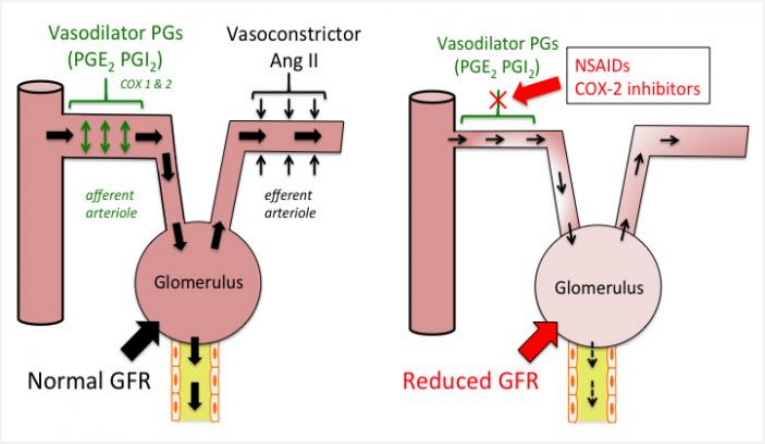


Salt & water retention

Explained below ↓

Renal ADRs:

NSAIDs cause **hemodynamically-mediated acute renal failure**. They prevent the synthesis of PGE2 & PGI2 by inhibiting COX-1 & COX-2 leading to the prevention of vasodilation, and reducing GFR(Glomerular filtration rate)



For better understanding:

- Prostaglandins (PGE2 & PGI2) cause **vasodilation** of the afferent arterioles of the glomeruli. This helps maintain normal renal blood flow and GFR.
- **NSAIDs** prevent the synthesis of PGE2 & PGI2 by Inhibition of both COX-1& COX-2 enzymes (mainly COX-2).
- Decreased synthesis of PGs results in retention of sodium and water, Causing edema of lower limbs in some patients, hyperkalemia & interstitial nephritis.
- Patients with a history of heart failure or kidney disease are at particularly high risk.

NSAIDs and Renal Function

Nonselective Cox-1/Cox-2 inhibitors

1. Aspirin [also known as acetylsalicylic acid (ASA)]

Mechanism of action

Non-selective inhibition of COX-1/COX-2.
Aspirin binds with the active site of COX enzyme and makes it inactive.
This process is irreversible.

Pharmacokinetics:

Aspirin is metabolized → By hydrolysis → to Salicylic acid → Hydroxylation / Conjugation with glycine / Conjugation with glucuronic acid

- Higher dose = more plasma- proteins binding
  = longer plasma half-life.
  Low dose: $t^{1/2}$ = 3h. Higher dose: $t^{1/2}$ = 15h.

Clinical uses:

1. Acute rheumatic fever (an inflammatory disease, treated mainly by Aspirin)
2. Chronic use of small doses reduces the incidence of colon cancer.
3. Prevents pre-eclampsia. pre-eclampsia=hypertension and tendency to thrombosis of pregnant women.
4. Reduces the risk of myocardial infarction (cardio-protective)

Low-dose aspirin(81mg) inhibits COX-1-mediated production of PGs, as well as TXA2. Thereby reducing TXA2-mediated **anti-platelet effect** (vasoconstriction and platelet aggregation) and the subsequent risk of cardiovascular events

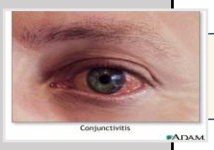
Contraindications:

1. Pregnancy. aspirin for pregnant women in the 3rd trimester should be avoided due to effects on the fetal cardiovascular system (closure of the ductus arteriosus).
2. Gout«النقرس» (**SMALL** doses can cause it, however, **LARGE** doses can cure it)
3. Patients with peptic ulcers.
4. Hemophilic patients, and patients taking anti-coagulants.
5. Children with viral infections. They will have Rey's syndrome if treated with aspirin.

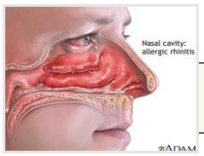
Aspirin (cont.)

Adverse effects (ADRs)

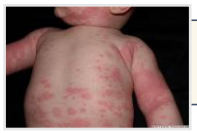
At clinical dose



1. Conjunctivitis



2. Rhinitis



3. Urticaria

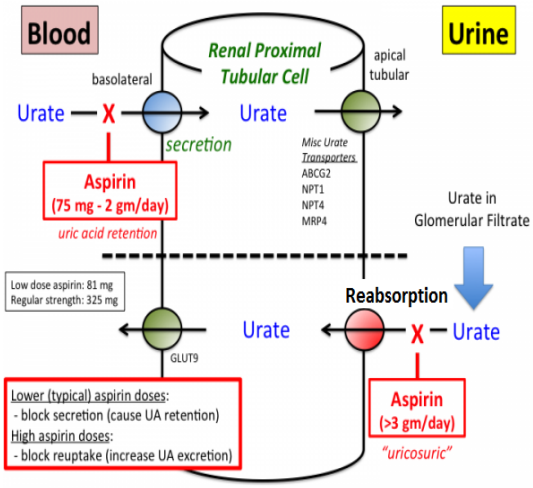
4. Impaired **hemo**stasis. For this reason, aspirin is often held, or not given, at least 1 week prior to surgery.
5. GIT side effects: dyspepsia (indigestion), Nausea, Vomiting.
6. **Reye's syndrome**. Which is a rare disorder, associated with consumption of Aspirin by children with viral infections. It usually causes Fatty liver with encephalopathy, and it is life endangering.
7. Mucosal damage which leads to hemorrhage. (Chronic use)
8. Hypersensitivity bronchospasm.

Mechanism of bronchospasm in aspirin-sensitive asthmatics:
Aspirin inhibits COX-mediated synthesis of prostaglandins but not of leukotrienes, which are responsible for bronchospasm. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of PGs synthesis can cause a shift toward leukotriene production and, therefore, increase the severity of asthma.

At overdose

1. Hyperthermia a toxic dose will increase heat production.
2. Gastric and ulceration bleeding.
3. Salicylism (Ringing of ear, vertigo). Treated by stopping the administration of Aspirin.

At low dose



- **Acute gouty arthritis:**

- SMALL dose of Aspirin:

Blocks secretion of urate to urine, leading to its accumulation in blood CAUSEING Gout.

- LARGE dose of Aspirin:

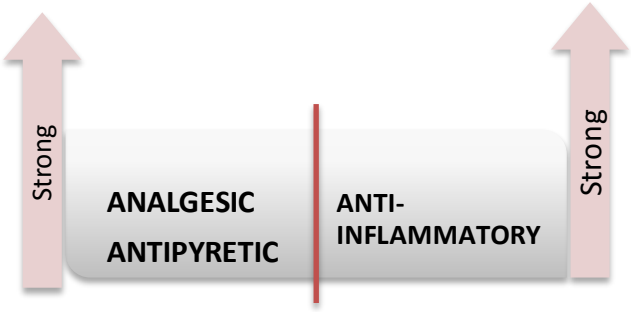
Blocks reuptake of urate and leads to its excretion in urine CUREING Gout.

2. Diclofenac

Mechanism of action:

nonselective COX-2 Inhibition

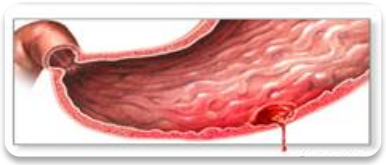
It has activity for both COX-1 and COX-2 but increased affinity for COX-2.



Clinical uses:

1. Acute gouty arthritis. remember, this is one of the adverse effects of low doses of aspirin.
2. **Locally** to prevent post-operative ophthalmic inflammation. (eye drops) for treating inflammation after operations on the eye. ophthalmic= related to the eye.

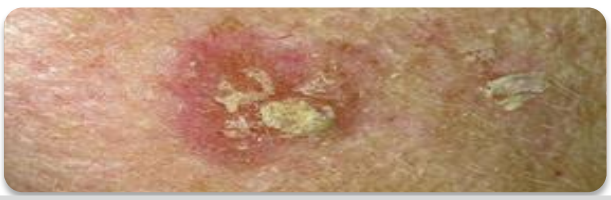
Preparations:



1. Diclofenac with **misoprostol** (a PGE1 analog) decreases upper gastrointestinal ulceration, but results in diarrhea.

2. Diclofenac with **omeprazole** to prevent peptic ulceration, and recurrent bleeding.

3. 0.1% ophthalmic preparation for postoperative ophthalmic inflammation.



4. A topical gel 3% for (solar keratosis), Which is a common skin condition resulting from skin damaged by the sun over many years.

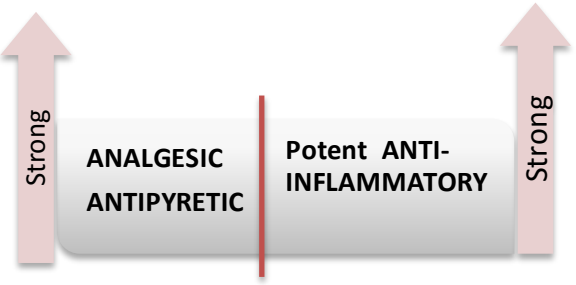
5. Oral mouth wash.
6. Intramuscular preparations .
7. Rectal suppository as analgesic.

Selective COX-2 inhibitors.

Example: CELECOXIB

Mechanism of action:

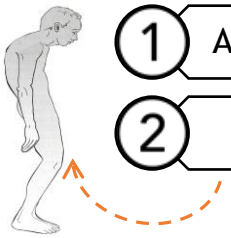
Selective reversible NSAID, blocks ONLY COX-2 which induces inflammation, and has little to no effect on COX-1 desirable functions (Homeostats of GIT, Renal tract and platelet functions), thus has lower incidence of gastric upsets and no effect on platelet function.



Pharmacokinetics:

- Half-life = 11 hours. Highly bound to plasma proteins
- Celecoxib is readily absorbed after oral administration. Thus, food decreases its absorption. It is extensively metabolized in the liver.

Clinical Uses:



1. Acute musculo-skeletal pain
2. Ankylosing spondylitis*
3. Short-term use in postoperative patients
4. Acute gouty arthritis

2* (inflammation in the joints of spine, leading to pain and stiffness)

Adverse Effect:

1. Renal toxicity
2. Dyspepsia & heartburn
3. Allergy
4. Cardiovascular abnormalities*

4* it does not offer the cardio-protective effects of the non-selective group.

Contraindications:

Should not be prescribed to:

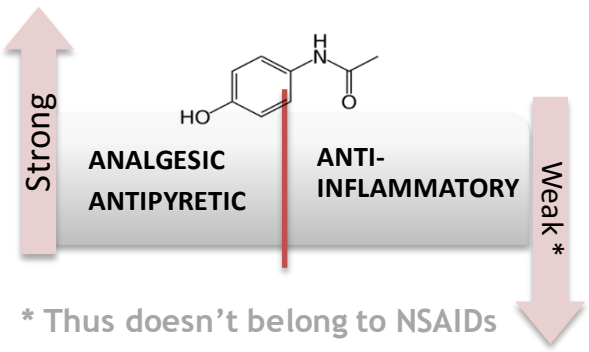
1. Patients with severe hepatic or renal disease.
2. patients who are hypersensitive to sulphonamides

Cox-3 inhibitors

Example: Paracetamol (acetaminophen)

General information:

- COX-3 inhibitor.
- Given **orally**, well absorbed
- t½ =2-4 h
- Metabolized by **conjugation** at therapeutic doses.



* Thus doesn't belong to NSAIDs

Clinical uses:

Commonly used analgesic antipyretic, for patients with **contraindications to aspirin** :-

1. Peptic or gastric ulcers
2. Pregnancy
3. Viral infections in children
4. Bleeding tendency
5. Allergy to aspirin

REMEMBER: aspirin can't be used in these cases.

1. An ADR of aspirin is peptic ulcer, therefore, consuming it by patients who already suffer from gastric ulcer will make it worse.
2. Can't be used by pregnant women because of its defects on the fetal cardiovascular system.
3. aspirin + kids with viral infections = Reye's syndrome.
4. aspirin also causes impaired hemostasis and leads to bleeding tendency.
5. it also causes hypersensitivity reactions.

Adverse drug reactions:

Therapeutic doses

Elevate liver enzymes, No significant ADR.

Large doses

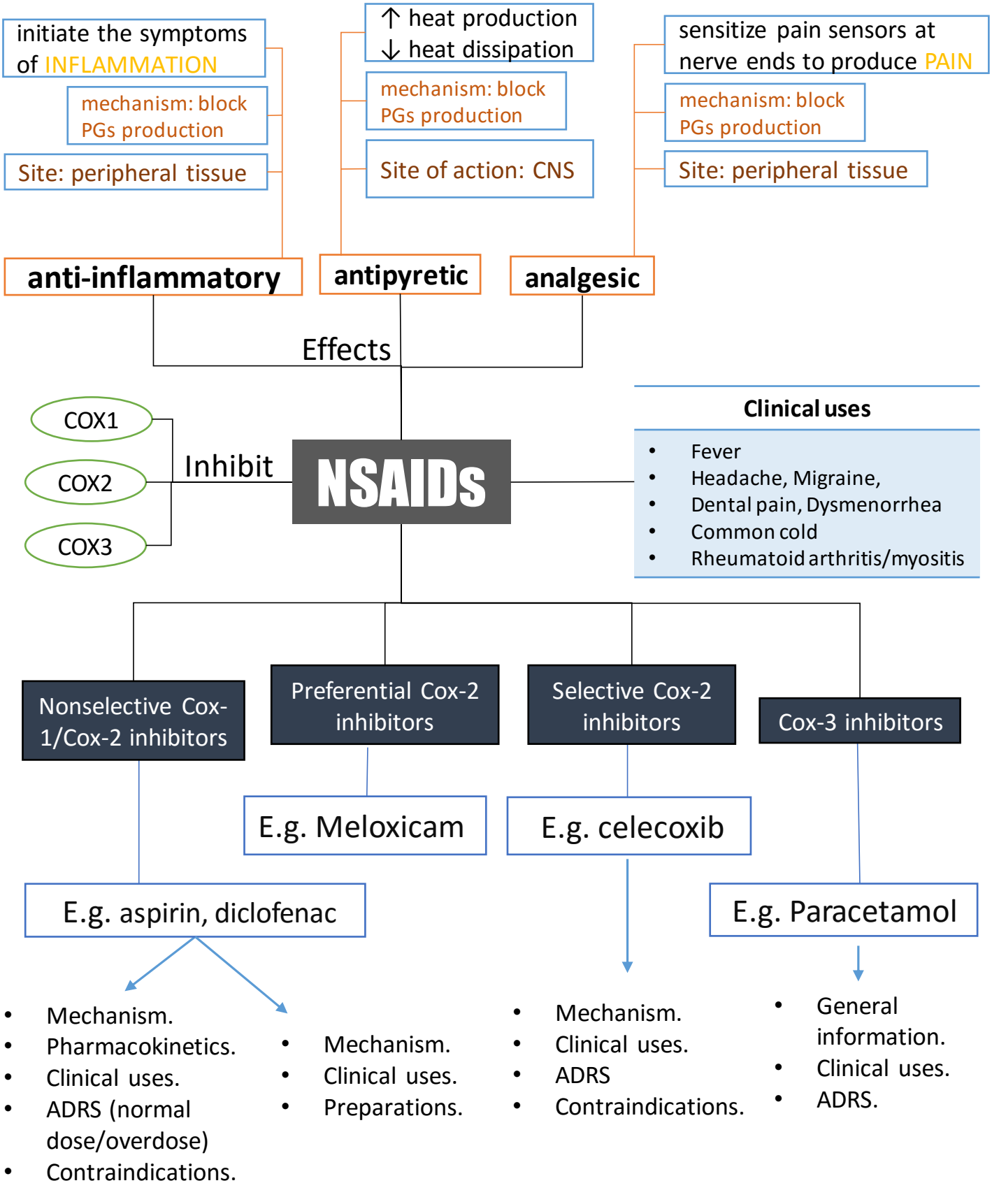
ADRs are mainly on liver, due to its toxic metabolite **(N-acetyl-p-benzoquinone),** which causes liver damage

Treatment of toxicity of paracetamol is by **N-acetylcysteine** to neutralize the toxic metabolite

Chronic abuse

Nephrotoxicity

Mind map


initiate the symptoms of INFLAMMATION
mechanism: block PGs production
Site: peripheral tissue
↑ heat production
↓ heat dissipation
mechanism: block PGs production
Site of action: CNS
sensitize pain sensors at nerve ends to produce PAIN
mechanism: block PGs production
Site: peripheral tissue
anti-inflammatory
antipyretic
analgesic
Effects
COX1
COX2
COX3
Inhibit
NSAIDs
Clinical uses
Fever
Headache, Migraine,
Dental pain, Dysmenorrhea
Common cold
Rheumatoid arthritis/myositis
Nonselective Cox-1/Cox-2 inhibitors
Preferential Cox-2 inhibitors
Selective Cox-2 inhibitors
Cox-3 inhibitors
E.g. Meloxicam
E.g. celecoxib
E.g. aspirin, diclofenac
E.g. Paracetamol
Mechanism.
Pharmacokinetics.
Clinical uses.
ADRS (normal dose/overdose)
Contraindications.
Mechanism.
Clinical uses.
Preparations.
Mechanism.
Clinical uses.
ADRS
Contraindications.
General information.
Clinical uses.
ADRS.

Summery of the drugs

	Aspirin	Paracetamol	Celecoxib	Diclofenac
Mechanism of action	Non-selective irreversible inhibition of COX	COX3 inhibitor	Selective COX-2 inhibitor	Semi-selective COX-2 inhibitor
Pharmaco kinetics	• Metabolized by Hydrolysis and then Conjugation. • Higher dose= longer plasma half-life.	• Metabolized by conjugation • Given orally, well absorbed • t½ =2-4 h	• Food decreases its absorption • Highly bound to plasma proteins. • t½ =11 h	---
Clinical uses:	• Acute rheumatic fever. • Reduces risk of myocardial infarction. • Prevents pre-eclampsia. • Colon cancer incidence is reduced.	• Peptic or gastric ulcers • Bleeding tendency • Allergy to aspirin • Pregnancy • Viral infections in children	• Short term use in postoperative patients • Acute gouty arthritis • Acute musculo-skeletal pain. • Ankylosing spondylitis.	• Acute gouty arthritis. • Post-operative ophthalmic inflammation (Locally used)
ADRS	**At normal dose:** • Hypersensitivity bronchospasm, rhinitis, conjunctivitis, urticaria. • Reye's syndrome. • Impaired hemostasis. • GIT side effects: dyspepsia, Nausea, Vomiting. • Mucosal damage. **At overdose:** • Salicylism (Ringing of ear, vertigo.) • Hyperthermia. • Gastric and ulceration bleeding. **At low dose:** • Acute gouty arthritis	**Therapeutic doses:** • Mainly on liver due to its active metabolite • elevate liver enzymes **Large doses:** • metabolized into N-acetyl-p-benzoquinone, which causes liver damage. • Treatment of toxicity of paracetamol is by N-acetylcysteine to neutralize the toxic metabolite **Chronic abuse:** • Nephrotoxicity	• Renal toxicity • Dyspepsia & heartburn • Allergy • Cardiovascular (does not offer the cardio-protective effects of the non-selective group).	**Preparations :** 1. Diclofenac + misoprostol decreases upper gastrointestinal ulceration, but result in diarrhea. 2. Diclofenac + omeprazole to prevent recurrent bleeding. 3. 0.1% ophthalmic preparation for postoperative ophthalmic inflammation. 4. Topical gel 3% for solar keratosis. 5. Oral mouth wash. 6. Intramuscular preparations. 7. Rectal suppository as analgesic.
Contra-indications	1. Aspirin-sensitive asthmatics 2. Peptic ulcer. 3. Pregnancy. 4. Hemophilic patients. 5. Patients taking anti-coagulants. 6. Children with viral infections. 7. Patients with gout.	---	• patients who are hypersensitive to sulphonamides.	

Quiz

THANK YOU FOR CHECKING OUR WORK

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