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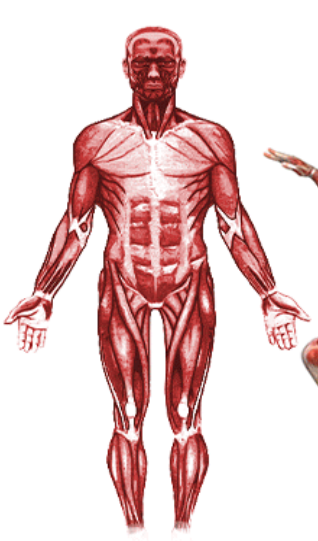

MSS

Musculoskeletal System

Pharmacology

Doctor 2018 | Medicine | JU

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Hello, this sheet will be long, but as a tip I recommend reading the first 20 slides beforehand, so that you have an idea what the important points are and read the sheet to understand, slides aren't 100% included, *good luck* ☺

Introduction to **NSAIDS** and **analgesics:**

Non-steroidal anti-inflammatory drugs, are a group of drugs that can **inhibit inflammation** and have other characteristics, an important one is that they cause **analgesia** (pain killing)

We call them NSAIDs specifically because steroids are also anti-inflammatory drugs that kill pain, and we want to distinguish the two since steroids are a different group that has a different mechanism of action (different pharmacological targets) and a different side effects.

↳ Aspirin and ibuprofen are bright members of the NSAIDs family.

Analgesics;

Are plain pain killers. We specifically added the term to include **Paracetamol**, which is a painkiller that affects the CNS with a similar mechanism of action to NSAIDS but without anti-inflammatory characteristics. Thus, it's a group on its own.

Opioids are other famous analgesics with a totally different MOA that NSAIDs that affects the CNS.

Why are these drugs very important?

Because they deal with **Pain,**

- Pain is the No. 1 reason people seek medical treatment and take medications.

It's an alarming sign of the body, which tells us that something is wrong, it's caused by a certain type of tissue damage → that gives this warning sign → which is permeated by certain cytokines or neurotransmitters → that would stimulate sensory neurons of pain → which would tell the body to GO seek help.

Pain is Universal, there are many kinds of pain and it's a Complex feeling that's very Subjective; as two people can have THE SAME injury but don't feel the same type of pain

Analgesics continued:

Derived from Greek **an-** "without" & **-algia** "pain".

An analgesic, or painkiller, is any member of the group of drugs used to achieve analgesia — **relief from pain.**

- They Act in various ways on the peripheral (drugs related to the musculoskeletal system) and central nervous systems.

Types of analgesics:

- **The non-steroidal anti-inflammatory drugs** (NSAIDs)
  Mild or moderate pain, that's happening peripherally (musculoskeletal pain)
- **Paracetamol** = acetaminophen (has a bit of both other groups)
- **Opioid drugs**
  They work on the **CNS**, and treat **all kinds of pain** (musculoskeletal, visceral(organs), pains related to cancer, after surgeries). The most common one is **morphine**, which is a very strong pain killer & is used for severe pain.

Sometimes, when a patient undergoes a surgery, we start with giving him opioids since he'd be in a lot of pain. Then as the pain naturally reduces, NSAIDs are given.

Comparison of Analgesics

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

comparison between NSAIDs+ paracetamol and opioids

Efficacy:

Morphine can inhibit pain by 99%, aspirin or ibuprofen 60-80%

kind of pain relieved and its location:

Visceral and peripheral VS. just peripheral (musculoskeletal)

- Exception is: **Paracetamol**, which works centrally but inhibits the same machinery (**cyclooxygenase enzyme**) of prostaglandin synthesis as NSAIDs.

Mechanism:

NSAIDs and paracetamol work by **inhibiting** the **prostaglandins synthesis**, while opioids work by **interacting** with certain **neurotransmitter receptors** centrally.

Danger/ risks:

To opioids:

Tolerance: **irresponsiveness** to the drug after a while.

The dose needed to induce the same effect is increased with each time the drug is taken, because there's a loss of the receptor's sensitivity

Dependence: is like **addiction**.

- The patient would feel the need to use the drug continuously.
- It could be psychological because of a **rewarding sensation** or physiological because the body has adjusted, and it would have a bad response upon withdrawal like certain **physiological signs and symptoms**, like **headache, hypothermia, shivering and aggressiveness.**

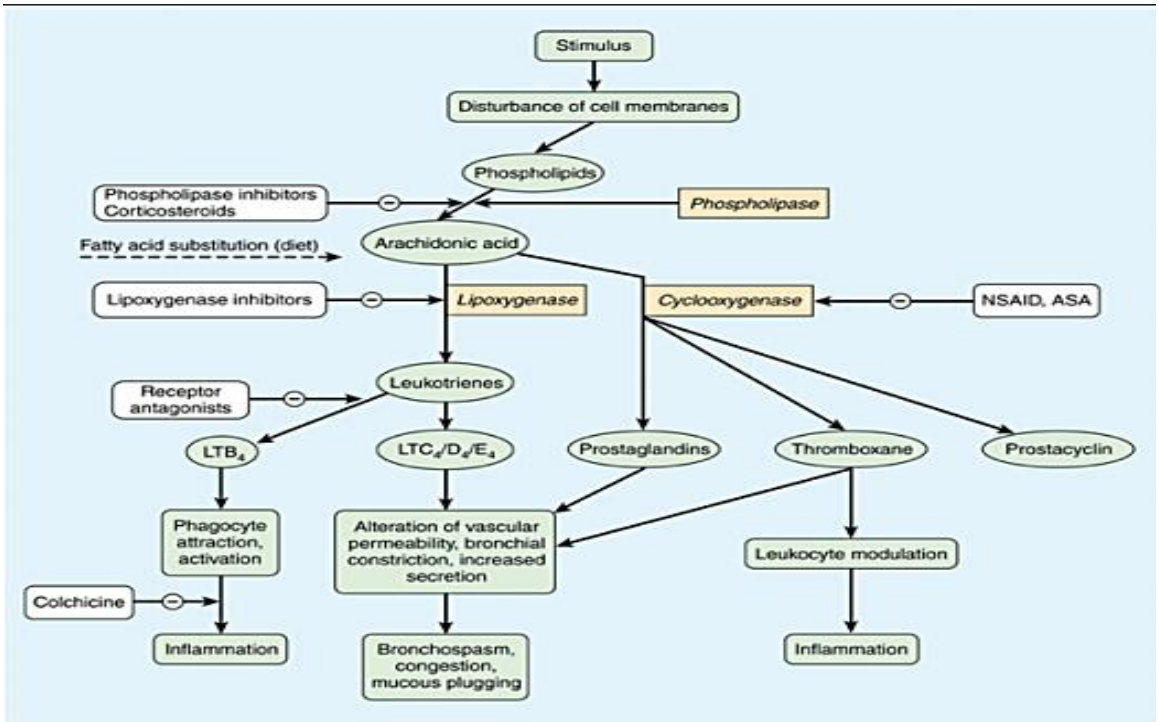
To NSAIDS:

GIT irritation.

*Like when you take ibuprofen, it's advised to take it after food, or with it (in these cases, food act as a protective barrier). It causes **GIT irritation** by **increasing the acid secretion** in the stomach. So, we give the patient drugs that work as **proton pump inhibitors** to decrease the gastric acid secretions.

Some NSAIDs have anti-inflammatory, antipyretic and anti-platelet activity, as opposed to opioids.

Some have anti platelet activity (like aspirin) because they inhibit the production of one of the prostaglandins (thromboxane A2)



* a lot of the explanation below is about this map, so keep coming back to view it*

Review of the inflammatory pathway in the body:

Course of the story:

Certain stimuli would cause the **release of phospholipids** like, phosphatidyl serine, which would be **worked upon** by some **enzymes** like phospholipase C, A2.

These are the most important, because corticosteroids for example can inhibit the action of these phospholipases. Thus, they will inhibit the product of this reaction which is arachidonic acid, the **father of prostaglandins**, one of the mechanisms of action of corticosteroids is inhibition of arachidonic acid synthesis and thus they're going to inhibit all these different pathways of inflammation that are activated by arachidonic acid generation. That's why they are used to treat asthma.

Corticosteroids have multiple mechanisms of action:

- modulating glucocorticoid receptors
- translocating to the nucleus modulating transcription of certain genes
- some unknown mechanisms (covered more in endocrine)

Arachidonic acid is a substrate for two enzymes, **cyclooxygenase** and **lipoxygenase**

1. **Cyclooxygenase (COX) pathway** of arachidonate metabolism produces prostaglandins (different kinds, PGE, C, I (prostacyclin) and thromboxane A2).

- They have different roles in the body which will help us understand what's the **effect of** inhibiting COX and the production of PGs on the body, whether a therapeutic effect or a side effect.
- These effects can be on blood vessels, on nerve endings, and on cells involved in inflammation.
- **NSAIDs** or **aspirin** work through **inhibiting** the **cyclooxygenase arm** of arachidonic acid metabolism, thus the effect will be a **decrease** in the leukocyte modulation, cytokine production, in the chemotactic, chemo-inflammatory response which are the processes that usually lead to inflammation.

2. The **lipoxygenase pathway** of arachidonate metabolism yields leukotrienes (B, D, E, C & A) *this topic is covered more in Respiratory system*

- **Leukotriene B** is involved in **phagocytosis**; it causes phagocytes attraction and activation, which is important for certain inflammatory responses, like the phagocytic engulfment of foreign material.
- **LTC,D,E** are involved in the **asthmatic reaction**; they cause modulation of certain receptors on the bronchi causing constriction of these bronchial smooth muscle cells (***bronchospasm***), induction of mucous production (***mucous plugging***), and increase in vascular permeability, which leads to edema (***congestion***), and all these effects will be responsible for the signs and symptoms we see in asthma or any allergic stimulation or condition.

- If we interfere with the LTs arm, we're going to inhibit this pathway, that's why agents called **leukotriene modifiers** are important in the treatment of asthma.
- To treat **asthma,** we have a variety of drugs *not exactly important in MSS*
    - LOX inhibitors, like a drug called *zelutin*

They work to treat asthma by modifying leukotriene pathway, they have limited side effect than other drugs like (antihistamines, corticosteroids)

- Receptor antagonist like *montelukast* or *zafirlukast*.

One thing about these receptor antagonists is that because they're newly developed, they're still very expensive, that's why they're rarely prescribed, unless other drugs are showing no effect in the treatment of that patient

Colchicine is a drug that inhibits **microtubule formation**, it inhibits the movement of phagocytes to engulf material, which works by continuous rearrangement of microtubules, disruption of microtubule structure inhibits movement of phagocytes, one use of colchicine is in **inflammatory disorders** like gout.

Another use, is in cancer, because microtubules are the building bone of the mitotic spindle which works in mitosis, so disruption of this mitotic spindle would inhibit separation of chromosomes and thus stop mitosis, and thus block the quick turnover (proliferation) of the cancer cells.

- Side effects of colchicine and its severity depend on the dose.

NSAIDs

- NSAIDs are a group of chemically dissimilar agents, which means that they differ in their chemical structure and also their antipyretic, analgesic, and anti-inflammatory activities.

Most of them have all of these capabilities but with varying degrees so their potencies and efficacies differ

- They work by inhibiting the cyclooxygenase enzymes that catalyze the first step in PGs biosynthesis → thus decreasing the PGs synthesis with both beneficial and unwanted effects.

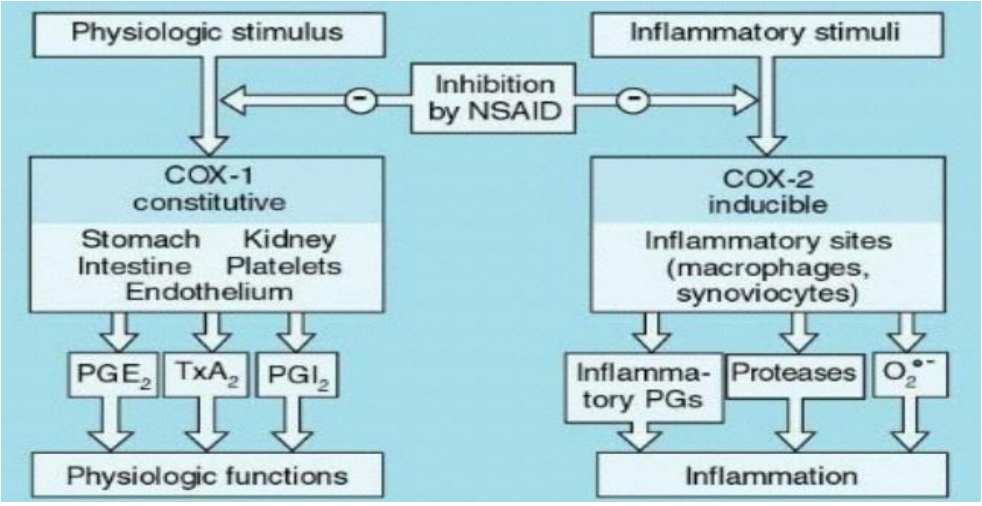
Cyclo-oxygenase (COX)

It exists in two isoforms COX-1 and COX-2 and the main difference is that:

- ***COX-1*** Exists in the tissue as a **constitutive isoform**, which means it's always produced in these tissues, like the stomach, kidneys, intestines, platelets and endothelium, it's always working to produce different prostaglandins to give a physiological effect.

- ***COX-2*** exists at sites of inflammation as an **inducible form**. Cytokines stimulate the induction of the 2nd isoform. An increase in the expression of it occurs in cases of inflammation. It is found in inflammatory sites (macrophages, synoviocytes). Upon its activation, it can produce inflammatory prostaglandins, certain proteases & superoxide radicles which all function in the phagocytotic process of what's been engulfed.

So, it's better to target the cyclooxygenase-2 pathway, because then It'll only affect the inflammation reactions happening without affecting the normal function of PGs in the body.



- Most NSAIDS used are non-selective for neither of the isoforms (aspirin, ibuprofen, diclofenac sodium (voltaren), diclofenac potassium (voltfast))
- One of the problems of non-selective is that they'll affect the stomach.

Normally, PGs have a protective effect on the stomach, they **decrease** the acid secretion and **increase** the mucous production, which is a way to help prevent the injury of the stomach from the acid secreted in it by producing a mucous membrane layer in the inside wall of the stomach.

If cyclooxygenase enzyme in the stomach is inhibited, it'll decrease that protective effect of prostaglandins & increase the acid secretions ⟹ reducing the protective mucous layer & leading to GI irritation.

- Thromboxane A2 is involved in platelet aggregation, inhibitors of COX-1 or non-selective inhibitors will help in utilizing the effect of them (specifically aspirin) on platelet aggregation, hence only **aspirin** is used to **prevent platelet aggregation**, but not the other NSAIDs nor other COX inhibitors.

Why aspirin? At the dose that's used (80 mg, small) of aspirin it's mainly targeting platelets without causing other side effects in the body, another thing is that it's an **irreversible inhibitor**, which binds to the target and keep inflecting its effect until the body produces new of it (in this case the target is COX-1 present in platelets) and as we all know platelets are shreds of cells not actual functional cells -they're devoid of nucleus- so, they CAN'T produce new COX-1 that's not bound to aspirin.

↳ The time of activity of aspirin in the body will equal the life span of that platelet which is 8-11 days, that's why aspirin has that good potential of being an excellent anti-platelet agent.

To have the anti-inflammatory, anti-pyretic and analgesic effects of aspirin altogether, we use it in higher doses, above 325-350 mg.

However, aspirin shows analgesic and anti-platelet effects at low doses.

- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.
- Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.

NSAIDs relieve pain, fever & Inflammation

- One of the PG's effects is that they cause **vasodilatation**, which means more permeability and more inflammatory signs and symptoms will be seen, so inhibiting that will inhibit these effects.
- Another effect is **erythema**.
- They also stimulate the release of histamine which increases **edema**, itching and some other inflammatory cytokine generation at the site of inflammation.

Anti-inflammatory action:

1) decreasing vasodilator PGs (PGE2, PGI2) leads to less vasodilatation and, indirectly, less edema.
2) The inhibition of activity of adhesion molecule, which is important for the recruitment of inflammatory cells.
3) Accumulation of inflammatory cells is also reduced.

Analgesic effect:

Normally prostaglandins will stimulate certain sensory neurons, or nociceptive nerve endings which will cause the feeling of pain.

▪ Decreased prostaglandin generation means decreased sensitivity of nociceptive nerve endings to inflammatory mediators and decreased sensation of pain.

▪ Headache is very hard to study in pharmacology. There are so many things that are opposite to each other that would cause headache.

For example: In hypertension one of the rare signs is headache, and this headache is caused by an increase in the intracranial pressure due to hypertension. I treat hypertension by inducing **vasodilation**, which will help in the signs and symptoms of hypertension which include headache.

However, vasodilation would also cause stretching of certain nociceptive nerve endings in the wall of the blood vessel that will stimulate the pain, meaning **vasodilation can also CAUSE headache**.

Inhibition of PGs is useful in the treatment of headache because it'll reduce this vasodilator effect of prostaglandins on the blood vessels.

↳ It's controversial comparing different kinds of headache.

Migraine is a kind of headache, one of the drugs used to treat it causes **vaso-constriction** to help relieve the pain that would be caused by stretching on nociceptor nerve endings in the walls of blood vessels.

However, there's a drug called propranolol, a beta blocker that is used to treat migraine and it causes **dilation of BVs**!!

- That's why for each patient suffering from headache, we have to use the proper treatment. We can use NSAIDs, because we relieve vasodilation which causes nociceptive feeling that causes pain, and we'd also use paracetamol which works centrally to relieve pain-causing headache.

To sum up: Relief of headache by NSAIDs is due to decreased prostaglandin-mediated vasodilatation.

Antipyretic effect:

PGs increase the production of certain interleukins. One of these is IL-1 which will cause re-setting of the thermo regulatory center in the hypothalamus of the brain and that would elevate body temperature,

- we'll have a higher set point of the thermoregulatory center and thus, what we do when we inhibit prostaglandin synthesis is that we induce blocking of IL-1 production and thus preventing this increase in body temperature.

Fever and increased temperature are hypothalamic problems. The antipyretic drugs we use just counteract the cascade effects of that. They don't affect the hypothalamus directly - So, NSAIDs do not decrease body T° if one took them without having a fever.

For example, if one took paracetamol or ibuprofen while having a fever they'll have a lowering of this fever, but if a nonpyrogenic person took it, their temperature will NOT reach below the normal range (37.2), Because we're blocking the resetting caused by prostaglandins and thus if no resetting caused by prostaglandins, no drop in temperature is induced.

- Fever is associated with an increase in brain PGs (pyrogenic).
  Aspirin prevents the temperature-raising effects of IL-1 by preventing the increase in brain PGs.

To sum up: the antipyretic effect is due to a decrease in the mediator prostaglandin that is responsible for elevating the hypothalamic set-point for temperature control in fever.

Effects on the stomach:

Inhibition of PG synthase in gastric mucosa causes GIT damage (dyspepsia, gastritis).

How to overcome this problem?

Tell the patient to take it after eating, because the food that's present in the stomach will form a barrier between the acid and the gastric mucosa helping the case, even though the effect of the decrease in PGs is not eliminated at the root.

- If given orally, it'll be **absorbed** then it'll go **all over the body** inhibiting COX including the stomach and causing GI irritation.
- It's not beneficial either to tell the patient to take it IM, because then it'll inhibit all the COX in the body including the stomach just the same.
- If given as a suppository it'll be absorbed and eventually reach the COX enzyme present in the gastric mucosa and it'll inhibit PG synthesis, so no protection either.
- ✓ We can give another drug alongside it like Nexium (generic name: esomeprazole) which is a **proton pump inhibitor**, a drug used to treat peptic ulcers, including the NSAIDs over-use associated peptic ulcer.

How does it work?

There's an ATPase pump that pumps H^+ inside the stomach while the Cl^- will diffuse in and the acid will form inside the stomach.

A drug decreasing this action will decrease the acid secretion, thus these two drugs together will have counteracting effect in this point, making it better (prototype of proton pump inhibitors: omeprazole)

> Proton pump inhibitors are indicated in the chronic use of NSAIDs among other things we'll learn in GIS.

Chronic NSAIDs use is associated with migraine & inflammatory conditions like rheumatism.

To treat these, drugs given would include corticosteroids because of their anti-inflammatory properties or NSAIDs. People taking NSAIDs would have damage of gastric mucosa, and this calls for prescribing them drugs to protect the stomach like proton pump inhibitors or H2 receptor antagonists like ranitidine (commercial name: the late 'zantac')

- ✓ We can also give something selective for COX-2 instead of nonselective because they would work at the sites of problem & not take the good with the bad like non-selective NSAIDs.

Examples on COX-2 selective include: Rofecoxib (withdrawn from the market) and celecoxib. We use it for the treatment of inflammatory conditions or chronic pain problems because it wouldn't cause side effects of gastric irritation.

Effects of NSAIDs on various organs/systems:

- Cardiovascular:
  - Platelets: Inhibition of TXA2 derived from platelet COX-1. Giving the net effect of **increasing bleeding time** (inhibition of platelet aggregation)
  - PGI2 derived from Endothelial COX-2 can inhibit platelet aggregation (inhibition augments aggregation by TxA2).
  - Aspirin (acetylsalicylic acid) covalently modifies and, irreversibly inhibits platelet COX. The enzyme is inhibited for the lifetime of the platelet (~8 -11 days). This effect is achieved at a very low dose. (as we said before)
    - Basis of therapeutic efficacy in stroke and MI (reduces mortality and prevents recurrent events).
  - PGI2 derived from Blood vessels/smooth muscle COX-2 can antagonize catecholamine- and angiotensin II-induced vasoconstriction (NSAIDs can elevate bp).
  - Atherosclerosis: Inhibition of COX-2 can destabilize atherosclerotic plaques (due to its anti-inflammatory actions)
- Renal:
  - COX-1 and COX-2 – generated PGs (TxA2, PGF2, PGI2 (from the glomeruli), PGE2 (from the medulla). Some of these PGs act as powerful vasodilators where they might be involved in the maintenance of renal blood flow.

- NSAIDs tend to promote Na+ retention and can therefore increase bp.
  - They can counteract effects of many anti-hypertensives (diuretics, ACE inhibitors and -AR antagonists).
- PGs have minimal impact on normal renal blood flow, but their functions become important in the compromised kidney.
- Patients (particularly elderly and volume depleted) are at risk of renal ischemia with NSAIDs.

- **Gastrointestinal:** (explained above)
  - PGs (generated via COX-1) are actually saviors  of the gastric mucosa, they:

- Inhibit stomach acid secretion,
- Stimulate mucus and HCO_3- secretion, vasodilation and therefore, they are Cytoprotective for the gastric mucosa.
  - Therefore, NSAIDs with COX-1 inhibitory activity will produce opposite effects, leading to: Gastric distress, gastric bleeding, sudden acute hemorrhage (effects however, are dose-dependent)

- **Gestation (pregnancy):**

PGs (generated from COX-2) are involved in the initiation and progression of labor and delivery, through the contraction of the uterus.

Therefore, inhibition of their production by NSAIDs can prolong gestation. And can be used to somewhat stabilize the pregnancy.

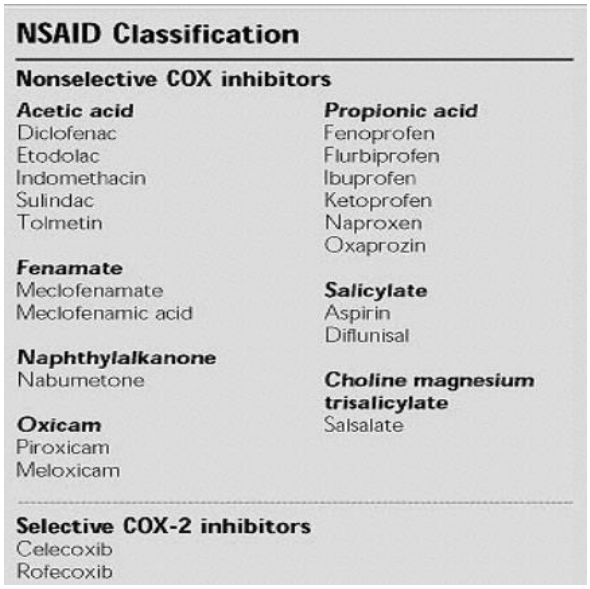
- **Respiratory system**

High doses of (salicylates) cause partial uncoupling of oxidative phosphorylation with increased CO2 production (COX-independent effects).

Increase in plasma CO2.

Hyperventilation → which leads to alkalosis

Even higher doses cause paralysis of respiratory muscles which leads to depression of respiration and thus causing acidosis



NSAID Classification

Nonselective COX inhibitors

Acetic acid
Diclofenac
Etodolac
Indomethacin
Sulindac
Tolmetin

Fenamate
Meclofenamate
Meclofenamic acid

Naphthylalkanone
Nabumetone

Oxicam
Piroxicam
Meloxicam

Propionic acid
Fenoprofen
Flurbiprofen
Ibuprofen
Ketoprofen
Naproxen
Oxaprozin

Salicylate
Aspirin
Diflunisal

Choline magnesium trisalicylate
Salsalate

Selective COX-2 inhibitors
Celecoxib
Rofecoxib

We have different chemical families of NSAIDs

Notes:

We'll talk about diclofenac and indomethacin from the acetic acid family, ibuprofen, ketoprofen and naproxen from the propionic acid family.

A note on the oxicam family is that Meloxicam is known to have more affinity towards COX-2 (selectivity) even though it's considered nonselective. GI side effects associated with it are less.

We'll talk about aspirin, the father of these drugs, which was discovered BC, as they used to use the bark of willow trees to relieve pains and aches of muscles peripherally.

Story time: The manufacturing of it started in 1903, by a chemist called Hoffmann who reacted salicylic acid to produce acetyl-salicylic acid, because his father was in pain (maybe rheumatism) and he wanted to help him.

Good luck