

First, we should know about Pain and Fever

- **Pain:**

Pain is a symptom of inflammation.

- **Fever:**

When temperature is above of 98.6 F. We know, when temperature is 100.4 F , it is called fever.

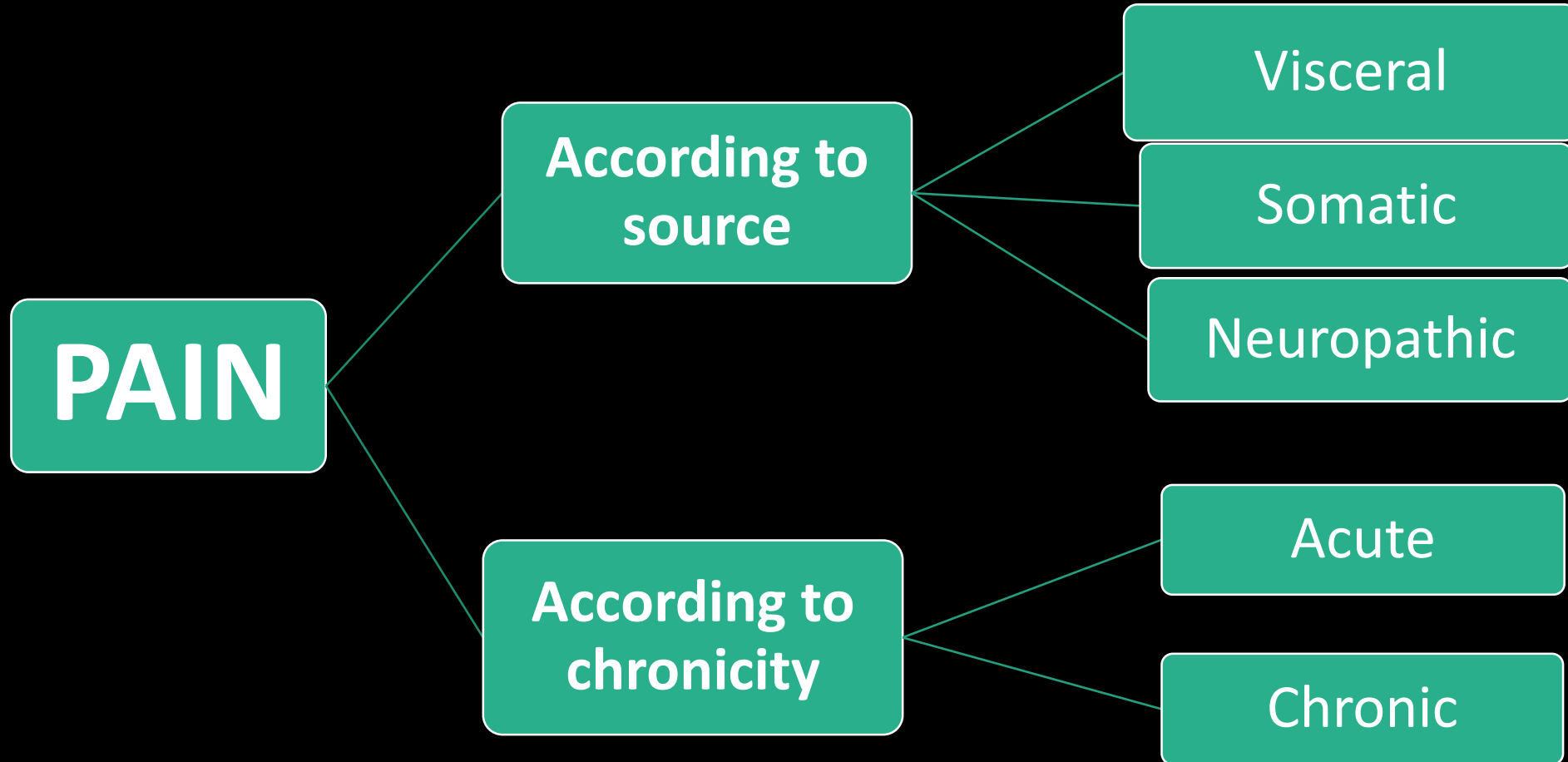
- **Analgesic:**

A drug that selectively relieves pain by acting on CNS or on peripheral pain mechanisms without significantly altering consciousness. It is a pain relive drug.

- **Antipyretic:**

A drug that reduces fever by lowering the body temperature (Some analgesic drugs have antipyretic activity).

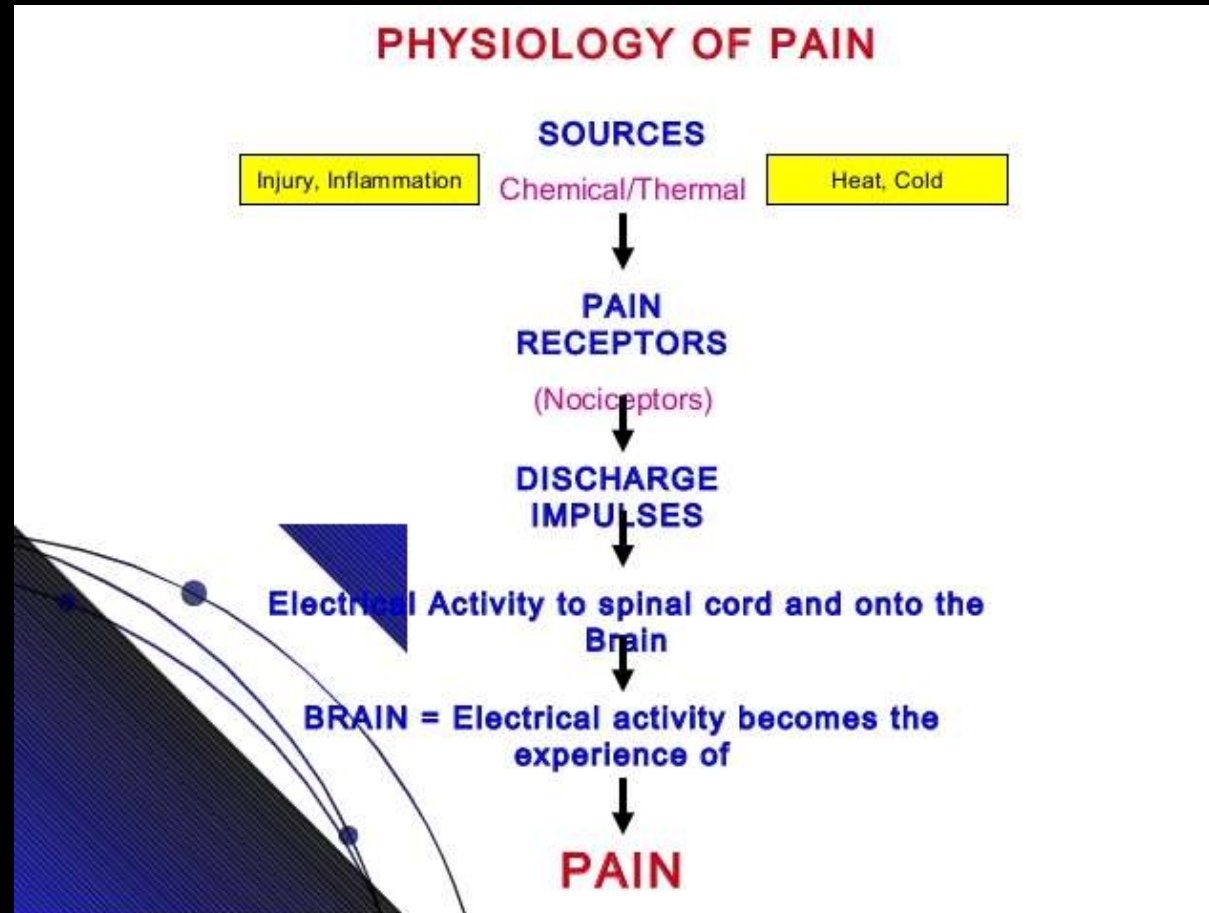
TYPES OF PAIN



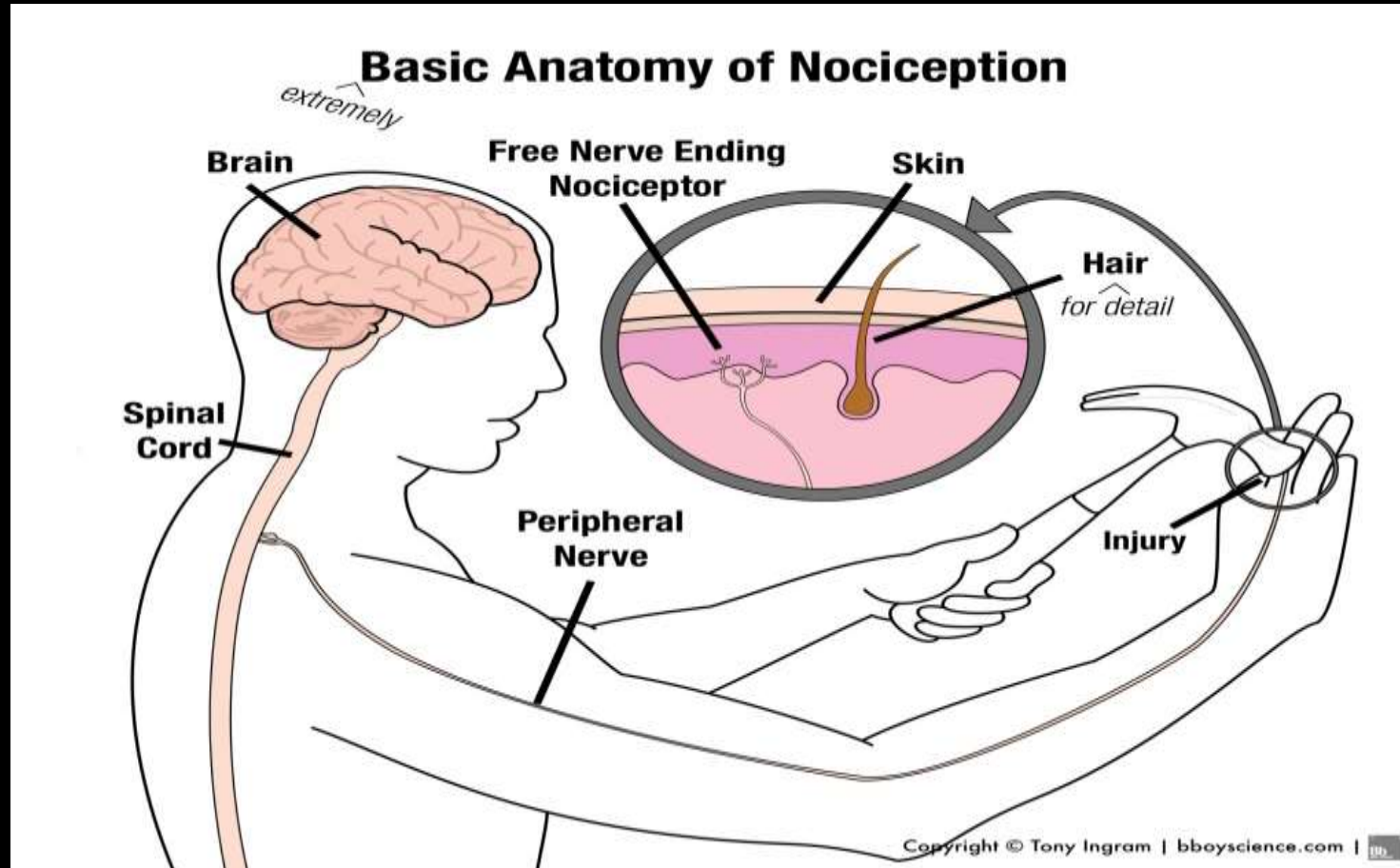
PAIN RECEPTOR

- Pain receptor in our bodies are nerves that transmit pain. These are free nerve endings located in various body tissues that respond to thermal, mechanical, & chemical stimuli.
- When tissue becomes injured, they release chemicals called prostaglandins and leukotrienes that make the pain receptor more sensitive and these causing pain.

PHYSIOLOGY of PAIN



BASIC ANATOMY of NOCICEPTION



CENTRAL ANALGESICS

❖ Opioids:

Morphine & morphine like
drugs



❖ Non-Opioid:

NSAIDs

Acetaminophen/PCM

Flupirtine

Ziconotide

DIFFERENCE

OPIOID ANALGESICS	NON OPIOID ANALGESICS(ANTIPYRETIC):
Act centrally	Act peripherally
Cause addiction	Do not cause addiction
Produce CNS depression	Do not produce CNS depression
Do not produce gastric irritation	Produce gastric irritation
Show no anti inflammatory effect	Show anti inflammatory effect. Reduce body temperature.
eg. Morphine, Tramadol, Pethidine etc.	Diclofenac, Ibuprofen, Aspirin etc.

OPIOID ANALGESIC

- ✓ “Opium” is a Greek word meaning “juice,” or the exudates from the poppy.
- ✓ Opium is extracted from poppy seeds (*Paper somniferum*)
- ✓ “Opioid” is a natural or synthetic drug that binds to opioid receptors producing agonist effects.
- ✓ Which are present in the central and peripheral nervous system, can cause numbness and induce a state of unconsciousness.

MECHANISM of ACTION

All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

They are also involved in

- Postsynaptic hyperpolarization (increasing K⁺ efflux)
- Reducing presynaptic Ca⁺⁺ influx

Thus inhibits neuronal activity.

OPIOID RECEPTOR:

All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase. They also facilitate opening of potassium channels (causing hyperpolarisation) and inhibit opening of calcium channels (inhibiting transmitter release).

They are of 4 types:

- μ receptor
- σ receptor
- δ receptor
- κ receptor

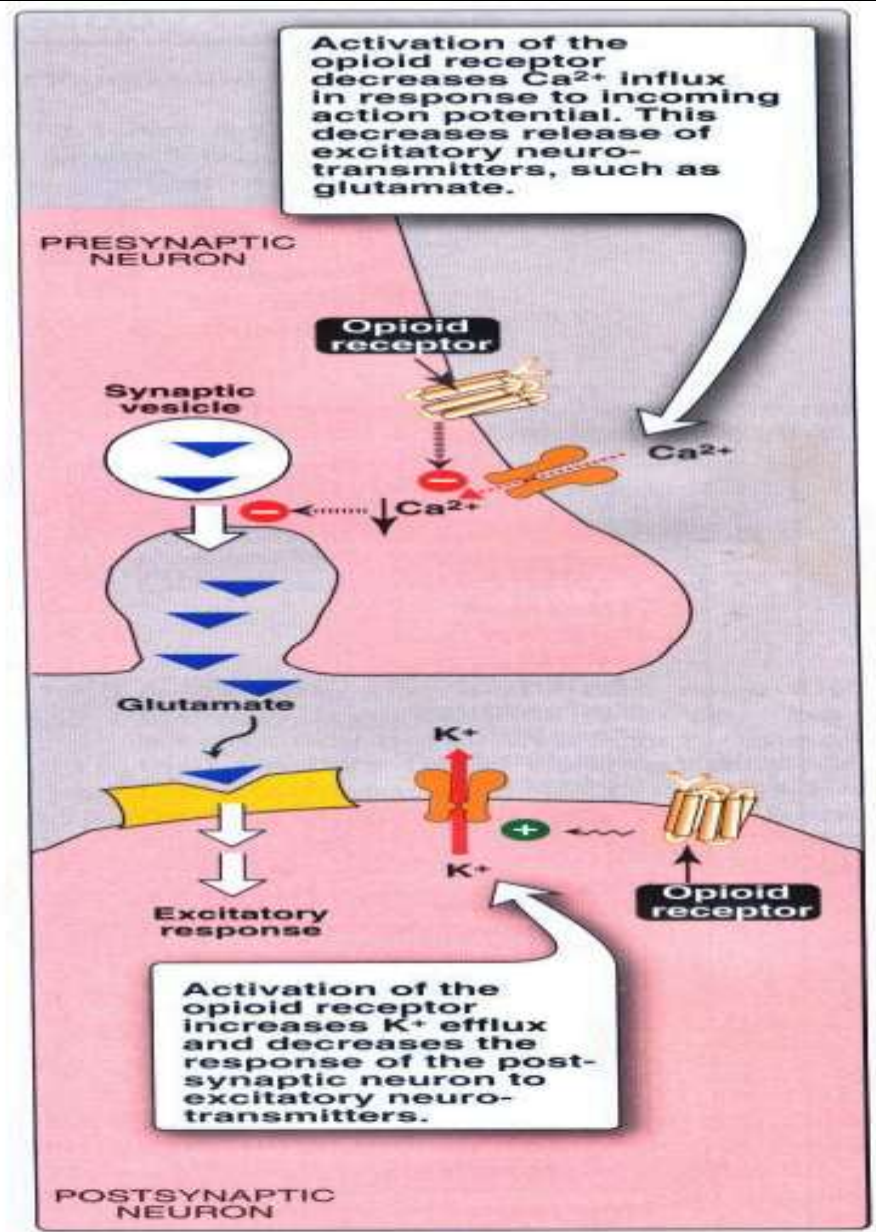
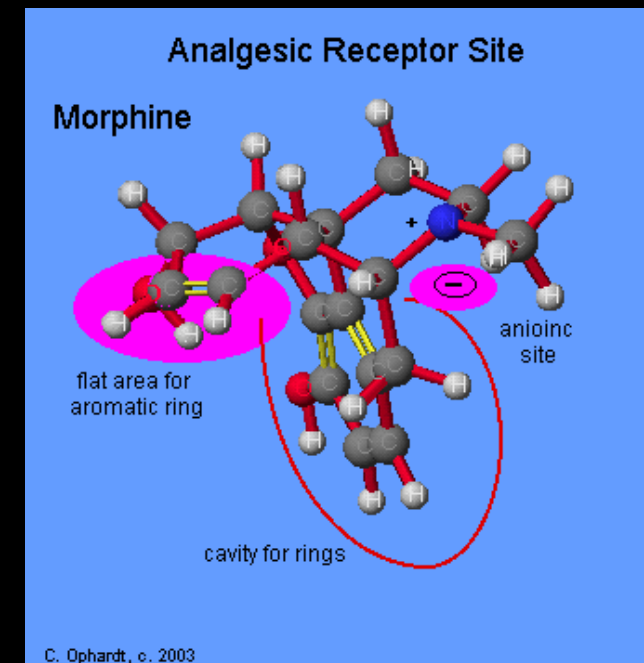
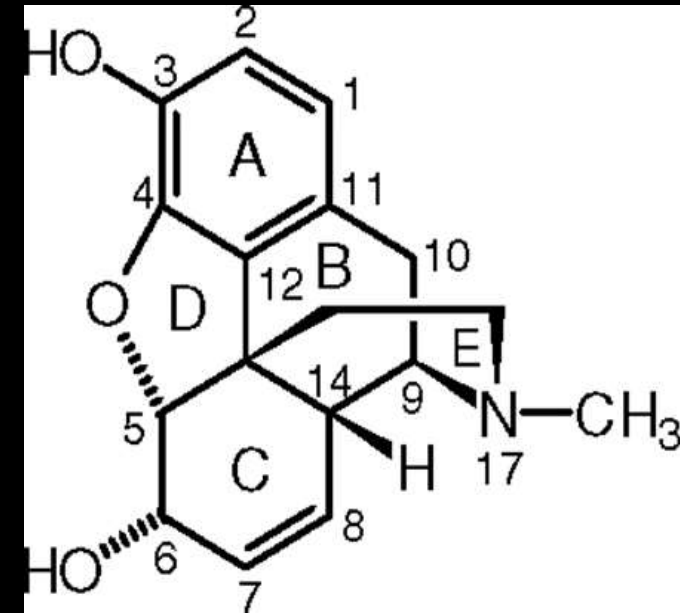


Figure 14.2
Mechanism of action of μ-opioid receptor agonists in the spinal cord.

RECEPTOR BINDING of MORPHINE

Morphine exerts a narcotic action manifested by analgesia, drowsiness, changes in mood, and mental clouding. The major medical action of morphine sought in the CNS is analgesia.

Opiates suppress the "cough center" which is also located in the brainstem, the medulla. Such an action is thought to underlie the use of opiate narcotics as cough suppressants.



RECEPTOR BINDING of MORPHINE

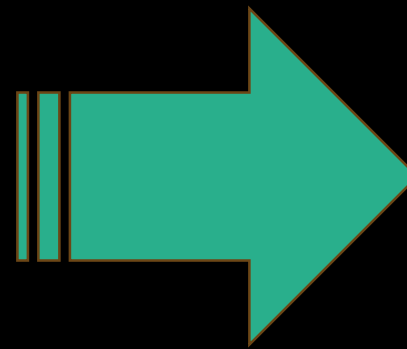
Morphine activates analgesic receptors in the CNS. Which leads to a reduction in the transmission of pain signal to the brain. There are 3 main types of analgesic or opioid receptor activated by morphine. Called the mu, kappa, delta receptors. Which are g-protein coupled receptor.

Morphine acts as an agonist at all three receptors and activation leads to :

Opening of potassium ion channel

Closing of calcium ion channels

Inhibition of Neurotransmitter release



Reduces the pain signal

Morphine has high affinity for mu receptor. Activation of the mu receptor results in sedation, which is the strongest analgesic effect. But activation of this receptor also leads to depression, euphoria, and addiction.

PHARMACOLOGICAL ACTIONS

- **Analgesia**
- **Respiratory depression**
- **Cough suppression**
- **Vagal stimulation (bradycardia)**
- **Sedation & hypnosis**
- **Hypothermia**
- **Itching**
- **Physical & psychological dependence**
- **Euphoria**
- **Histamine release , hypotension....etc.**

ADVERSE EFFECTS

- Morphine can produce a wide range of adverse effects like **nausea, vomiting, dizziness, mental clouding, respiratory depression, constipation, dysphoria, urinary retention, & hypotension, allergic reactions.**
- **Tolerance**- Repeated administration of morphine results in the development of tolerance to some of its effects including respiratory depression, analgesia, sedation, etc .
- **Dependence**- Opium has been a drug of addiction for many centuries. Its ability to produce euphoria makes it a drug of addiction. Opioids produce both physiological & pshycological dependence. Manifestations are lacrimination, sweating, yawning, anxiety, restlessness..etc.



Non-Opioid Analgesics (NSAID's)-as Antipyretic Drug

- ✓ Non steroidal anti-inflammatory drugs are aspirine-type or non-opioid analgesics.
- ✓ In addition, they have **anti-inflammatory, anti pyretic & uricosuric** properties without addiction liability.
- ✓ The active principle is **salicin**, that is converted into **salicylic acid** in body.

Drugs for antipyretic

- Aspirin
- Paracetamol / Acetaminophen

CLASSIFICATION

Non selective COX inhibitor

- Salicylic acid derivatives. Eg: aspirine
- Para aminophenol derivatives. Eg: paracetamol
 - Pyrazolone derivatives. Eg: Sphenylbutazone
- Indole acetic acid derivatives. Eg: sulindac
- Arylacetic acid derivatives. Eg: diclofenac
- Propionic acid derivatives. Eg: ibuprofen
- Anthralinic acid derivatives. Eg: flufenamic acid
 - Oxicams. Eg: piroxicam
 - Alkanones. Eg: nabumetone

Selective COX-2 inhibitors

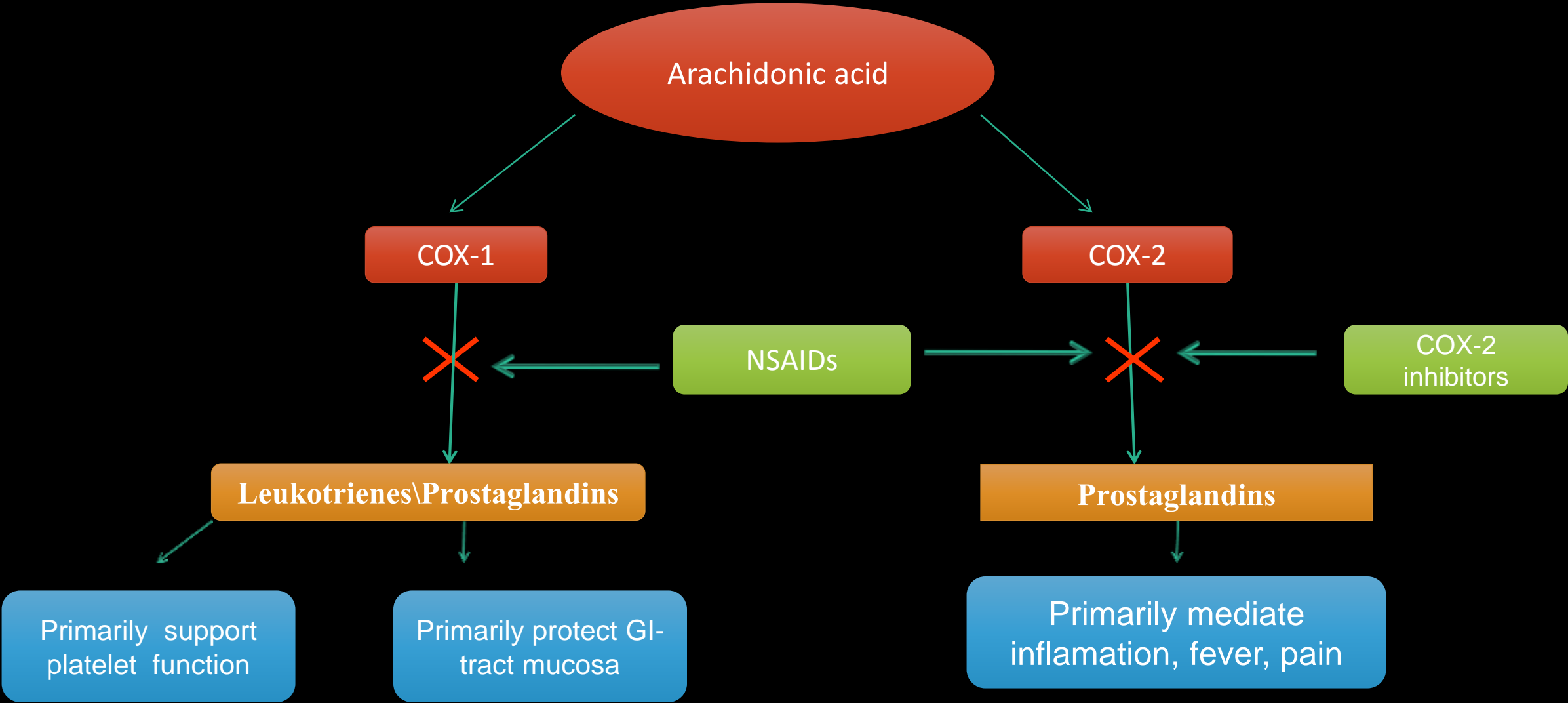
- Nimesulidde, celecoxib, rofecoxib...etc

MECHANISM of ACTION

Activities of antipyretic:

- Used to treat fever.
- Inhibits the enzyme COX.
- Fever → release of endogenous pyrogens (*e.g.*, interleukin-1) released from leucocytes → acts directly on the thermoregulatory centers in hypothalamus → increase body T° .
- This is assoc with increase in brain PGs (pyrogenic).
- Aspirin prevents the T° -rising effects of interleukin-1 by preventing the increase in brain PGs.

MECHANISM of ACTION



ADVERSE EFFECT

Analgesics doses are usually well tolerated but anti-inflammatory doses are usually associated with adverse effects when used for a long period.

A. G.I tract:- Epigastric distress, nausea, vomiting, erosive gastritis, peptic ulcer, increase occult blood loss in stools are common

B. Allergic reactions are not common and may be manifested as rashes, photo sensitivity..etc

C. Haemolysis

D. Nephrotoxicity

E. Reye's syndrome

F. Salicylism

G. Acute salicylate intoxication

SIDE EFFECTS of ANALGESICS & ANTIPYRETIC DRUG

- Risk of experiencing side effects depends on the type of analgesic what we take, and how long we take it.
- Side effects of analgesics may include:
 - Constipation
 - Drowsiness
 - Dizziness
 - Upset stomach
 - Ringing in your ears
 - Skin itching or rash
 - Dry mouth