# ANALGESIC
# Drugs part 2

Semester II

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# Learning Outcomes

By the end of the lecture, the students will be able to:

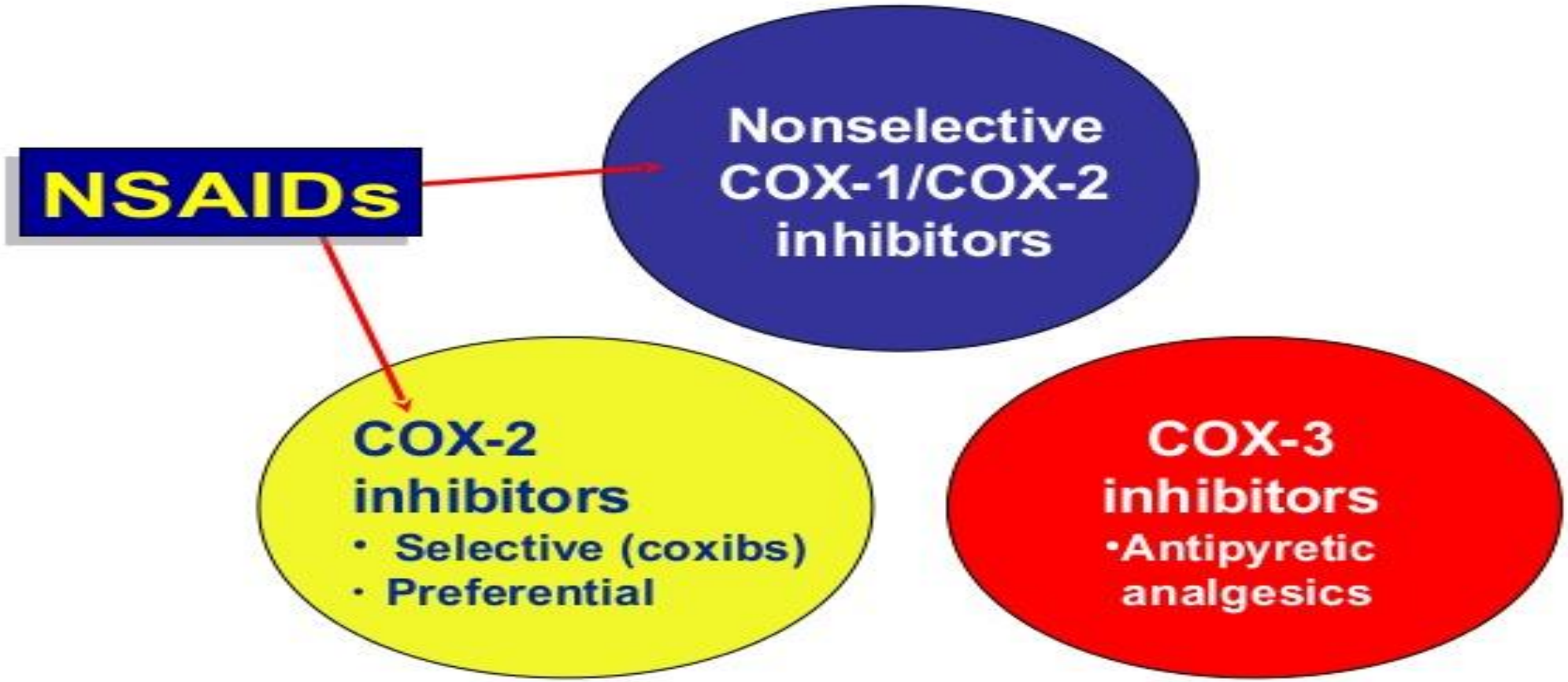
1. Describe the effects of NSAIDs on prostaglandin synthesis.
2. Contrast the functions of COX-1 and COX-2.
3. Compare the actions and toxicity of aspirin, the older nonselective NSAIDs, and the COX-2-selective drugs.
4. Explain why several of the highly selective COX-2 inhibitors have been withdrawn from the market.
5. Describe the toxic effects of aspirin and NSAIDs.
6. Describe the effects and the major toxicity of acetaminophen (paracetamol).

# Selective COX-2 inhibitors: Celecoxib

- Selective COX-2 inhibitors are newer forms of NSAIDs that directly target COX-2 enzyme responsible for inflammation and pain. Celecoxib is approximately 30 times more potent at inhibiting COX-2 than COX-1.
- Selectivity for COX-2 reduces the risk of peptic ulceration but does not seem to affect other adverse-effects of NSAIDs (especially the risk of renal failure).
- Selective COX-2 inhibitors may also increase the risk of **cardiovascular accidents** (myocardial infarction, thrombosis and stroke) due to relative increase in $TXA_2$ and platelet aggregation.

| | Non-selective COX inhibitors | Selective COX-2 inhibitors |
|---|---|---|
| **Mechanism:** | **They inhibit COX-1 (non-inducible) and COX-2 (inducible) enzymes** | **They inhibit COX-2 (inducible) enzyme only** |
| **Pharmacological effects:** | **Both classes have equal analgesic and antipyretic effects** | |
| **Gastric side effects:** | **Frequent** | **Less frequent** |
| **Renal side effects:** | **Frequent** | **Frequent** |
| **CVS side effects:** | **Decreased** | **Increased** |
| **Hypersensitivity reactions:** | **Frequent** | **Less frequent** |

# COX inhibitors



# Acetaminophen (Paracetamol)

- **Mechanism & Pharmacological effects**
- It is a **selective Cox III inhibitor** so it inhibits PGs synthesis in **the brain only** and has **analgesic & antipyretic** actions **without** effect on peripheral PGs and so it has **no anti-inflammatory action.**
- It has **little or No** effects on the GIT, or respiratory.
- **Therapeutic uses**
- As **analgesic and antipyretic** **when aspirin is contraindicated**

  (e.g. patients with peptic ulcer, asthma…….etc).
- Acetaminophen can be administered in **pregnancy**

  with greater safety than aspirin.

# Adverse effects

- **At therapeutic doses:** It is well-tolerated but may cause:
  - Skin rash & drug fever (as an allergic reaction).
  - Hemolytic anemia in patients with G-6-PD deficiency.
- **In toxic doses:** **Dose-dependent hepato-toxicity**:

➢It occurs with large doses ( **15 gm** in adults and **4 gm** in children).

➢***Treatment of toxicity:***

- **G**astric lavage better with activated charcoal.
- **Sulfhydryl (-SH) donors** **e.g. acetylcysteine** to enhance hepatic synthesis of glutathione.
- **Hemodialysis:** better within the first 12 hrs after ingestion.

# Case Discussion/reflection

- a. Paracetamol taken in adequate doses (upto 2.6 g per day) is the most suitable analgesic for relieving knee pain in the given patient. Unlike many NSAIDs, it does not increase the risk of myocardial infarction/stroke. Paracetamol does not inhibit endothelial PGl 2 synthesis, does not affect platelet function and does not nullify the cardioprotective effect of low dose aspirin. Moreover, it is a first-line drug for osteoarthritic pain, and is well tolerated with minimal gastric side effects.
- b. The selective COX-2 inhibitors (celecoxib, etoricoxib) are not suitable for this patient, because they increase the risk of heart attack and stroke by inhibiting endothelial PGl2 synthesis. Diclofenac is also not free of such risk. Though propionic acid NSAIDs (ibuprofen, etc.) are nonselective COX inhibitors which do not increase thrombotic risk, they block the cardioprotective effect of low dose aspirin that this patient is taking.
- c. Topical NSAIDs, e.g. diclofenac/ketoprofen gel can afford adjuvant symptomatic relief in this patient. Since blood levels of NSAIDs after local application are low, they are well tolerated and do not increase cardiovascular risk.

# Summary and wrap up

- NSAIDs should be taken after food.
- NSAIDs should be avoided in patients with peptic ulcer as it may aggravate the condition.
- Preferred analgesics for patients with peptic ulcer are paracetamol and selective COX-2 inhibitors.
- Patients on aspirin should inform the doctor if surgery/dental procedure is planned.
- Educate patient about adverse effects and drug interactions of aspirin. Advise patient to report signs of bleeding, if any.
- The preferred analgesic in patients with chronic renal failure is paracetamol.

# Quiz

- **A 52-year-old man with chronic low back pain. He is complaining from severe hyperacidity. Which of the following agents may improve his pain without worsening his gastrointestinal symptoms?**

  **(A) Aspirin**

  **(B) Celecoxib**

  **(C) Ketorolac**

  **(D) diclofenac**

# Quiz

**Which one of the following analgesic agents inhibits mainly COX in CNS?**

a) Morphine

b) Paracetamol

b) Ketorolac

d) Ibuprofen

# Quiz

- **The pharmacologic effects of acetylsalicylic acid include:**

A- Reduction of high body temperature

B- Promotion of platelet aggregation

C- Reduction of pain by stimulation of PGs synthesis

D- Less gastric irritation than other NSAIDs

# Quiz

- **Acetaminophen**

a) is primarily used in ischemic heart diseases

b) is an aspirin substitute for analgesia and antipyresis in children

c) has no associated liver toxicity with chronic use of large doses

d) is not given to children because it causes flu-like symptoms

# MCQ

**Acetaminophen is a potent analgesic and antipyretic NSAID but differs from other agents in that it has no anti-inflammatory action. Which of the following reasons explains this unique aspect of acetaminophen?**

A. the distribution of acetaminophen does not reach peripheral sites of inflammation
B. acetaminophen is not an inhibitor of the COX enzyme
C. antiinflammatory doses of acetaminophen are too high and toxic
D. it is selective for a newly discovered isozyme of COX
E. acetaminophen undergoes significant first-pass metabolism

- **Which of the following statements concerning the anti-inflammatory effect of NSAIDs are TRUE?**

A. Anti-inflammatory effect of NSAIDs results from inhibition of cyclooxygenase

B. Anti-inflammatory effect of NSAIDs results from inhibition of phospholipase A2 and reducing prostaglandin and leukotriene synthesis

C. Anti-inflammatory effect of NSAIDs results from induction of cyclooxygenase II expression which results in reducing the amount of an enzyme available to produce prostoglandins

D. All of the above

- **The following statements concerning aspirin are true, EXCEPT:**

A. In contrast to most other NSAIDs, aspirin irreversibly inhibits COX
B. Aspirin interferes with the chemical mediators of the kallikrein system
C. Aspirin inhibits phospholipase A2
D. Aspirin inhibits tromboxane A2 formation

- **Indication for aspirin administration are the following, EXCEPT:**

A. Inflammatory conditions
B. Decreasing the incidence of transient ischemic attack, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting
C. Relieving severe visceral pain( myocardial infarction, cancer pain condition, renal or biliary colic )
D. Reducing elevated body temperature

- **Which of the following NSAIDs is a selective COX-2 inhibitor?**

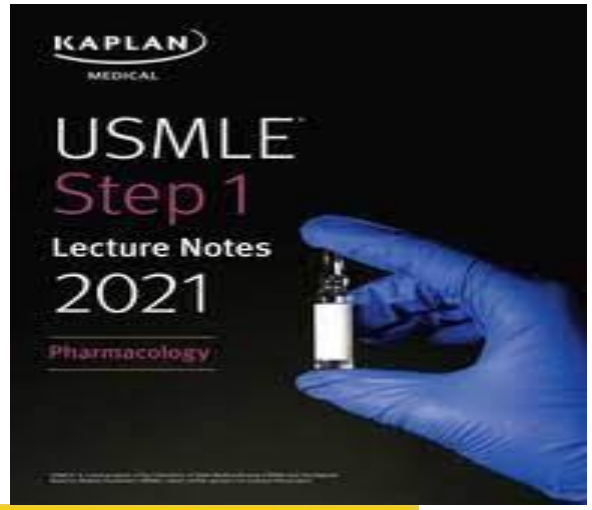
A. Piroxicam
B. Indomethacin
C. Celecoxib
D. Diclofenac

- **Which of the following NSAIDs is a nonselective COX inhibitor**

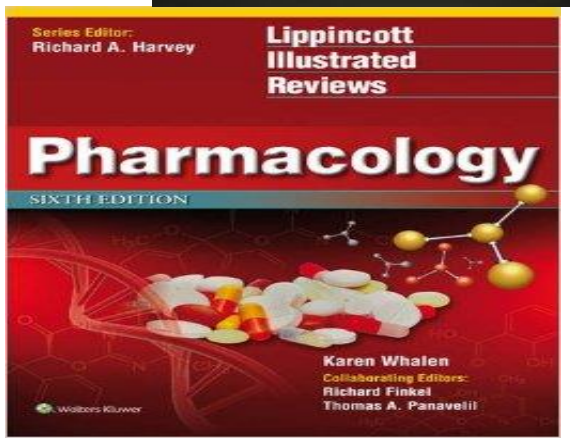
A. Piroxicam
B. Rofecoxib
C. Celecoxib
D. All of the above

# References or further readings

1) **Kaplan USMLE STEP1, lecture notes Pharmacology latest edition.**



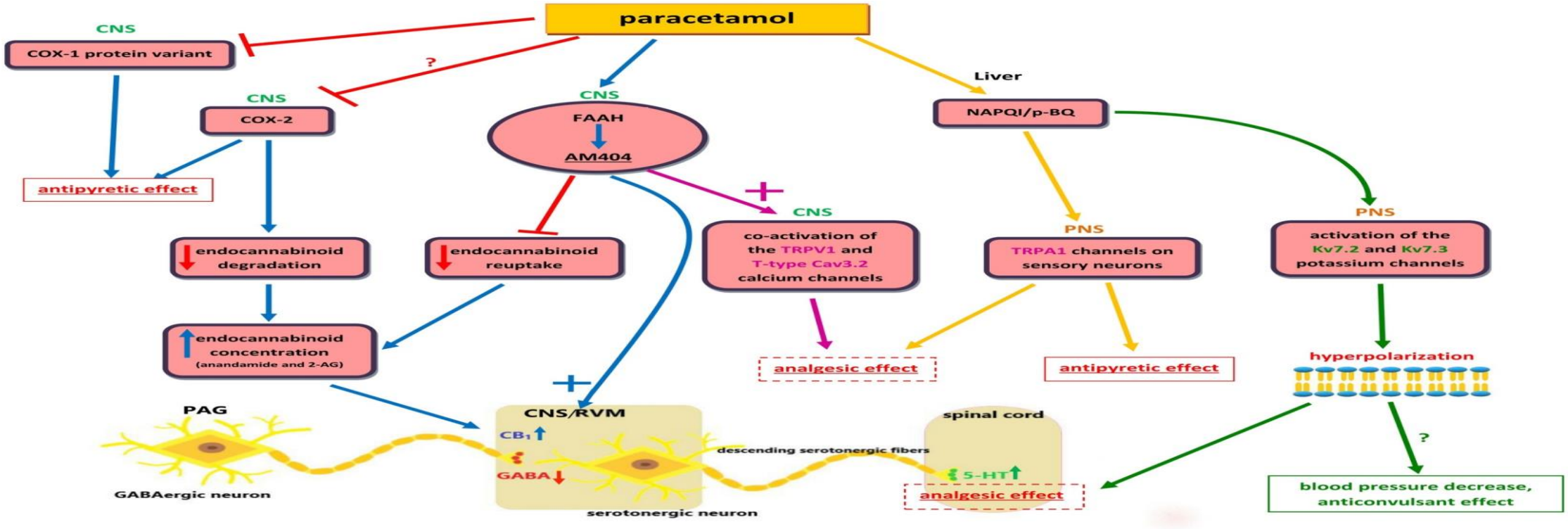

2) **Lippincott's illustrated review: Pharmacology, latest edition**




Thank you

# nice to know

## **Paracetamol –** An old drug with new mechanisms of action




Hypothetical scenario of paracetamol action in central nervous system (CNS) and liver. 2-AG, 2-arachidonoylglycerol; 5-HT, 5-hydroxytryptamine receptor (serotonin receptor); AM404, N-arachidonoylphenolamine; CB1, cannabinoid receptor type 1; CNS, central nervous system; FAAH, fatty amide hydrolase; NAPQI, cN-acetyl-p-benzoquinoneimine; p-BQ, p-benzoquinone; PAG, periaqueductal gray; PNS, peripheral nervous system; RVM, rostral ventromedial medulla; TRPA1, transient receptor potential subfamily ankyrin 1; TRPV1, transient receptor potential subfamily vanilloid-1