Evaluation of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (Lab 4)

Asst. Lec. Zakariya A. Mahdi

Department of Pharmacology & Toxicology
Mustansiriyah University

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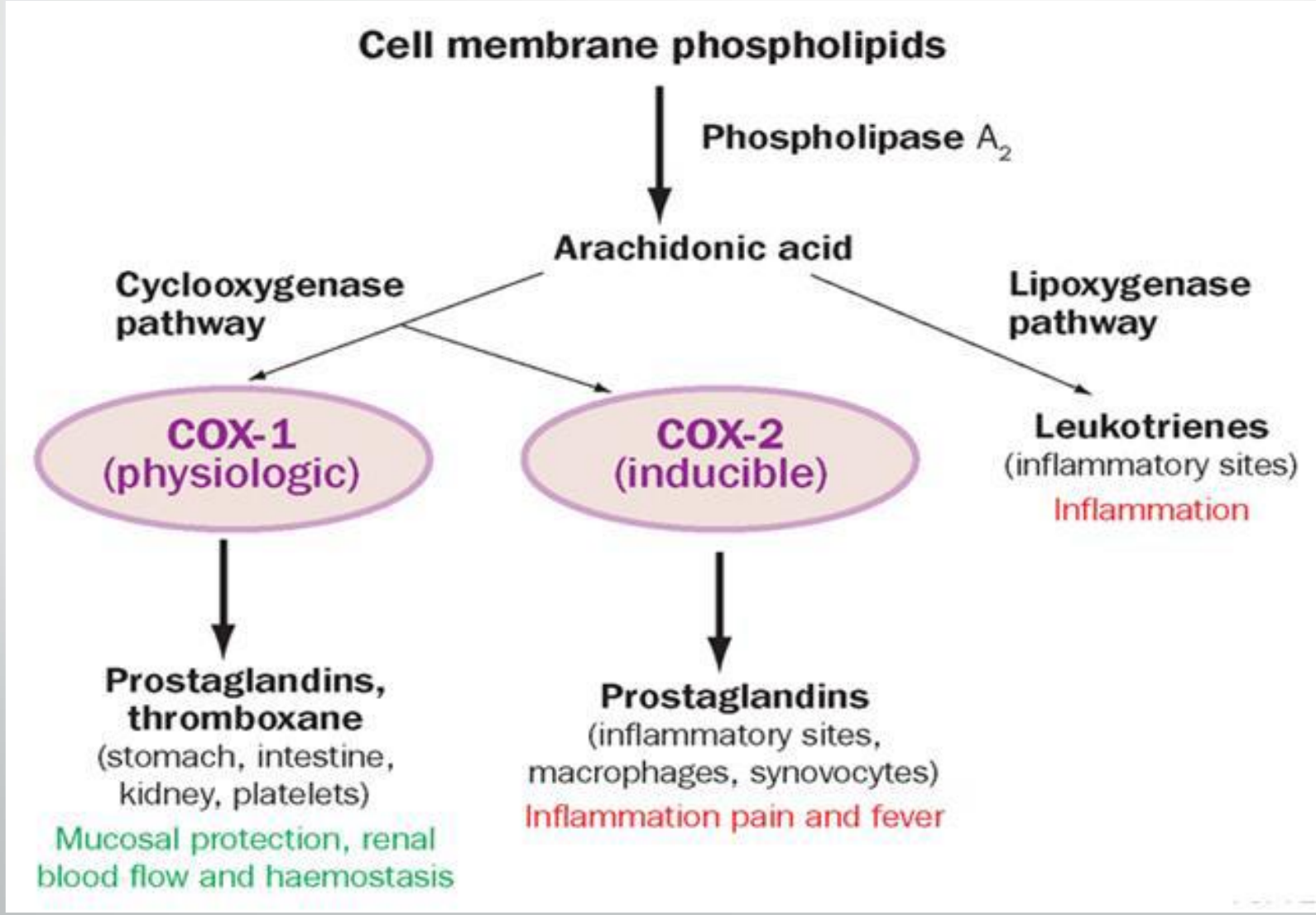
Synthesis of prostaglandins & leukotrienes:

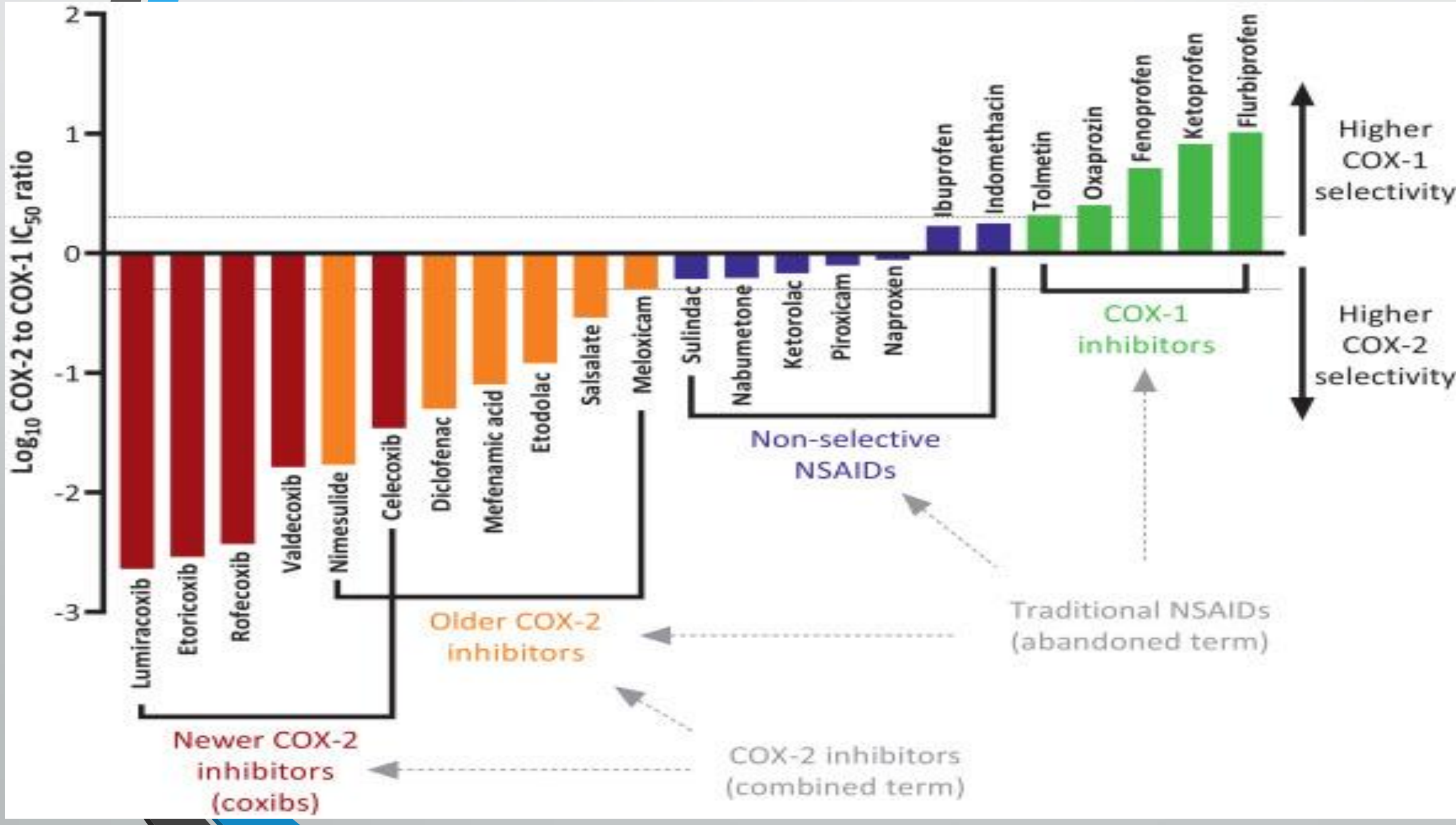


Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

- The NSAIDs are a group of chemically dissimilar agent that differ in their activities. antipyretic, analgesic, & anti-inflammatory.
- They act primarily by inhibiting the cyclooxygenase (COX) enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial & unwanted effects.
- Traditional NSAIDs include aspirin, ibuprofen, naproxen & many other generic & brand name drugs.

NSAID

- A newer NSAID like celecoxib, is a "COX-2 inhibitor" or a "COX-2 selective" NSAID.
- NSAIDs are used to relieve pain & reduce signs of inflammation.
- NSAIDs also are a common treatment for chronic (long-term) health problems such as rheumatoid arthritis & osteoarthritis.


Log10 COX-2 to COX-1 IC50 ratio
2
1
0
-1
-2
-3
Lumiracoxib
Etoricoxib
Rofecoxib
Valdecoxib
Nimesulide
Celecoxib
Diclofenac
Mefenamic acid
Etodolac
Salsalate
Meloxicam
Sulindac
Nabumetone
Ketorolac
Piroxicam
Naproxen
Ibuprofen
Indomethacin
Tolmetin
Oxaprozin
Fenoprofen
Ketoprofen
Flurbiprofen
Higher COX-1 selectivity
Higher COX-2 selectivity
COX-1 inhibitors
Non-selective NSAIDs
Older COX-2 inhibitors
Newer COX-2 inhibitors (coxibs)
Traditional NSAIDs (abandoned term)
COX-2 inhibitors (combined term)

Selectivity	Drugs
Weak COX inhibitors	Acetaminophen,Salsalate
Inhibitors of COX-1 and COX-2	Acetylsalicylic acid, Piroxicam, Indomethacin, Sulindac, Tolmetin, Ibuprofen, Naproxen, Fenoprofen, Meclofenamate, Mefenamic acid Diflunisal, Ketoprofen, Diclofenac, Ketorolac, Etodolac, Nabumetone, Oxaprozin, Flurbiprofen
Preferential COX-2 inhibitors	Nimesulide, Meloxicam
Selective COX-2 inhibitors	Celecoxib, Rofecoxib,Valdecoxib, Etoricoxib, Parecoxib, Lumiracoxib

General unwanted effects of NSAIDs:

- Dyspepsia, nausea & vomiting. Gastric damage may occur in chronic users, with risk of haemorrhage.
- Skin reactions.
- Reversible renal insufficiency seen mainly in individuals with compromised renal function.
- All NSAIDs (except COX-2 inhibitors) prevent platelet aggregation & therefore may prolong bleeding.

In vivo analgesic evaluation techniques:

❖ Principle:

Pain is induced in a suitable animal & the response of the animal to the painful stimuli is recorded with or without administration of the analgesic agent.

❖ Classification of methods:

1. Methods for central analgesic activity:

- Hot plate method
- Tail immersion method
- Tail clip method

2. Method for peripheral analgesic activity:

- Writhing method
- Formalin test in rats

Writhing method:

- The painful stimulus is induced by IP injection of an irritant substance (e.g. acetic acid).
- The animals create a characteristics stretching behavior, which is called writhing. (writhing is constriction of abdomen, turning of trunk (twist) & extension of hind legs).
- The number of writhes for each animal is counted during certain time period (eg, during 30 minutes), beginning 5 minutes after injection of acetic acid.

Experimental protocol:

- Groups of animals are the control & the treated mice.
- The control group is given acetic acid IP & after 5 minutes the number of writhes is recorded for each

animal during 20 minutes.

- Treated animals are administered the drug (diclofenac or piroxicam) IP, 5 minutes prior to acetic acid

administration. Then acetic acid is given IP.

- Five minutes are allowed to elapse, the mice are then observed for a period of 20 minutes & the number of

writhes is recorded for each animal.

- If the drug possesses analgesic activity, the animal that received the drug will give lower number of writhes than the control, i.e. the drug having analgesic activity that inhibits writhing.
- Calculate % inhibition:

% inhibition = [No. of writhing in control group - No. of writhing in treated group] / No. of writhing in control group] × 100

Writhing test		
Group	**No. of writhing**	**% inhibition**
Control	**40**	**0**
Group I: Drug A	**20**	**50%**
Group II: Drug B	**30**	**25%**

THANK YOU FOR YOUR ATTENTION