NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Sources:

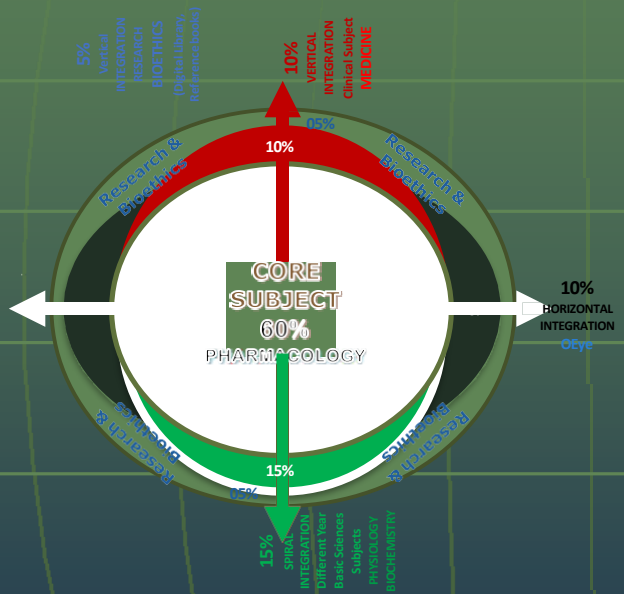
Bertram G. katzung Basic & Clinical Pharmacology 15th Edition

Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



4rd Year Pharmacology LGIS		
Core Subject – 60%		
Pharmacology		
Horizontal Integration – 10%		
Same Year Subjects	•	Eye • Pathology
Vertical Integration – 10%		
Clinical Subjects	•	Medicine • Surgery
Spiral Integration – 15%		
Different Year Basic Sciences Subjects	•	Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%		

Learning Objectives

- ✓ At the end of the lecture, students should be able to:
- Classify NSAIDs
- Describe the mechanism of action of NSAIDS.
- Describe the shared toxicities of NSAIDs.
- Differentiate between non selective COX inhibitors and selective COX-2 inhibitors

Spiral Integration- Physiology

EICOSANOIDS

- **PGs, TXA_2 LTs, prostacyclin,** all derived from precursor fatty acid, arachidonic acid, are called eicosanoids (eikosi, Greek word, means twenty)
- Are short-lived, extremely potent & formed in almost every tissue of body

PROSTANOIDS

PGs, Prostacyclin, TXA_2 collectively called as prostanoids

CYCLOOXYGENASE (COX)

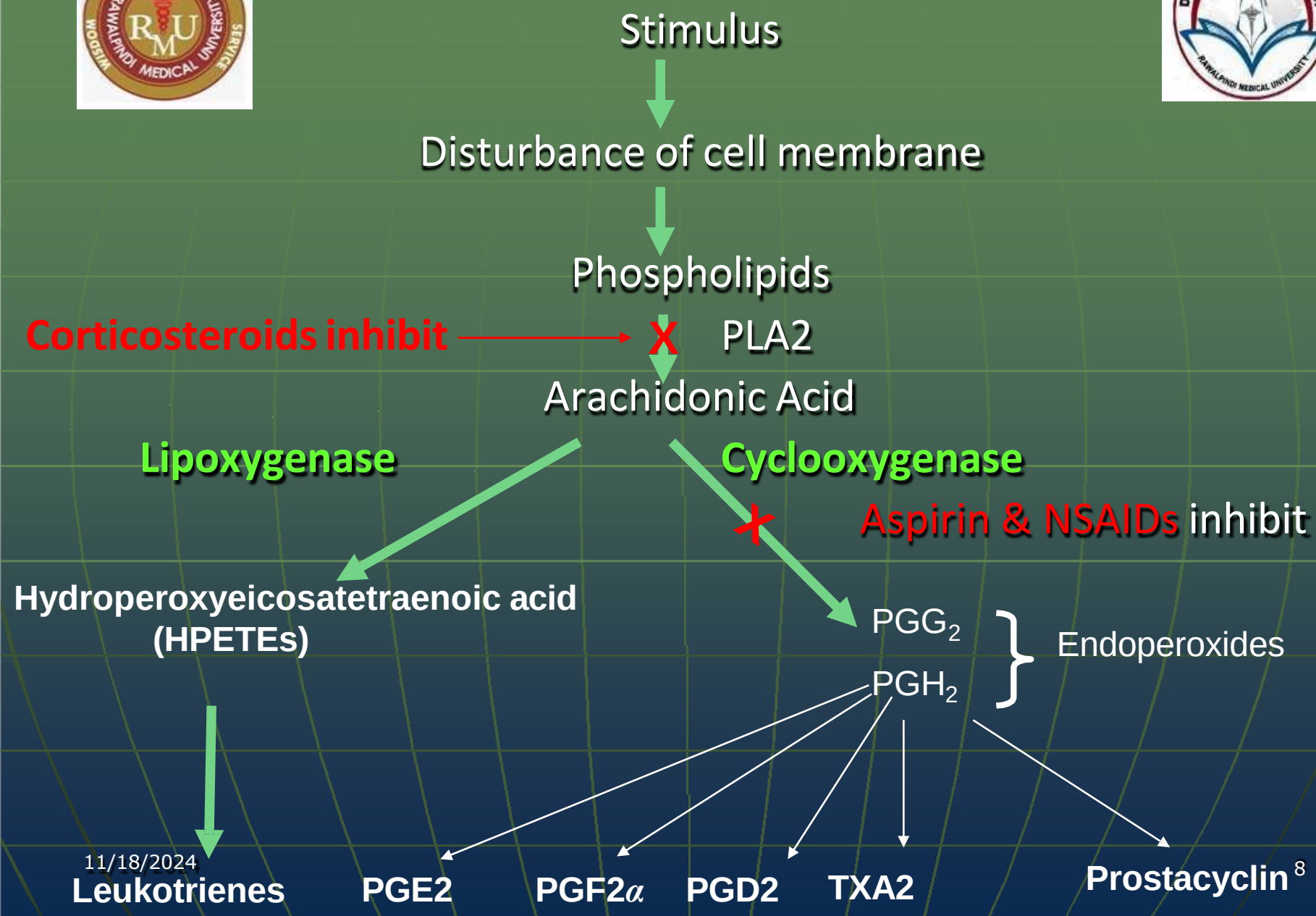
COX, found bound to endoplasmic reticulum, exists in 3 isoforms:

COX-1: expressed constitutively in most cells, is "House keeping" enzyme, regulates normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation & kidney function

COX-2: constitutively expressed in brain, kidney, bone & ***induced during inflammation & cancers***

COX-3: (in brain)

Scheme for Prostaglandin Biosynthesis with inhibitors



PGD2	• Vasodilatation
PGE2	• Affect hypothalamus temperature regulating system produces fever • Increases water electrolytes & mucus secretion in GIT
PGF2α	• Produces contraction of uterine smooth muscles & bronchi
PGI2	• **Vasodilatation & inhibition of platelet aggregation**
TXA2	• **Vasoconstriction & stimulates platelet aggregation**
LTC4 AND LTD4	• Bronchoconstriction • Increased capillary permeability

CORE SUBJECT

NSAIDs

Non – Narcotic Analgesics

Non-opioids, Aspirin like drugs

Compared to opioid analgesics:

- Weaker analgesics
- Do not depress CNS
- Do not produce physical dependence
- No abuse liability

CLASSIFICATION

A. NONSELECTIVE COX INHIBITORS (Traditional NSAIDs)

i. SALICYLIC ACID DERIVATIVES

Aspirin (Acetyl salicylic Acid)

Sodium Salicylate Diflunisal

ii. ACETIC ACID DERIVATIVES

Diclofenac Sulindac

Indomethacin Etodolac

Tolmetin Ketorolac Nabumetone

iii. FENAMIC ACID DERIVATIVES (FENAMATES)

Meclofenamic Acid Flufenamic Acid

CLASSIFICATION

iv. PROPIONIC ACID DERIVATIVES

Ibuprofen Ketoprofen Fenoprofen
Flurbiprofen Naproxen

V. PYRAZOLONE DERIVATIVES

Phenylbutazone Oxyphenbutazone

vi. OXICAMS (ENOLIC ACID DERIVATIVES)

Piroxicam Meloxicam

CLASSIFICATION

B. SELECTIVE COX-2 INHIBITORS

Celecoxib Valdecoxib Parecoxib

Rofecoxib Etoricoxib Lumiracoxib

C. PREFERENTIAL COX-2 INHIBITORS

Nimesulide Diclofenac

Meloxicam Etodolac

D. PREFERENTIAL COX-3 INHIBITOR

Acetaminophen (Paracetamol)

ASPIRIN

- Prototype drug
- Acetyl salicylic acid
- Obtained from willow bark & leaves but is now synthesized

NSAIDs/ASPIRIN- PHARMACOKINETICS

- All NSAIDs are weak acidic drugs except nabumetone
- All are well absorbed from GIT
- Can cross both the BBB & placenta
- Mostly NSAIDs have high PPB--- 98%
- Widely distributed, penetrate arthritic joints, cross BBB
- Half life varies among NASIDs
- Aspirin------ $t_{1/2}$ 15 min
- Mostly metabolized in liver & have renal excretion
- Aspirin is hydrolyzed to salicylate & acetic acid by esterases in tissues & blood

MOA OF ASPIRIN / NSAIDs

- NSAIDs inhibits biosynthesis of PGs, by reversible inhibition of COX enzymes
- Aspirin is **non selective COX inhibitor, *irreversibly inhibit cyclooxygenase activity***, inhibiting PGs synthesis
- While most of NSAIDs act as reversible competitive inhibitor of COX activity
- Do not inhibit lipoxygenase pathway of AA metabolism so not suppress LT formation

VERTICAL INTEGERATION-MEDICINE

THERAPEUTICS USES OF ASPIRIN & OTHER NSAIDs

- All NSAIDs, including selective COX-2 inhibitors, are antipyretic, analgesic & anti-inflammatory ***EXCEPT*** acetaminophen, which is antipyretic & analgesic but devoid of anti-inflammatory activity

ANALGESIC

- Aspirin & other NSAIDs used for relief of mild to moderate pain especially arising from integumental structures rather than from viscera
- Severe pain, not controlled by NSAIDs
- Used in pain like:

Toothache, Headache, Myalgia, Arthralgia Neuralgia, Dysmenorrhea

ANALGESIC

- Nociceptors, that senses pain, activated by noxious stimuli, causing release of inflammatory mediators, which increase sensitivity of nociceptors & potentiate pain perception
- PGs reduce threshold to stimulation of nociceptors, causing ***peripheral sensitization***
- Aspirin & Other NSAIDs inhibit COX enzyme , reduce production of PGs → decrease sensation of pain
- A central subcortical action, raising threshold to pain perception also contributes
- ***No sedation, tolerance & dependence are produced***

DYSMENORRHOEA

- Pain arising from hollow viscera not relieved by NSAIDs, exception to this is menstrual pain
- Release of PGs by endometrium during menstruation cause severe cramps
- NSAIDs are effective by decreasing PG release

RESEARCH

- Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA. Aspirin use to prevent cardiovascular disease and colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. Jama. 2022 Apr 26;327(16):1585-97.

- Dear JW, Bateman DN. Developing new antidotes for poisons with existing effective treatments: a case study of fomepizole in paracetamol poisoning. Clinical toxicology. 2023 Sep 22:1-3.

FAMILY MEDICINE

- Wallis KA, Elley CR, Moyes SA, Lee A, Hikaka JF, Kerse NM. Safer Prescribing and Care for the Elderly (SPACE): a cluster randomised controlled trial in general practice. BJGP open. 2022 Mar 1;6(1).

ARTIFICIAL INTELLIGENCE

- Ravikumar, C., Sanganal, J.S., Shridhar, N.B., Sunilchandra, U. and andMoonoshree Sarma, R.S., 2023. An overview of NSAID loaded nanomaterials.

BIOETHICS

- Johnson CF, Maskrey M, MacBride-Stewart S, Lees A, Macdonald H, Thompson A. New ways of working releasing general practitioner capacity with pharmacy prescribing support: a cost-consequence analysis. Family Practice. 2022 Aug 1;39(4):648-55.


THANK
YOU!