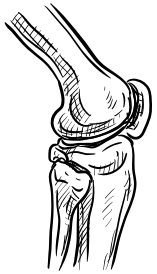
بسم الله الرحمن الرحيم



PHARMACOLOGY

MID | Lecture 1

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم

اللهم استعملنا ولا تستبدلنا

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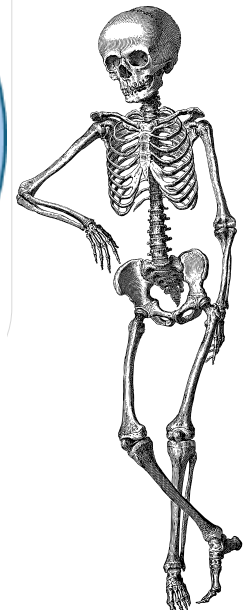
Mahmood Alabsi

Reviewed by: Laith Joudeh



REMEMBER FROM GENERAL PHARMACOLOGY

Efficacy vs. Potency:

- Efficacy refers to the maximum effect a drug can produce regardless of the dose. It represents the drug's ability to achieve a maximal biological response, often quantified by its E_{max} value.
- Potency describes the amount of a drug needed to produce a given effect. A more potent drug achieves the desired effect at a lower dose compared to a less potent one.
- E_{max} is the maximum effect that can be achieved with a drug when all available receptors are activated. It is a direct measure of the drug's efficacy.

Pharmacodynamics is the branch of pharmacology that studies how drugs affect the body. It focuses on the interaction between drugs and their biological targets, such as receptors, enzymes, or ion channels, and explains how these interactions lead to therapeutic and adverse effects.

Key concepts include:

- Drug-Receptor Interactions: Understanding how drugs bind to and activate or inhibit receptors (agonists vs. antagonists).
- Dose-Response Relationship: Illustrating the relationship between drug concentration and effect, using parameters like efficacy (E_{max}) and potency.
- Signal Transduction: Examining the cascade of intracellular events following receptor activation.
- Therapeutic Window: Defining the dosage range where the drug is effective without causing significant side effects.

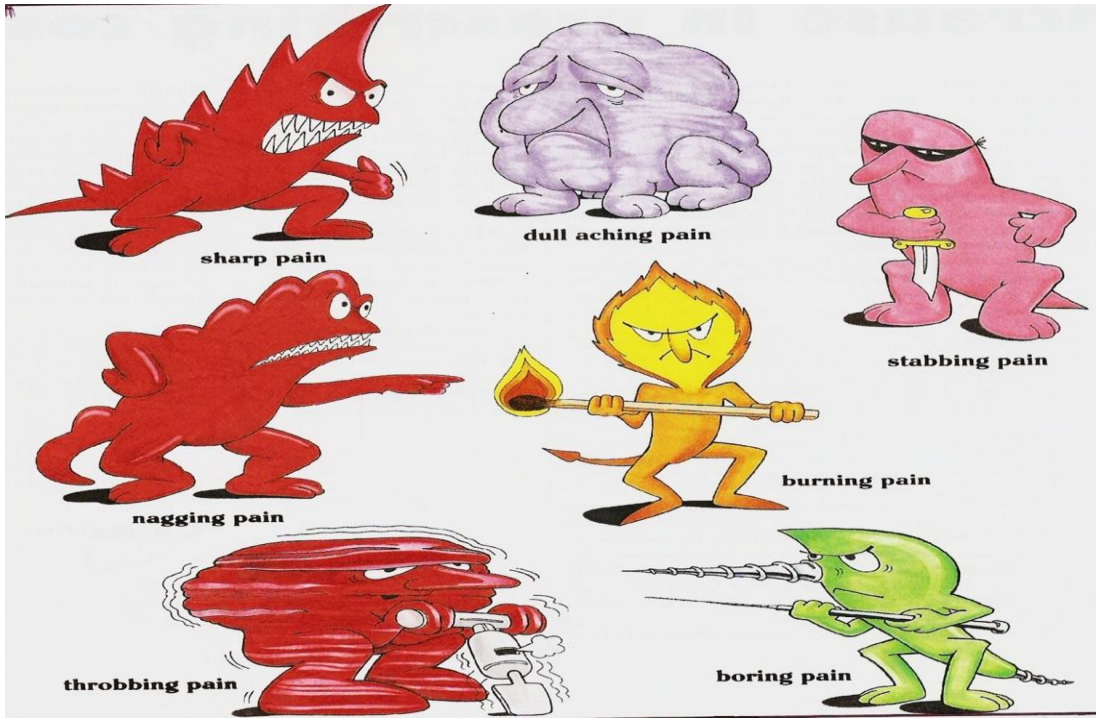
This framework helps in optimizing dosing regimens and improving patient outcomes.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

Dr. Alia Shatanawi

Pain

- Universal, Complex, Subjective experience
- No. 1 Reason people take medications
- Generally, is related to some type of tissue damage and serves as a warning signal



- Pain serves as an alarming indicator that something may be amiss within the body, often prompting individuals to seek medical treatment.
- Typically, pain is associated with tissue damage, which activates specific signaling pathways that stimulate nociceptor nerve terminals and convey pain signals to the central nervous system.

Analgesics

- Pain killers
- 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.
- Act in various ways on the peripheral and central nervous systems.
- Analgesics differ from anesthetics in both systemic and local applications (such as during dental procedures). Analgesia refers to the alleviation or removal of pain, whereas anesthesia involves the loss of sensory perception. Consequently, anesthesia suppresses various types of nociceptive signals, not just pain.

Analgesics

- The **N**on-**S**teroidal **A**nti-**I**nflammatory **D**rugs (NSAIDs)
- Paracetamol = Acetaminophen
- Opioid Drugs

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

Analgesics: Compared

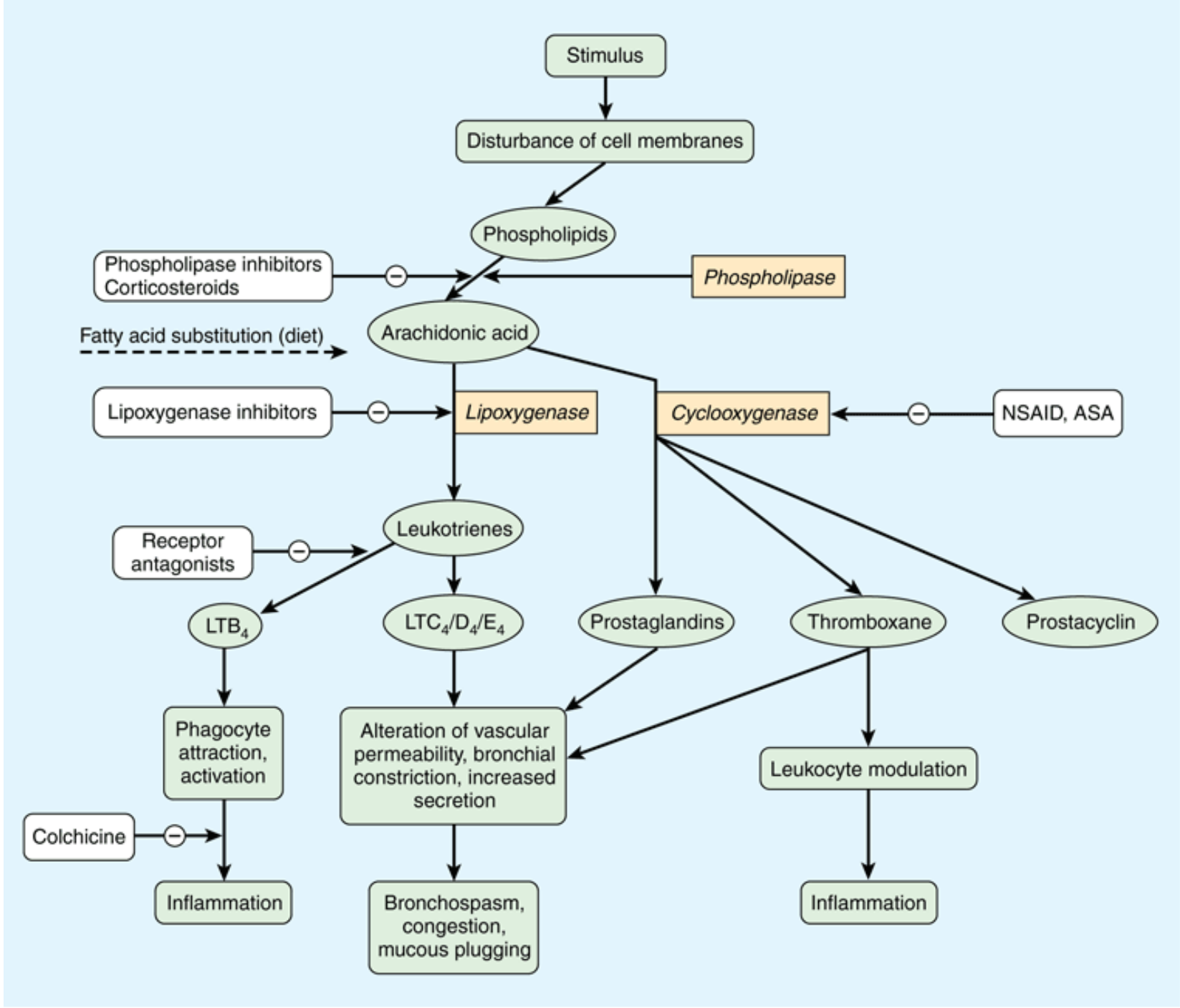
- For instance, when an individual experiences dental pain, headaches, or standard back pain, morphine is typically avoided due to its potential for serious side effects, such as addiction. In such cases, simpler analgesics like NSAIDs are generally sufficient for pain relief.
- Morphine is administered to patients undergoing major surgery and to those with cancer, as it effectively relieves visceral pain. In contrast, NSAIDs are primarily used to alleviate superficial pain, such as headaches and muscle pain.
- Ibuprofen should be taken on a full stomach, typically after food, to reduce the risk of gastrointestinal irritation.

Inflammatory Pathways

- Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins
- Effects on blood vessels, on nerve endings, and on cells involved in inflammation.
- The lipoxygenase pathway of arachidonate metabolism yields leukotrienes
- have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.
- **Prostaglandins are key mediators of redness, swelling, pain, and related inflammatory responses. Therefore, when evaluating a drug that inhibits prostaglandin synthesis, it is essential to understand the consequent effects on these processes.**

The glucocorticoids also have powerful anti-inflammatory effects and when first introduced were considered to be the ultimate answer to the treatment of inflammatory arthritis.
Although there are data that low-dose corticosteroids have disease-modifying properties, their toxicity makes them less favoured than other medications, when it is possible to use the others.

5-LOX inhibitor (zileuton) and selective antagonists of the CysLT 1 receptor for leukotrienes (zafirlukast, montelukast, and pranlukastare) used clinically in mild to moderate asthma.



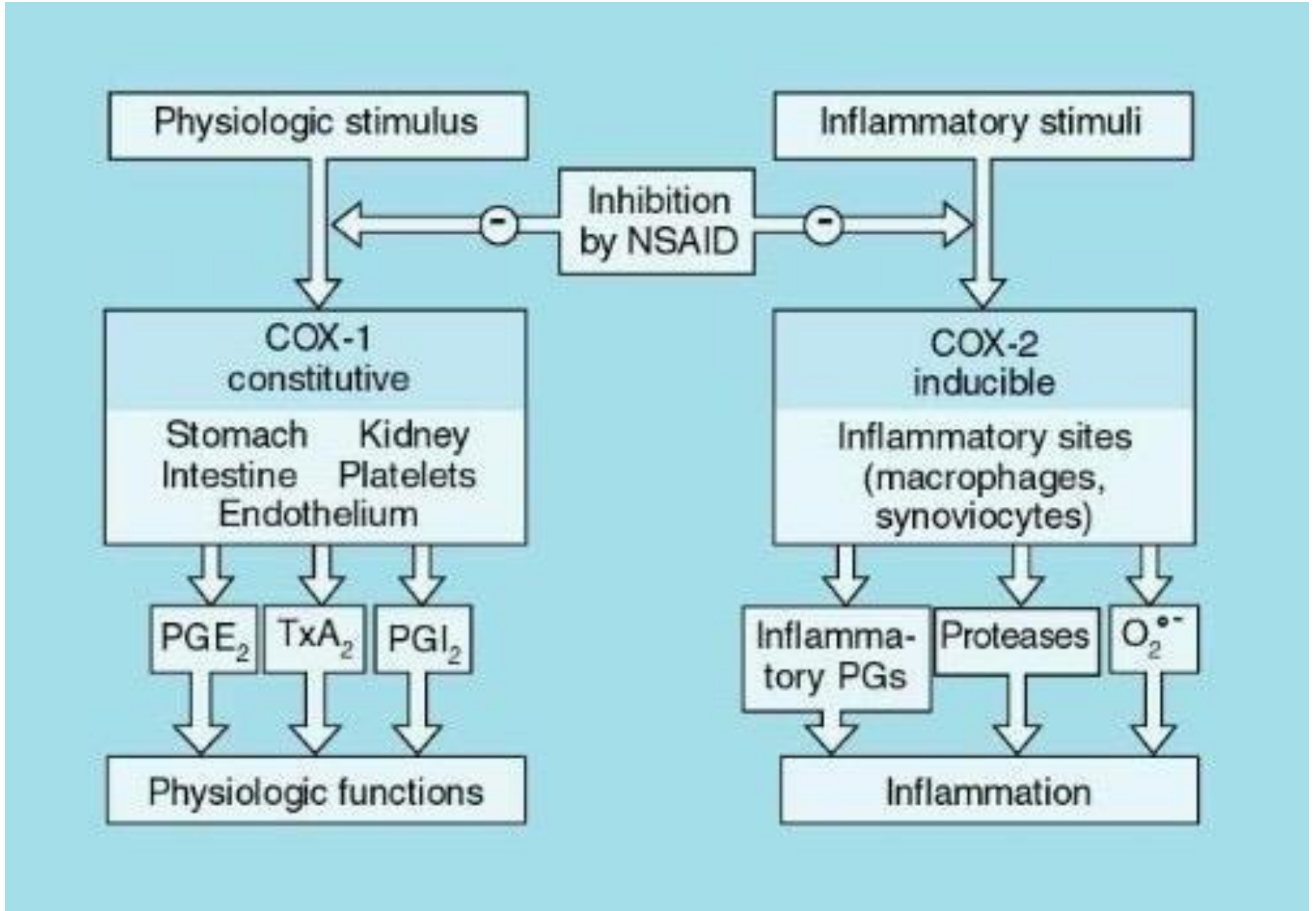
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition:

Arachidonic Acid Pathways and Inflammation

- When an individual experiences certain stimuli or injuries, damage to the cell membrane occurs, which activates phospholipase enzymes. This activation releases arachidonic acid, which can then follow two distinct metabolic pathways. In one pathway, arachidonic acid is converted into prostaglandins—such as prostacyclin (a vasodilator) and thromboxanes (which promote vasoconstriction). Prostaglandins alter vascular permeability, leading to edema, redness, itching, and pain. They also stimulate the production of various interleukins, including IL-6 and IL-1. IL-1, in particular, activates the thermoregulatory center in the hypothalamus, causing changes in body temperature, while prostaglandins increase the sensitivity of nociceptor nerve endings.
- Conversely, arachidonic acid can be metabolized via the lipoxygenase pathway to produce leukotrienes, which are key mediators in the pathophysiology of asthma. As a result, anti-inflammatory medications such as corticosteroids—often administered locally via inhalers—are used to mitigate leukotriene-induced inflammation in asthmatic patients.

Arachidonic Acid Pathways and Inflammation

- Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation, where autoantibodies target specific receptors. Consequently, treatment strategies focus on reducing this inflammatory process to facilitate improved mobility.


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2°-
Physiologic functions
Inflammation

Prostaglandins: Protective and Physiological Roles

- Prostaglandins play a protective role in the stomach by promoting mucus secretion and reducing hydrochloric acid (HCl) levels, thereby preventing irritation. However, when HCl production is high and mucus secretion is low, the stomach lining can become irritated, potentially leading to peptic ulcers. This is why it is advisable to take ibuprofen with food—to help preserve the beneficial effects of prostaglandins while minimizing irritation.
- Extra explanation:
  Ibuprofen works by reducing the production of prostaglandins, which are chemicals that contribute to pain and inflammation. However, prostaglandins also help protect your stomach by increasing mucus production and decreasing stomach acid. When you take ibuprofen on an empty stomach, you may lose some of this protection, which can lead to irritation or even ulcers. Taking ibuprofen with food helps protect your stomach lining by providing a buffer against these effects.
- Another common role of prostaglandins is in regulating uterine contractions during menstruation, which can lead to dysmenorrhea (period pain). Many women experience painful cramps and bleeding during their menstrual cycle due to these contractions. Since prostaglandins are responsible for inducing smooth muscle contractions, inhibiting their synthesis can help alleviate dysmenorrhea.

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-1).
- At site of inflammation, cytokines stimulates the induction of the 2nd isoform (COX-2).
- 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.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

قال صلى الله عليه وسلم: "من سلك طريقاً يطلب فيه علماً سلك الله به طريقاً من طرق الجنة، وإن الملائكة لتضع أجنحتها لطالب العلم رضاً بما يصنع، وإن العالم ليستغفر له من في السموات ومن في الأرض، والحيتان في جوف الماء، وإن فضل العالم على العابد كفضل القمر ليلة البدر على سائر الكواكب، وإن العلماء ورثة الأنبياء، وإن الأنبياء لم يورثوا ديناراً ولا درهماً إنما ورثوا العلم، فمن أخذه أخذ بخط وافر"