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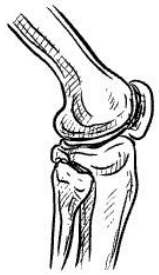

PHARMACOLOGY

MID | Lecture 2

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

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Mais alrahahleh

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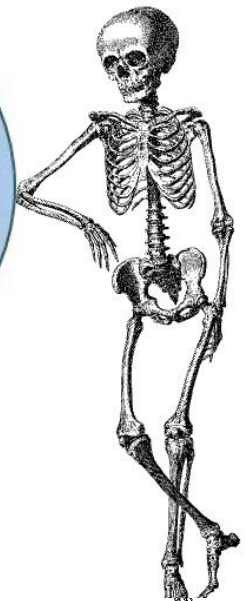
﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا



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QUIZ

Remember from General Pharmacology

- **Irreversible** effects of drugs occurs due to **covalent** bonds between drug and enzyme (slide 16).
- Drugs which work irreversibly have long duration of action (slide 17).
- Increasing the dose will cause side effects to appear, and lose the selectivity of drug.
- There is variability for drug response between individuals, some patients not all of them may experience exacerbated asthma (slide 22).

The first 2 slides belong to the previous lecture. We included them for confirmation.

TABLE 36–1 Properties of aspirin and some other nonsteroidal anti-inflammatory drugs.

Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-Inflammatory Dosage
Aspirin	0.25	<2%	1200–1500 mg tid
Salicylate[1]	2–19	2–30%	See footnote 2
Celecoxib	11	27%[3]	100–200 mg bid
Diclofenac	1.1	<1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	<1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	<1%	300 mg tid
Ibuprofen	2	<1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	<1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[4]
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone[5]	26	1%	1000–2000 mg qd[6]
Naproxen	14	<1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[6]
Piroxicam	57	4–10%	20 mg qd[6]
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

NSAIDs

- The NSAIDs are a group of chemically dissimilar agents that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

- **inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

>>>> decreased prostaglandin synthesis with both **beneficial** and **unwanted** effects.

In this lecture, we will discuss these drugs:

Examples of commonly used NSAIDs and brand names (not an exhaustive list)

Generic name	Brand name
Aspirin	Bayer, Aspir-Low, Aspir-Trin, found in Excedrin, Goody's, Alka-Seltzer
Ibuprofen	Advil, Motrin
Naproxen	Aleve, Naprosyn, Anaprox
Indomethacin	Indocin
Diclofenac	Voltaren
Celecoxib*	Celebrex
Etodolac	Lodine and Lodine XL
Ketorolac	Toradol
Meloxicam	Mobic
Piroxicam	Feldene

Non-steroidal anti-inflammatory drugs (NSAIDs)

- NSAIDs are used to reduce:

pain

fever

Inflammation

By inhibition of cyclo-oxygenase enzymes COX1 & COX2. (Non-selective inhibition)

NSAIDs

An anti-inflammatory action:

(1) decrease Vasodilator PG (PGE_2, PGI_2) leads to less vasodilatation and, indirectly, less edema.

- PGE2 and PGI2 (prostacyclin) are vasodialtors. Once their synthesis is inhibited by NSAIDs, there will be less vasodilation and less leakage.

(2) The inhibition of activity of adhesion molecule involved in chemotactic process.

(3) Accumulation of inflammatory cells is also reduced.

NSAIDs

An analgesic effect:

- Decreased prostaglandin generation means decrease sensitivty of **nociceptive** nerve endings to inflammatory mediators.
  - NSAIDs reduce pain by acting on nerve terminals. PGE2 is thought to increase the sensitivity of nerve endings, so if PG levels are reduced, the pain threshold will increase, leading to less sensitivity in the nerves, and, consequently, less pain perception.
- Relief of **headache** is due to decreased prostaglandin- mediated vasodilatation.
  - One theory of headache development suggests that headaches are caused by dilation of cerebral vasculature, which results in stretching on the nerve endings of vessel walls, stimulating pain.
  - Effect of NSAIDS: Reduced production of PG -> less dilation -> less stretching -> more constriction -> less pain.

Analgesic action:

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.

- management of pain of <u>low to moderate</u> intensity arising from musculoskeletal disorders rather than that arising from the viscera.

  - For visceral pain, opioids like morphine are recommended.

Antipyretic Effects

- The antipyretic due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.
  - The thermoregulatory centers in hypothalamus is set at a specific temperature, although environmental factors may influence body temperature but the hypothalamus reset it back to set- point temperature (37 Celsius approximately).

- It induces a decrease in interleukin-1 modulation of the hypothalamic control of body temperature.

- The hypothalamic control on body temperature returns… vasodilation occurs and dissipates and fever decreases

Go to the next page for explanation…

Illustration :

- When the body is exposed to pathogen, such as bacterial Infection, there is a release of PGs, which in turn stimulate leukocytes to produce certain ILs such as TNF-alpha and IL-1. These mediators then act on the hypothalamus, which resets the body temperature to a higher level, such as 39°C instead of 37°C, leading to fever.

- what do NSAIDs do? They inhibit PG Synthesis. Therefore, the hypothalamus will reset body temperature to 37°C.

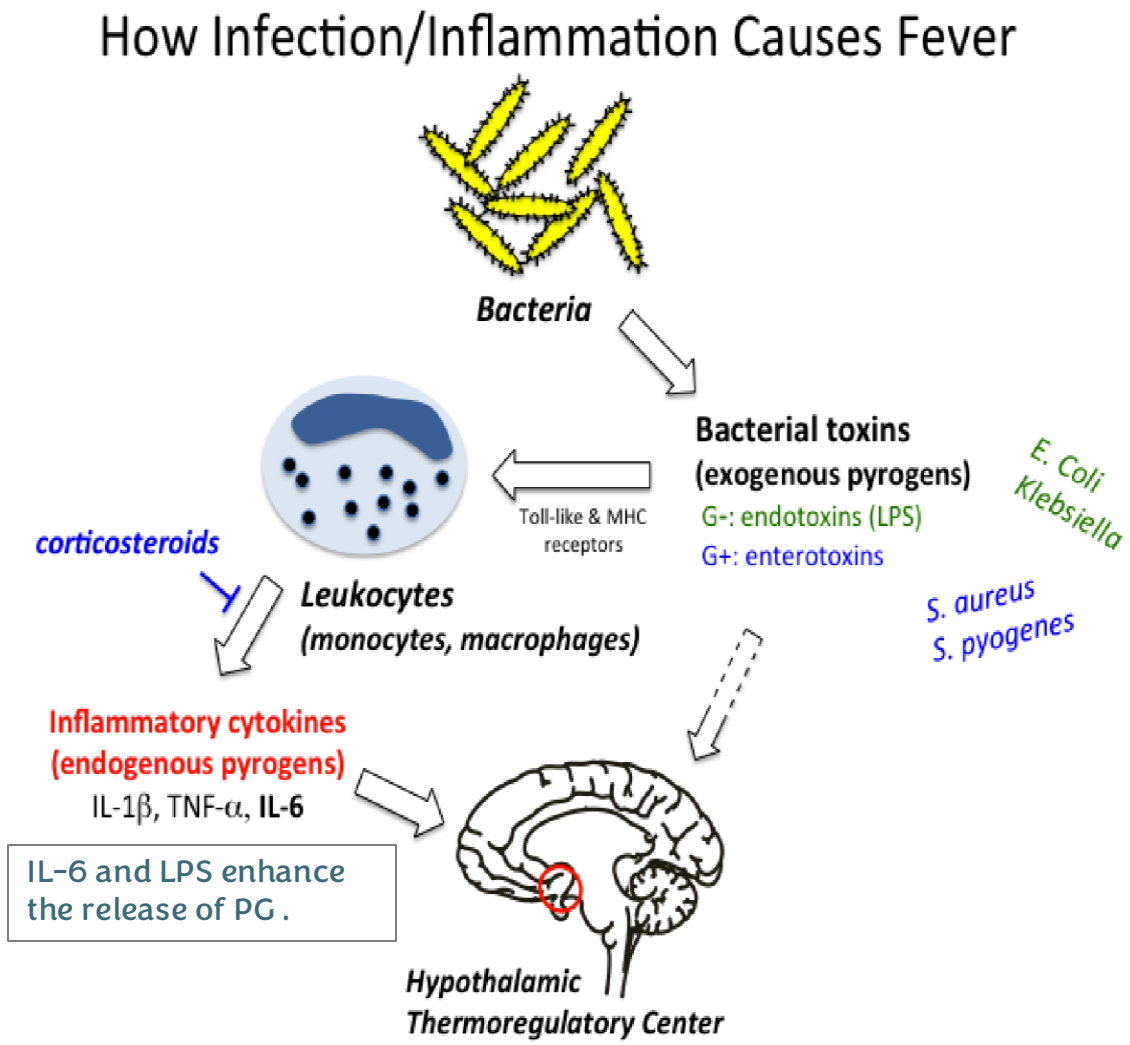
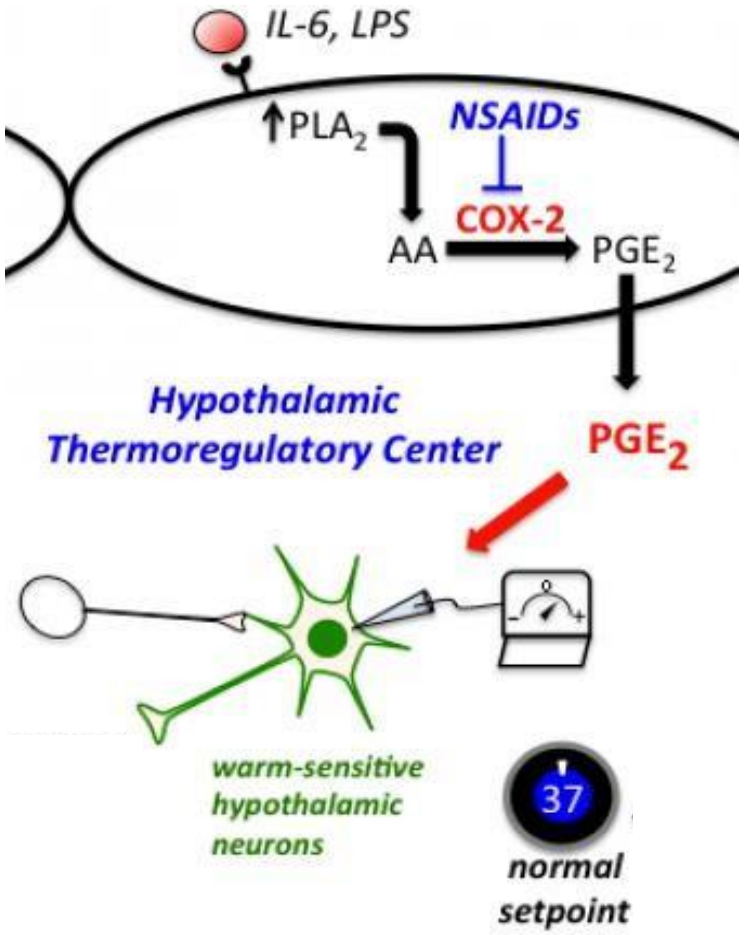
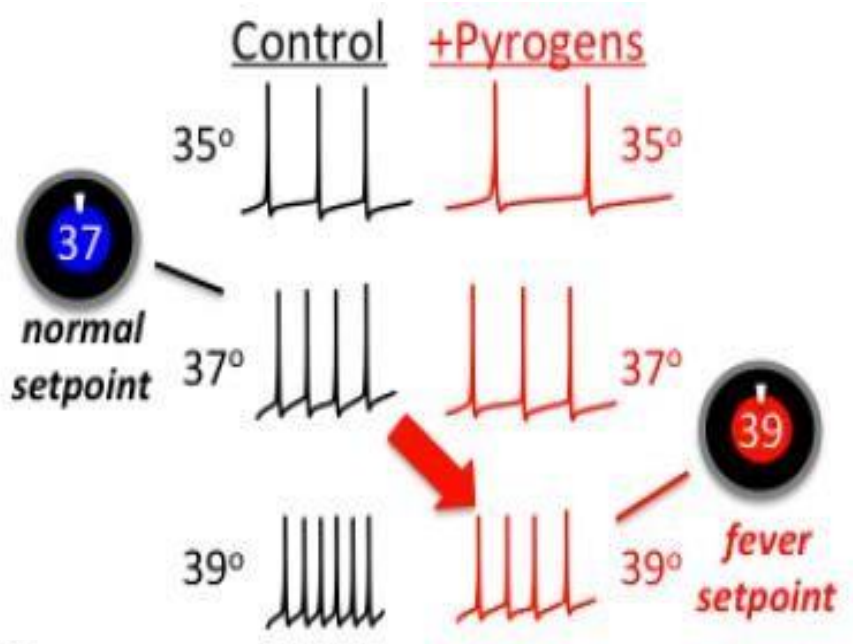


Illustration :



- IL-6 and LPS (lipopolysaccharides) can stimulate the PG synthesis from AA which directly affect the thermoregulatory center of brain.



Antipyretic action:

- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated.
- When aspirin is impeding PGE_2 synthesis and release it resets the hypothalamus toward normal.
- **<u>Aspirin has no effect on normal body temperature.</u>**
  - Aspirin only prevents the inducer of the reset mechanism. This means that if your body temperature is at its normal set point (37°C) and you administer aspirin, your body temperature will not go below (37°C).

Aspirin

- ✦ It can cause **irreversible** inactivation of COX-1 and COX-2.

- Aspirin is the prototype of **traditional** NSAIDs and was officially approved by the FDA in 1939.

  ❖ Aspirin is antiplatelet not anticoagulant.

  What is the difference?
  - ➢ Antiplatelet: prevent platelet aggregation.
  - ➢ Anticoagulant: Inhibit coagulation cascade proteins.

  But both pathways work together towards blood clot formation.

Mechanism of action

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly** inactivates cyclooxygenase.

- The other NSAIDs are all reversible.

- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.

  - The body can counteract the effects of aspirin (as an antipyretic and analgesic drug) by producing new COX enzymes (since aspirin binds covalently and irreversibly), This process takes 6 to 48 hours, which is the time that is required to transcribe and translate the proteins.

Aspirin as an antiplatelet:

- The effect of aspirin as an antiplatelet lasts in the body for about 7-10 days. This means that the duration of the antiplatelet effect lasts for the lifespan of platelet.

- Since platelets are not true cells (they lack a nucleus), they are unable to synthesize new proteins (specifically COX enzymes) to eliminate the drug-protein complex and its effect. Therefore, the only way to eliminate the effect of aspirin is for the platelets to die, which takes 7-10 days.

- Clinical advice: When a patient comes to your practice and is taking aspirin, and you are performing a minor procedure, the patient may bleed if you do not take a thorough drug history. You must take the duration of action of drug into consideration and consult his CV doctor.

Aspirin as an antiplatelet:

All NSAIDs have antiplatelet effects, but **aspirin is the only one used as an antiplatelet drug.** Why is that?

All NSAIDS are non-selective (except for celecoxib) and they work on both COX-1 and COX-2. However, they may have higher selectivity for one type of enzyme rather than the other, so it is found that...

- Aspirin has greater selectivity forCox-1, which means less TXA production and a stronger antiplatelet effect.

- new research indicates that all other NSAIDs (other than aspirin) increase cerebrovascular events (such as blood clots, stroke, MI, heart attack).

The dose of aspirin used for:
① antiplatelet effect: 80-100 mg.
② anti-inflammatory, antipyretic, analgesic effect: 325mg-700mg (2 pills).

This emphasizes that at low doses, aspirin has selectivity for COX-1, and as the dose increases, the selectivity is lost.

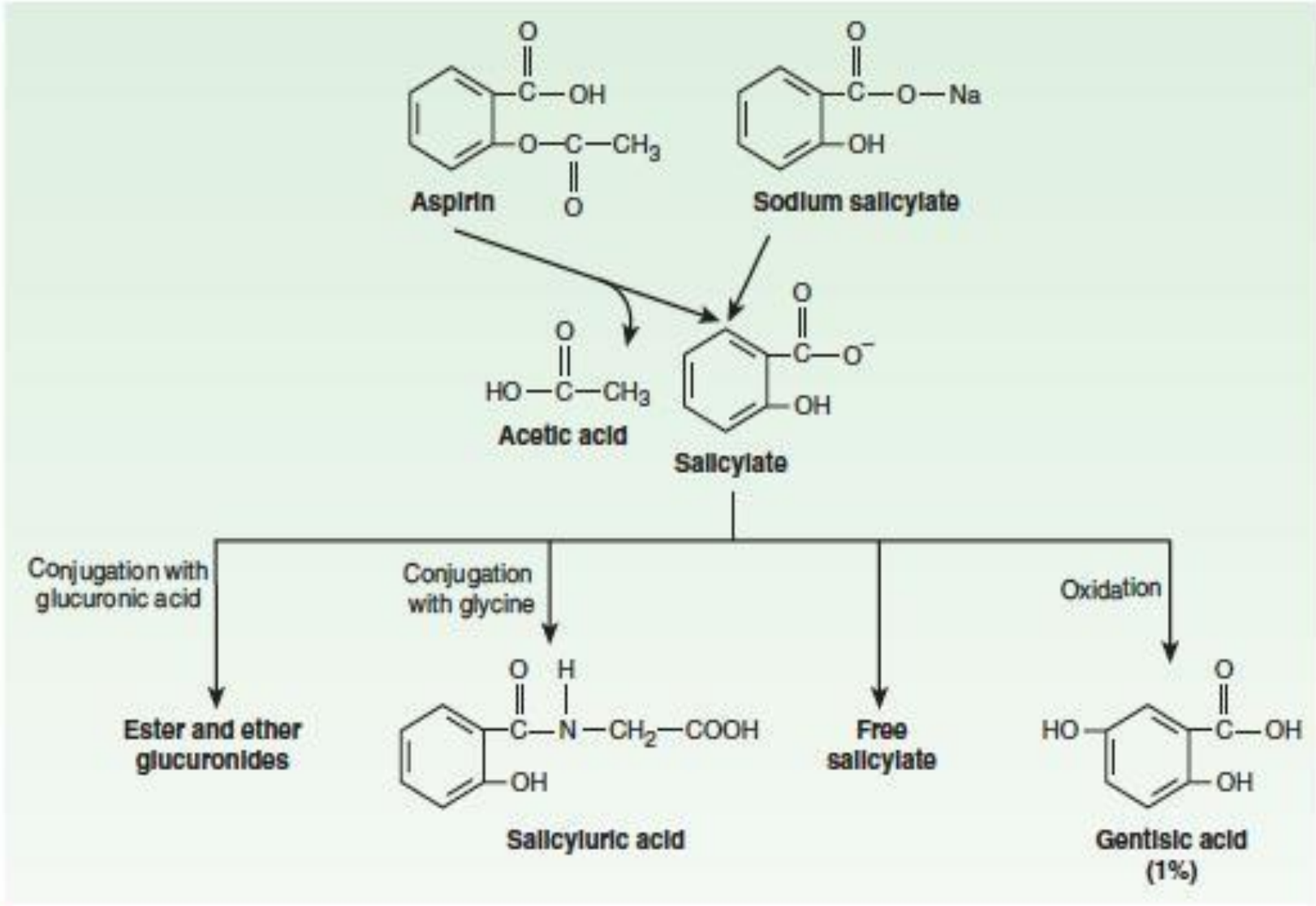


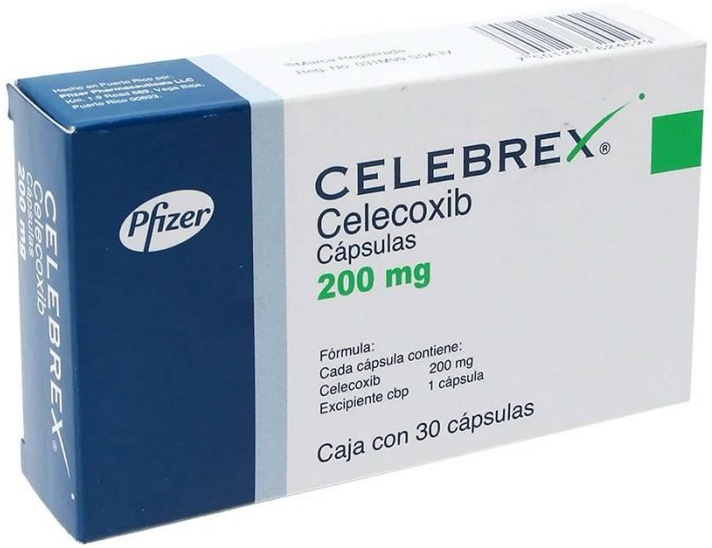
FIGURE 36–3 Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

Celecoxib

Celecoxib is a selective COX-2 inhibitor. Although it dosen't cause gastric irritation, it unfortunately increases the risk of thrombotic events. How?

(1) When it inhibits the COX-2 pathway, the load on COX-1 Pathway increases, leading to more more production of TXA, which results in platelet aggregation·

(2) With no prostacyclin produced by COX-2, the vasodilation effect is blocked.



Respiratory actions:

Aspirin can cause bronchoconstriction in some asthmatic patients through increased production of proinflammatory mediators, particularly leukotrienes.

Aspirin may exacerbate the condition of asthma, How?

- By blocking the COX pathway, the load on LOX pathway increases, resulting in more production of leukotrienes. These leukotrienes play a significant role in the symptoms of asthma (vascular permeability alternation, edema, bronchoconstriction, and increased mucus production).

Clinical Uses

Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting

Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.

Go to the next page for explanation...

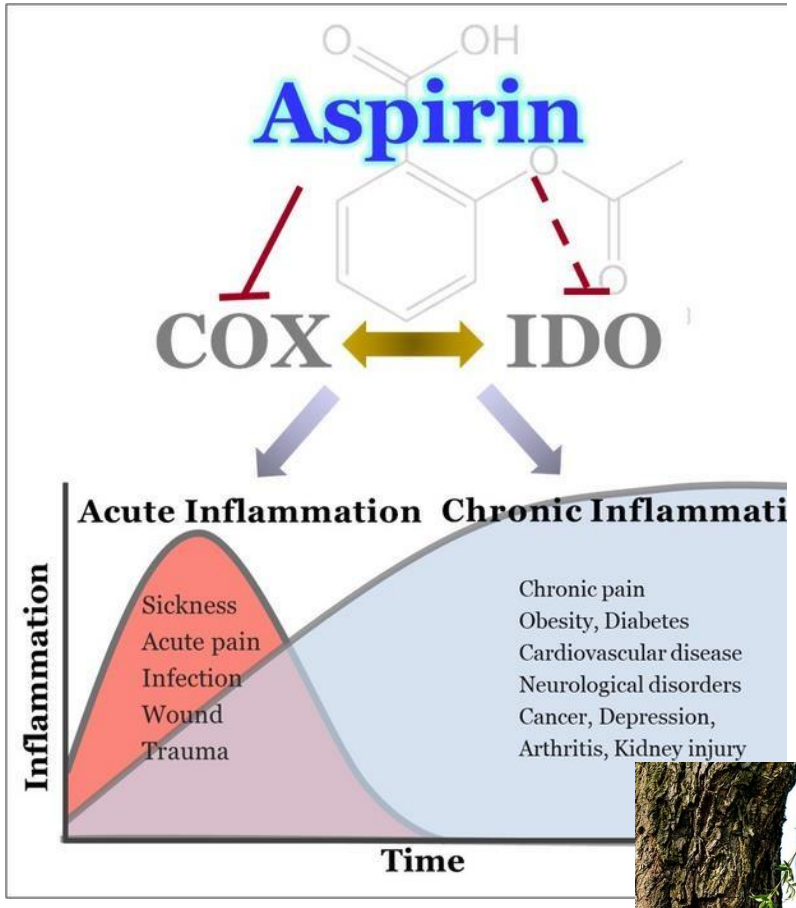
- Transient ischemic attacks are caused by microthrombi, which can be prevented by administering aspirin prophylactically.
- Unstable angina is caused by the accumulation of cholesterol in the blood vessel that nourishes the heart (the coronary artery). This cholesterol can detach from the blood vessel wall and lead to clot formation, so aspirin is used to reduce the risk of unstable angina.
- Clinicians also recommend aspirin for patients at high risk of developing cardiovascular diseases, such as diabetic patients, hypertension patients, and elderly smokers.
- An observational study was conducted on patients who take aspirin (for reasons other than colon cancer prevention). It showed that they have a lower incidence of developing colon cancer. However, this remains an area of research, and more studies must be done to see if really inhibiting COX enzymes truly has an effect on colon cancer prevention.

Not required for the midterm exam!

New insights into an old drug: Scientists discover why aspirin works so well

"We found that aspirin downregulates IDO1 expression and associated kynurenine production during inflammation," Mandal said. "Since aspirin is a COX inhibitor, this suggests potential interplay between COX and IDO1 during inflammation." **IDO1 is an important target for immunotherapy.** Because COX inhibitors modulate the COX–IDO1 axis during inflammation, the researchers predict that COX inhibitors might also be useful as drugs for immunotherapy.

IDO: Indoleamine 2,3-dioxygenase.



A chemist called Felix Holffmann modified salicylic acid to acetylsalicyic acid so that it could be taken orally.

BAYER

Aspirin is very old drug. Ancient Egyptians used the bark of willow tree to treat pain and inflammation.

Adverse effects

Gastrointestinal effects:

- **PGE2** stimulate synthesis of protective **mucus** in both the stomach and small intestine and decrease acid secretion.

- In the presence of aspirin, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection.

- Agents used for the prevention of gastric and/or duodenal ulcers include **p**roton-**p**ump **i**nhibitors (**PPIs**). Some examples are esomeprazole, lansoprazole, omeprazol.

- To find solutions for these side effects, a selective COX-2 inhibitor was developed (celecoxib). Although it has its own adverse effects, other solutions have been developed for patients who cannot take this medication, such as drugs that reduce the acidity of the stomach that cased by aspirin. Therefore, chronic users of aspirin are often prescribed PPIs, which inhibits the production of HCL.

Effect on platelets:

Aspirin irreversibly inhibits platelet COX so that aspirin's anti platelet effect lasts 8–10 days (the life of the platelet).
In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6–12 hours.

Actions on the kidney:

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 that are responsible for maintaining **renal blood flow.**

- Decreased synthesis of prostaglandins can result in **retention of sodium and water** and may cause **edema** and **hyperkalemia** in some patients.

Go to the next page for explanation...

NSAIDs can have detrimental effects on the kidneys since PGE2 is a vasodilator. One of its important functions is dilating the blood vessels in the glomeruli, particularly the afferent arteriole. Inhibiting PG synthesis leads to vasoconstriction, which reduces renal blood flow and can cause kidney damage.

- This damage does not typically occur with a single use of NSAIDs but is more common with prolonged use. Additionally, individuals with risk factors such as advanced age, cardiovascular disease, or diabetes with existing kidney issues should avoid NSAIDs to reduce risk of kidney impairment.

Prostaglandins also play a role in regulating electrolyte balance, particularly sodium and potassium, by acting on kidney transporters that control the execration and reabsorption, of sodium, as well as by influencing the renin-angiotensin system. When this effect is inhibited, the body retains excess salts and water, leading to hyperkalemia (high potassium levels), hypernatremia (high sodium levels), as well as increased water retention. This can be harmful to patients with congestive heart failure, as it worsens edema and congestion. Additionally, in hypertensive patients, increased fluid volume within fixed-capacity blood vessels raises blood pressure. The heart is especially affected by elevated potassium levels, which can be dangerous for patients with heart failure or cardiac arrhythmias.

***From a question in the lecture, taking aspirin along with V-A derivative drugs are avoided since aspirin increases blood vessel fragility, thereby increasing the risk of bleeding

Common Adverse Effects

- Platelet Dysfunction.
- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)

GIT bleeding, along with decreased mucus production and increased acid secretion, can lead to peptic ulcer formation, which may propagate to perforation.

- Acute Renal Failure in susceptible individuals. While we previously mentioned that it typically results from prolonged use, there are rare exceptions where NSAIDs can cause sudden renal failure, particularly in children and adults.
- Sodium+ water retention and edema.
- Analgesic nephropathy refers to deterioration of kidney function caused by use of analgesics and here it refers to NSAIDs.
- Prolongation of gestation and inhibition of labor occur because PGs induce contractions in the smooth muscles of the uterus. Therefore, reducing PGs levels decreases uterine contractions, leading to delayed labor.
- GIT bleeding and perforation.

PGs have diverse effects depending on their site of action, (uterus, GIT, etc..).

Adverse effects

These effects are related to the salicylate itself, as it is a weak acid.

Gastrointestinal:

- The most common GI effects of the salicylates are **epigastric distress**, nausea, and vomiting.
- Microscopic **GI bleeding** is almost universal in patients treated with salicylates.
- At stomach pH, aspirin is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing **direct damage to the cells.** **This may explain why aspirin is more harmful to the stomach than other drugs.**

Hypersensitivity: Approximately 15 percent of patients taking *aspirin experience hypersensitivity reactions.*

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

Reye's syndrome:

- Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema.

- This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin

- Aspirin's chemical name is acetylsalicylic acid. Other salicylic acids are also used in skin conditions as a keratolytic agents. Additionally, a drug called Bismuth subsalicylate (as Pepto-Bismol, which is pinkish in color with a strong flavor) is mostly used by travelers for digestion issues and travel-related diarrhea.
- In cases where both medications are needed, such as a viral infection, a patient with a respiratory viral infection may be given aspirin to lower their temperature. If the patient also has stomach flu caused by a virus from contaminated food, they may take Pepto-Bismol. The concern arises when the patient is a child, as this combination increases the risk of developing Reye's syndrome, a potentially serious condition associated with salicylate-containing drugs.

Reye's syndrome is a very rare but potentially fatal condition that occurs in children with viral infections. The risk increases with the use of salicylates.

**Note: Salicylic acid drugs are associated with Reye's syndrome due to their chemical structur, not because of their kinetics or mechanism of action.

Reye's syndrome

- Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, nausea, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

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:

Reference Used:
(numbered in order as cited in the text)

1. Doctor’s Recorded lecture (S1 & S2).

Extra References for the Reader to Use:

1. https://youtu.be/Lo6-5w95_xA?si=RJmAal4p0SVbgVob

رسالة من الفريق العلمي:

لقد عَزِمنا منذُ كُنّا أن نَكون
نحنُ الذينَ اختار الله لنا الطريق أولًا، وحين وقفنا بمنتصفهِ حيَارى مُثقلين ألهمنا الاستمرار، كُلّما انحنت أكتافنا تخليًا واستسلام أرسلَ لنا من فيضِ حكمته ما نتعافى به من مرار الأيام، وينفض عن الروح غبار التعب، لِيُربّي فينا رغبة التمسُّك والمُحاربة، إله الرحمة والجبر، حاشاهُ أن يخذلنا أو يكسر بنا أغصان الأمل.

رمضان مبارك عليكم ♡

لا تنسونا من صالح دُعائِكم