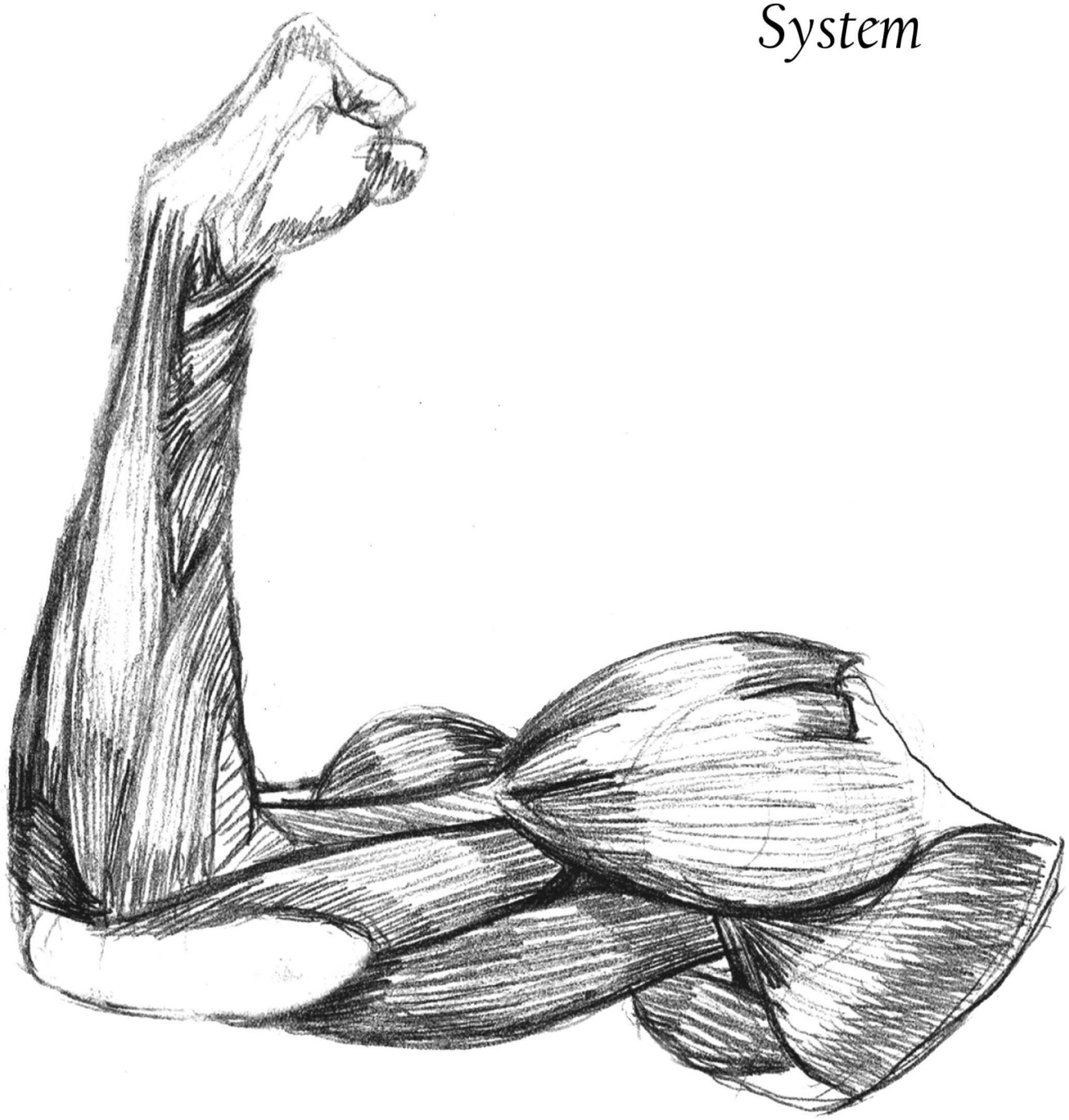
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # 2

DOCTOR: **Omar Shaheen**
DONE BY: **Mohammad Abu Alia**

BY MOHAMED F. ABU ALIA

Anti-Rheumatic Drugs

Prostaglandins and NSAIDs

Anti-rheumatic drugs, usually called non-steroidal anti-inflammatory drugs, are non-steroidal drugs used in the treatment of rheumatoid arthritis.

The corticosteroid hormone (a steroid) cortisone is used as a very critical drug in the treatment of some stages of rheumatism.

Mechanism of action

All NSAIDs act by their effect on the synthesis of prostaglandins, so they are involved in any pathology concerned with prostaglandins and the enzymes that synthesize prostaglandins and alike substances.

A deeper look into prostaglandins

Prostaglandins and alike substances (like histamine) are autocoids (or autacoids), which means they are substances produced in almost all body tissues and act locally within the tissue they are produced by, without circulating in the blood –they are thus described as local mediators. While hormones –which are similar to autocoids but not the same- are produced by specific organs (glands) and circulate in the blood affecting almost all cells in the body.

The effects induced by prostaglandins and autocoids generally are terminated by being locally metabolized at the site of production, and actually, a very small amount reaches the circulation and gets to other tissues.

Examples to these substances are: prostaglandins, thromboxanes, leukotrienes, Hydroperoxyeicosatetraenoic acids (HPETEs), and Hydroxyeicosatetraenoic acids (HETEs).

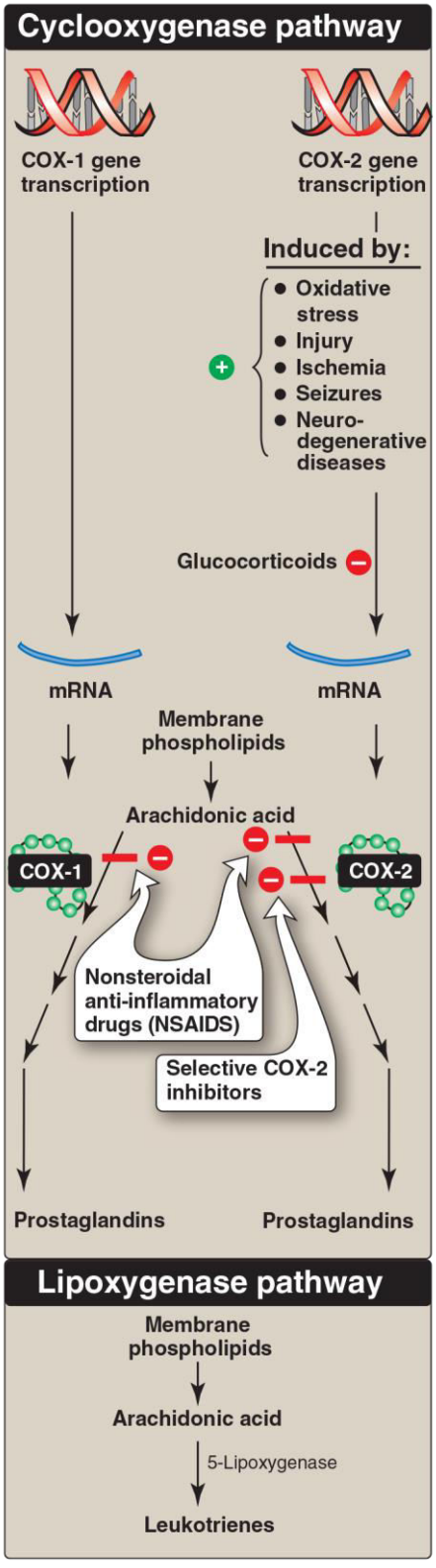
All of these substances are involved in rheumatic and rheumatoid diseases, and are all related to each other since they are synthesized by almost the same route of metabolism from arachidonic acid, and they use interrelated pathways.

Synthesis of prostaglandins:

Prostaglandins are a product of the metabolism of a part of a phospholipid that is present in the cell membrane, called arachidonic acid. Arachidonic acid is actually a 20-carbon fatty acid, an eicosanoid (eicosanoid; meaning it has 20 carbon atoms, Latin). It is the precursor of prostaglandins and alike substances.

So prostaglandins can be considered as eicosanoids that are present in an inactive form as a part of the phospholipids in the cell membrane. The first step in their synthesis is to liberate this part (arachidonic acid) from the membrane by certain inducers; this is catalyzed by the enzyme phospholipase A2, and other factors as acyl hydrolases. This happens in the case of the normal physiological need for these autocoids, but under some pathological conditions like rheumatic fever (an autoimmune disease), other factors, sometimes stress factors, lead to the release of arachidonic acid and trigger the process of making autocoids.

The free arachidonic acid will take one of two pathways for the synthesis of autocoids that are involved in rheumatoid arthritis. One of them is the cyclooxygenase pathway. Knowing that these pathways, in addition to their involvement in abnormal conditions and pathology where we need to deal with them with pharmacological agents, are needed normally under physiological conditions for the maintenance of the integrity of each individual cell in the body, a process known as housekeeping.



Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase.

The cyclooxygenase pathway, using the cyclooxygenase enzyme (COX), produces the prostaglandins, thromboxane and prostacyclin. The other pathway, the lipoxygenase pathway, produces leukotrienes.

Actually, the cyclooxygenase pathway involves two types of this enzyme depending on two genes that trigger the transcription of two different mRNAs. The first of these two isomers is cyclooxygenase 1 (COX1), it is involved in the normal physiologic production of prostaglandins (the housekeeping process). Cyclooxygenase 2 (COX2) is also involved in the same physiologic process and is a normal constituent of tissues such as the brain, kidney and bone. Regarding the presence of COX2 in the kidney, it is the main site of the toxic effects that kill people when these drugs (COX2 inhibitors) are used for a long period of time by inhibiting the normal physiology in the parenchyma of the kidneys creating renal failure and a fatal effect. This point has to be emphasized since most people consider them as OTC (over-the-counter) drugs, and they are very commonly used.

> The discovery of the two types of COX enzyme was during the study of the mechanism of action of one of their inhibitors; aspirin, an antiplatelet drug.

Our area of interest however, is the function of COX2 in the production of prostaglandins in pathological states, such as inflammation at the inflammatory site. So where ever rheumatism is found, COX2 will be involved, whither in joints (not all joints though) or any tissue that is affected by this autoimmune disease. The inducer of COX2 in the pathological state can be oxidative stress; this explains that people who are always under stress suffer later from the catabolic effect of these substances (products of COX2).

Other factors that may induce COX2 include: injury (any type of pathologic injury), ischemia in the heart, seizures in the brain, and neurodegenerative diseases of the nervous system.

So, eventually, the main difference between the two enzymes is that COX1 is only functioning during physiologic states where COX2 functions also during

pathologic states. Another difference is found in the configuration of the two enzymes: 60% of the cascade of amino acids in the two enzymes are similar (homologous). The other 40% is different, this includes the substrate binding sites and their conformation. In fact, the binding site at COX2 is larger than that at COX1, from this rises the specificity and differentiation between types of these enzymes. What interest us in the substrate binding sites –as well as the catalytic sites- are the pharmacological agents (inhibitors) of these enzymes.

So among these catabolic enzymes, COX2 has larger and more flexible substrate channels and a large space at the site of binding for its selective inhibitors. From this we see that COX1 lacks specificity in its inhibition, meaning that the drugs that affect COX1 are the same that affect the larger site at COX2, such as aspirin, an inhibitor of both COX1 and COX2. While the specific COX2 inhibitors do not affect COX1, so they inhibit certain substances in the arachidonic acid catabolism – only the COX2 products.

COXs are found in all body tissues, but they have different functions in different tissues, by producing different specific autocoids in each tissue that provide a local, short action. For example: prostaglandin E2 (PGE2) in the parietal cells of the stomach is involved in the maintenance of the normal integrity of the mucous cells in the fundus mainly, it is produced in the pyloric cells by stimulation from peptic acids (HCL). So when there is an increase in HCL (induced mainly by food), PGE2 is produced to end this process, PGE2 increases mucous production by gastric mucosa, this mucous will protect the cellular wall from the acid by forming a lining layer, this also will provide feedback inhibition to the fundal cells that produce HCL, decreasing HCL production (autoregulaion of HCL production via this autocoid). This is an example on how PGs are involved in the physiologic maintenance of normal tissue homeostasis. So when, for example, the production of PGE2 is inhibited by a drug such as aspirin, the mucous production will be reduced, and HCL production will increase because of the lack of negative feedback inhibition to its production by PGs, the final result will be peptic ulcer that maybe goes to perforation and bleeding.

Another example is the importance of COX in platelet aggregation regulation: PGs increase –physiologically or pathologically- platelet aggregation which is the first step in the formation of a thrombus (in the case of injury for instance).

The main idea of all these examples is to understand that these **autocoids actually have a normal function in the body**, involved in normal homeostasis. But when an injury (such as a physical injury, an infection or an autoimmune disease) and its stress factors induce the release of these autocoids by COX2 we start to see the pathological actions of them, such as pain and platelet aggregation, which are yet defense mechanisms against injury.

The problem with autoimmune diseases (including rheumatoid arthritis) is that in them, the body releases defense mechanisms against itself for unknown reasons (yet), which makes stopping these mechanisms including PGs a target in pharmacology.

The Agents that act on cyclooxygenases

There are many agents (inhibitors) that are non-selective in inhibiting both COX1 and COX2 producing a large variety of side effects. That takes us to demand specificity for inhibiting COX2.

Next time, acetyl salicylic acid (aspirin) and acetaminophen (paracetamol) will be discussed.

The End

A dedication for my biostatics team, my friends, and all colleagues for supporting me in the difficult time, thank you