PATHOLOGY

◉ Sheets ○ Slides

Number: Sheet 8

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Subject: Inflammation 3

Doctor: Hyamawad **00/00/0000**

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In the last two lectures, we talked about vascular changes and cellular changes that happen during inflammation.

In this lecture and next lectures, we are going to talk about chemical mediators.

- Chemical mediators: are the molecules and proteins that mediate the inflammation.
- As we said in last lecture, chemical mediators can be:
  a- produced from a cell
  b- can be found in the plasma in the inactive form.

- If they are secreted from cells →
  a- they are either not present in the cells and need to be synthesized. (newly synthesized molecules)
  b- they are present in the cell but found inside granules, so they don't act in resting states (in cases of no inflammation) and they need to be released during inflammation. (preformed mediators in secretory granules).

  - WBCs are either granulocytes or agranulocytes → Some of them have granules in their cytoplasm and some of them don't.

- If they are in the plasma → they will be in an inactive state and will be activated during inflammation → so this makes these proteins ready to be activated and used whenever there's inflammation.

  - Question: Why are these mediators not active during resting states? Why do we need them to be only activated at the time of inflammation?

Answer: Because they are very potent mediators. They have many effects in our cell and may destroy our normal cell, that's why we don't want them to act during resting state.

That's why if the chemical mediators are present in normal state, they will be either stored in granules (in the case of cell-derived mediators) or they are in inactive form (Plasma-protein derived).

❖Action of mediators :

- ❖ The mediators like any other protein will act through receptors and those receptors will be found on several cell types.
- ❖ So a single molecule can have several receptors in several cell types.
- ❖ Example : 1. histamine can act on endothelial cells and platelets .
- ❖ 2. Cytokines can act on endothelial cells , white blood cells , mast cells and many other cells .
- ❖ So in each cell these mediator will have a receptor.
- ❖ Mediators that act through receptors may act on different cells and these cells should have a receptor for that mediator.
- ❖ one mediator can cause :
  a- diverse actions in different cells. (if it has receptors on different cell types).
  b- can cause one action (if they act on only one or a few cell types).

❖Regulation of mediators actions :

These mediators need to be regulated because they are not ready to act → a- either because they are inside granules
b- or because they are inactive.
Once there is inflammation, they start acting and when they start acting they should be regulated .

As the doctor said before the war must end at a certain point, so we also need to stop these mediator How ??

1 .quick decay: they just spontaneously decay such as (arachidonic acid metabolites).

2. enzymatic inactivation (e.g bradykinin) bradykinin is a very important mediators that cause pain and vasodilation and it needs to be inactivated enzymatically by kininase enzyme , another example histamine which is inactivated by an enzyme called histaminase.

3. elimination: e.g oxygen free radicals they will be eliminated by antioxidants .

4. inhibition: they are inhibited not enzymatically by certain inhibitory mechanisms e.g (complement inhibitory proteins)

- ❖ so all these four mechanism , one of them , or more will cause regulation of mediators , so mediators act only when they are needed and then regulated by one of these mechanism .

- ❖ The principle chemical mediators of inflammation :
  As we said there is a lot of mediators and you are not supposed to memorize all of them, but they are very important because if we understand what each mediator causes we can control certain diseases or symptoms.

- ❖ Example from last lecture interleukin_1 we said if we control it we, can modify the course of the disease .
- ❖ So it's important to know how mediators work in order to know how to treat inflammatory diseases.

In this lecture and next one, we will focus on some important mediators and their important effects.

As we said some mediators are cell-derived and others are plasma protein-derived that circulate on the plasma ;

1. Cell derived :

- ❖ The mediators which are found in cells are either preformed and found in secretary granules or they are newly synthesized.
- ❖ Preformed mediators include histamine and serotonin (vasoactive amines) , newly synthesized include a lot of things which we will talk about next lecture.

- ❖ 2.Plasma derived: 1. Complement proteins 2. Proteins of Hageman factor activation.

In this lecture we are going to focus on vasoactive amines and arachidonic acid metabolites .

❖Vasoactive amines :

Vasoactive amines are very important inflammatory mediators and the include :

1. Histamine 2. serotonin

Vasoactive : means they have **activity** to regulate blood **vessels**.

❖ Histamine :

- found manly in the mast cells.
- can be found in platelets and basophils.
- histamine is a preformed molecule which means it's found in granules of these cells → it act quickly.

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- it’s one of the earliest mediators to be secreted and to act during inflammation .

❖ Effect of histamine : 1. Vasodilation 2.increases vascular Permeability (by endothelial cell contraction).

→ it’s responsible for edema .

- Histamine is inactivated by histaminase.

❖ Serotonin: its effect is the opposite of histamine effect. serotonin causes vasoconstriction, especially during clotting. So, serotonin is mainly secreted during clotting not during inflammation (clotting is a part of repair, so we may consider it a part of inflammation).

- it’s mainly stored in platelet granules .

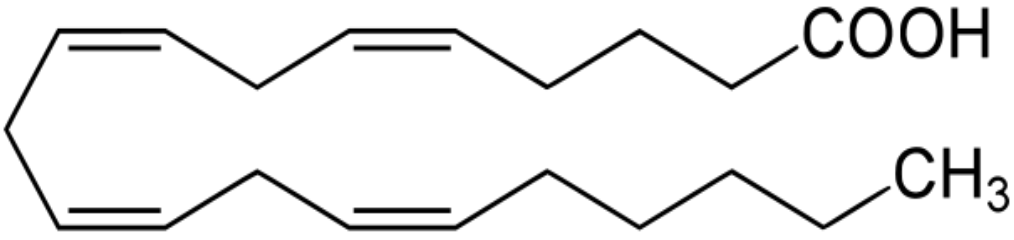
❖ Serotonin is also a neurotransmitter, so serotonin is also called neurohormone because it works as a neurotransmitter and has hormonal function.

❖ Now arachidonic acid :

It’s a very important component in our body and many important mediators are derived from it .

Arachidonic acid is a polyunsaturated fatty acid

- it’s polyunsaturated because it has four double bond .



It’s a very important fatty acid because it’s important for cell membrane, so we need it for our cell membrane and we take it

from several foods that contains fat such as eggs , especially fish .
- because it's present in the cell membrane → it doesn't cause inflammation by itself.
- the metabolites of arachidonic acid cause inflammatory effect.

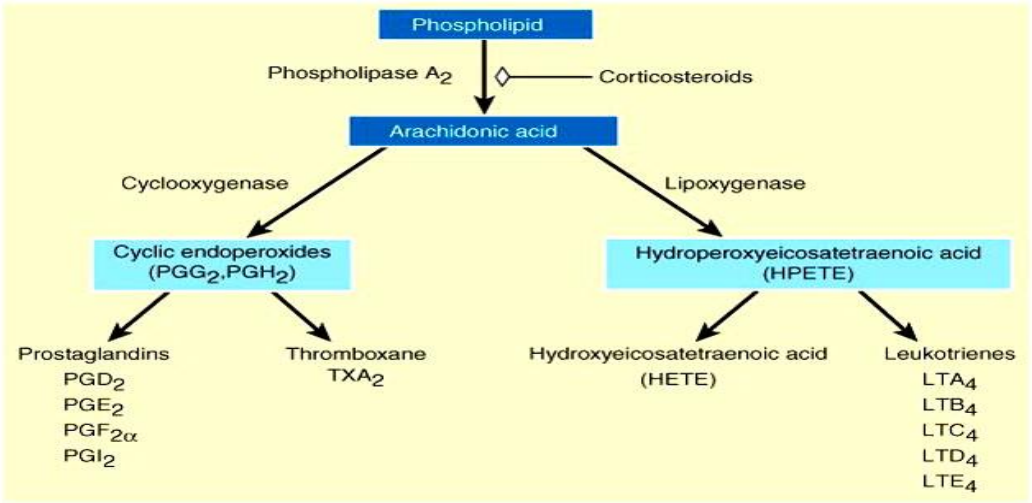
To synthesize the metabolites, we have to separate arachidonic acid from the membrane and take it to the cytoplasm. Why ?

Because the enzyme that acts on the arachidonic acid can't act on it when it's integrated on the cell membrane → we need an enzyme (phospholipase enzyme) which separates arachidonic acid from the cell membrane and takes it to the cytoplasm.
- When it's in the cytoplasm, certain enzymes can act on it in order to produce inflammatory mediators .

We have two enzyme families that act on the arachidonic acid
1. Cyclooxygenases 2 .lipooxygenases
in order to produce mediators which are important for inflammation.

The metabolite mediators contain 20 carbon atoms so they are called eicosanoids (eico means 20)

The arachidonic acid metabolites again (the picture) to show you phospholipase a2 is important to separate the archidonic acid from the phospholipid present in the cell membrane .



Schematic diagram of arachidonic acid metabolism. LT = leukotriene; PG = prostaglandin; TXA_2 = thromboxane A_2.

So this is the first step (phospholipase-a to separate the arachidonic acid and bring it to the cytoplasm). Now we have to use enzymes (cyclooxygenases and lipoxygenases) .

❖Cyclooxygenase pathway :

Cyclooxygenase will produce prostaglandins and thromboxane A2 (considered as a prostaglandin) .

Why do we call it cyclooxygenase? because its product has a cycle .

We have different type of prostaglandins :

1.(PGE2) 2. (PGI2) 3.(PGD2) 4. Thromboxane A2.

- PGE and PFD2 have the same functions : **1.vasodilatation**
2. Edema and redness because of vasodilatation
- also they cause **3. Pain 4.fever** .

They cause fever because they interact with cytokines .

So I need to control their effects because we don’t want the patient to suffer from fever and pain but also I need the effect

of inflammatory mediators to kill the bacteria so I treat the paient by anti-inflammatory drugs

- ❖ What the different between prostaglandins and histamine ?

1- Histamine has a ripid action but PG needs to be synthesized , so they take time.

2- histamine causes vasodilatation only but PGs cause pain ,fever and vasodilatation.

3- histamine is produced from granules in mast cells and some other cells but PG are synthesized from cell membranes.

- cell membrane and arachidonic acid are found in all cells but prostaglandins are only synthesized in the cells that have cyclooxygenases.

- ❖ There are different types of Cyclooxygenases.

- each kind is found in a specific cell , so each cell can produce one or more type of PGs .

- ❖ Example 1. PGI2 (prostacyclin) is produced from endothelial cells because endothelial cells have prostacyclin synthase which is a cyclooxygenase .

2. Platelets can synthesize thromboxane A2 by thromboxane a2 synthase which is also a cyclooxygenase.

- ❖ What's the importance of this (that each kind of cyclooxygenases is present only in a specific cell ? We will talk about prostacyclin and thromboxane A2.

We need thromboxane A2 which is produced in platelets during the process of clotting → during the clotting process, we need contraction of vessel wall to stop bleeding and also need to increase the aggregation of platelets , so thromboxane A2 causes these two effects .

Thromboxane a2 causes **vasoconstriction** and **platelets aggregation** , that's why it produced from the platelets and important in clot formation .

- PGI2 is produced from endothelial cells and causes **vasodilatation** and **inhibits platelets aggregation** .

So it's the balance between PGI2 and thromboxane A2 that makes things smooth , and prevents clotting normally.
- If this balance is disturbed :
if thromboxane increases → we will have clotting
if the pg i2 is increased → we will have bleeding .

In injury , there will be increase in the production of thromboxane A2 to make aggregation and endothelial cells will continue producing PGI2 to prevent excessive clotting .

Lipoxygenase pathway :

Will produce leukotrienes and lipoxins.

- We have different type of leukotrienes:
  1.(LTB4) 2.(LTC4) 3.(LTD4) 4. (LTE4)
  - the 4 means that they have 4 double bonds and in PG, number 2 means they have 2 double bonds.
- LTB4 is a very important chemotactic agent to neutrophils.
  - mainly produced in neutrophils and it affects another neutrophil.

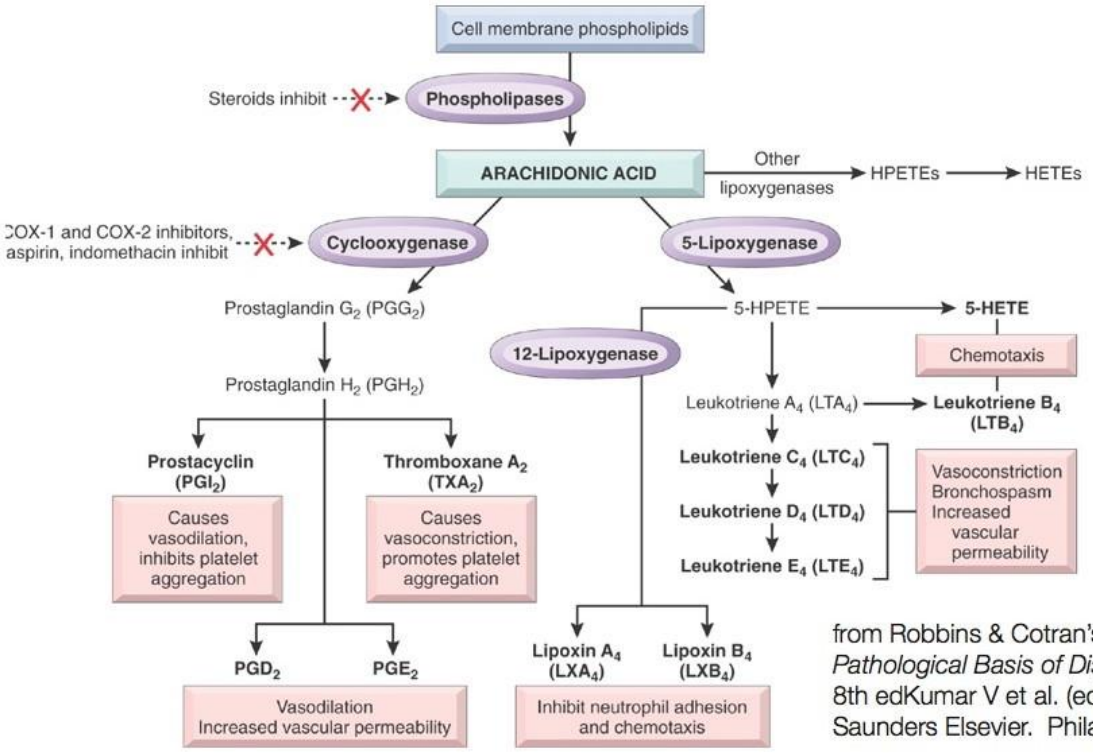
- So the first neutrophili to come will produce LTB4 to attract more neutrophils to come to the area.
- Their main effect is chemotaxis.
- LTC4 , LTD4 , LTE4 have the same function which is bronchospasm and increased vascular permeability .
- They are important in lung disease and mainly in bronchial asthma.

❖ Lipoxins (lx) :

They are the other product of the lipoxygenase pathway.
- they have anti-inflammatory effect.
- they are the first mediators until now that have anti-inflammatory effect.
- we said that when the process of inflammation begins , anti-inflammatory effect starts→ it's an important anti-inflammatory mediator.

- LXA4 and LXB4 inhibit neutrophil adhesion and chemotaxis → this is how they have anti-inflammatory effect.
- So lipooxygenase produces leukotrienes which give inflammatory effect and lipoxins which have ant-inflammatory effect.
- Anti-inflammatory effects don't stop inflammation once it occurs but control it.

Arachidonic acid metabolites and inflammation



from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)

Action	Eicosanoid
Vasodilation	PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2,
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4

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- Anti-inflammatory drugs :
- When we have anti-inflammatory treatment we target arachidonic acid metabolites.
  - there are many drugs that target arachidonic acid metabolites .
- Drugs that block the phospholipase such as : steroids → so arachidonic acid doesn't go to the cytoplasm → so the cycloxygnase pathway and lipooxygenase pathway won't proceed → so we blocked the inflammation .
- non-steroidal anti-inflammatory drug (ex ; ibuprofen and aspirin): these block the whole cycloxygnase pathway so we won't have prostaglandins but we will have lipooxygenase pathway working normally.
  The patients who take non-steroidal pills will have stomach ulcers complication and heart burn but why ??
  Because they found that cyclooxygenase family is divided into small family cyclooxygenases 1 and cyclooxygenases 2 (cox1 and cox2) so there are two types of cyclooxygenases: cox1 and cox2 .
  Cox1 enzymes normally act inside our cells and produce certain prostaglandins which protect our tissues.
  - some of them protect our GI TRACT by increasing mucous secretion , some important for renal function , and some important for platelets function .
- So cox1 product are important in physiologic processes.
  - cox2 products cause inflammation , cause pain and fever , so if I have a drug which inhibits only cox2 , I won't have the side effect of non-steroidal anti-inflammatory drugs .
- As a conclusion these drugs will inhibit all cyclooxygenases so they won't produce protective prostaglandins or inflammatory prostaglandins because of

that they will have ulcer because there is no prostaglandins that is beneficial for stomach .

- so they divided cox family into cox1 and cox2 , cox1 are beneficial for me we won't inhibit them but the prostaglandins that are produced by cox2 are the problem → so we want to inhibit them so they made a drug that affects cox2 only (cox2 inhibitors) → so I reduced the side effects of steroids but we face another problem that cox2 produces prostaglandins I2 and cox1 produces thromboxane → so we inhibit producing PGI2 but we produce thromboxane A2 → so we disturbed the balance then clotting occurs .

➔ This may increase the probability of having stroke or myocardial infarction.

- lipooxygenase inhibitors → these block the lipooxygnase pathway .where do we use them ?

For asthma patients .

Sorry for any mistake ☺