University of Jordan
Faculty of Medicine

Medical Committee
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Biochemistry

● Sheet ○ Slides

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Title: Metabolism of Sphingolipids

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in this lecture we will continue talking about

the alteration of polar head group **slide #1**

. Methylation of Phosphatidyl Ethanolamine

methylation : adding methyl group

what's the product of methylation of Phosphatidyl ethanolamine? Mean when adding methyl group what's the resulting compound ?

it's Phosphatidyl Choline

also the donor of the methyl group is a compound called S- Adenosyl Methionine (SAM) it's activated carrier (activated donor) of the methyl group .

many of the reactions in the body are methylation reactions for example synthesis of epinephrine from norepinephrine

so many reactions are methylation reactions and involved S- Adenosyl Methionine

(SAM) so what's the methionine ? it's amino acid join to adenosine (adenine ribose) and adenosine link to methionine by S and become SAM it's activated donor of methyl group .

why SAM not just simply methionine ?

when look to structure; the sulfur atom is joined to 3 atoms (it's forming 3 covalent bonds) it's unusual because sulfur like oxygen form 2 bonds so this is makes the methionine or compound unstable it will be much more stable when it lose methyl group so simply methyl group transfer into the ethanolamine forming Phosphatidyl Choline .

what's the difference between SAM and S- Adenosyl Homocysteine ?

the methyl group is released the S- Adenosyl Homocysteine do not have methyl group .

what's homocysteine ? exactly like cystein except it has one more (CH_2) so remove one (CH_2) become cystein

also Homocysteine could be responsible for development of atherosclerosis (increased homocysteine level cause atherosclerosis)

so the homocysteine like cholesterol high level causes atherosclerosis .

there is diseases where the homocysteine metabolism is unusual or defective it's accompanied by atherosclerosis myocardial infarction early in life .

how many S- Adenosyl Homocysteine do to require for conversion Phosphatidyl Ethanolamine to Phosphatidyl Choline ?

three why ? because we have replacing 3 methyl groups

Remodeling Phospholipids: Changing the Fatty Acid slide #2

the fatty acid that's usually change is the own that's found at position 2

lysophosphatidylcholine it does not have fatty acid so phospholipase A2 is responsible for it . to put it again , add arachidonyl coA is the donor of arachidonic acid to replace it.

this reaction series in two purposes :

1) we can change the fatty acid at position 2 (number of double bonds) and can change fluidity of the membrane by membrane components if mono unsaturated fatty acid replaced by poly unsaturated fatty acid you change the fluidity of the membrane.
2) phospholipase A2 act to release arachidonic acid for synthesis of prostaglandins.

SO remodeling : changing identity of fatty acid usually at position # 2

Structure A AND B slide #3

structure A) ethanolamine is not phosphatidyl why ?

because there is a double bond plus the functional group is ether not carboxylic group .the ether bond is not hydrolyze by water so this is ether glycerophospholipid that's resistant to hydrolysis

structure B) ether bond + fatty acid it’s just acetic acid (short chain) called platelet activating factor . so phospholipids have platelet ; remember the main function of phospholipids are the membrane components , emulsification , micelles formation and here another function , they can act as signal molecule (platelet activating factor , it has to do with the function of the platelets) " phosphatidalethanolamine " .

what's the function of platelets ? stop bleeding (homeostasis).

Surfactant Action of Phospholipids slide #4 ,5,6

What’s the surfactant ?(detergent)

Is the agent that reduce surface tension .

surface tension of water due to presence of large number of hydrogen bonds among water molecules

imagine the surface tension ...when we put drop of water on a glass plate the drop of water stay drop like dome but another molecules just spread on glass like spray use for glass cleaning because no surface tension

presence of surfactant in the water make water very thin layer and this is important in the function of the lung

the smallest units of the lung are alveoli ; it's filled with air in the inspiration and in expiration and it is partially deflated. due to presence of surfactant the lung remain at end of expiration partially deflated and not

collapsed . but if the surfactant is not present small water molecules will bring the wall of the alveoli together due to totally collapsed causes need much larger negative pressure to re inflate the alveoli.

this is important for the normal function of the lung . surfactant action of phospholipids responsible by compound called dipalmitoyl lecithin (lecithin with the two fatty acid are palmatic acid)

this substance is synthesized by neomosites and the synthesis start at the late age (late fetal age) at the end of the fetal life at 36-37 weeks of gestation the surfactant synthesis start in the neomosites .if the fetus was born as premature (before 36 week) he may suffer from respiratory distress why? the inadequate amount of the surfactant.

another function of phospholipids is precursor as signal molecule (phosphatidylinositol group with two addition phosphate group called phosphatidylinositol 4,5-bisphosphate)

which is found in the membrane if it's acted upon by phospholipase C what happens ? inositol 1,4,5-trisphosphate will be produced that cause increase in the calcium concentration in the cell due to opening Ca channels and diacylglycerol it's activator of an enzyme . the cleavage of phosphatidylinositol occurs in the response to hormonal signals exactly like synthesis of CAMP and produce second messenger ,all in response to hormonal signals

the last functions of phospholipids to join or to link protein with the membrane (it can act as anchor to the protein) and this protein is link to membrane but is not part of it .

Metabolism of Sphingolipids **slides(7 to 27)**

what's Sphingolipids ? it contains 2 groups : 1-Sphingophospholipids 2-Glycosphingolipids

Sphingolipids are group of compound that contain Sphingosine of glycerol and may or may not contain phosphate .

its name Sphingolipids because the alcohol is sphingosine and we put glycerol behind it in order to compare the sphingosine with glycerol (in the slides for comparison)

we notice that the structure of sphingosine contain hydroxyl group ,amino group ,and another hydroxyl group , and it's along chain compound contain 18 carbons.

in sphingosine you can easily see the functional group and you can compare it with structure of glycerol, it's like glycerol with one fatty acid . it has hydroxyl group at carbon number one , amino group at carbon number two, hydroxyl group at carbon number three .

if we joined fatty acid to amino group we get Ceramide : it's fatty acid joined to sphingosine... the bond in it is amide bond ,it's more resistance to hydrolysis than ester bond .

Ceramide "from its name" amide means there's amide bond . if we add Phosphocholine to ceramide we got compound it's name Sphingomyelin . Sphingomyelin is found in the myelin sheath in the plasma membrane it is rich with the Sphingomyelin .

ceramide look like diacylglycerol . so Sphingosine is one large molecule if it's joined with fatty acid will give us ceramide which joined with Phosphocholine give us Sphingomyelin .

what's the function of Sphingomyelin ?

Sphingomyelin it's component of the phospholipids of plasma membrane .(the slide which talk about the structure of phospholipids and Sphingomyelin just want to show us the similarity between them)

all animal cells and RBCs have Sphingomyelin, but it's particularly rich in neuronal cells around axon of the neurons there's myelin sheath (schwan cell around the cell) the function here is insulation of the axons help the rapid transmission of the nerve signal.

what's the synthesis pathway of the Sphingomyelin ?

1) palmitoyl coA condensation with serine give us sphinganine (derivative of sphingosine) + co2

why this reaction give ATP ? two things make this reactions favorable reaction :

A) Release of co2 from serine B) cleavage of the thioester bond in palmitoyl coA , these two thing contribute to the irreversibility of the reaction .

you will notice that many reactions involving amino acid required pyridoxal phosphate which is vitamin B6 as coenzyme ." you have to know the structure of sphingosine and from where the hydroxyl group and amino group .

2)befor it becomes sphingosine , fatty acid is added we get derivative of ceramide (dihydroceramide) it's differ from ceramide that it doesn't have double bond, and it got two hydrogen extra .

3) the last step it introduction of the double bond to give us ceramide . so the synthesis start with serine + palmitoylic acid then addition of fatty acid then introduction of double bond so we have 3 steps to get ceramide .

now we will add Phosphocholine, here unlike the synthesis of phospholipids ,here transfer Phosphocholine to ceramide produces sphingomyelin .

what's the source of Phosphocholine ? we can say the compound very similar to it, ceramide + Phosphatidylcholine will give sphingomyelin and the other product it's Diacyl Glycerol.

so just transfer of Phosphocholine from Phosphatidylcholine to ceramide will give us sphingomyelin.

what's about glycolipids ? glycolipids don't have phosphate ,so we don't add Phosphatidylcholine we add sugar or oligosaccharide or anther components.

so the first addition of Glucose or Galactose to ceramide to produce Cerebroside from its name you can know that it insulated from brain tissues and contain sugar (glycosidic bond). addition of sulfate group on galactose give us Sulfoglycosphingolipids .addition of Oligosaccharide give us Globoside and the last one addition Oligosaccharide with NANA give Gangliosides.

What's the NANA ?its N-Acetylneuraminic Acid or sialic acid , its sugar derivative, open chain like carbon sugar ,it's contain amino group, and it's carboxylic acid ,aldehyde group it's carboxylated .it's in glycolipids and glycoproteins .

We said if there's (NANA) with Oligosaccharide give Gangliosides. GM1,GM2,GM3 are all Gangliosides . G - Gangliosides because it's from the nerve ganglia

M - mono (it's contain only one molecule of NANA)

1,2,3 - this is the sequence of Oligosaccharide named by 3,2,1 and this is contrary to the logic , it's like 3 smaller than 2 and 2 smaller than one .

the synthesis act by adding one sugar at the time . the sugar always should be in activated form. and what's activated for sugar in the glycoprotein synthesis or in the disaccharide synthesis ? always it's UDP ,it's active donor it's carrier of the sugar like(UDP-Glucose ,UDP-Galactose,UDP-N-Acetylgalctoseamine) except NANA it's donate by CMP .

for example, ceramide we can add to it UDP-Glucose give glucocerebroside ,or UDP-Galactose and give galactocerebroside . what's determinant if we have to add UDP-Glucose or UDP-Galactose ?? it's the enzymes there's enzymes specific for glucose and another one specific for galactose ,the difference is very miner . the difference just the hydroxyl group in carbon-4 . but they have different function thus they have different synthesis by different enzymes .

remember glycolipids are bound on the outside of the membrane (outer layer) . Transfer of Sulfate Group to Galactocerebroside Produces Sulfo -Galactocerebroside (Sulfatide) . why sulfate ? sulfate as we know is negatively charged and strong acid (sulfuric acid) .sulfate is added to galactose . the sulfate group donor is PAPS it's like structure of ADP but is not ADP . ((PAPS use for the synthesis of Sulfatide and for GAGs)).

if there is no enzyme, there is no synthesis, so no life ((no defect in the synthesis to continue life)).

Degradation of Sphingolipids **slides(28 to the last slide)**

degradation is much more important because may cause diseases (may defect) degradation occurs by Hydrolytic Enzymes these specific for the sugar .

we have several enzyme because we have several sugars .for example; α Galactosidase, β Galactosidase, neuraminidase, Hexoaminidase. for each sugar there is specific enzyme also if the bond α or β glycosidic bond we have different enzyme . there's enzyme for degradation of each which reflects the importance of degradation.

the degradation occurs in the lysosomes .the lysosomes contain enzymes that are firmly Bound to Lysosomal membrane (part of the membrane). they act at PH between 3.5-5.5 Optimum PH (acidic PH). remember the lysosomes have low PH (acidic PH). this indicate if one of this enzyme (firmly bound) if it escapes it can't change anything and directly become deactivation . Stepwise Sequential Process

"Last on, First off" (that's mean the last one added the first one will be remove) .

the example in the slide β-Galactosidase will remove galactose then β-Hexoseaminidase remove NAcGal then neuraminidase will remove NANA . so the degradation is more important than the synthesis because the first sequence "1,2,3" according to degradation not synthesis . the degradation if it's defective it will lead to group of diseases called Sphingolipidoses or 1- Lipid Storage Diseases (lipid stay store in the cell because they are not degraded), 2-Defect in one of the Enzyme (one of the enzyme is not present), 3-Inherited as Autosomal Recessive Disease

why it's recessive ? because the turnover it's not rapid process but it's important if the enzyme is absent the lipid will be not degraded but if the enzyme is present in variation quantities the person will be ok the individuals will be ok if you inherit abnormal gene from one of your parent and normal gene from other parent you are ok because the level of enzyme 50% and 50% is enough so it's recessive , if the disease occurs by having only one mutual gene (dominant) in this case having an abnormal gene it's sufficient to produce the disease , but here having one normal gene it's sufficient so it's recessive also most enzymes deficiency are recessive . 4- Accumulation of Specific Lipid which is the substrate of the Defective Enzyme .5- Brain is Mostly Affected. 6- Extent of Enzyme deficiency is the same in different tissues.

Degradation of Sphingomyelin : Sphingomyelinase that convert sphingomyelin into ceramide if the Sphingomyelinase is absent the sphingomyelin will accumulate in the nerve cells.

In the last slide three diseases (in the red cycle)you should know about them recognize their name and don't memorize the symptoms.

1) **GAUCHER DISEASE : most common lysosomal storage disease**

2) **TAY-SACHS DISEASE : most common in Jewish population due to inheritance**

3) **NIEMANN-PICK DISEASE : inability to degrade Sphingomyelin**

GOOD LUCK ☺