Phopholipid Compounds of Physiological Importance

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PHOSPHOLIPID COMPOUNDS OF PHYSIOLOGICAL IMPORTANCE

Most importantly : SURFACTANT

Remember: **LIPID** a heterogenous group with relatively weak-insoluble"soluble in NONPOLAR" Except ketone bodies.

SIMPLE LIPIDS:
- Fatty acids
- Ketone bodies
- Triacylglycerol
- Cholestrol

COMPLEX LIPIDS:
- **Phospholipids**
- Lipoproteins
- Glycolipids

STRUCTURE OF PHOSPHOLIPIDS

Back bone made up of either glycerol or shpingosine (determines the type, glycero- or sphingo-phospholipid) + fatty acid branches + phosphate group with variable base attachment (determines the phospholipid)

FUNCTIONS OF PHOSPHOLIPIDS

Membrane-bound

Structural: lipids of cell membrane (bilayer) (Amphipathic → hydrophobic in the center Hydrophilic inward and outward)

Anchoring: attaching proteins to membrane

Signaling: source of secondary messengers Ex: IP3 and DAG

Specific functions: Ex: myelin sheaths Insulator & speed up nerve impulse

Non-membrane-bound

Lung Surfactant: re-inflation of alveoli by air

Detergent effect: (washing effect) essential component of BILE:
1. solubilize cholesterol →prevent gallstone
2. emulsify lipids and help digest them

emulsify: blend

Structural: Coat of lipoprotein (outer)

PHOSPHOLIPIDS BASED ON THEIR STRUCTURES

1. GLYCEROPHOSPHOLIPIDS: glycerol + phospholipid

Parent compound: PHOSPHATIDIC ACID

A) **Phosphatidylcholine (lecithin)** ➔ surfactant "dipalmitolylecithin" "dipalmitophosphatidylcholine"

** Major lipid component of lung surfactant

-Synthesis & secretion: by granular pneumocytes (type II)

SURFACTANT:

Is made of dipalmitolylecithin (65%) + other phospholipids, cholesterol & protein (35%)

Function: Decreases surface tension of fluid lining of alveoli➔decreases pressure against inflation by air ➔ PREVENT ALVEOLAR COLLAPSE ="atelectasis"

CONGENITAL RESPIRATORY DISTRESS SYNDROME (RDS)

Insufficient production of lung surfactant <in pre-term babies> ➔ causing neonatal death

Prenatal diagnosis by:

Lecithin/sphingomyelin ration (L/S) in amniotic fluid

Ratio= 2 or above ➔lung maturity and no RDS [normal: shift from sphingomyelin to lecithin synthesis by pneumocytes by 32nd week of gestation ➔ [L higher than S]

Lower than 2 ➔ RDS [sphingomyelin is higher]

Prevention: glucocorticoids to pregnant mother (with low L/S ratio) shortly before delivery

Treatment: intratracheal administration of surfactant to pre-term infants with RDS (airway catheter –tubular instrument- in the trachea to assist breathing)

B) **Phosphatidylinositol 4,5 bisphosphate** [PIP_2 system]

**Is broken down by the enzyme: phospholipase C to give the 2nd messengers:

1. DAG "Diacylglycerol" 2. IP_3 "inositol triphosphate"

Signal: hormones or neurotransmitters

Ex: ACh

Anti-diuretic hormone (V_1 receptor)

Catecholamines "E.g. epinephrine, norepinephrine and dopamine" (α_1 actions)

Receptor: G-Protein coupled receptor

Effects: activation of phospholipase C ➔yielding of DAG + IP_3 (Ca^{2+} release from endoplasmic reticulum) ➔activate protein kinase C

Response: phosphorylation (activation or inactivation) of cellular proteins and response to hormones

PROTEIN ANCHORING: attach proteins to membranes via CARBOHYDRATE-PHOSPHATIDYLINOSITOL BRIDGE

Ex: 1. Alkaline phosphatase (attaches to surface of small intestines)

2. Acetylcholine esterase (attaches to postsynaptic membrane)

**these proteins can be cleaved (removed) from their attachment to membranes by Phospholipase C.

2.SPHINGO-PHOSPHOLIPIDS: <<myelin sheath>> sphingosine + phospholipid

**Parent compound: Ceramide

MYELIN SHEATH

80% lipid (glycolipids and sphingomyelin) + 20% Protein

Function: insulates nerve axon ➔ prevent signal leakage

speed up transmission of impulses

LIPOPROTEIN STRUCTURE

Outer part [coat]: - apoprotein/apolipoprotein <<AMPHIPATHIC PHOSPHOLIPIDS>>

-Free cholesterol: hydrophilic (relatively)➔ allow lipid transport in aqueous plasma

Inner part [core]:

According to type of lipoproteins

Different lipid components in various combinations

PHOSPHOLIPASE FAMILY

Phospholipases are specific to the type of phospholipid it breaks down

Glycerophospholipids: A1, A2, C & D* (found in mammalian tissue, except D> in plants only)

Sphingophospholipids: lysosomal phospholipase & sphingomyelinase

TYPES:

1. Phospholipase A_1:
   - Found in many mammalian tissue
   - Breaks the bond between the 1st fatty acid and the 1st C of the backbone
2. Phospholipase A_2:
   - Found in many mammalian tissues, pancreatic juice and snake & bee venom
   - Breaks down the 2nd fatty acid of the backbone
   - Acts on phosphotidylinositol to release arachidonic acid, which is the precursor for prostaglandins
   - Pancreatic secretions [digestive enzyme] is a proenzyme, hence requires activation by trypsin. Bile salts are also needed for activity.
   - Is inhibited by glucocorticoids (ex: cortisol)

3. Phospholipase C:
   Found in liver lysosomes and some bacterial toxins
   Some are membrane bound and are activated by the PIP_2 system to produce the second messengers IP_3 and DAG
   Breaks down bond between backbone and phosphate group
4. Phospholipase D:
   Found primarily in plants [non-mammalian]
   Breaks the base off the phosphate group

- Sphingomyelinase breaks down sphingomyelin into ceramide and phosphocholine

Functions of phospholipases

Degradation of phospholipids:

- Production of second messengers (type C)
- Digestion by pancreatic juices (type A_2)
- Degradation of membranes by pathogenic bacteria to spread infection (type C)

Remodeling of phospholipids:

Specific phospholipases that remove fatty acids from the backbone to yield another type of phospholipid

Fatty actyl CoA transferase replace fatty acid by an alternative fatty acid

EX: Binding of 2 palmitic acids in dipalmitoylphosphatidylcholine (DPPC-Lecithin)
Binding of arachidonic to carbon # 2 of PI or PC

Questions

Degree of relevance: * * * * *

1- An infant, born at 28 weeks of gestation, rapidly gave evidence of respiratory distress. Lap and x-ray results supported the diagnosis of infant respiratory distress syndrome (RDS). Which of the following statements about this syndrome is true?

A. It is unrelated to the baby's premature birth.
B. It is a consequence of too few Type II peumocytes (granular pneumocytes).
C. The lecithin/sphingomyelin ratio in the amniotic fluid is likely to be greater than two.
D. The concentration of dipalmitoylphosphatidylcholine in the amniotic fluid would be expected to be lower than that of a full-term baby.
E. RDS is an easily treated disorder with low motility.

Degree of relevance: * * *

2- Aspirin-induced asthma (AIA) is a severe reaction to nonsteroidal anti-inflammatory drugs (NSAIDs) characterized by bronchoconstriction 30 minutes to several hours after ingestion. It is seen in as many as 20% of adults. Which of the following statements best explains the symptoms seen in patients with AIA?

A. NSAIDs inhibit the activity of Cystic fibrosis transmembrane conductance regulator (CFTR protein) resulting in thickened secretion that block airways.
B. NSAIDs inhibit COX but not lipoxygenase, resulting in the flow of arachidonic acid to leukotriene synthesis.
C. NSAIDs activate the COX activity of PGH synthase, resulting in increased synthesis of prostaglandins that promote vasodilation.
D. NSAIDs activate phospholipases, resulting in decreased amounts of dipalmytoylphosphatidylcholine and alveolar collapse (atelectasis).

Correct Answers:

1- D.

DPPC (surfactant) is reduced in baby with RDS

2- B.

NSAIDs inhibit COX but not lipoxygenase, so any arachidonic acid available is used for the synthesis of bronchoconstrcing-leukotrienes. NSAIDs have no effect on CFTR protein, defect in which are the cause of cystic fibrosis.