

Lipids III

Phospholipases

- Phospholipase A1, A2, C and D all hydrolyze (know the reaction) at specific sites on phospholipids
- Phospholipases C and D are specific for PI and PC respectively
- Some of the functions of phospholipases are housekeeping - constitutively active
- Other functions are biochemically important - usually under hormonal control
 - PLA2 often responsible for release of arachadonic acid. The free fatty acid is then metabolized to various eicosanoids. Lysophosphatidic acid (LPA) is also produced. LPA is a potent mitogen (causes cell growth) and at high concentrations can act as a detergent - lysing the cells
 - PLC - releases inositol and diacylglycerol. Inositol increases intracellular release of calcium. DAG activates protein kinase C.
 - PLD - Increases the production of phosphatidic acid. PA can be a potent mitogen and PA can be further metabolized to DAG
 - Phospholipids preferentially hydrolyze substrates that are located in bilayer membranes. They carry out interfacial catalysis at the boundary of water and a lipid phase

Plasmalogens

- Different than the other phosphoglycerides - contains an ether linked FA at the sn1 position
- These are typically involved in platelet aggregation and vasodilation

Sphingolipids

- Another class of phospholipids
- Do not contain glycerol as a backbone instead an amino alcohol called sphingosine.
- Add one fatty acid and it is ceramide
- Add an head group (choline or ethanolamine) and it is a sphingophospholipid
- These are very different in location and concentration than the glycerolipids
- They do contain similar shapes to phosphoglycerides
- Ceramides and certain sphingomyelin can bring about apoptosis - programmed cell death.
- Some phosphatases - opposite of protein kinases are activated by sphingolipids. A different family of protein kinases are also activated by various sphingolipids
- Cerebrosides and gangliosides are modified sphingomyelins
 - both are ether linked sugars and are neutral - no phosphoric acid
 - Gangliosides have several carbohydrates modified in place of the head group
 - Gangliosides - important in forming the myelin sheaths. Gray brain matter.
 - Constitute up to 6% of the total lipids

- Tay-Sachs disease - symptoms are weakness and retarded motor developments by one year of age. By two, dementia and blindness set in and by three the child is dead.
- The concentration of Gm2 is very high - usually in the lysosome
- Victims are missing an enzyme to hydrolyze one of the sugars
- 1/30 Jewish Americans have this disease vs 1/300 non-Jews

Eicosanoids

- These are a diverse group of hormone-like molecules produced in nearly all mammalian cells
- Stem from the greek word eikosi meaning twenty
- Because they act on the same organ they are produced in they are autocrines, vs a paracrine which act distal to the site of origin
- Most are derived from arachidonic acid 20:4 ^{5,8,11,14}
- Source if from the hydrolytic actions of PLA2

- Leukotrienes are hydroxylated fatty acid derivatives of arachidonate
 - Initially found in leukocytes - white blood cells
 - Often congugated
 - Secreted by damaged cells during anaphylaxis
 - Promotes bronchioconstriction and vasioconstriction
 - Acts as a chemotractant to bring white blood cells to fight infection

- Aspirin inhibits the formation of cyclic ecosanoids
 - Inhibition is by NSAIDs
 - The Serine in the active site of the enyme cyclooxygenase is acetlyated by aspirin

- Prostaglandins have a cyclopentane ring and is hydroxylated at various carbons. There are several versions each with a different effect. Different types and concentrations of prostaglandins are found in different tissues.
 - Induce inflammation and cause fever and pain
 - Ovulation and uterine contraction during conception and labor
 - Antiplatelet aggregation
 - Vasiodialation
 - Smooth muscle contraction

- Thromboxanes produced by platelets to cause aggregation at sites of cardiovascular injury. Leads to clot formation and foam cell formation (platelets differentiate into cells that cause plauques in arteries)
 - Alterations in double bonds in arachidonate still leads to TxB formation but they are less able to aggregate platelets
 - These fatty acids are found in some cold fish oils omega 3 fatty acids

- Prostacyclin produced by blood vessels and inhibit platelet aggregation
 - These are antagonistic to thromboxanes
 - The omega 3 fatty acids leads to a more potent antiagregant activity