Biochemistry Summary

Chapter 18 and 19

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Special Thanks to Bilal Marwa.

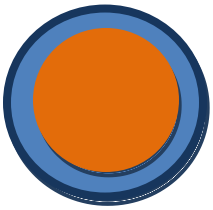
Chapter 18

- Plasma Lipoprotein and Steroid Hormones.

Plasma Lipoprotein and Steroid Hormones

- Spherical macromolecular complexes of lipid and specific proteins (apolipoproteins or apoproteins).
- The function of lipoprotein is to provide a transport system for its hydrophobic lipids in the plasma from and to tissues.
- The different lipoproteins are differing in their lipid and protein composition, size, density, and site of origin.

Composition of plasma lipoproteins:



= apolipoproteins, phospholipid, nonesterified cholesterol.

= lipid (Triacylglycerol, cholesteryl esters)

Size and density of lipoproteins:

BY SIZE :	BY DENSITY :
1] Chylomicrons	1] HDL
2]VLDL	2] LDL
3] LDL	3] VLDL
4] HDL	4] Chylomicrons

✓ Plasma lipoproteins can be separated by:

1. Their **electrophoretic mobility**.
2. On the basis of their density by **ultracentrifugation**.

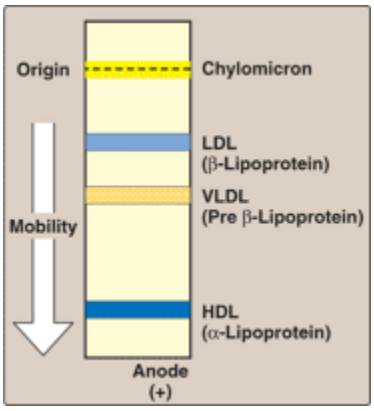


Figure 18.15 Electrophoretic mobility of plasma lipoproteins.

The order of LDL and VLDL is reversed if ultracentrifugation is used as the separation technique.

Apolipoprotein function:

1. Provide recognition sites for cell-surface receptors.
2. Activators or Co-enzyme for enzymes involved in lipoprotein metabolism.
3. Some of them are essential structural components, whereas others are transferred freely between lipoproteins.

✓ They are divided by structure and function into 5 major classes (A, B, C, D, E) with some of them having sub-classes.

I. Chylomicrons

B. Metabolism of chylomicrons :

- Chylomicrons are assembled in intestinal mucosal cells.
- They consist of: dietary triacylglycerol (90%), cholesterol, fat-soluble vitamins, and cholesteryl esters.
- They carry it to the peripheral tissues.

Synthesis of apolipoproteins B-48 :

- Unique to chylomicrons.
- Its synthesis begins on the rough ER.
- It is glycosylated as it moves through the RER and Golgi.

Assembly of chylomicrons :

- The enzymes involved in triacylglycerol, cholesterol, and phospholipid synthesis are located in the smooth ER.
- The formation of chylomircrons needs a microsomal triacylglycerol transfer protein which loads (يحمل) apo B-48 with lipid.
- Then the particles transition from ER to Golgi, where they packed in a secretory vesicles.
- These fuse with the plasma membrane releasing the lipoproteins, which then enter the lymphatic system and, ultimately, the blood.

C- Modification of nascent chylomicrons particlals:

- "Nascent Chylomicrons": particles of chylomicrons released by the intestinal mucosal cells.

When it reaches plasma, it will receive apo E & apo C-ll ➔ from HDL

- *NOTE:* apo C-ll function is activation of lipoprotein lipase -----> degrade the TAG in the chylomicrones .

D-Degradation of TAG by lipoprotein Lipase:

- It is an extracellular enzyme in (adipose tissue & cardiac M. & skeletal M.)
- It is activated by apo C-ll.
- The result of degradation -----> TAG hydrolyzed :

1. FATTY ACID :

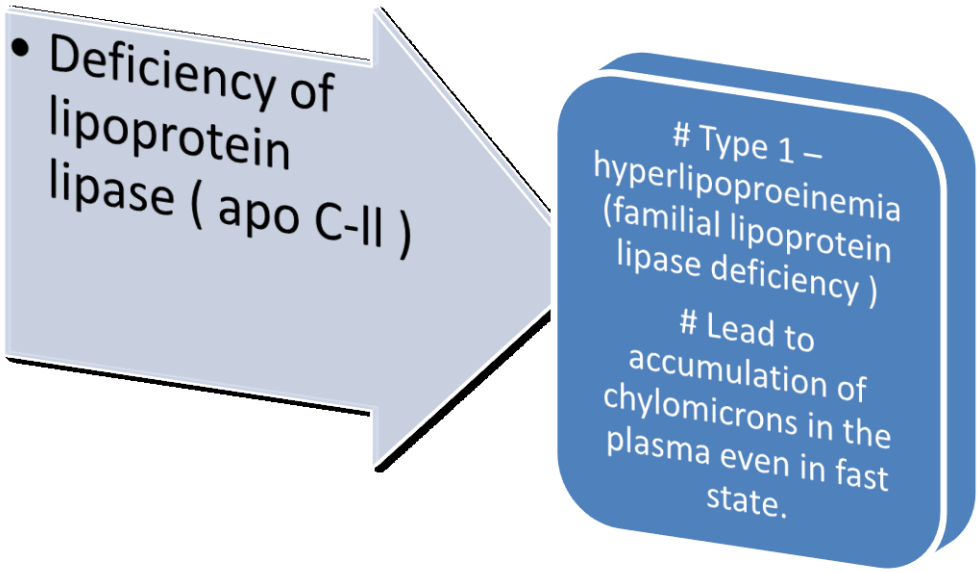
a. Either stored by adipose tissue.
b. Or used for energy by muscle.

- If they are not immediately taken up by a cell, the Long Chain Fatty Acid will ➔ transported By serum albumin until their uptake occur.

2. GLYCEROL:

- Used by liver in:
  a. lipid synthesis
  b. glycolysis
  c. gluconeogenesis

NOTE:



E- Regulation of lipoprotein lipase activity:

- Stimulated by insulin.
- Isomers of Lipoprotein lipase:

1. Adipose Enzyme :

a) Because of the High Km

❖ only when there is an increase in plasma lipoprotein ------> The enzyme can remove F.A from ➔"lipoprotein particle + stored TAG"

2. Heart Muscle :

a) Because of it's low Km

❖ Even when there is a decrease in plasma lipoprotein ➔ Heart muscle has continuing access to the circulating fuel.

Formation of chylomicron remnants:

❖ As the chylomicron circulates degraded by lipoprotein lipase, the particle decreases in size and increases in density.
❖ The C apoproteins (but not apo E) are returned to HDL.
❖ The remaining particle, called a "**remnant**," is removed from the circulation by the liver, using it's lipoprotein receptors that recognize apo E.
❖ They are taken into the hepatocytes by endocytosis. The endocytosed vesicle then fuses with a lysosome.
❖ The components of the remnant are hydrolytically degraded, releasing amino acids, free cholesterol, and fatty acids.

- The receptor is recycled.

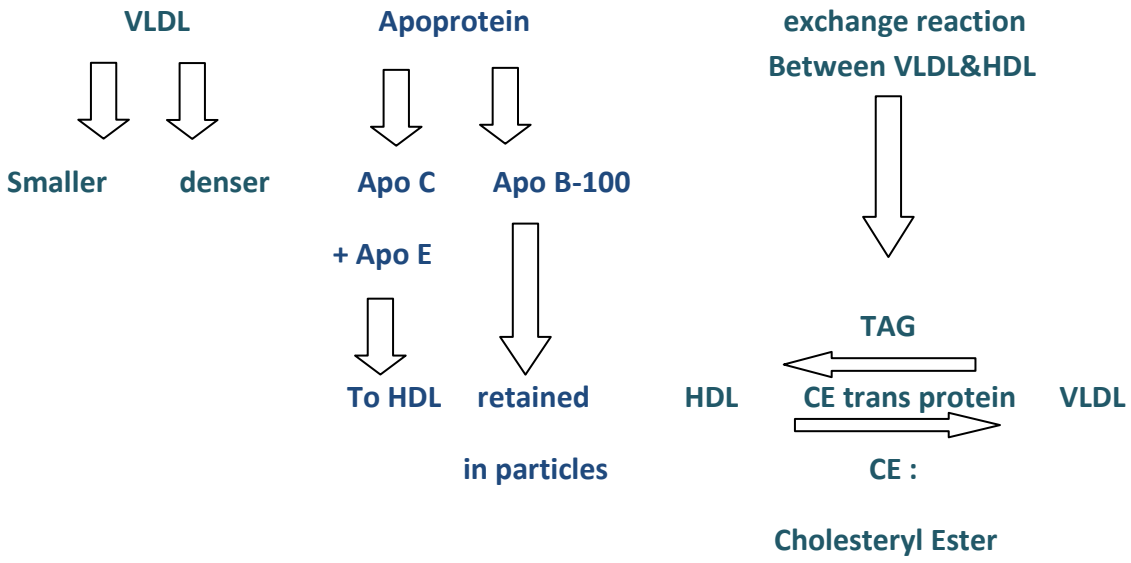
II. VLDL

VLDL:

1. Lipoprotein lipase :

a. Activated by Apo C||

b. Enzyme degrade TAG causing 3 changes :



c. The end result : VLDL converted to LDL

2. IDL (VLDL remanents)

a. Observed during LDL transition

b. Can be taken up by cells through receptor mediated endocytosis .

3. Apo E :

a. Used as ligand in receptor mediated endocytosis .

b. Present normally in 3 isomers :

i. **Apo E-2**
   - Binds poorly to receptors

ii. **Apo E-3**

iii. **Apo E-4**
   - Not yet understood the fact of the E-4 isoform confers increased susceptibility to and decreased age of onset of late onset Alzheimer disease , doubling the lifetime risk.

4. Diseases regarding VLDL :

i. Fatty liver :

- No balance between synthesis of hepatic TAG & secretion of VLDL
- Causes :

obesity , uncontrolled Diabetes Mellitus & chronic ethanol ingestion .

ii. Abetalipoproteinemia :

- Also = Rare hypolipoproteinemia ..
- Hypolipoproteinemia is : low lipoprotein level in blood which means → low TAG are found in blood

❖ TAG accumulate in its site of formation (liver & intestine)

❖ no chylomicrons , no VLDL are formed → because the loading of Apo B with lipids is unable ..

- Defective TAG transfer protein .
- No chylomicrons → ⇩ TAG in blood → ⇧ TAG in small intestine
- No VLDL → no LDL → ⇩ cholesterol .

iii. Type ||| hyperlipoproteinemia

❖ Also = dysbetalipoproteinemia or broad beta disease .

- Accumulation of chylomicrons remnants & IDL in plasma.
- Abnormal Apo E

❖ Patient with homozygous E-2

- Deficient in the clearance of chylomicrons remnant & IDL.
- It causes : hypercholesterolemia & premature atherosclerosis .

III. LDL

Metabolism of LDL:

Primary function of LDL particles is to provide cholesterol to peripheral tissues by mechanism of receptor mediated endocytosis ..

The Mechanism of Receptor Mediated Endocytosis :

5 steps :

1st step: clustered of LDL receptors in pits on cell membranes .

The intracellular side of the pit is coated with protein clathrin .-

Clathrin stabilizes the shape of the pit .-

2nd step: internalization of LDL receptors by endocytosis .

3rd step: the vesicle containing the LDL rapidly loses clathrin coat and fuses with other similar vesicles called endosomes .

4th step: separation of the LDL from it's receptors by falling of PH of endosome . The receptors then migrate to one side of endosome , where the LDL stay free within vesicle .

5th step: the receptors can be recycled , where the lipoprotein remnants in the vesicle are transferred to lysosomes and degraded by lysosomal enzymes releasing : free cholesterol , AA , FA and phospholipids .

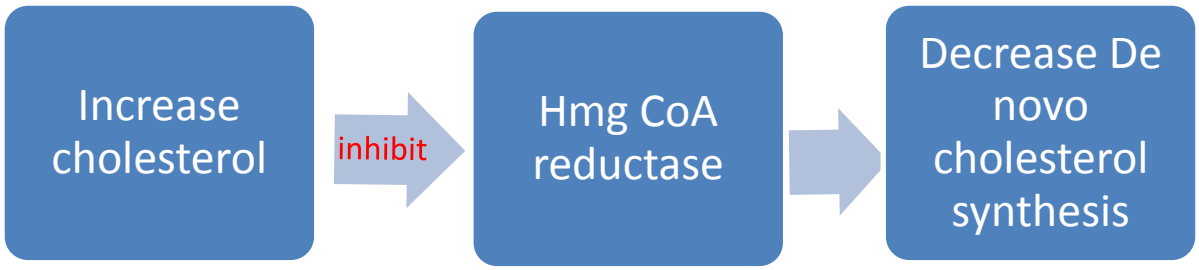
Diseases	Causes
1- Type II Hyperlipidemia	Deficiency of functional LDL receptors
2- Wolman Disease	Autosomal recessive deficiencies in ability to hydrolyte lysosomal cholesteryl esters
3- Niemann Pick Disease	Autosomal recessive deficiencies in ability to transport unesterified cholesterol out of lysosome

Effect of endocytosed cholesterol on cellular Cholesterol homeostasis:

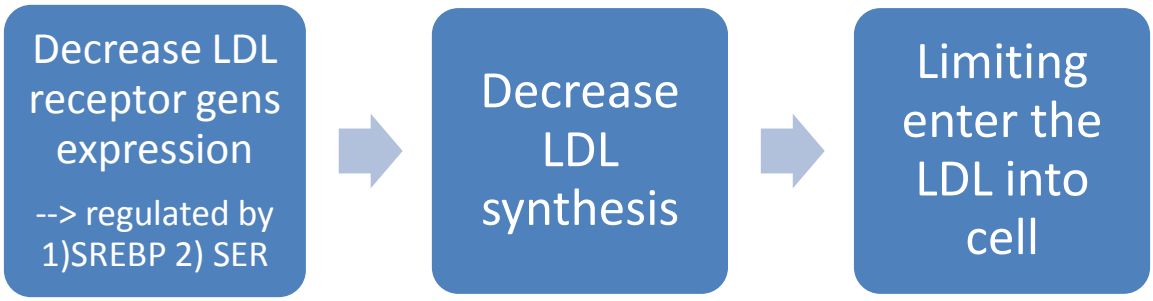
1. Chylomicron remnant
2. IDL
3. LDL

} affect cellular cholesterol

First:

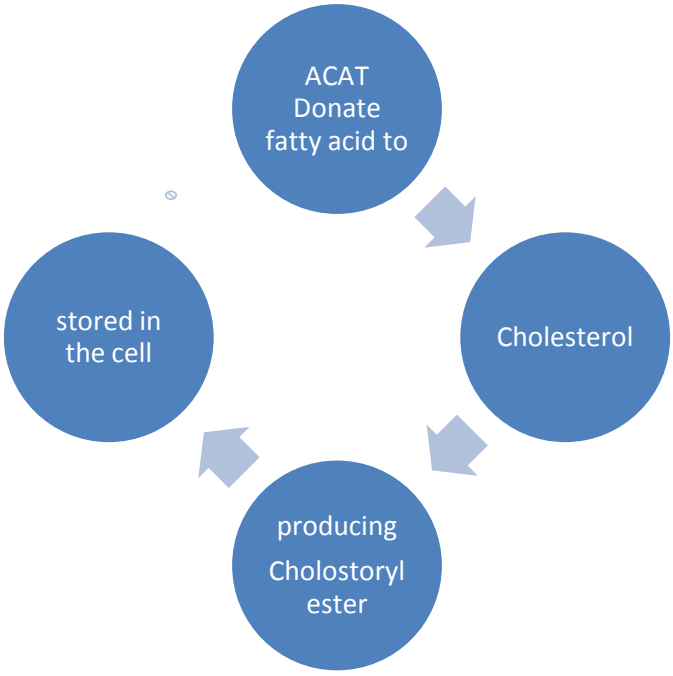


Second:



Third:

- When cholesterol is not required immediately for some structural or synthetic purpose it is esterified.
- Remove fatty acid from Fatty acyl CoA derivative By:
  - Acyl CoA: cholesterol acyltransferas (ACAT) ➔ increase intracellular cholesterol

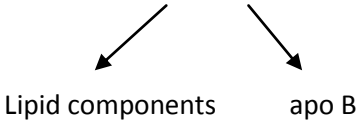


Uptakes of chemically modified LDL by macrophage scavenger:

- Macrophage possess high levels of scavenger receptor activity (Scavenger receptor class A (Sr-A)

The receptor → bind a broad range of ligands

⇨ Mediate endocytosis of modified LDL
By oxidized



Lipid components apo B

N.B scavenger is not down regulated in response to increased intracellular cholesterol.

- cholesteryl ester accumulate in macrophages ----> form ---- > **FOAM** cell ----> cause ➔ a atherosclerotic plaque.

IV. HDL

Components:

Phospholipid largely phosphatidylcholine and apoproteins A, C, and E.

Functions of HDL:

1. HDL is a reservoir of apolipoprotiens
2. HDL are excellent acceptor s of unestrefied cholesterol from both other protein particles and from cell membrane
3. Esterification of cholesterol
4. Reverse cholesterol transport :selective transfer of cholesterol from peripheral tissue to HDL…and from HDL to the liver.

Metabolism of HDL:

- HDL is formed in blood by the addition of lipid to apoA-1.
- Apo A-1: apolipoprotien made by the liver and intestine → secreted into blood
- Apo A-1 account for about 70% of the apoprotiens in the HDL .

1-HDL is a reservoir of apolipoproteins:

- HDL serve as circulating reservoir of apo c-II and apo E
- apo c-II ➔ apolipoprotein that is transferred to VLDL and chylomicrons ,,,and is activator of lipoprotein lipase.

- apo E ➔ apolipoprotein required for the receptor mediated endocytosis of IDLs and chylomicrons remenants.

2-HDL uptake of unesterified cholesterol:

- Nascent HDL are disk shaped particles containing phospholipid (phophatidylcholine)
- They are rapidly converted to spherical particles as they accumulate cholesterol.
- HDL particles are excellent acceptors of unesterified cholesterol (both from other lipoproteins particles and from cell membranes) As a result of their high concentration of phospholipids, which are important solubilizers of cholesterol.

3-Esterification of cholesterol:

1-when cholesterol is taken up by HDL, it is immediately esterified by plasma enzyme phosphatidylcholine: cholesterol acyltransferase(PCAT, also know LCAT, in which "L" stands for lecithin.) this enzyme is synthesized by the liver.

2-PCAT binds to HDL and is activated by apo A-I.

3- PCAT transfer the fatty acid from carbon 2 of phophatidylcholine to cholesterol.

4-This produces a hydrophobic cholesteryl ester, which is sequestered in the core of the HDL and lysophosphatidylcholine which binds to albumin.

5- Cholesteryl ester-poor HDL3 and *cholesteryl ester-rich HDL2 particle that enters to the liver.

6-the cholesterol ester transfer protein CEPT moves some of the cholesteryl esters from HDL to VLDL in exchange for TAG.

- because VLDL are catabolized to LDL ,the cholesteryl esters are ultimately by the liver.

4-Reverse cholesterol transport:

- The selective transfer of cholesterol from peripheral cells to HDL,,,and from HDL to the liver for bile acid synthesis or disposal via the bile,,and to steroidogenic cells for hormone synthesis.
- The transfer of HDL to to steroidogenic cells for hormone synthesis is a key component of cholesterol homeostasis.
- Reverse cholesterol transport involves:

1. efflux of cholesterol from peripheral cells to HDL1
2. esterification of cholesterol by PCAT2
3. binding of the choesteryl ester-rich HDL(HDL2) to the liver and steroidogenic cells3
4. the selective transfer of the cholesteryl esters into these cells (liver and steriodogenic) and the release of lipid-depleted HDL(HDL3)

Hint= The 4th point means that cholesteryl esters moves from HDL 2 and go to liver and steriodogenic cells and finally give us HDL 3 which is very small, after than it load again with cholesteryl ester and become HDL.

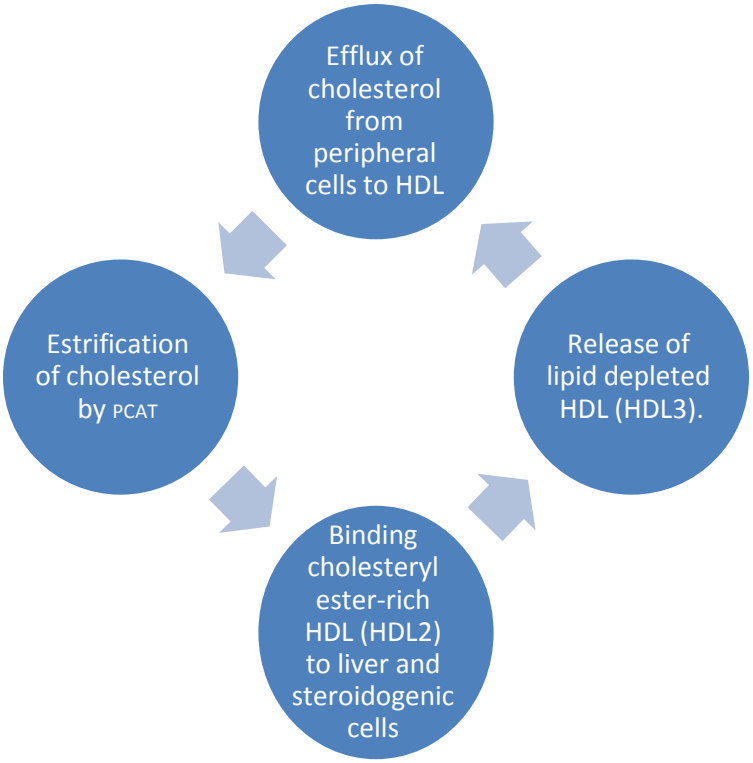


Figure18.23

- The efflux of cholesterol from peripheral tissue cells is mediated by the transport of protein ABCA1.

❖ *Disease:* TANGIER disease is a very rare deficiency of ABCA1 and is characterized by the virtual absence of HDL particles due to degradation of lipid –poor apo A-1.

- The uptake by the liver is mediated by the cell surface receptor SR-B1 (scavenger receptor class B type 1) that binds HDL.
- Hepatic lipase with its ability to degrade both TAG and phospholipids, participates in the conversion of HDL2 to HDL3.
- ABCA1 is an ATP –binding cassette (ABC) protein, ABC protein use energy from ATP hydrolysis to transport materials, including lipids, in and out of the cells and cross intracellular compartments.

-In addition to tangier disease, defects in specific ABC proteins result in X-linked adrenoleukodystrophy (respiratory distress syndrome due to decrease surfactant secretion, and cystic fibrosis.

5-Role of lipoprotein (a) in heart disease:

- Lipoprotein (a) or Lp (a) is a particle when present in large quantities in the plasma, is associated with an increased risk of coronary heart disease.
- LP (a) is nearly identical in structure to an LDL particle.
- Its distinguishing feature is the presence of an additional apolipoprotein molecule apo (a) that is covalently linked at a single site to apo B-100.
- Circulating levels of Lp(a) are determined by genetics. However, some factors such as diet (Trans fatty acids) show increase in LP (a), and estrogen decreases both LDL and LP (a).
- apo(a) is structurally homologus to plasminogen plasminogen is the precursor of a blood protease whose target is fibrin,,the main protein component of blood clot.
- Elevated LP (a) slows the breakdown of blood clots that trigger heart attack because it competes with plasminogen for binding to fibrin.

	VLDL	LDL	HDL
Formation	In liver	From VLDL	In blood
Components	Rich in TAG " 60 % "	Less TAG High cholesterol High cholesteryl ester	Lipids
Apoproteins	➢ Mainly apoB-100 ➢ Apo E & apo C || << from circulating HDL	Remnant of VLDL → Apo B-100	Heterogenous family of lipoproteins ➢ Apo A 70% ➢ Apo C || ➢ Apo E
functions	Carry TAGs from liver to peripheral tissues	Provide cholesterol to peripheral tissues	1. Reservoir of apoprotein 2. HDL uptake of free cholesterol = unesterified cholesterol 3. Esterification of cholesterol 4. Reverse cholesterol transport.

V. Steroid Hormones

Classes of Steroid Hormones:

1- glucocorticoid → cortisol

2- mineralocorticoids → aldosterone

Corticosteroid

3- Sex hormones → androgen, estrogen & progestin

- the precursor of all classes of steroid hormones is '' Cholesterol ''

Synthesis & Secretion:

1. Adrenal cortex → cortisol , aldosteron & androgen
2. Ovaires & Placenta → estrogen & progestin
3. Testes → testosteron

Transport of steroid hormones ;

Because of its hydrophopbicity they must be complexed with plasma protein

1. non-specific carrier → plasma albumin
2. specific steroid carrier

a. Synthesis of steroid hormones

1-mechanisem:

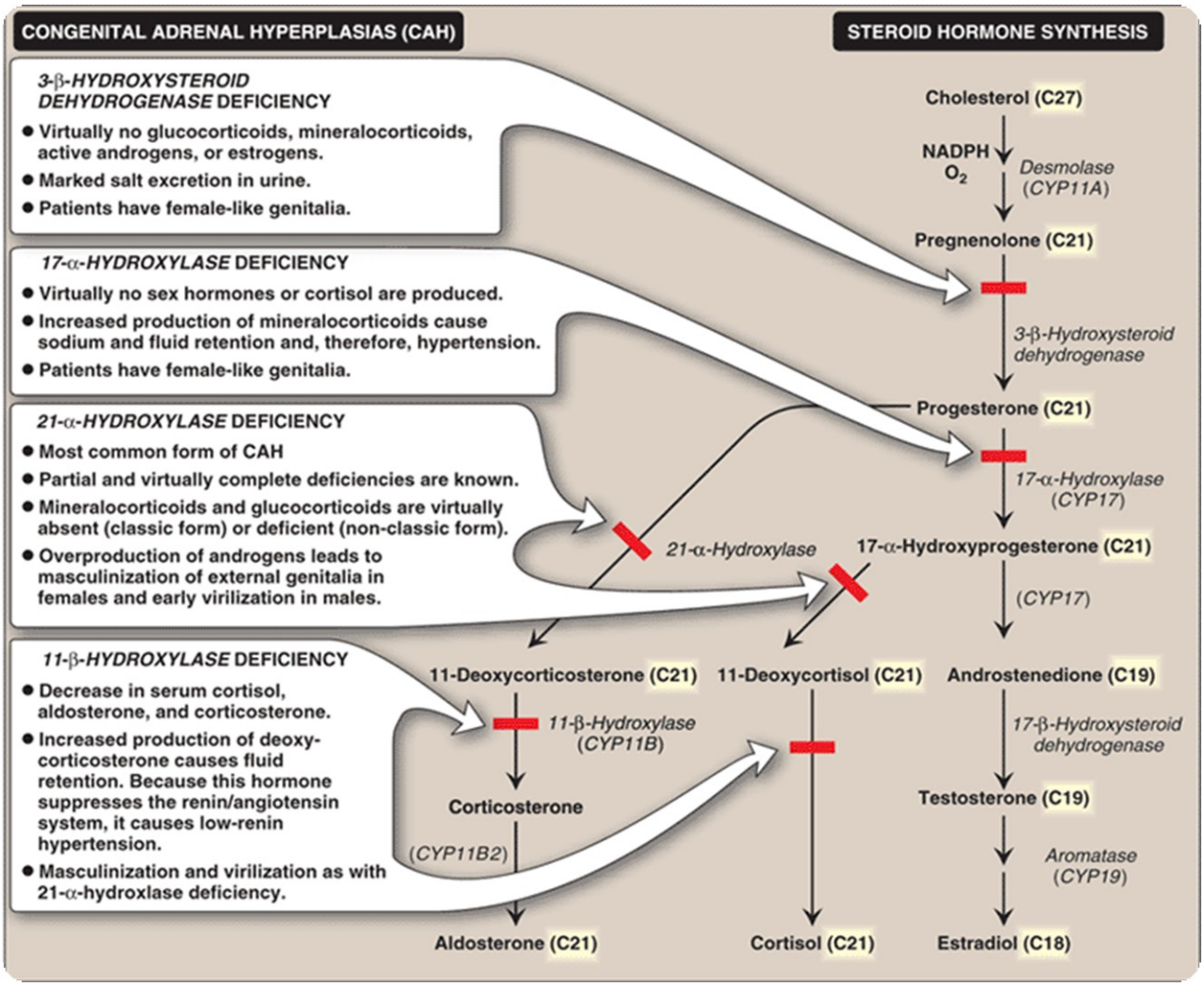
a- shortening the hydrocarbon chain of cholesterol
b- hydroxylation of the steroid nucleus

2-initial & rate limiting step

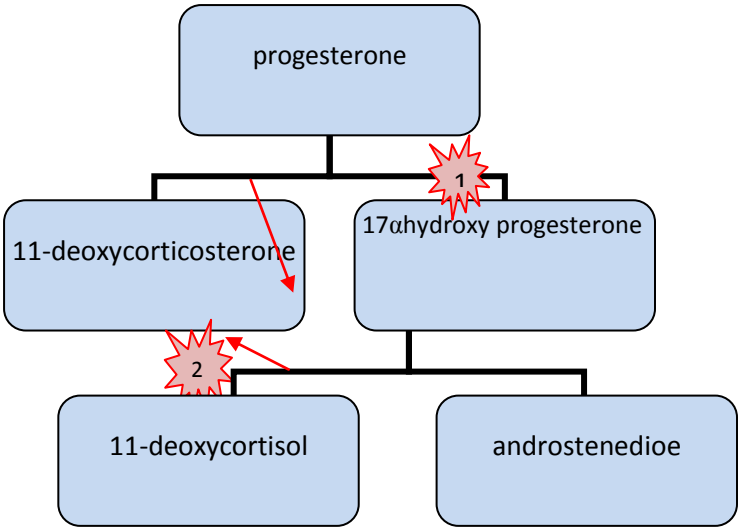
The convertion of cholesterol to 21 carbon pregnenolone

Catalyzed by:	Cholesterol side chain cleavage enzyme complex "desmolase"→ CYP11A	→CYP mixed function oxidase of inner mitochondria membrane
Coenzyme:	NADPH	Molecular oxygen

The following steps: fig18-25



Associated disease:



1

17- α hydroxylase deficiency:

1-sex hormoe &cortisol → will not be produce "virtually" →patients with ♀ like genitalia

2-intead ↑ the mineralcorticoids"11 deoxycorticosterone"→ Na & fluid retention → hypertentsion

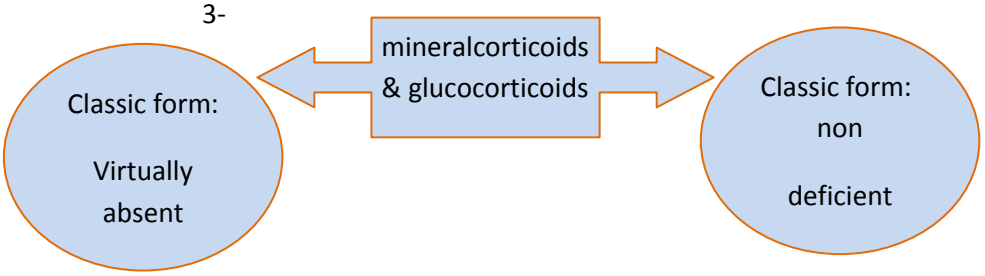
2

21- α hydroxylase deficiency:

1-the most common form of CAH "congenital abnormal hyperplasias"

2- complete deficiency: "virtually & partial"

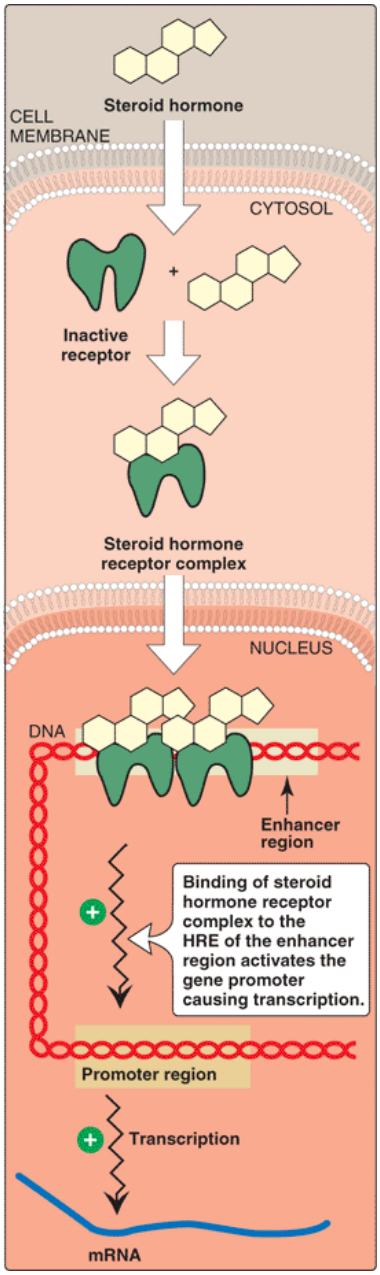
3-



4- over production of androgens lead to

Female	Masculinization of external genital
Male	Early virilization ""البلوغ

Mechanism of steroid hormone action:



Summary of some important diseases:

- Type I hyperlipoproteinemia (Familial lipoprotein lipase deficiency or Hypertriacylglycerolemia)
  - Due to deficiency of lipoprotein lipase or apo C-II
  - ⇨ Will lead to accumulation of chylomicrons in plasma. Even in fasted state.

- Type II hyperlipidemia (Familial hypercholesterolemia)
  - Deficiency of functional LDL receptors
  - ⇨ Will lead to elevation of plasma LDL and therefore plasma cholesterol but plasma TG remains normal. And a premature atherosclerosis.

- Type III hyperlipoproteinemia (Familial dysbetalipoproteinemia or broad Beta disease)
  - Abnormal apo E
  - ⇨ Will lead to accumulation of chylomicron remnants & IDL in plasma.
  - ⇨ There's hyperchloesterolemia with premature atherosclerosis .

- <u>Abetalipoproteinemia</u>
  - Defective triacyglycerol transfer protein
  - ⇨ Will lead to No chylomicrons → ↓TG& ↑ TG in small intestine & liver

    No VLDL

    No VLDL → no LDL → ↓ cholesterol

- <u>Fatty liver</u> :
  - there's imbalance between hepatic TG synthesis & secretion of VLDL
  - ⇨ Will lead to hepatitis ,DM, chronic ethanol ingestion

- 2nd Causes of Hypercholesterolemia
  - ✓Familial Hypercholesterolemia, diabetes mellitus, nephritic syndrome, obstructive jaundice, and hypothyroidism (cretinism in infants, and myxedema in adults)

Chapter 19

- Amino Acids: Disposal of Nitrogen.

Amino Acid: Disposal of Nitrogen

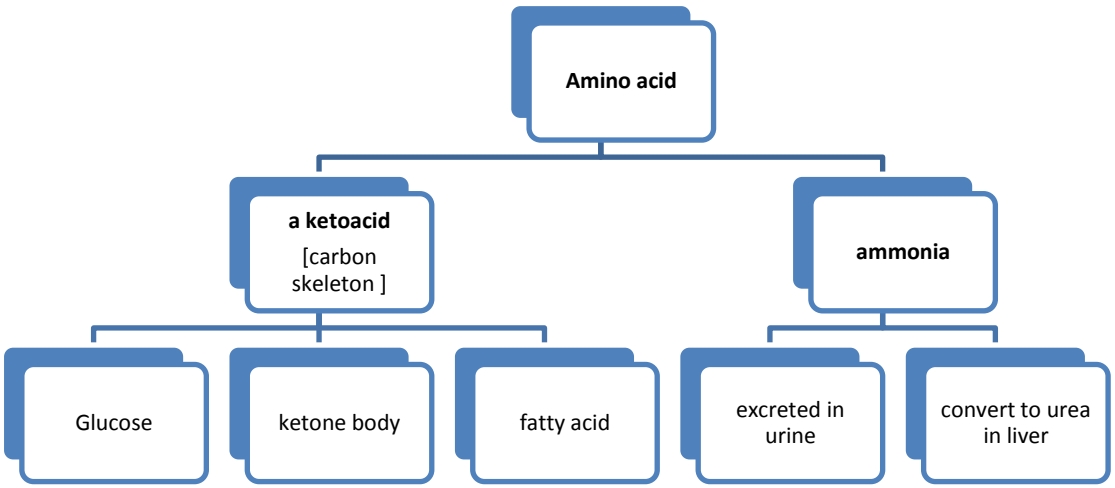
1- Overview

Amino acids are not stored in the body, but the excess amounts either used in amino acid pool or excrete in urine.

-The sources of amino acids are:

- Diet
- De novo synthesis of amino acids
- Degradation of normal protein

-The amino acid degrades to give:



There are 2 types of amino acids:

- ✓ Essential : only obtained from diet
- ✓ Non essential : can be obtained from diet or by de novo synthesis

2- Over All Nitrogen Metabolism

- Nitrogen enters the body in form of different compound in diet.
- Nitrogen leaves the body as urea or ammonia.

A) Amino acid pool:

- Free amino acid are present in all the body.
- All the amino acids in the body belong to single entity called amino acid pool.
    - ***the sources of amino acid pool :***

1. degradation of body proteins
2. amino acid from diet
3. synthesis of non – essential amino acids

- ***The amino acid pool is depleted by :***

1. synthesis of body proteins
2. synthesis of nitrogen containing molecules e.g. : purine , pyrimidine
3. conversion to glucose , glycogen & fatty acids

- The amino acid pool is the center of whole body nitrogen metabolism.
- In healthy people , the input of amino acids should be equal to the output.

B) Protein turn over:

- Protein turnover: constantly degraded & synthesis of body protein, because some proteins are abnormal or unneeded by the body, and they must be degraded “amount of protein is constant ".
- Regulation of the synthesis, determine the concentration of protein in the cell.
    - Cellular levels of protein are controlled by selective degradation.

1: rate of turnover:

- 300 – 400 g of body protein are hydrolysis and resynthesis per day.
- The rate of turnover varies for individual protein.

➢ ***half – lived protein :***

a) short – lived protein:

e.g.: regulatory protein, misfolded protein.

- Rabidly degraded.
- Half – lives: minutes to hours.

b) long – lives protein :

- Majority of protein in the cell.
- Half – lives: days to weeks.

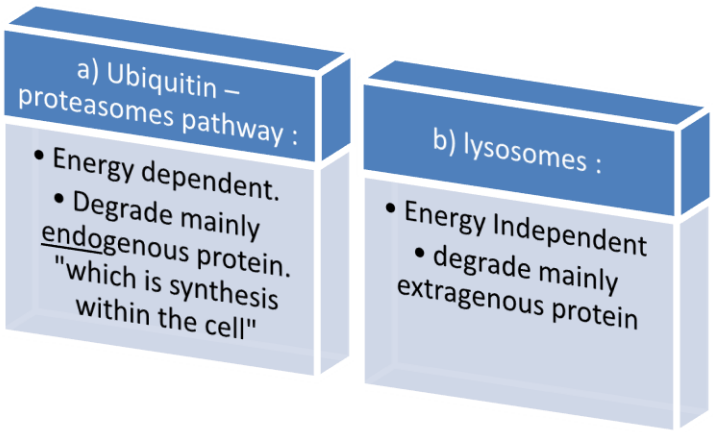
c) Structural protein:

e.g.: collagen.

- Metabolically stable.
- half-lives: months to years .

2: Protein degradation:

There are two major enzyme systems responsible for degradation of damaged or unneeded protein.



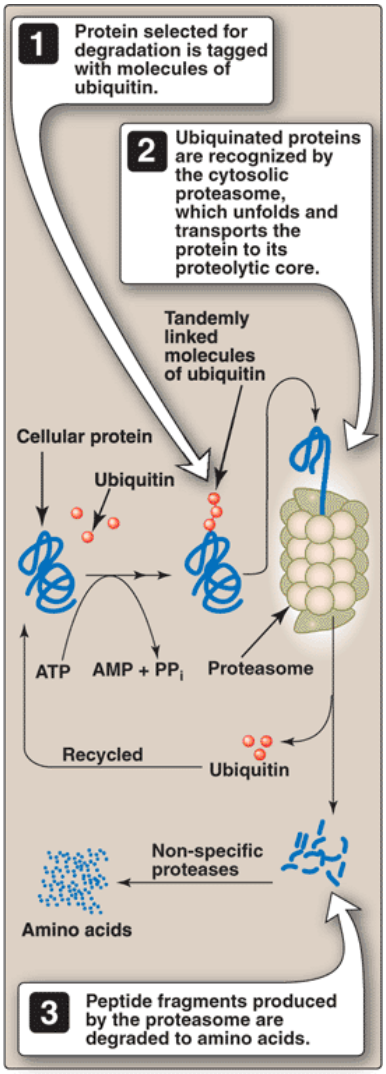
- **The extragenous protein :**

e.g.:

1) Plasma protein: taken by endocytosis .

2) Cell surface membrane protein: used in receptor – mediated endocytosis .

A) Ubiquitin – proteasome proteolytic pathway:



○ ubiquitin: small , globular protein will attach covalently to protein .

○ This attachment is occur by linked of alpha - carboxyl glycin of ubiquitin to E – amino group lysine of protein m by 3 steps.

○ The addition of more ubiquitin from polyubiquitin.

○ The polyubiquitin make tag to unneeded protein.

○ This tag are recognizable by proteasome , a large , barrel – shaped proteolytic complex .

○ The proteasome cut target protein into fragment.

○ These fragments are further degraded to amino acid "which enter the amino acid pool".

○ The ubiquitin are recycled.

○ This pathway requires energy "ATP".

B) Chemical signal for protein degradation:

○ The half – life of protein is influenced by the nature of N – Terminal residue.

○ If the N – Terminal of protein is:

- serine : has half – life more than 20 hours
- Aspartate : has half – life for 3 minutes
- PEST " Proline , Glutamate , Serine , Threonine " has short half – life

3- Digestion of Dietary Protein:

- Proteins are large molecule, so it should be degraded to small molecule “Amino Acid" to be absorbable.
- Newborn can absorb protein " anti – body in breast milk"

A) Digestion of protein by gastric secretion:

- The digestion of protein starts in stomach.
- Stomach secret gastric juice which has :

➢ Hydrochloric acid "HCL” and pepsinogen.

1) Hydrochloric acid: has many functions:

- make the stomach acidic environment " PH 2 _ 3 "
- hydrolys the hydrogen bonds of protein , but not digest Protein .
- kill bacteria .
- activate the pepsinogen .

2) Pepsin:

- Acid-stable endopeptides enzyme.
- Secreted by serous cell of stomach as pepsinogen.
- Pepsinogen is activated to pepsin by:
  - ✓HCL.
  - ✓pepsin.
- The activation of pepsinogen involves of extra amino acid in pepsinogen remove of extra amino acid in pepsinogen sequence, which inactivate it.
- Pepsin release peptides + few amino acids.

B. Digestion of protein by pancreatic enzymes:

The polypeptides which come from stomach are further degraded by action of pancreatic proteases.

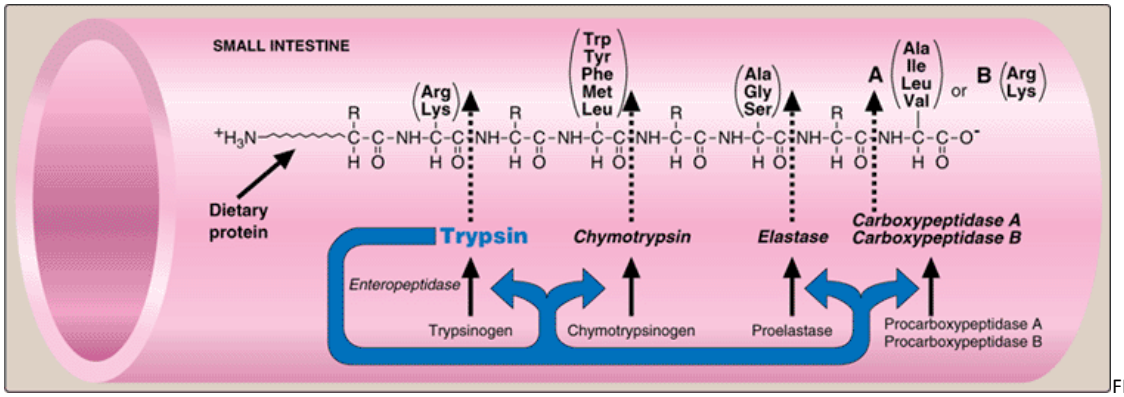


FIGURE (19.5)

1- *Specificity:*

- Each pancreatic enzyme has different specificity for amino acid R-group.

2- Release of zymogens:

- The digestive tract release hormones "CCK, secretin", that activate the release of pancreatic zymogens.
-

3- Activate of zymogens:

- The intestine mucosal cells secrete **Enteropeptidase**, an enzyme that activate trypsinogen to trypsin.
- The activation occurs by removal of hexapeptide from NH^2-terminus of trypsinogen.
- Trypsin Activate other pancreatic zymogens, although it convert trypsinogen to trypsin!

4- Abnormality in protein digestion:

- Deficiency of pancreatic secretion (due to: chronic pancreatitis, cystic fibrosis, or surgical removal of pancreas) will affect the digestion of protein and lipid.
    - ➔ This result in the abnormal appearance of lipid "**Steatorrhea**" and undigested protein in feces.

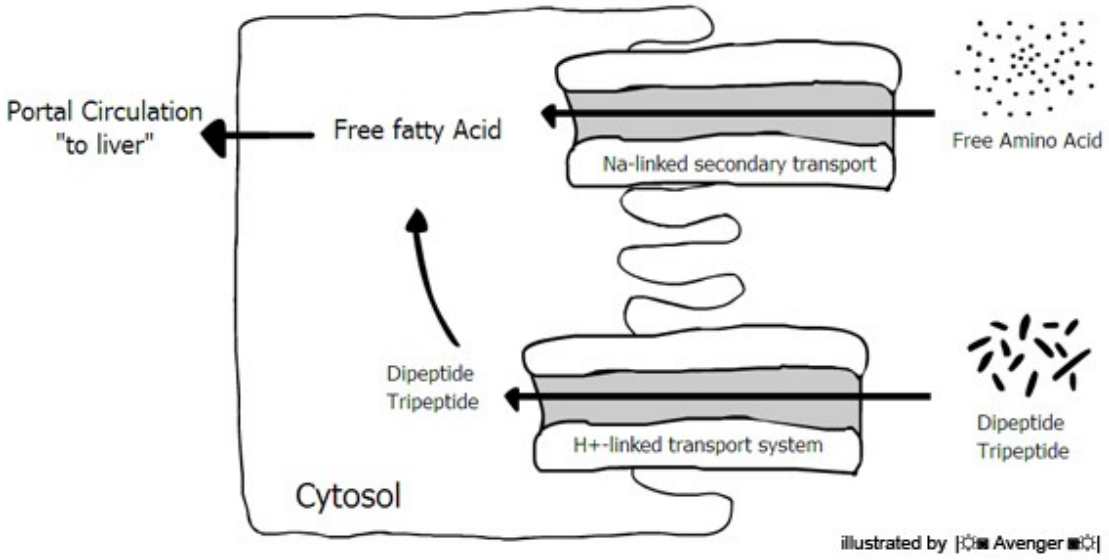
Celiac Disease

- *is* a disease of mal-absorption resulting from immune-mediated damage to small intestine in response to ingestion of protein called "**Gluten**"

C. Digestion of oligopeptides by small intestine`s enzymes:

- Aminopeptidase, an exopeptidease released by intestinal cell.
- This enzyme cleaves the N-terminal residue of oligopeptides to produce free amino acid + smaller peptides.

D. Absorption of amino acid and dipeptides:



- Amino acid in portal circulation either 1- Metabolized by liver or 2- Released in general circulation.
  - ❖ **Note:** Branched amino acid "e.g. Valine, Leucine and Isolecine" are not metabolized by liver, but they sent into general circulation.

4- Transport of A.A Into Cells :

There're at least 7 active transport systems that are responsible for moving A.A from ECF into the cells [driven by hydrolysis of ATP] & maintain concentration of A.A in ECF lower than its conc. within the cells. Small intestine & kidneys have common transport systems. If there is any defect in these systems , there will be inability to transport specific A.A

Case :

- *Normal Condition:* there's a system which is responsible for the uptake of Cystiene, Orthinine, Arginine, & lysine (known as COAL sysem)

-*Defect:* in disorder cystinuria (most common genetic disease of A.A) , all four A.A appears in urine & causes stones in kidneys (calculi).

Treatment : Oral hydration

- ***Hartnup disorder*** is caused by defect in transport of tryptophan & causes dermatological & neurological symptoms.

5- Removal of Nitrogen from A.A :

a-amino group of A.A keeps the A.A away from any oxidative reactions. Once removed, nitrogen & carbon skeleton will enter different types of reactions.

A- Transamination:

It's the transfer of a-amino group of A.A to a-ketoglutarate , & production of a- keto acid(carbon skeleton) & Glutamate. It's catalyzed by aminotransferase (found in cytosol & mitochondria of all cells especially in liver, kidney, intestine, & muscle). Glutamate can be oxiditavely deaminated or used as amino group donor. This reaction is applied for all A.A except for lysine & threonine (they lose their a-amino group by deamination). Each aminotransferase is specific for one or few a-amino group donors. Most common : ALT (for Alanine) & AST (for Aspartate).

ALT:

Alanine + a-Ketoglutarate ⟷ Pyruvate + Glutamate

Alanine gives its amino group to a-Ketoglutarate (alanine will be pyruvate , and a-Ketoglutarate will be glutamate). The enzyme will function in glutamate direction during A.A catabolism.

AST:

Glutamate + Oxaloacetate ⟷ a-Ketoglutarate + Aspartate

This reaction is an exception because glutamate transfers its amino group to oxaloacetate (instead of a-ketoglutarate) & produces aspartate (from OAA) which is the source of nitrogen, and a-ketoglutarate (from glutamate).

Mechanism of action of aminotransferases :

All aminotransferases needs pyridoxal phosphate (coenzyme that's covalently linked to e-amino group of lysine residue in active site) for the reaction to achieve.

1- aminotransferases transfer amino group to pyridoxal-P forming pyridoxamine-P

2- pyridoxamine-P gives the amino group to a-keto acid (OAA in the upper example) , forming A.A (aspartate in the upper example). pyridoxamine-P will also return to its original aldehyde form (pyridoxal-P) by giving this amino group.

Equilibrium:

After eating, reaction functions in A.A degradation by removal of amino groups.

When supply of A.A isn't enough, reaction will function in biosynthesis of A.A by addition of amino groups to a-keto acids.

Diagnostic value of plasma aminotransferases;

It's low in normal conditions, if elevated it will indicates damage in specific tissues as live, heart, & muscle (which are rich in aminotransferases)

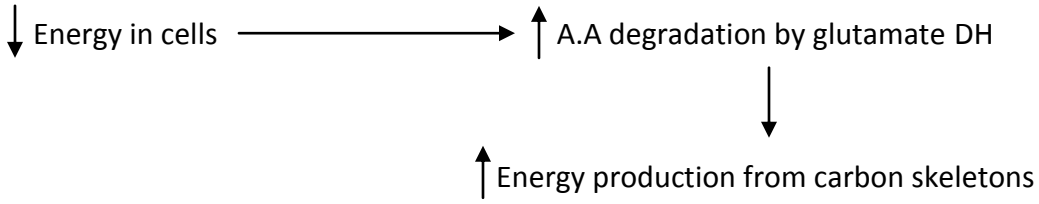
Elevated plasma ALT & AST indicates liver diseases (necrosis, viral hepatitis, toxic injury, & prolonged circulatory collapse). ALT is more specific but AST is more sensitive because liver has high amounts of AST.

Oxidative deamination of A.A:

- Occurs primarily in liver & kidneys by glutamate dehydrogenase. Provide a-keto acis & ammonia (nitrogen source)
- Sequential action of transamination by transferring of amino groups from A.A to form glutamate , and oxidative deamination of glutamate both provide a pathway in which amino groups of most amino acids can be released as ammonia.
- Glutamate DH can use NAD+ as coenzyme (in oxidative deamination) or NADPH (in reductive amination).

- *Direction of the reaction depends on:* concentration of glutamate, a-ketoglutarate, ammonia, & the ratio of oxidized to reduced coenzymes.

•*Guanosine triphosphate* is an allostric inhibitor of glutamate DH, while adenosine diphosphate (ADP) is an activator.

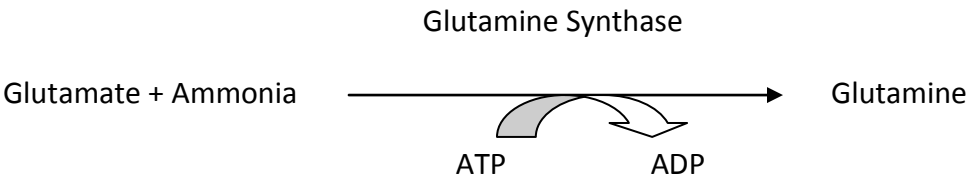


• *D-amino acids* are found in plants, microorganisms, & diet. Not present in mammalians proteins. When this type enters our bodies it will be metabolized in liver & kidneys by D-amino acid oxidase (FAD-dependent peroximal enzyme) which catalyzes oxidative deamination of these A.A producing a-keto acids.

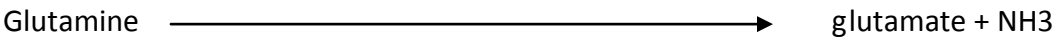
Transport of ammonia to the liver:

There're two mechanisms for transferring A.A from peripheral tissues to liver:

1- in most tissues by these two reactions:



Glutamine goes to the liver where it cleaved by glutaminase to glutamate & ammonia



2- second method , mostly in muscles , involves formation of alanine from transamination of pyruvate. Alanine goes to the liver where it is reconverted to pyruvate by transamination., again. Then, pyruvate can be used to synthesize glucose which can enter the blood & be used up my muscles. This pathway is known as glucose-alanine cycle.