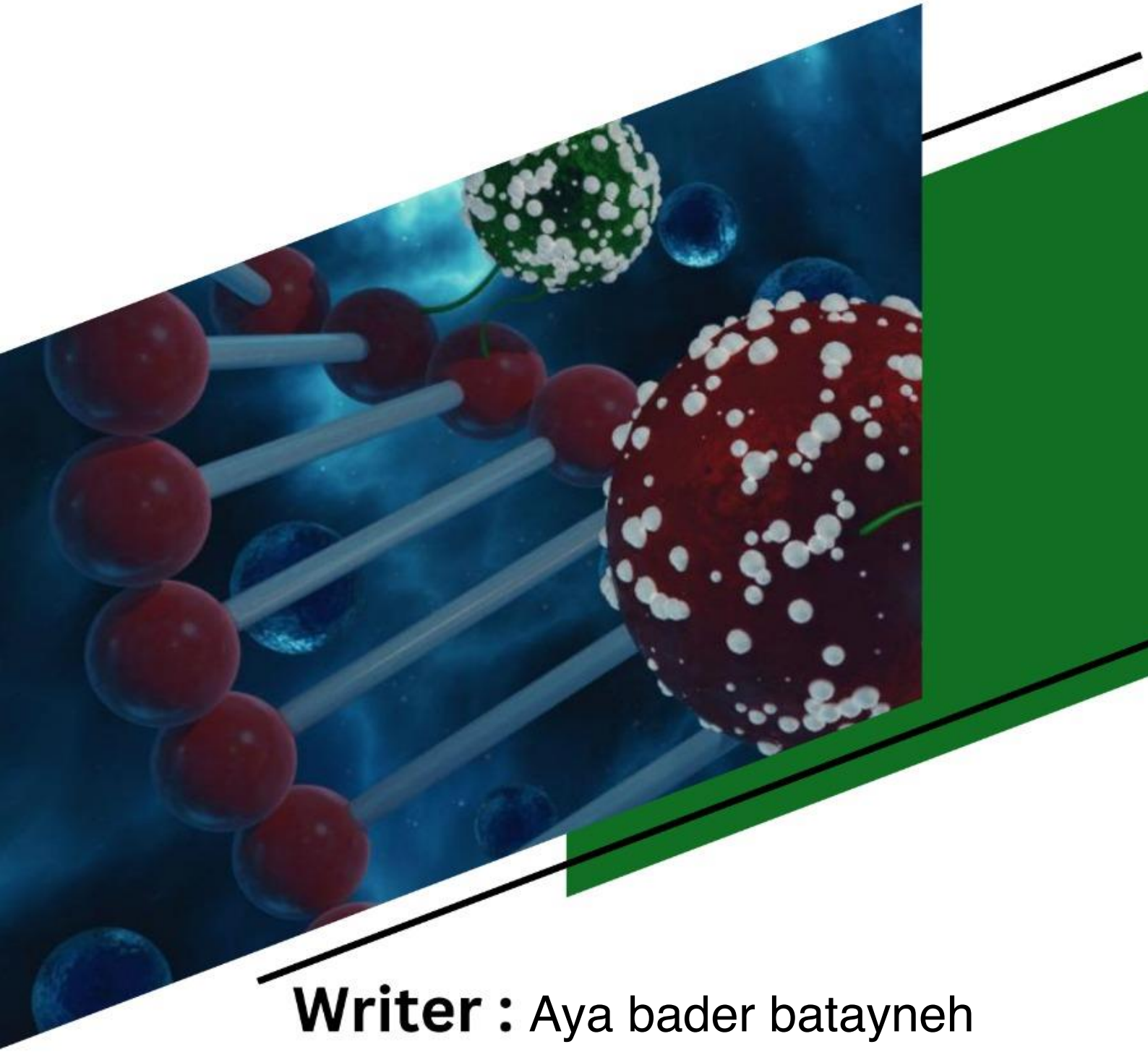
Doctor 021

METABOLISM

Sheet no. 27



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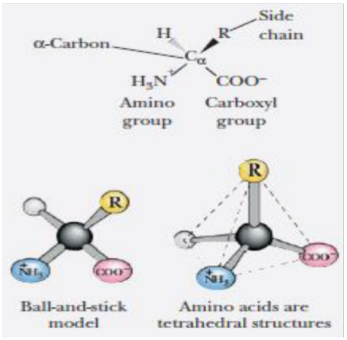
AMINO ACID DIGESTION & METABOLISM

AMINO ACID STRUCTURE:

Amino acids are carbon molecules; each one has a carboxyl group, amino group, H atom and R- group bonded to the α-carbon atom (4 bonds).

- Amino acids =AAs



~ Only 20 AAs are usually found in proteins

That's mean: We have 20 AAs in protein structure,

But there are other AAs that can be present as free AAs,

They can't be incorporate in the protein structure.

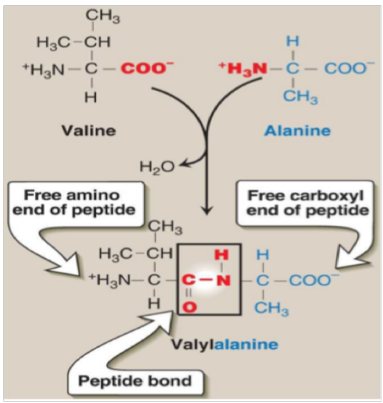
-The 20AAs in the protein are present in D or L configuration

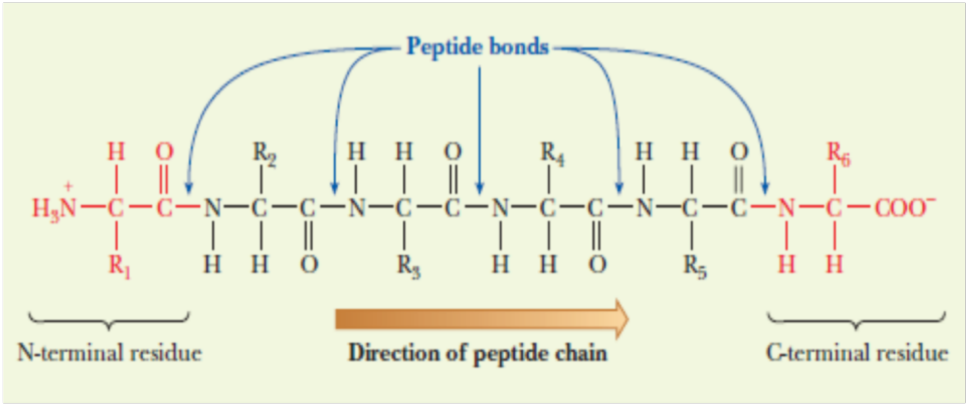
However; all cells can deal with AAs if we obtained them from other sources.

PEPTIDE AND POLYPEPTIDE CHAINS:

In proteins, amino acids are joined covalently by peptide bonds, which are amide linkages between the α-carboxyl group of one amino acid and the α-amino group of another (dehydration reaction).

In this reaction the peptide bond or oligopeptide or polypeptide bond can form and that can perform a wide range of functions.





- **Peptides: two to several dozen AA.**
- **Polypeptide chain: many amino acids (usually more than a hundred).**

-Naming the peptide: By convention, the free amino end (N-terminal) of the peptide chain is written to the left and the free carboxyl end (C-terminal) to the right Therefore, all amino acid sequences are read from the N- to the C-terminal end.

➢ AMINO ACIDS (AAS)

- **AAs are NOT stored in the body.**

However they have a pool, this is pool has input &output (sources that can supply this pool & fates that can take AA from this pool.

- **AAs sources are: diet, de novo synthesis or protein degradation.**
- **AA metabolism overview:**

1. a-amino group removal by transamination then oxidative deamination (N leaves the body as urea, ammonia or other compounds)

2. The resulting a-keto acids are converted to energy producing intermediates

3. Intermediate metabolism to CO2, water, glucose, fatty acids, or ketone bodies

-The metabolic processes have to keep harmony between amino acid pool and protein turnover

- in order to prevent accumulation the AAs in the cells , we are going to use either in the synthesis of protein or synthesis of other molecules (nitrogen containing compound) and also it can be degraded (the degradation can be a source of substrate for gluconeogenesis).

SOURCES AND FATES OF AMINO ACIDS

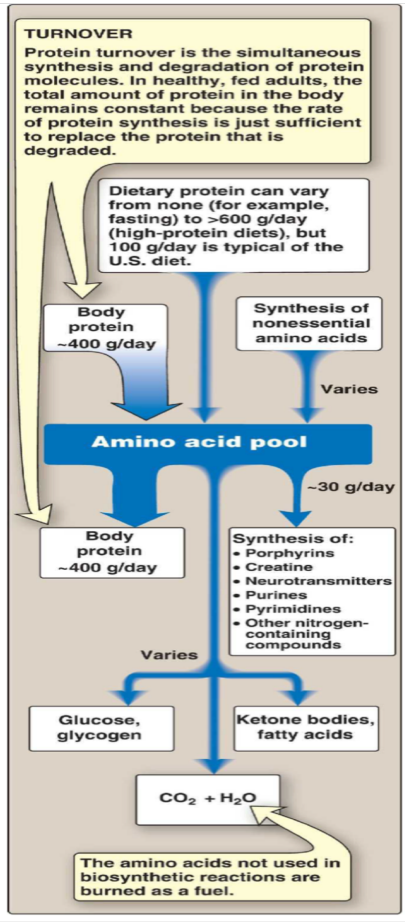
Some note:

- **The AA pool is small ~about 90-100gof AAs.**

That's mean it's not a store because it's not a high quantity

- **The amount of protein in the body is about 12 kg in A70-kg man.**
- **Normally, the amount of AAs in the AA pool is balanced by the output (constant amount)**
- **The amino acid pool is in a steady state, and the Individual is in nitrogen balance.**

-it has to be maintains in a steady state (supply & Consumption must be close to each other) because



this is going to affect the balance of nitrogen because Nitrogen from amino acid degradation is released as ammonia and its very toxic specially to the CNS.

AMINO ACID POOL

➢ **AA sources :(where do AAs come from?)**

1. Endogenous (body) protein degradation (which is constantly taking place to eliminate misfolded, non-functional proteins or a protein that has finished its function)

2. Exogenous (dietary) protein digestion

3. Nonessential amino acids synthesized from metabolic intermediates.

AMINO ACID POOL DEPLETION ROUTES

➢ **AAs are depleted by 3 routes:**

1) Synthesis of body protein

2) AAs consumed as precursors of nitrogen-containing small molecules

Like heme group and other hormones.

3) Conversion of AAs to glucose, glycogen, fatty acids, ketone bodies, or $CO_2 + H_2O$.

PROTEIN TURNOVER

-Protein turnover is the process in which the rate of protein synthesis is sufficient to replace the degraded protein (protein synthesis & degraded constantly all the time (turned over) so it's a dynamic process).

1-RATE OF PROTEIN TURNOVER

- **Each day, 300-400 g of body protein is hydrolyzed and resynthesized in healthy adults, so the rate of protein synthesis is just sufficient to replace the protein that is degraded so the total amount of protein in the body remains constant.**
- **Turnover varies widely for individual protein**

(because of their 1- **functions**& the protein has a **half-life** ,this is half-life is also depended on function &it's also related to the **structure** like collagen lives more than one year without degradation but the enzyme it has to be degraded faster it has a shorter half-life Compared to the structural protein, There are some structural elements in these proteins make them live longer to maintain their function.2- **mode of expression** that affects protein turnover, it means how and when this gene is expressed. So for example,

housekeeping genes are considered as constitutive genes they are constantly expressed, but there are certain proteins that are only synthesized under certain condition and stimulators, so they are called induced proteins, such as insulin and glucagon, which regulate metabolic pathways.

- **Most proteins are long-lived proteins (t1/2 days to weeks).**
- **Structural proteins, such as collagen, are metabolically stable (t1/2 months or years).**
- **For many proteins, regulation of synthesis determines the [protein in the cell] and protein degradation is minor.**
- **For other proteins, the rate of synthesis is constitutive, or relatively constant, and [protein in the cells] is controlled by selective degradation.**

2-PROTEIN DEGRADATION

-Two major enzyme systems are responsible for degrading damaged or unneeded proteins:

a. The ATP-independent degradative enzyme system of the lysosome.

b. The ATP-dependent ubiquitin-proteasome system of the cytosol mainly endogenous proteins (proteins that were synthesized within the cell).

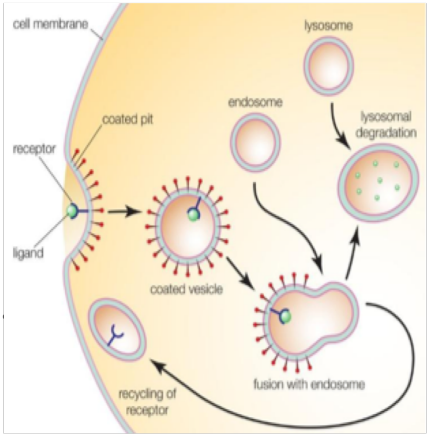
a. THE ATP- INDEPENDENT DEGRADATIVE ENZYME SYSTEM OF THE LYSOSOME:

➢ **Lysosome enzymes (acid hydrolases) degrade primarily:**

1. Extracellular proteins found in ECM, interstitial fluid, etc., such as plasma proteins, by endocytosis

2. Cell-surface membrane proteins by receptor-mediated endocytosis,

-forming a vesicle called endosome which fuses with lysosome that starts degrading.

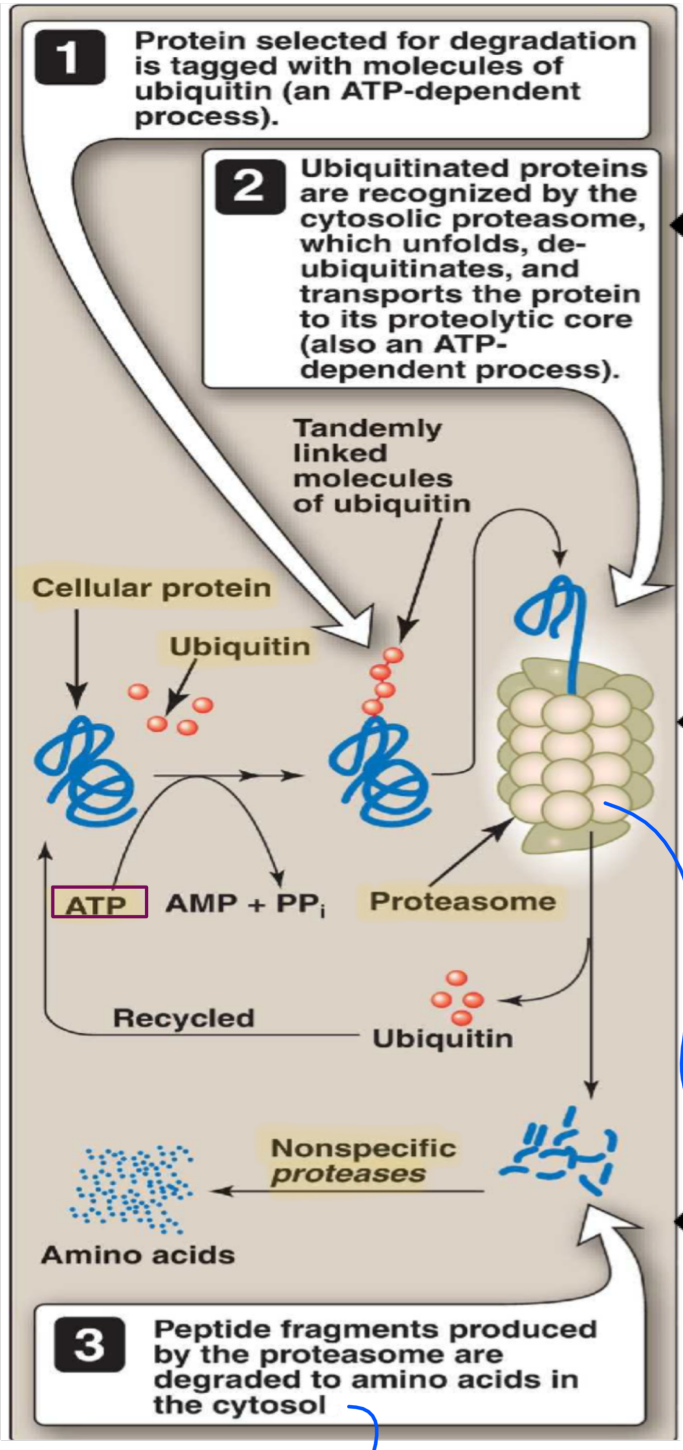


-The lysosome is the digestive system of the cell;

it contains acid hydrolases which work in the acidic environment of lysosomes that have a ph of around 5, which is acidic relative to the cytosol's pH of around 7.

-This system is ATP independent.

b- UBIQUITIN-PROTEASOME PROTEOLYTIC PATHWAY:



that intracellular proteins can be degraded by this mechanism; however, extra cellular proteins as well as cell membrane proteins are degraded by the lysosome system.

(Ub) Ubiquitin:
small ,nonenzymes ,globular protein use to (labeling(tagging) the target proteins.

-Tagging is done by attaching several molecules of ubiquitin to the protein to be degraded, this process is called polyubiquitination

-Tagging process needs energy in the form of ATP, that's why this whole pathway is considered ATP dependent.

proteasome: a hollow,large,macro molecular, barrel- shaped structure that has a core and is composed of many
complex protein structures (proteolytic complex). It is machinery rather than an organelle!
The proteins are targeted to this structure for degradation (the degradation (hydrolysis)inside it is ATP-independent)

by nonspecific proteases & the the Ub is recycled because it was not degraded & consumed .

These entire pathways for **endogenous protein** (originate from within a living system) SO, now we will discuss the degradative pathways for **dietary** &**exogenous protein** (originate from outside of an organism):

DIGESTION OF DIETARY PROTEINS

Some note:

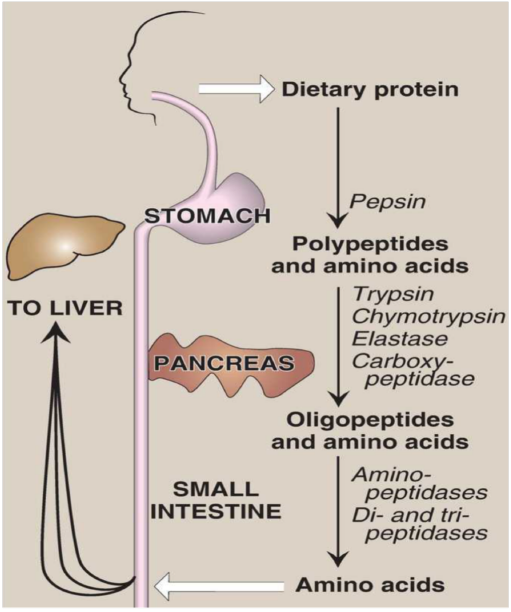
~70-100 g/day in the American diet

(How much we consume proteins)

~Proteins are too large to be absorbed by the intestine.

~Protein digestion begins in the stomach

(no digestion in the mouth)



~Stomach secretes the gastric juice that contain hydrochloric acid (acidic environment) **and the proenzyme, pepsinogen.**

A. DIGESTION OF PROTEINS BY GASTRIC SECRETION

In the stomach:

1.Hydrochloric acid: **-** decreases the PH 2-3 to hydrolyze proteins.

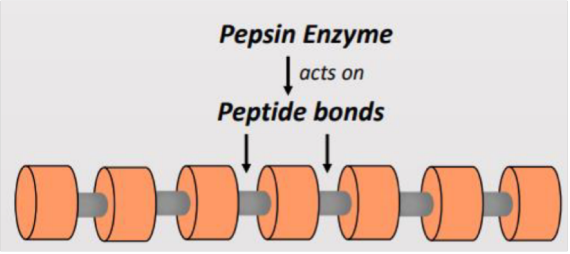
(because it's very strong acid)

- HC1 is secreted by the parietal cells
- HC1 functions:(what's the advantages of hopping very acidic environment in the stomach ?)

A. kills some bacteria (this acidic environment works as a sterilizer for pathogenic microbes that may enter the stomach).

B. denatures proteins to make them more susceptible to subsequent hydrolysis by digestive enzymes proteases. (By denaturation, proteins lose their 3D shape, but the primary sequence is maintained & the peptide bonds aren't broken (proteins will be open structure which has more spaces for a binding &action of digestion enzyme(exposing the active sites)) look at the pic to know what I mean).

C. Activates pepsinogen to become pepsin



After the HCL unfold the proteins into a chain of AAs to be more accessible to enzymatic action :

2. Pepsin (the enzyme that is present in the stomach):

- **this** acid-stable endopeptidase, Is secreted by the chief cells of the stomach as an inactive zymogen (in order to prevent their action in the chief cells) or proenzyme, pepsinogen.
- Pepsinogen is activated to pepsin, either by HCL or auto catalytically by other activated pepsin molecules (to cleave the proteins by exposing the active site & hydrolysis the peptide bonds, but not all bonds, so we don't need to Cleave the whole polypeptide To single AAs)
- Pepsin releases peptides and a few free amino acids from dietary proteins.
- Pepsin catalyzes the **partial** digestion of the protein and it produces smaller fragments .

✓ **NOTE** : pepsin+ HCl + partially digested proteins (oligopeptide chaines)= is called Chyme, and this chyme moves from the stomach to the small intestine (duodenum).

B. DIGESTION OF PROTEINS BY PANCREATIC ENZYMES IN SMALL INTESTINE

✓ This chyme will move to the duodenum where inactivation of pepsin takes place& activation pancreatic enzymes because of the increase in pH which reaches around 6.

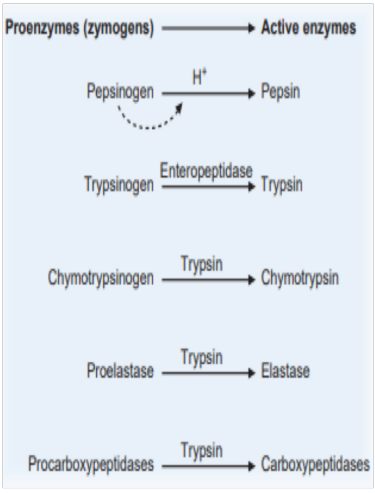
➢ **Pancreatic enzymes (proteases) in the duodenum:**

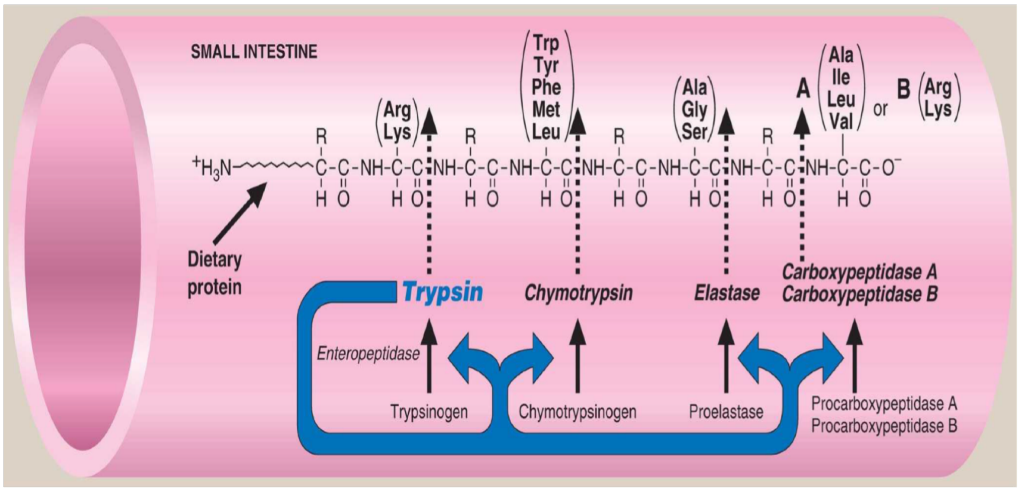
1- exopeptidases include Carboxypeptidase A & B (they cut next to the C terminus(in the end)).

2- endopeptidases(Serine) include Trypsin,Chymotrypsin &Elastase,

(" endo" because they cleave within).

❖ Each is produced from an inactive zymogen because when it was in active form,it will degrade the pancreatic structure & proteins) .





(the position of cleavage for these enzyme are not required)

1.Specificity: Each of these enzyme has a different specificity for the amino acid R-group adjacent to the susceptible peptide bond so that's why we have all these enzymes and not a single enzymes that runs the whole process.

2. Zymogens release: The release and activation of the pancreatic zymogens is mediated by the secretion of cholecystokinin and secretin (two polypeptide hormones of the GIT).

3. Zymogen activation : Enteropeptidase (also called enterokinase),serine protease synthesized by & present on the luminal surface (apical) of intestinal mucosal cells (enterocytes) of the brush border converts the pancreatic zymogen trypsinogen to trypsin (by removal of a hexapeptide from the N-terminus of trypsinogen) thus, enteropeptidase unleashes a cascade of proteolytic activity because Trypsin iS the common activator of all pancreatic zymogen.

C. DIGESTION OF OLIGOPEPTIDES BY SMALL INTESTINE ENZYMES

- **the luminal surface of the intestine (enterocyte)contains aminopeptidase is an exopeptidase that repeatedly cleaves the N-terminal residue from oligopeptides to produce smaller peptides and free AAs.**

✓ **Note :** Amino peptidase is an intestinal enzymes (not pancreatic).

- **The digestive enzymes digest themselves as well as dietary protein. They also digest the intestinal cells that are regularly sloughed off into the lumen.**

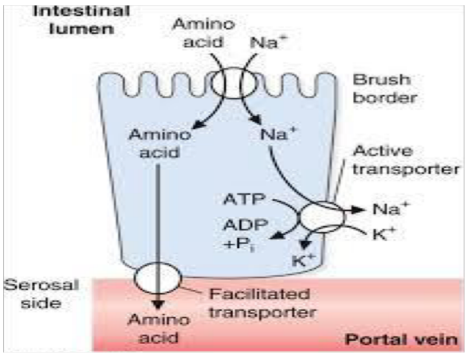
D. ABSORPTION OF AMINO ACIDS &SMALL PEPTIDES

✓ After all these enzymes, we end up with single amino acids or at most di-tri peptides , so now these molecules are ready for absorption (transport of these molecules from the lumen → enterocytes→ portal circulation→ liver).

- Recall that enterocytes are polar cells;

with 1. a brush border and

2. a baso-lateral surface.



➢ **Most free amino acids are taken into enterocytes via a sodium-dependent (linked) secondary transport system at the apical membrane** (has to be coordinated to the Na-K pump to maintain the charges across the membrane) **. Di- & tripeptides, however , are taken up by a proton (H^+)-linked transport system .**

➢ **The peptides are then hydrolysed in the cytosol to free amino acids,**Regardless of their source, Free amino are released from enterocytes in to the portal system by sodium-independent transporter of the basolateral membrane(Therefore, only free amino acids are found in the portal vein) .**these amino acids are either metabolized by the liver or released into general circulation.[NOTE: branched -chain amino acids are not metabolized by the liver but ,instead, are sent from the liver to muscles via the blood .]**

-these molecules concentration increases inside the enterocyte, so the concentration gradient will lead to the transport of these amino acids to the portal vein using facilitated diffusion (with no need of energy).

-When amino acids reach the body cells, each amino can have its own transporter or a single transporter can be shared between different amino

acids, that depends on the amino acid itself. the most popular transport system is COAL (Cystine ,Ornithine, Arginine , Lysine).

-يلي مكتوب فوق هو الصح لكن للطلاب يلي بحبوا يعتمدوا كلام الدكتورة فالاختصارات ذكرتهم الدكتورة كالتالي:

(Cystine , Ornithine, Alanine, Leucine) skippp…….

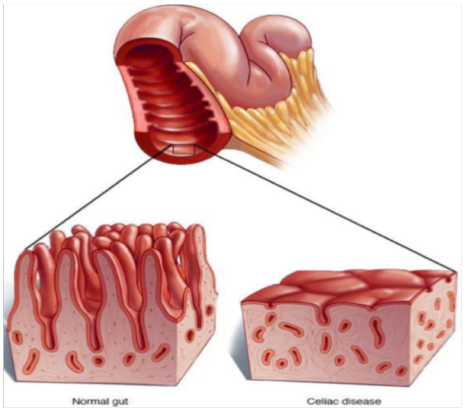
E. DIGESTION ABNORMALITIES

1. Pancreatic secretion deficiency due to chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas, results in incomplete fat and protein digestion.

- **Symptoms: abnormal appearance of lipids (steatorrhea), and undigested protein in the feces**

2. Celiac disease (celiac sprue)(حساسية القمح):

is a disease of malabsorption resulting from immune-mediated damage to the small intestine in response to ingestion of gluten (or gliadin produced from gluten), a protein found in wheat, barley and rye.



Notice the figure → the difference between normal gut and celiac gut, the brush border of enterocytes provides higher surface area for absorption and higher concentration for enzymes and transporters but this structure has changed due to frequent destruction of enterocytes that affects absorption and causes malabsorption which happens only when consuming gluten.
But digestion won't be affected in this case, because most digestive enzymes come from the pancreas that is not affected by celiac.
~ <u>The treatment is to have gluten-free diet</u>.

Thanks a million