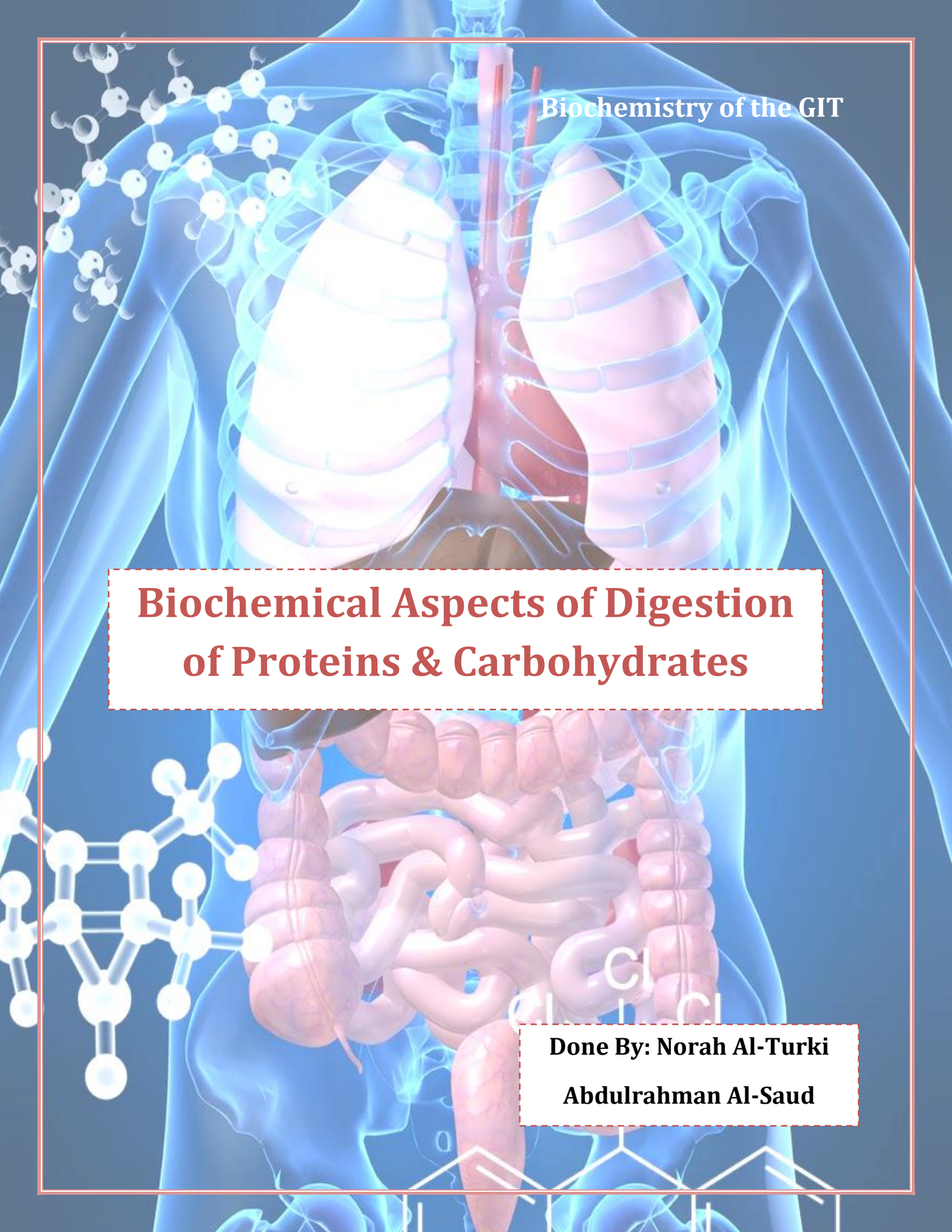

Biochemistry of the GIT

Biochemical Aspects of Digestion of Proteins & Carbohydrates

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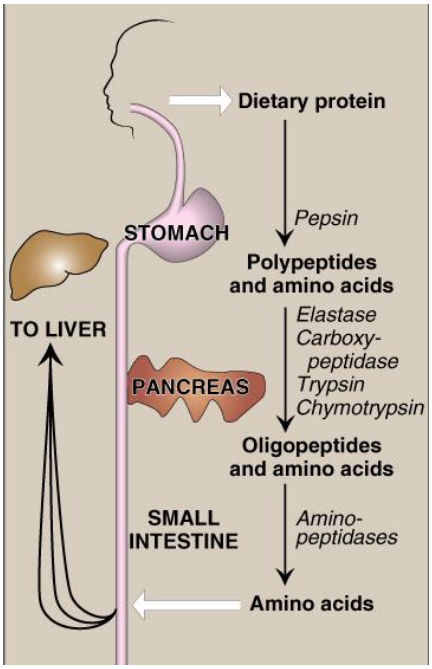
Protein Digestion:

- Dietary proteins constitute **70-100** g/day. (The average consuming of Protein per person per day)
- Proteins are generally **too large** to be absorbed by the **intestine**.
- They must, therefore, be **hydrolyzed** to their **constituent amino acids**, which can be absorbed

The source of proteolytic enzymes responsible for degrading dietary proteins:

1. The stomach (Gastric Secretions)
2. The pancreas (Pancreatic enzymes)
3. The small intestine (the last step)

First, you have to know that there are three **sources** of the secretions responsible for Protein digestion



Digestion of proteins <u>in general</u>:

1. In mouth: (only cutting of the food, no digestion) →
2. Stomach: (stomach enzymes: Pepsin and Renin, they are Endopeptidase)→ polypeptides
3. Intestine:
(pancreatic proteases in duodenum)→ oligopeptides and amino acids →(<u>aminopeptidase</u> in small intestine)→ di- & tripeptides and amino acids →absorption→(small intestine cell cytosol)→ amino acids → blood and portal Circulation

❖ **So what is the difference between an "endopeptidase" and an "exopeptidases"?**

We have 2 types of Proteases(peptidase): any enzyme that help in protein catabolism by hydrolysis of the peptide bonds

1. Endopeptidases: break peptide bonds WITHIN a polypeptide/Protein. (e.g. Elastase, Trypsin, Pepsin, and Chymotrypsin)

2. Exopeptidases: break peptide bonds which are located at the end of the polypeptide/Protein (e.g. Carboxypeptidase and Aminopeptidases)

- Aminopeptidases: degrade the building blokes to Amino Acids

To understand more:

For example, if there was a polypeptide made of a chain of 100 amino acids, an endopeptidase may break the peptide bond between amino acids number 30 and 31, giving us a 30 amino acid chain and a 70 amino acid chain, however, an exopeptidase may break the peptide bond between amino acid 1 and 2, or 99 and 100, giving us 1 amino acid and a 99 amino acid chain.

* So basically what you need to know is that endopeptidases give us 2 shorter polypeptides (or oligopeptides) while exopeptidases give us a single amino acid and a polypeptide. So exopeptidases release amino acids.

1- Digestion of Proteins by Gastric Secretion:

— The gastric juice contains 3 components important for protein digestion:

1. **Hydrochloric acid HCL** (in stomach plays a role in protein digestion + stimulates Trypsinogen into Pepsin)
2. **Pepsin**
3. **Rennin** (in neonates and infants)

Protein digestion by stomach→ Polypeptides

We already took this in the past lecture; this is just a quick revision.
You just need to keep in mind that stomach enzymes break down proteins into smaller polypeptides, then it enters the duodenum.

2- Digestion of Proteins by Pancreatic enzymes:

— The digestion in small intestine is hormonally controlled.

— Two small peptide hormones are released from cells of the upper part of small intestine:

A. Cholecystokinin (CCK):

1. Secretion of pancreatic enzymes
2. Bile secretion
3. Slow release of gastric contents

B. Secretin: (simulated by the Acidity of the chime; the digested form that came from the stomach)

Release of watery solution rich in bicarbonate by pancreas

Summary the gut hormones:

The gut hormone	Stimulus for secretion	Effects
1- Cholecystokinin (CCK)	The presence of partially digested proteins (& lipids) in the upper small intestine	1. Stimulates the release of pancreatic digestive enzymes 2. Stimulates the contraction of the gall bladder & release of bile 3. Decreases gastric motility → slower release of gastric contents into the small intestine
2- Secretin	Low pH of the chyme entering the intestine	Stimulates the pancreas to release a watery solution rich in bicarbonate to neutralize the pH of the intestinal contents (to reach the optimum pH for digestive activity by pancreatic enzymes)

Pancreatic enzymes for Digestion of Proteins

- The pancreatic secretion contains a group of pancreatic proteases

  Why there is a "group" of enzymes (proteases)?

- Because: Each of these enzymes has a different specificity for the cleavage sites
- These proteases are synthesized and secreted as inactive zymogens

  * Zymogen = inactive digestive enzyme

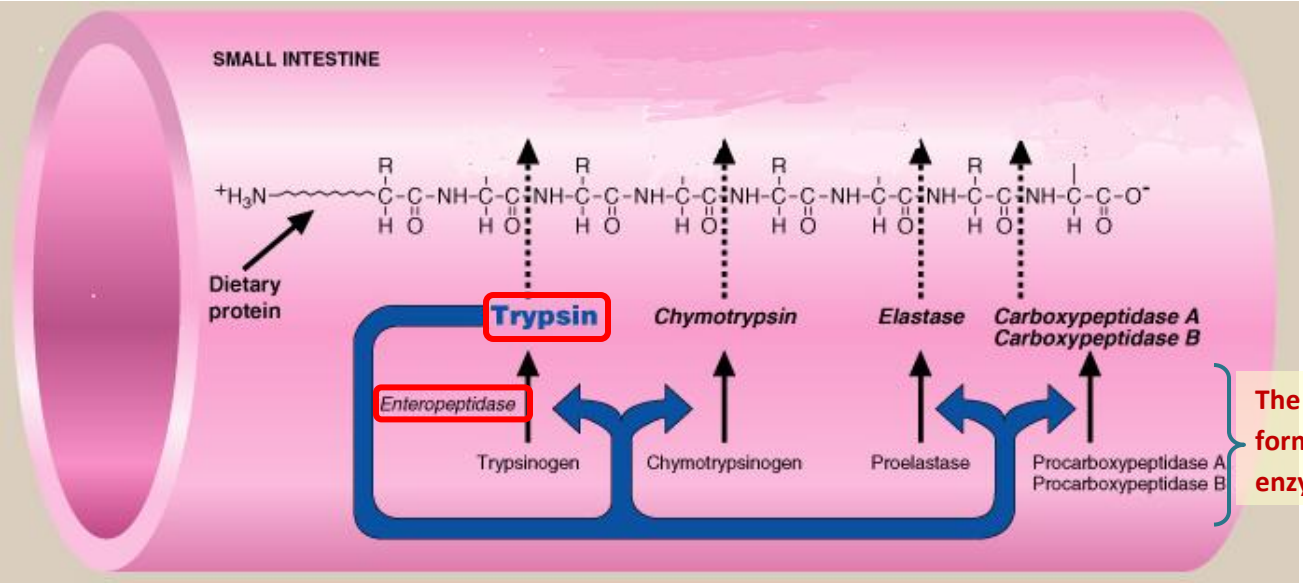
Explanation of specificity here (just to understand, not important):
We all know that polypeptides are made of amino acids which are connected by peptide bonds, and the peptide bonds are basically an amino group (NH2) from one amino acid connected to a carbonyl group (COOH) of another amino acid by dehydration (peptide bond = -CO-NH-). So when we say here that each of the pancreatic proteases has a different specificity, we mean that each of them break specific peptide bonds, depending on the amino acid associated with the peptide bond. For example, trypsin cleaves only when the carbonyl group of the peptide bond is associated with arginine or lysine (specific amino acids), and another protease may only cleave when the peptides bond is associated with an acidic amino acid, and so on.. [See the pink picture below]

Activation of Pancreatic enzymes:

- **Enteropeptidase** activates trypsin:
  It converts trypsinogen into trypsin
- Trypsin then activates all the other pancreatic zymogens (including itself)
- Enteropeptidase is an enzyme synthesized by, and present on the luminal surface of intestinal mucosal cells of the brush border membrane

* Enteropeptidase is very important because it starts the whole process

Activating enzyme	Active enzyme	zymogen
1- Enteropeptidase **2- other trypsin molecules (autocatalysis)**	Trypsin (endopeptidase)	Trypsinogen
Trypsin	Chymotrypsin (endopeptidase)	Chymotrypsinogen
Trypsin	Elastase (endopeptidase)	Proelastase
Trypsin	Carboxypeptidases (exdopeptidases)	ProCarboxypeptidases



They all need **Trypsin** to be activated (it is the key for activation of all the other enzymes)

At the end, why do we need all these enzymes to be activated?

Because each one of them has specificity for a bond to cleave (been explained before)

*** So until this point the outcome is:** oligopeptides and a few free amino acids.

The few free amino acids are because of the action of Carboxypeptidase (the exopeptidase).

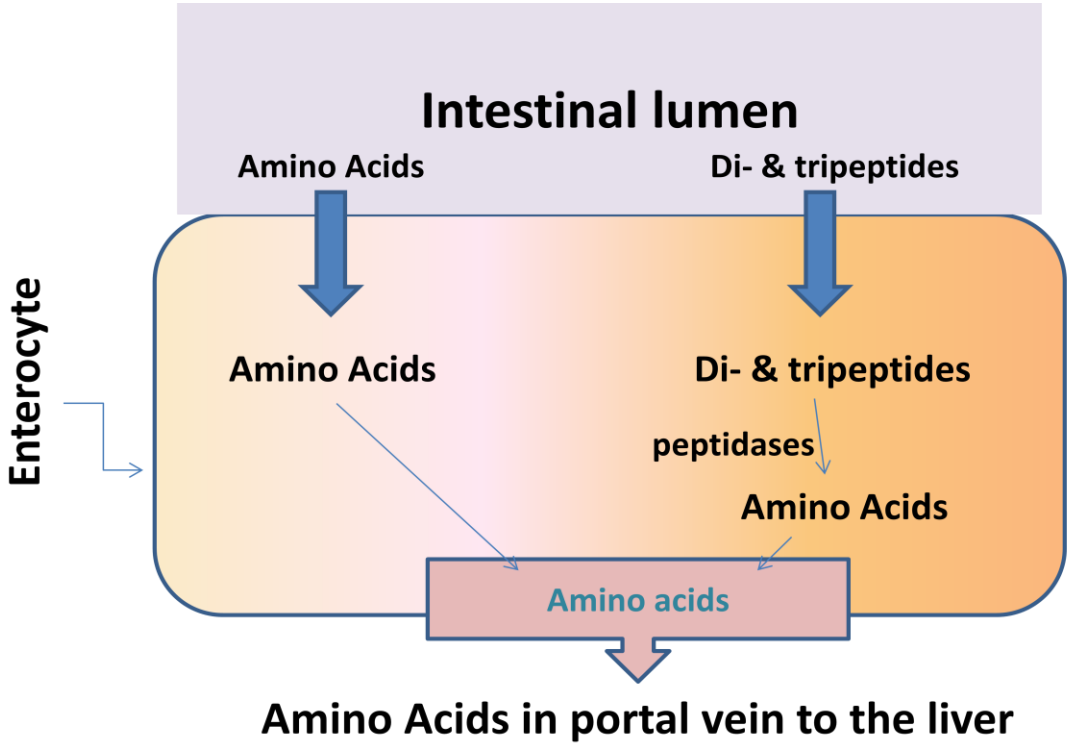
3- Digestion of proteins in small intestine:

— Oligopeptides that result from the action of pancreatic proteases are cleaved into free amino acids and smaller peptides (di- & tri-peptides) by

intestinal aminopeptidase

(an exopeptidase on the luminal surface of the intestine, as we said before)

Absorption of digested proteins:



Explanation:

As said before that from the action of pancreatic proteases we get oligopeptides and a few free amino acids. The few amino acids are directly absorbed into the enterocytes (small intestine cells) and passes directly to the portal vein heading to the liver, however, the oligopeptides need to be broken down into di- or tripeptides first so they can get taken up by the enterocytes. That's what the aminopeptidase does, it breaks down oligopeptides (on the intestinal cell surface) into smaller oligopeptides and free amino acids (because it's an exopeptidase) and it keeps breaking the oligopeptides until there's only di- and tripeptides and free amino acids. Now the di- and tripeptides can be taken up by the enterocyte into the cytosol, where it is finally broken down into single amino acids which can pass to the portal vein.

Thus only free amino acids are found in the portal vein after a meal containing protein.

❖ Abnormalities in protein digestion:

— Pancreatic insufficiency (decrease in Pancreatic digestive enzymes)

— e.g. in chronic pancreatitis, cystic fibrosis, surgical removal of the pancreas → incomplete digestion & absorption of fat & protein → abnormal appearance of lipids (steatorrhea) & undigested protein in the feces.

❖ Celiac Disease (Celiac sprue)

- It is a disease of malabsorption resulting from immune-mediated damage to the small intestine in response to ingestion of gluten.
- Gluten is a protein found in wheat, rye, and barley

Wheat: قمح
Rye: نوع من أنواع الحبوب
Barley: الشعير

* Gluten is a protein found in these plants,

The presence of Guten in these patients' intestine will stimulate the Immune system to react with the small intestine aggressively.

- As prevention, Celiac patients should avoid any food that contains Gluten.

Carbohydrates Digestion:

Carbohydrates digestion in general:

Ingested carbohydrates →(salivary and pancreatic alpha-amylase)→ oligosaccharides and disaccharides → (disaccharidases and alpha (1,6) glucosidases in small intestine)→ monosaccharides (The building blocks of carbohydrates) → absorbed → portal vein

- **Carbohydrates digestion is rapid:**

  Generally completed by the time the gastric contents reach the junction of the duodenum & jejunum.

- **Sites for digestion of dietary carbohydrates:**
  - The mouth
  - The intestinal lumen

Dietary carbohydrates:

Mainly:

- **Polysaccharides**:
  - Starch from plant origin
  - Glycogen from animal origin

  } Contain α (1→4) & α (1→6) bonds

  - Cellulose from plant origin → Contains β (1→4) bonds
- **Oligosaccharides**
- **Disaccharides:**
  - Sucrose
  - Lactose
  - Maltose
- **Monosaccharides:** Little amounts

* Beta (1→4) bonds cannot be cleaved by our digestive enzymes (they can only cleave alpha(1→4) and alpha(1→6)), that's why we cannot digest cellulose (when we eat it we excrete it as it is). So it's good for preventing constipation.

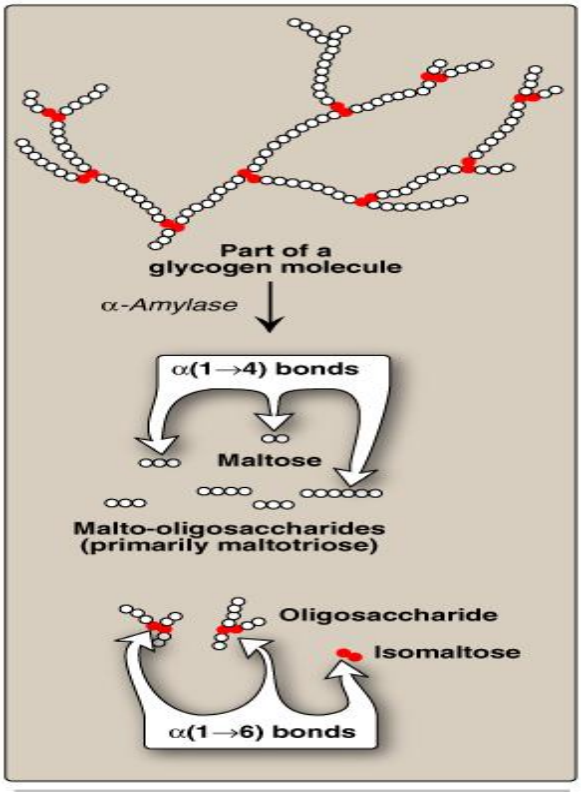
Enzymes for digestion of dietary carbohydrates:

- **α-amylase** (Both salivary & pancreatic):
  Substrate: **Polysaccharides**
- **Disaccharidases** (Intestinal):
  Substrate: **Disaccharides**
- **Isomaltase** & **α(1,6) glucosidase** (Intestinal):
  Substrate: **Branch points of oligo- and di-saccharides**

- α-amylase cleaves alpha(1,4) glycosidic bond
- Isomaltase cleaves isomaltose.
  - Isomaltose: 2 glucose units joined by alpha(1,6) glycosidic bond.
  - Maltose: 2 glucose units joined by alpha(1,4) glycosidic bond.)

Effect of α-Amylase on Glycogen:

- **Hydrolysis of:**
  α(1,4) glycosidic bonds
- **Products:**
  A. Mixture of short **oligosaccharides** (both branched & unbranched)
  B. **Disaccharides:** Maltose and isomaltose



(Mentioned already in past lectures.)
Applies to salivary and pancreatic alpha-amylase.
It's important to remember the outcome which is oligosaccharides and disaccharides.
(a "mixture" of short oligosaccharides because it's both branched and unbranched)
- Maltose (unbranched) isomaltose (branched)

- No dietary carbohydrate digestion occurs in the stomach (the high acidity of the stomach inactivates the salivary α–amylase).
- **Pancreatic α–amylase** continues the process of starch & glycogen digestion in the small intestine (They are not Monosaccharides yet)
  (Secreted by pancreas and worked in small intestine)

Serum level of α-Amylases (This is important for the practical class).

— Normal level in serum:

- 25 -125 U/L (U/L → unit per liter)

— The clinical significance of rising circulating levels of α-amylase activity:

- **Diagnosis of acute pancreatitis** (damage, necrosis, or rupture of pancreatic cells → release & activation of the intracellular enzymes into the blood)
  - Its level starts to rise within few hours
  - Reaches a peak within 12- 72 hours
  - Then returns to normal within few days

- In **normal conditions** pancreatic enzymes are released inside the intestinal lumen, but in pancreatitis, cells rupture and enzymes leak to the blood. (causes maldigestion and malabsorption because levels will be decreased in intestinal lumen)
- If a person has abdominal pain and his blood test shows rising levels of alpha-amylase or lipase, it's likely that he has acute pancreatitis
- These rising levels do not cause big problems nor that they function in the blood, we just use it for diagnostic purposes.
- Sometimes we might find low levels of alpha-amylase or lipase in the blood, that would be a cause of normal cell death (wear and tear) i.e. Because of ageing.
  (most important thing in this slide is to know that high levels of alpha-amylase or lipase in the blood indicate acute pancreatitis)

Final digestion of carbohydrates by intestinal enzymes in the small intestine

— **Enzymes:**
  - Secreted by & remain associated with the luminal side of the brush border membranes of the intestinal mucosal cells

— Location of their action:
  - the mucosal lining of the jejunum

— They include:
  - Disaccharidases
  - α(1,6) Glucosidase (for branched oligosaccharides)
    — Digestion is fast and ends in jejunum (does not reach ileum)

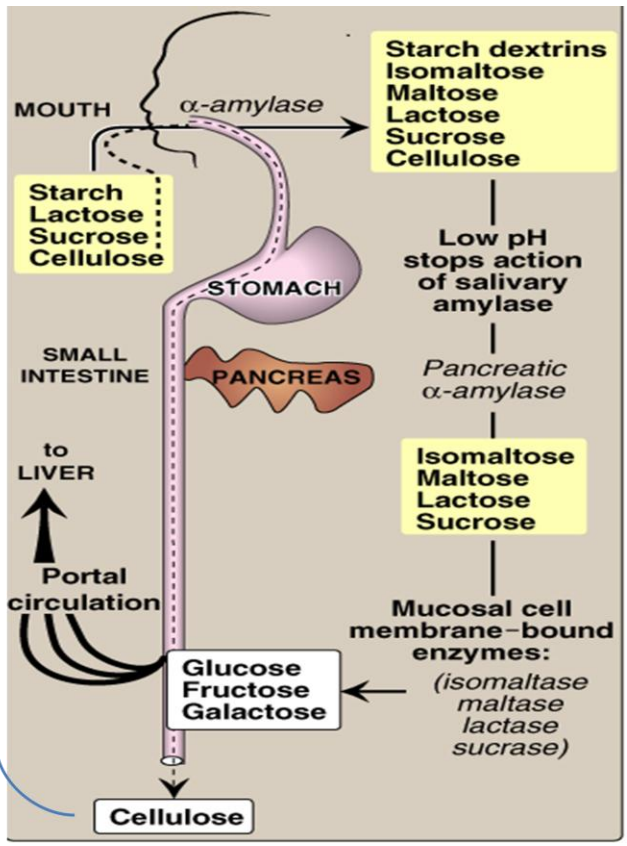
Intestinal disaccharidases

Enzyme	Substrate	Product
Isomaltase	isomaltose	2 Glucose
Maltase	maltose	2 Glucose
Sucrase	Sucrose	Glucose & fructose
Lactase (β-galactosidase)	lactose	Glucose & galactose

- Isomaltase (subtype of alpha (1,6) glucosidase) breaks alpha (1,6) bond

- Maltase breaks alpha (1,4) bond
  - Sucrase breaks alpha(1,2) bond between glucose and fructose
  - In general: disaccharides are cleaved by disaccharidases, and branches are cleaved by alpha(1,6) glucosidases.

Digestion of Carbohydrates:



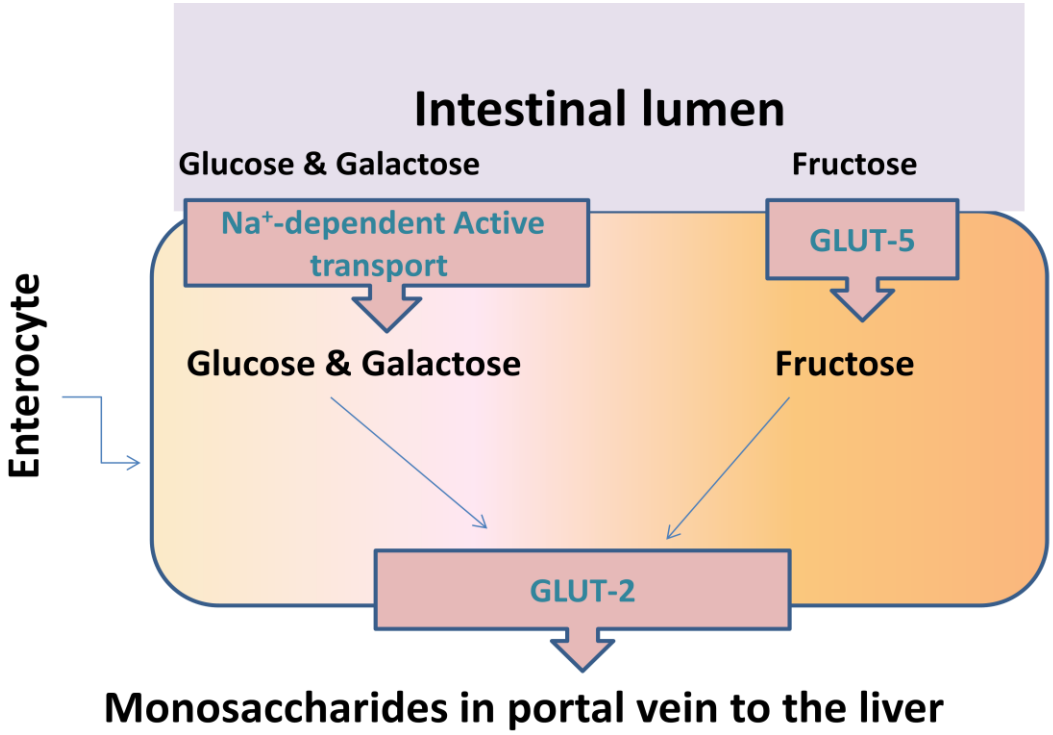
Dietary cellulose cannot be digested due to the absence of enzyme that can cleave β (1-4) bonds. It passes through the GIT largely intact. Despite that, it has several beneficial effects.

*** Yellow boxes are the final products..**

Absorption of Monosaccharides by Intestinal Mucosal Cells

- Location:
  - Duodenum & upper jejunum
- Insulin is **not** required for the uptake of glucose by intestinal cells
- Different Monosaccharides have different mechanisms of absorption

Absorption of digested carbohydrates



- **How are monosaccharides absorbed?**

  By glucose transporters (GLUT)

- There are 14 different members of GLUTs, depending on type of monosaccharide transported, tissue specificity and insulin sensitive (like GLUT-4 in skeletal muscle and adipose tissue) or resistant (insensitive)

- Monosaccharides are either transported by facilitated diffusion (GLUT, across concentration gradient) or active transport requiring energy (against concentration gradient)

- **GLUT-5 is specific for fructose**

- Na dependent active transport: Na passes outside the cell in exchange of **glucose and galactose** passing inside the cell (co-transport)

Abnormal digestion of disaccharides (e.g. of lactose):

Lactose intolerance (Lactase deficiency)

Lactase deficiency → Undigested carbohydrate (lactose) in large intestine → osmotic diarrhea. Bacterial fermentation of the undigested compounds in the large intestine → CO_2, H_2 **gases** → abdominal cramps, diarrhea & flatulence

- People with lactose intolerance should avoid milk and milk products
- In congenital lactose intolerance you'll see the baby crying after drinking milk (avoid dairy products)
- There are formulas available for people with lactose intolerance, e.g. Lactose-free milk.

Take home message Digestion of dietary proteins:

- **Proteolytic enzymes** responsible for digestion of dietary proteins are produced by the stomach, the pancreas & the small intestine.
- The **digestion of proteins in the stomach** is the result of the action of HCl, pepsin & rennin
- Pancreatic proteases are, like pepsin, synthesized and secreted as inactive zymogens
- The **intestinal digestion of proteins** occurs in the small intestine's lumen, on the luminal surface of the small intestine, and is completed intracellularly to produce free amino acids
- In **pancreatic insufficiency**, the digestion and absorption of fat & protein is incomplete → steatorrhea & appearance of undigested proteins in the feces
- **The story of proteases (peptidase) :**
    1. Elastase, Trypsin, Pepsin, and Chymotrypsin are endo
    2. Carboxy-peptidase is an exo
- **Salivary α-amylase** acts on dietary glycogen & starch in the mouth
- **Pancreatic α-amylase** continues the process of polysaccharide digestion in small intestine
- The **final digestive processes** of carbohydrates into monosaccharides occur at the mucosal lining of the small intestine by **disaccharidases & α(1,6) glucosidase**
- Dietary cellulose cannot be digested due to the absence of enzyme that can cleave β (1-4) bonds, so it passes through the GIT largely intact. Despite that, it has several beneficial effects.
- **Absorption** of the **monosaccharides** requires specific transporters **(GLUTs)**
- **Lactose intolerance** is due to deficiency of lactase enzyme and causes abdominal cramps, diarrhea & flatulence