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SUBJECT REVIEW PHASES OF SUGAR METABOLISM AND THE EFFECT OF HORMONES ON IT

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Abstract
Sugar metabolism is the biochemical processes that imply formation, breakdown, and conversion of sugar in human body. Several biological processes are involved during Sugar metabolism. This report discusses comprehensively both sugar metabolism phases and digestion pathways. The biological activities related to sugar metabolism in every relevant human body organs, chemical reactions, hormones and enzymes effects, transport routes and absorption mechanisms have been highlighted.

Keywords Sugar, metabolism phases, energy-consuming, digestion,

INTRODUCTION

Chemical composition of sugar

Glucose is on of a group of carbohydrates, simply known as sugar. It has a molecular formula $C_6H_{12}O_6$. It belongs to monosaccharide carbohydrates,[4] . Glucose is basicallysynthesised by plants during photosynthesis process[1][2][9]. When glucose enters the body, it moves through theblood circulatory systemto every cell in the body. Glucose is decomposedin the cellsduring biochemical reactions to release energy (ATP) to provide energy to all biological processes in the body. Furthermore, the glucose is the energy input of eukaryotes. The glucose is decomposed first during anaerobic process of glycolysis, leading to the production of some ATP, hence energy is provided, iether in anaerobic or aerobic conditions. [1][2][4][7].

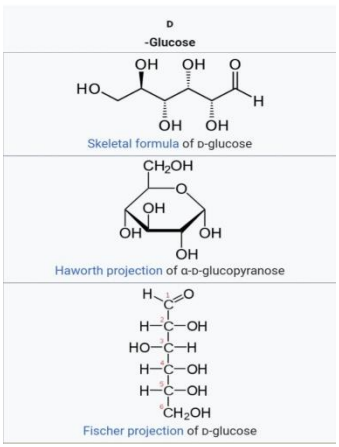


Figure1: chemical Format for glucose

Where are dietary carbohydrates: it is the largest source of energy and makes up about (50%) of the total energy of the body Balanced food containing carbohydrates is in the form of : lactose starch , sucrose , glucose starch consists of amylose and amylopectin , Amylose consists of glycosyl units that form a spiral linear chain linked by glycosidic bonds (1.4 _ α) with branches connected by glycosidic (α _ 1.4) as for amylopectin, the chains are polysaccharides composed of hundreds to millions of glycosyl units bonds (α_1.6) [8][9][11][15] .**lactose** : consists of glucose and galactose and the bonds between them is glycosidic (β_1.4) Sucrose : it is a binary sugar consisting of glucose and fructose between which there is a glycosidic bonds of type (1.2 _ α) [8][9][11][15] .
Carbohydrates are organic molecules that present abundantly in nature. They provide dietary calories for most organisms, act as a storage form of energy in the body, and serve a cell membrane components. Carbohydrates also supplystructural constituentof many other organism including insects, the cell walls of bacteria and the exoskeleton

Sugar metabolism phases

Digestion and absorption of sugars :

Mouth :

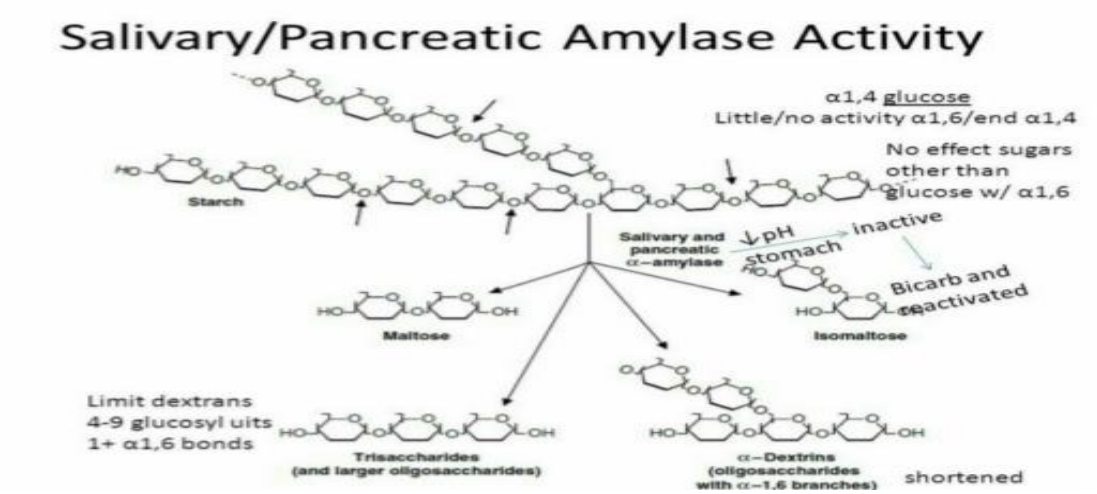
Saliva is secreted by the salivary glands the latter consists of 99.5 % water; ph =6.8 moderate medium so that carbohydrates undergo a partial glycolysis process by salivary alpha-amylase where it breaks glycosidic bonds (1.4 _α)
But the action of this enzyme is low, due to the short stay of food in the mouth
So a small amount of starch turns into Alpha-dextrins
The catalytic action of this enzyme is directly disrupted by ph = 4 immediately after it reaches the stomach, which explains the absence of any chemical digestion of sugars in the stomach (because it does not contain digestive enzymes for sugars) [9][7][11][3]

In the intestine:

The successive digestion of the previous sugary compounds begins where pancreatic amylase (alpha-amylase dehydrogenase)converts
Amorphous starch and dextrins are converted into maltoses by dissolving Alpha- bonds glycosidic bonds to obtain disaccharides.
For the bonds (. Alpha) are present at the removal points, the enzyme (α _ 1. 6) glycosidase cleaves them to obtain binary sugars
In turn, disaccharides are converted by disaccharide enzymes secreted from the pancreas and intestinal mucosa into sucrose-maltose-lactose to obtain monosaccharides, which is the final product of the digestion of sugars .[5][16][18][20]

Salivary and pancreatic alpha-amylase :

The digestion of starch starts in the mouth, where both chewing and mixing of food with saliva is perform, the salivary glands release into the mouth at a volume rate of about one liter per day, which has the enzyme alpha-amylase and other components .
Alpha-amylase is one of the enzymes that dissolve the internal glycosidic bonds
(α _ 1.4) within the starch molecule.[7][9][4][3]



The short chains of complex polysaccharides resulting from the action of salivary amylase are called alpha-dextrin

Salivary alpha-amylase is inhibited when it reaches the stomach due to the high acidity of Hcl secreted from gastric parietal cells .

After that, the acidic gastric juice enters the duodenum (which is the upper part of the small intestine) , where digestion continues

Secretions from the pancreas with external secretion continue and are secreted per day about 1.5 liters and enter the duodenum as well, and these secretions include:

Bicarbonate HCo3:

modifies the acidic pH of the contents of gastric juice

The enzyme pancreatic alpha-amylase: which continues to dissolve starch and glycogen, forming maltose, triple sugars (maltotriose) and oligosaccharides called limited dextrins .

Dextrins usually contain limited from to glycosidic alcohols and contain or more branches(1.6 _ α) The two sugars of the glycoside whose bond(will turn into the sugar diisomaltose (1.6 _ α

Alpha-amylase cannot hydrolyze oligosaccharides branched laterally to isomaltose.

Alpha-amylase does not show an active bond direction (α _1.6) at the binding points .

It also has a weak activity in the direction of the bond (1.4 _ α) at the end of the series

Binary enzymes located in the membrane of the intestinal villi :

Both lactose as well as sucrose are present in the diet, together with the products of starch digestion are converted into simple monosaccharides by glycosidase enzymes associated with the membranes of intestinal cells in the intestinal villi .

Note :

Maltase Cannibalize of maltose to glucose + glucose

The final result of digestion of starch is free glucose ; more than 90% of the final Digestion products of sugars are glucose

Absorption :

Monosaccharides are absorbed only as glucose, which makes up 90 % of the absorbed sugars, is absorbed in the small intestine

The mechanisms of absorption are numerous, the most important of which occur in the intestinal villi .

Absorption is carried out depending on sodium-based qualitative vectors

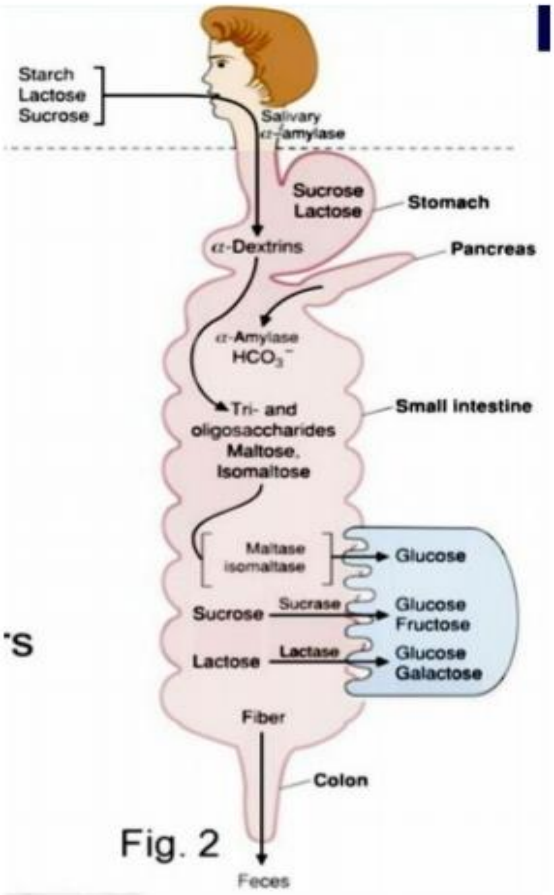


Fig. 2

Sodium-dependent transporters are present in the intestine and are responsible for the transport of glucose and galactose and are not responsible for the transport of fructose

Sodium-dependent glucose transporters are located in the lumen side of the adsorbed cells. So that the carrier receives both glucose and sodium (another sugar), as is known, the concentration of sodium electrolytes outside the cells is high and therefore glucose must be brought with it to the inside of the cell .

Thus, in order for the process to continue and maintain the concentration difference, it is regulated through the sodium-potassium pump that the ATP pumps sodium out of the cell into the blood and thus transfers glucose from the low-Lumen concentration to the high concentration in the cell .

Which enhances the tendency of sodium concentration from a high concentration in the lumen to a lower concentration in the cell (secondary active transport), the intestinal villi cell is at rest and when eating a meal rich in sugar, this sugar is broken down by the intestine into its simple components (glucose and fructose), and then its concentration rises inside the intestinal lumen.

Sodium in the normal state, its concentration outside the cell is high and inside the cell is low when sugar is absorbed, sodium enters with simple sugar from a high concentration to a lower concentration without spending any energy.

But when absorption increases, the concentration of glucose inside the vellus cell becomes high compared to the lumen, so it needs energy to enter from a low concentration in the lumen to a high concentration inside the villi

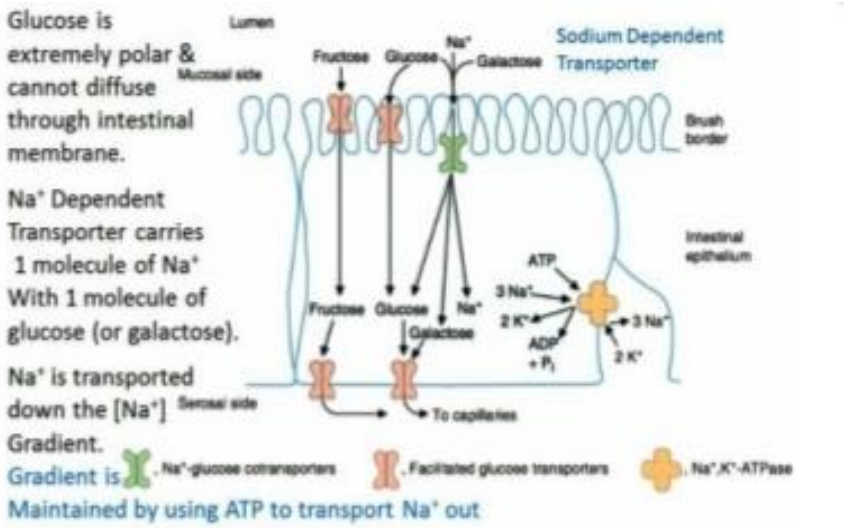
Here the energy comes from the electrochemical

gradient of sodium (sodium in the Lumen is high) and intracellular is low as it depends on the charge difference and the difference of the concentration gradient of sodium on both sides of the membrane [44][2][35]

The mechanism is called: secondary active transfer where:

Active: because it's the opposite of boring focus

Secondary: because he does not need energy from the atp, but took it from the electrochemical gradient teams [13][17][22] .



Facilitated glucose transporters.

Do not rely on sodium located in the serous side of the cells

Glucose has the ability to move from a high intracellular concentration to a lower concentration in the blood without having any Energy Exchange

These transporters work in parallel with sodium-dependent transporters for glucose transport and are the direction quality of cells

It turns out that there are 5 types of glucose-facilitating transporters, and they share the same structure with each other by being proteins consisting of a transmembrane membrane 12 Helix .

The sodium-based carrier does not belong to the previous group .

During fasting, these vectors are localized in vesicles in the cytosol .

When insulin is stimulated, the vesicles move to the surface and activate glucose transporters .[13][14][7][45]

Facilitated transporters, during fasting, are dormant in the cytosol of cells and are grouped in the form of vesicles

The facilitated transporters of the cytosol return after the blood glucose returns to its normal level .

The only glucose transporter that needs sodium is only the one that is in the intestine [9][4][8]

The most important types of glucose transporters and their properties.

SGLT: It can basically be located in the renal tubules and intestinal epithelia. They are essentialfor glucose reabsorption and absorption. Secondary active transport governs this transporter function wher ATP is required to pump sodium out of the cell and into the lumen,

which enablescotransport of glucose.

GLUT1: It can basically be located in the pancreatic beta-cells, red blood cells, and hepatocytes. It is essential factor for glucose detectingby the pancreas, and has an important propertyin controlling blood glucose with endogenous insulin.

GLUT2: It can basically be located in hepatocytes, pancreatic beta-cells, intestinal epithelium, and renal tubular cells. This bi-directional transporter is essentialfor controlling glucose metabolism in the liver.

GLUT3: It can basically be located in the CNS. This transporter has a very high attractionto glucose, in line with the brain's metabolic demands.

GLUT4: It can basically be located in skeletal muscle, cardiac muscle, adipose tissue, and brain tissue. This transporter is accumulatedin cytoplasmic vesicles (inactive), which will mergewith the cell membrane when induced by insulin..[3][4]

Table 12.1 The GLUT gene family

Isoform designation*	Class*	HUGO gene nomenclature	Major tissue distribution	Characteristics
GLUT1	I	SLC2A1	Brain microvessels, erythrocytes, placenta, kidney	Ubiquitous, functions as basal transporter, predominates in cultured cell systems
GLUT2	I	SLC2A2	Liver, kidney, β cell, small intestine	High K_m transporter
GLUT3	I	SLC2A3	Brain, placenta, fetal muscle	Low K_m transporter, found in tissues metabolically dependent on glucose
GLUT4	I	SLC2A4	Skeletal muscle, adipocytes, heart	Sequestered intracellularly and translocates to cell surface in response to insulin
GLUT5	II	SLC2A5	Testes, small intestine	High affinity for fructose
GLUT6	III	SLC2A6	Spleen, leukocytes, brain	Transports glucose
GLUT7	II	SLC2A7	Unknown	
GLUT8	III	SLC2A8	Testes, blastocyst, brain	Transports glucose, mediates insulin-stimulated glucose transport in blastocyst
GLUT9	II	SLC2A9	Liver, kidney	
GLUT10	III	SLC2A10	Liver, pancreas	
GLUT11	II	SLC2A11	Heart, muscle	Fructose-inhibitable glucose transport
GLUT12	III	SLC2A12	Heart, prostate	
GLUT13	III	SLC2A13	Brain	Myoinositol transporter, also referred to as HMIT
GLUT 14		SLC2A14	Testes	Alternatively spliced long form and short form which is a duplicon of GLUT3

*Isoform designation and class conforms to nomenclature proposed by Joost HG et al.: *American Journal of Physiology* 2002;**282**:E974–E976.
Note: Four untranslated pseudogenes have been reported including a pseudogene previously designated as GLUT6.

Glucose in the cell with an aldehyde group > uncharged cardiomyocytes > can return to the plasma .

So when it enters it is activated by phosphorylation to prevent its exit into the

plasma

Sugars activate enzyme kinases: the second row of kinases that transfer the phosphate group from ATP to another compound .

There are two types of kinases :

It activates all sugars, both aldehyde and ketone, at Site 6 called hexokinase .

Specific to the liver and other organs called fructo / galacto / mano kinase is active . except glucokinase is active in situ

Upon phosphorylation, we give the molecule a negative charge, i.e., the energy stored in the ester bond, to convert it into an ester .

After the activation of sugars by phosphorylation, one of the following metabolic pathways enters :

The pentose phosphate pathway .

The way to synthesize glucogen .

The way of synthesis of glucuronic acid

The way of glycolysis

* Glucose is introduced into adipose tissue and muscles directly by the action of insulin.

* Both glucose and galactose are absorbed from one of the main methods, which are methods based on sodium electrolytes

* A vector that directly affects insulin is GLUT4, which is found in adipocytes and skeletal muscle cells .

* Note: *

The number and location of these vectors varies with the concentration of glucose, as they increase with increasing glucose concentration.

The goal of the vectors is to irreversibly introduce glucose into the cells in order to return the glucose in the blood to its normal level .

All sugars are activated by phosphorylation and the source of phosphate is ATP, where its triple form ATP is converted into the binary form ADP and the enzymes contributing to this belong to the second class of enzymes (kinases)

Ways of glycolysis

Glycolysis takes place in the cytosol and may possibly occur in the mitochondria, if acetyl coenzyme A enters it in the case of aerobic decomposition only, which is a quick process to save energy, despite the low yield, and some of its averages can be used as a starting point for artificial pathways in good nutrition conditions; it includes many steps or reactions that take place sequentially until it reaches the end of the pathway .

Note

: the process of glycolysis consists sequential and ordered enzymatic reactions with so-called enzymatic sentences starting with glucose and ending with two molecules of pyruvate .Ways of glycolysis Aerobic glycolysis: it occurs in the container cells potentials ; where pyruvate is converted to acetyl coenzyme A which enters the Krebs ring.

Anaerobic glycolysis

Pyruvate is converted to lactate which is used as a substrate for another route .

They are used by aerobic and anaerobic tissues and organs such as erythrocytes, muscles and for most cytosolic reactions.

The way of glycolysis begins aerobic, but when there is a lack of oxygen it turns into anaerobic.

Three chemical reactions occur in the process of glycolysis

. the path of carbon atoms : 1

The carbon structure of glucose is realized to give pyruvate.

the path of the phosphate clique :2

LATP is formed from the ADP during the formation of high-energy compounds .

3 _ transfer of hydrogen atoms and electrons :

Production of reference equivalents .

The respective organ systems

Glucose is of vital importance in all the roles played by organs, for example :

Liver

The liver is an important organ that controls levelsof blood glucose. Glycogen, is a polysaccharide of glucose, is the stored form of glucose,which is basically accumulated in both the liver and skeletal muscles. Both glucose and triglycerides paly important role in storing energy;the first is being for short term while the other presentsa long-term storage capacity in adipose tissue. Release of glucose (the so called glycolysis) from glycogen is a biological effect that causes rise to glucose levels in blood. It is basically occurred both when glucagon activates liver glycogen and during fasting state. Insulin Insulin regulates glucose levels and determines whether to consume it (as energy source) or store it as glycogen to insure stability of blood sugar levels.

Pancreas

The pancreas plays an essential rolein releasing hormones that controls levels of blood glucose. Releasing of insulin occurs when glucose level increases withinthe beta cells,, hence blood glucose amountis reduced under well-known biological processes, which will be discussed later. On the other hand, alpha cells release glucagon under low glucose or low insulin conditions , , which helps raising the blood glucose level considering well-known biological processeslikesomatostatin that is released by delta cells in pancreasto reduce levels of blood glucose.[5][6][7][23][30].

Adrenal gland

The adrenal gland is made of two main parts; the cortex; the outer part and medulla; inner part, and it produces hormones that controls many biological functionsincluding glucose homeostasis. The adrenal cortex releases glucocorticoids that are responsible for increasing levels of blood glucose considering well-known biological processes.Cortisol is the most important glucocorticoid, for being the mosteffectiveand abundant. On the other hand, the adrenal medullaresponses to low levels of blood glucose and releases epinephrine to increase blood glucose levels considering well-known biological processes.[8]

The thyroid gland

The thyroid gland produces and releases hormones that controls many biological functionssuch as thyroxine, a thyroid hormone,, including raising blood glucose levels considering well known biological processes.[9]

Anterior pituitary gland

The anterior pituitary gland controls releasing both adrenocorticotropic and growth hormones, which increase levels of blood glucose.[10]

Hormones

Many hormones are involved with glucose homeostasis. The biological processes that govern their reactions are crucial. It is an important issue to understand each hormone influence on glucose levels. for example,both insulin and somatostatin decrease glucose level While the others increase it .

Insulin: is an essential hormone and helps controlling blood glucose level through increased extractionof both GLUT4 and glycogen synthase, deactivationof phosphorylase kinase, and reducingthe release of rate-limiting enzymes involved in gluconeogenesis.[33][45][27][26]

Glucagon: raisesblood glucose viaincreased both glycogenolysis and gluconeogenesis.

Somatostatin: reduces blood glucose levels bycontrolling release of both glucagon and gastrin and pituitary tropic hormones. This hormone also reduces insulin release; yet, a reductionin blood glucose levels is included.[14][21][22]

Cortisol: raisesblood glucose levels by promotinggluconeogenesis and by antagonism of insulin.

Epinephrine: raisesblood glucose levels by glycogenolysis (breakdown of glycogen to glucose) and enhanced fatty acid release from adipose tissues.

Thyroxine: rises blood glucose levels by glycogenolysis and enhanced absorption in the intestine.

Growth hormone: enhances gluconeogenesis, preventsliver uptake of glucose, motivatesthyroid hormone, constrainsinsulin. [34][38][25]

ACTH: motivatescortisol release from adrenal glands, acceleratesthe release of fatty acids from adipose tissue, which can then feed into gluconeogenesis.[34][38][25]

Clinical Significance

The symptoms associated with glucose in blood happensfrequentlywhen blood glucose levels are altered about normal range. Next sections present a brief discription of some of the more common medicalstates regardingabnormal levels of glucose and the related pathophysiology.

Hyperglycemia:

Hyperglycemia is associated with elevated blood glucose levels and can be serious if not well treated. Diabetes mellitus refer to group of complaints that influence sugar intake in the body. They are classified as I and II, where type I is associated with genetic, environmental, and immunological factors. Theinsulin cannot be made at all in the pancreas since producing cells have been attacked and destroyed by the patient's immune system. On the other hand, type II is associated with comorbid conditions as well as genetic factors. In this type of diabetes, insulin is not made enough and body becomes resistant to insulin. In both cases, improperlyhigh blood glucose is prompted, which causes pathology by a variety of mechanisms including osmotic damage, oxidative stress and non-enzymatic glycation[11][1][37][23]

The elevated glucose level causes adverse biological effects in circulatory systemwhere both microvascular and macrovascular complaints are reported. These basically include peripheral neuropathies, poor wound healing/chronic wounds, retinopathy, coronary artery disease, cerebral vascular disease, and chronic kidney disease..[12][13][44]

Additionally, high blood glucose levels can cause acute pathology, especially with type II diabetes. This conditionwas noticed when severehigh blood glucose level is found in elevated plasma osmolality, whichinitiatesboth osmotic diuresis and dehydration. Other symptoms including altered mental status, motor abnormalities, focal & global CNS dysfunction, nausea, vomiting, abdominal pain, and orthostatic hypotension have been reported.[14][50]

Hypoglycemia:

Hypoglycemia is a body state associated with decreased blood glucose levels, and normally associated with administration of glucose-lowering drugs by diabetic patients. It also occurs during inpatient care, as a consequence of changing usual diet of the patient. The reported symptoms are classified as either neuroglycopenic or neurogenic. The latter can be further categorizedinto either cholinergic or adrenergic. Some common symptoms of hypoglycemia are listed:

Neuroglycopenic: confusion, weakness or fatigue, coma, seizure and deathNeurogenic - Adrenergic: anxiety, tremor, and palpitations.

Neurogenic - Cholinergic: paresthesias, diaphoresis, and feeling of hunger.[15][45][48][49]

After previous overview regarding glucose, one can realize glucose metabolism considering a case when a carbohydrate-dense meal is consumed. Initially, glucose components will be decomposedfirst in saliva and later in intestines, hence free glucose is released. Absorption of glucose is occurred atintestinal epithelium (through Sodium-glucose transporters SGLT across the apical membrane). Later, the glucose and then arrivesbloodstream (through Glucose Transporter GLUT on the basolateralbarrier). Shortly,the level of blood glucose will build up in the bloodstream; the so called blood sugar spike.This will cause accumulative glucose amount in the pancreas and then stimulate releasing of the insulin. This initiates several processes, involvingextractionof enzymes in the liverlike glycogen synthase. The glucose will be released into hepatocytes cells in liver and will be incorporated to glycogen chains. Additionally, insulin will motivatereleasing of GLUT4toenhance basal glucose uptake into both muscle and adipose (body fat) tissue. When amount of blood glucose begins to decrease), insulin levels will drop as well consequentlyto the normal quantity. When insulin reaches lower levels, alpha-cells in the pancreas will release glucagon to properly increase blood glucose levels to last until the next meal. Finally, if fasting conditions are applied, the adrenomedullary system will release both cortisol together with epinephrine, to help establishing normal concentration of glucose in the blood (the so called euglycemia).[16][5][17][18][34]

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