Endocrine system 9

physiology

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Please read the information below photos, because the doctor read it and it will be meaningless to write it again in another paragraph.

Enjoy 😊

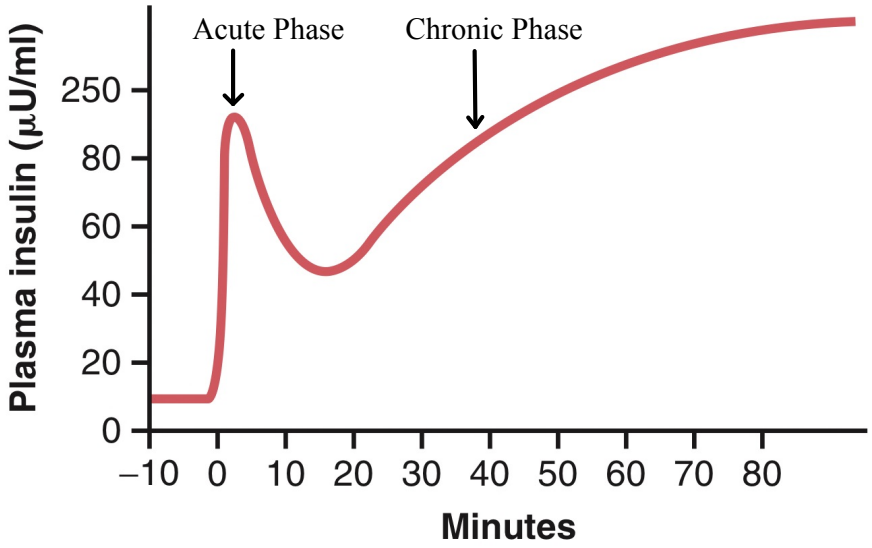


Figure 79-8. An increase in plasma insulin concentration after a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.

Why insulin is secreted in this way?

Sensing a rapid rise in plasma glucose concentration, the beta cells first secrete their stores of presynthesized insulin. Following this acute phase, the cellls begin to secrete newly synthesized insulin in the chronic phase, which lasts as long as the glucose challenge.

In vitro studies of isolated islet cells and the perfused pancreas have identified a third phase of insulin secretion, commencing 1.5 to 3.0 hours after exposure to glucose and characterized by a spontaneous decline in secretion to 15% to 25% of the amount released during peak secretion: a level maintained for more than 48 hours.

Principal Actions of insulin:

Insulin affect adipose tissue, muscle cells, and the liver on all food elements (carbohydrates, lipids and proteins).

TABLE 24–2 Effects of insulin on various tissues.

Adipose tissue
Increased glucose entry
Increased fatty acid synthesis
Increased glycerol phosphate synthesis
Increased triglyceride deposition
Activation of lipoprotein lipase
Inhibition of hormone-sensitive lipase
Increased K^+ uptake
Muscle
Increased glucose entry
Increased glycogen synthesis
Increased amino acid uptake
Increased protein synthesis in ribosomes
Decreased protein catabolism
Decreased release of gluconeogenic amino acids
Increased ketone uptake
Increased K^+ uptake
Liver
Decreased ketogenesis
Increased protein synthesis
Increased lipid synthesis
Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis
General
Increased cell growth

Effect of insulin on glucose uptake in tissues in which it has been investigated:

Insulin is needed by almost all cells in the body to facilitate glucose uptake →

Tissues in which Insulin facilitates glucose uptake
Skeletal muscle
Cardiac muscle
Smooth muscle
Adipose tissue
Leukocytes.
Crystalline lens of the eye
Pituitary
Fibroblasts
Mammary gland
Aorta
A cells of pancreatic islets

But there are some cells which don't need insulin to facilitate glucose uptake → (which are vital organs)

Tissues in which insulin does not facilitate glucose uptake
Brain (except probably part of hypothalamus)
Kidney tubules
Intestinal mucosa
Red blood cells

Glucose Homeostasis:

The normal glucose concentration in the blood ranges between 70 mg/dL – 110 mg/dL. The doctor mentioned that the normal glucose concentration is actually 80 mg/ dL – 100 mg/dL , but we widen the range to take into account the variability among individuals and so we consider it to be (70- 110).

There is an important concept related to glucose called **the renal threshold**. Basically, under normal conditions, when the glucose level is 70 mg/dL for example, glucose is not supposed to

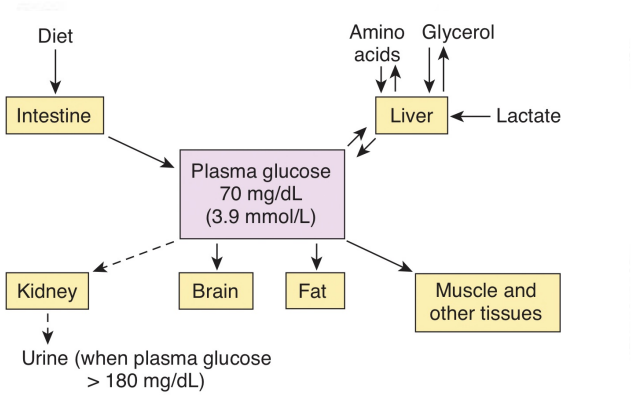


FIGURE 1–25 **Plasma glucose homeostasis.** Notice the glucostatic function of the liver, as well as the loss of glucose in the urine when the renal threshold is exceeded (dashed arrows).

*You should know from this figure the sources and destiny of blood glucose.

Sources: Diet & Liver.

Destiny: Brain, fat cells, liver, and muscles and other tissues. (notice that normally it shouldn't go to the kidneys)

*Memorize the percentages please 😊

The doctor mentioned in 2022 lecture that the normal glucose concentration is actually 90 mg/ dL – 100 mg/dL. 🙂🙂

appear in urine. However, when the concentration is excessively high (above 180 mg/dL), glucose will start to appear in urine and this is what we call the renal threshold. This is known as **glycosuria**. This is why if we suspect that a person has diabetes (excessively high blood sugar) a urine test can assist us in determining that.

The gluconeostatic function of the liver:

During fasting, liver glycogen is broken down and the liver adds glucose to the blood. With more prolonged fasting, glycogen is depleted and there's increased gluconeogenesis from amino acids and glycerol in the liver.

Insulin deficiency:

Actually the human needs very little insulin so as the metabolism level occur normal, but when it's deficient these changes happen:

1. Hyperglycemia.
2. Glucosurea.
3. Within certain limits of blood glucose in human being, brain glucose is'nt affected.
4. fat synthesis and the use up of glucose by muscles and other tissues will become blocked.
5. more liver glycogen will be broken down to supply us with glucose (Liver gives glucose more than what it takes).

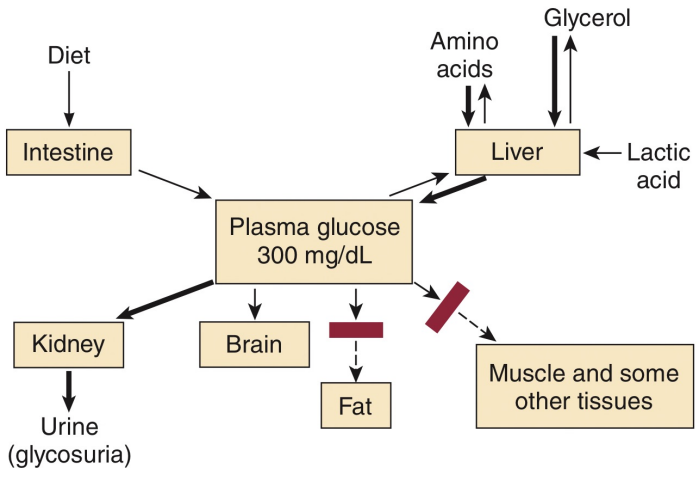


FIGURE 24–8 Disordered plasma glucose homeostasis in insulin deficiency. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reactions that are blocked.

Consequences of Insulin Deficiency:

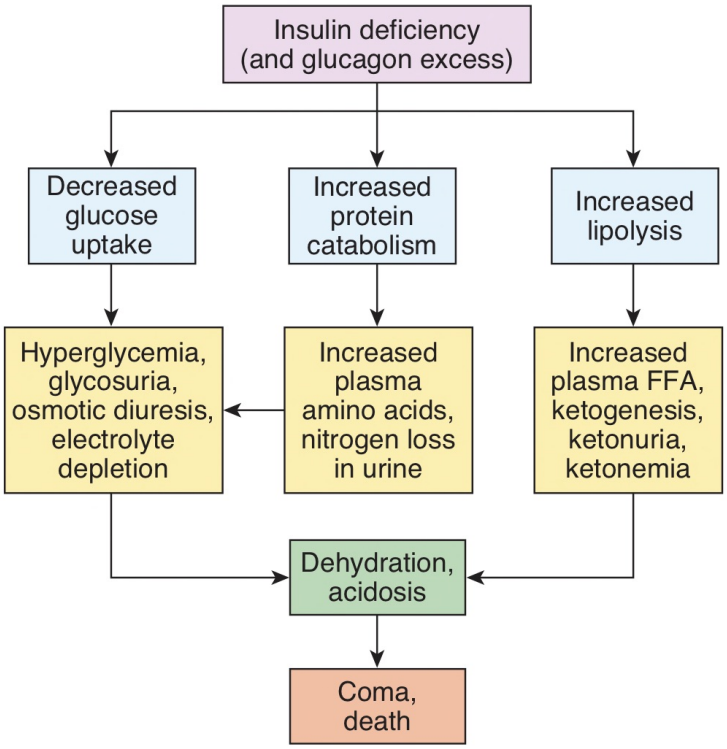


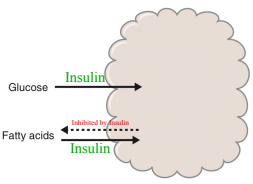
FIGURE 21–9 **Effects of insulin deficiency.** (Courtesy of RJ Havel.)

1. Effect on lipolysis of storage fat and release of free fatty acids:

In the absence os insulin, all the effects of insulin noted above causing storage of fat are reversed. The most important effect is that the enzyme hormone-sensetive lipase in the fat cells becomes strongly activated. This causes hydrolysis of the stored triglycerides, releasing large quantities of fatty acids and glycerol into the circulating blood. Consequently, the plasma concentration of free fatty acids begins to rise within minutes. This free fatty acid then becomes the main energy substrate used by essentially all tissues of the body besides the brain.

-When the body depends almost entirely on fat for energy, the level of the keto acids, aceto acetic acid, and β-hydroxybutyric acid in the body fluids may rise from 1mEq/L to as high as 10 mEq/L. All of this extra acid, obviously, is likely to result in acidosis.

(β-hydroxybutyric acid and acetone along with the acetoacitic acid are called ketone bodies).



-Ketoacids can be excreted in the urine, very little of them in the acidic form, but instead is excreted combined with Na+ from ECF. Part of the Na+ is replaced by H+ ions, thus adding greatly to the acidosis

2. Protein depletion and increased plasma amino acids:

Virtually all protein storage comes to a complete halt (terminate) when insulin is not available. The catabolism of proteins increases, protein synthesis stops, and large quantities of amino acids are dumped into the plasma.

The plasma amino acid concentration rises considerably, and most of the excess amino acids are either used directly for energy or as substrates for gluconeogenesis.

This degradation of the amino acids also leads to enhanced urea excretion in the urine. The resulting protein wasting is one of the most serious of all of the effects of severe diabetes mellitus. It can lead to extreme weakness as well as to many deranged functions of the organs.

3. Diabetes mellitus:

Diabetes mellitus is a systemic disease in which the body doesn't produce and/or use insulin and is characterized most notably by **hyperglycemia**. In addition to abnormal glucose metabolism, disorders in the metabolism of lipid and protein intensity the seriousness of the disease.

Superimposed on the disorders of carbohydrate, fat, and protein metabolism are diabetic- specific microvascular lesions in the retina, renal glomerulus, and peripheral nerve.

The cause of diabetes continues to be a mystery, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles.

-There are 23.6 million children and adults in the US, or 7.8% of the population, who have diabetes. Although an estimated 17.9 million have been diagnosed with

diabetes, unfortunately 5.7 million people (or nearly ¼) are unaware that they have the disease. Diabetes has several clinical forms, each of which has a distinct etiology, clinical presentation, and course.

Diagnosis:

Diagnosing diabetes mellitus isn't difficult to do. Symptoms usually include frequent urination, increased thirst, increased food consumption, and weight loss.

We'll talk about diabetes in more details in the next page after finishing the last consequence of insulin deficiency.

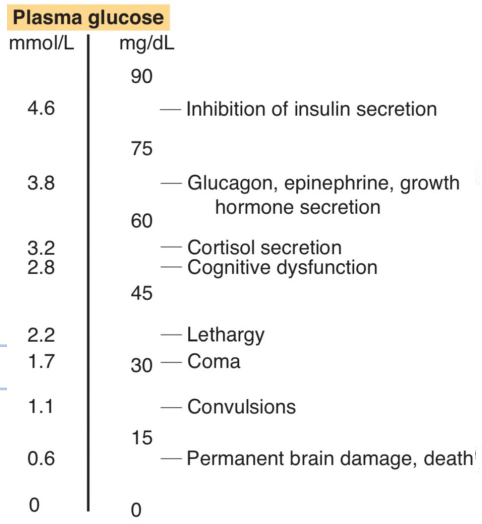
4. Coma:

Coma in diabetes can be due to **acidosis and dehydration**. However, the plasma glucose can be elevated to such a degree that independent of plasma pH, **the hyperosmolarity of the plasma** causes unconsciousness (hyperosmolar coma). **Accumulation of lactate in the blood** (lactic acidosis) may also complicate diabetic ketoacidosis if the tissues become hypoxic, and **lactic acidosis** may itself cause coma.

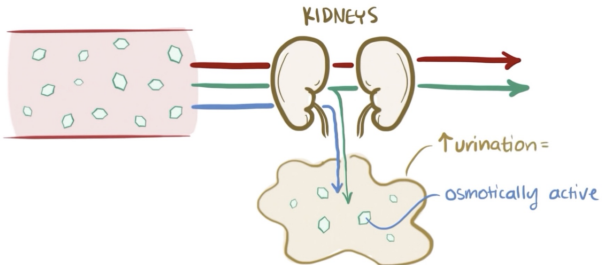
Brain edema occurs in about 1% of children with ketoacidosis, and it can cause coma. Its cause is unsettled, but it's a serious complication, with a mortality rate of about 25%.

This means that diabetic coma can occur by one of these ways:

1. Acidosis and dehydration which will affect plasma pH.
2. The hyperosmolarity of the plasma because of the high level of glucose molecules in plasma.
3. Accumulation of lactate in the blood (lactic acidosis) which can cause coma by itself or by the diabetic ketoacidosis it can cause.



(Both severe hyperglycemia and hypoglycemia can causes coma, so when glucose level become 40 mg/dl or below, coma may occur due to hypoglycemia).



Now we will talk more about diabetes…

Obesity and insulin resistance:

Obesity is closely linked to insulin resistance. The marked increase in the prevalence of obesity has played an important role in the prevalence of diabetes. According to data from the National Health and Nutrition Examination Survey, 2/3 of the adult men and women in the US with a diagnosis of type 2 diabetes had a body mass index (BMI) of 27 kg/m2 or greater.

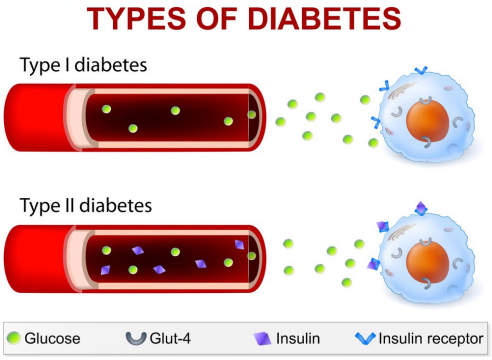
Diabetes:

There are two types of diabetes:

Type 1 (juvenile diabetes or insulin-dependent diabetes IDDM)

Type 2 (non insulin-dependent diabetes or insulin resistant or maturity onset diabetes).

Here's a comparision between the two types:



Feature	Type 1	Type 2
Age at onset	Usually <20 yr	Usually >40 yr
Body mass	Low (wasted) to normal	Visceral obesity
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

(The doctor didn't mention this but I think it's usefull: Usually type 1 is very easy to treat since it occurs due to absence of insulin, so supplying the patient with insulin would solve the whole problem. However, in the case of type 2, it occurs because of desensitization of the insulin receptors on target tissues towards insulin and so no matter how much you supply this patient with insulin; it would be of no use. Accordingly, the treatment is much more complicated.)

Type 2 diabetes treatment:

Early on, or in mild cases, diet, weight loss, and exercise can be extremely effective in diabetes therapy and may be the only treatment necessary.

Commonly however, lifestyle intervention is supplemented by treatment with one or more oral agents. Multiple classes of drugs independently address different

pathophysiologic featured that contribute to the development of type 2 diabetes. The available oral antidiabetic agents can be divided by mechanism of action into:

1. Insulin sensitizers with primary action in the liver (e.g. biguanides).
   Insulin sensitizers: Facilitate the action of insulin in the liver.
2. Insulin sensitizers with primary action in peripheral tissues (e.g. glitazones).
3. Insulin secretagogues which stimulate beta cells to secrete more insulin (e.g. sulfonylureas).
4. Agents that slow the absorption of carbohydrates (e.g. alpha- glucosidase inhibitors).

(These drugs are also used if diet, weight loss, or exercise didn't work)

In some cases, persons with type 2 diabetes may be treated with insulin, just like the patient with type 1 diabetes. Although insulin therapy apparently provides some benefit to type 2 diabetics, this approach is limited in controlling elevated glucose levels or in controlling obesity that predisposes to this disease.

Diabetes, if untrained, leads to renal failure, erectile dysfunction, blindness, coronary arterial disease, and increased risk of cancer. Of these, cardiovascular disease (CVD) is yhe most prominent. For example, more than 65% of people with diabetes die from heart fisease. In fact, adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes. Also, stroke accounts for approximately 20% of diabetes-related deaths, and the risk for stroke is also 2-4 times higher among people with diabetes.

Obesity:

How obesity can be measured?

1. Measuring the Ideal weight (Ideal weight = height - (100 if male or 105 if female))
2. Measuring the waist size in centimeters. We then compare that to half the measurement of the height. To have an ideal weight, your waist size should

be less than half the measurement of the height. (Waist measurement < ½ height)

3. The most practical way is the BMI (body mass index) which gives an idea about obesity.

BMI

One approach for gauging the extent to which human body mass is appropriate for body height is to compute the body mass index (BMI):

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

BMIs fall into four major categories:

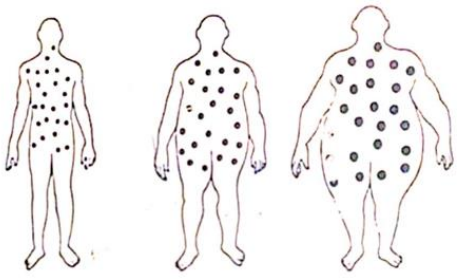
1. Underweight: less than 18.5
2. 2. Normal weight: 18.5 – 24.9
3. Overweight: 25 – 29.9
4. Obesity: 30 or more

Obesity is the most common and the most expensive nutritional problem in the USA:

A convenient and reliable indicator of body fat is the BMI. Values above 25 are abnormal. Individuals with values of 25-30 are overweight, and those with values > 30 are obese. In the USA, 55% of the population are overweight and 22% are obese. The incidence of obesity is also increasing in other countries. Indeed, the Worldwatch Institute has estimated that although starvation continues to be a problem, in many parts of the world, the number of overweight people in the world is now as great as the number of underfed.

This table shows the effect of weight on fat cells:

Notice that the number of cells is the same while the size increases with weight increase



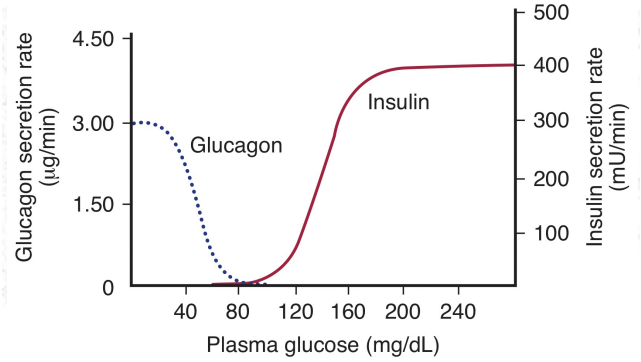
Body weight	165 lb	227 lb	328 lb
Fat cell size	0.2 µg/cell	0.6 µg/cell	0.9 µg/cell
Fat cell number	75 billion	75 billion	75 billion

Glucagon

*Glucagon is a single peptide of 29 AA with molecular weight of 3500, and the biological activity resides in 1-6 AA.

We've talked about hormonal interactions (permissive, synergistic, antagonistic).

Insulin is the only hypoglycemic hormone while glucagon is the most potent hyperglycemic hormone. They oppose each other which means that when glucose level increases, insulin increases while glucagon decreases. So they are apply antagonistic effect on each other.



-Glucagon is the other major pancreatic islets hormone (the second most important hormone of the pancreatic islets) that is involved in the regulation of body fuel metabolism.

-Ingestion of protein appear to be **the major stimulus** secretion of glucagon.

Although the amino acids released by digestion of a protein meal appear to be the major glucagon secretagogue, glucagon's main actions on the liver appear to involve the regulation of carbohydrate and lipid metabolism.

-Glucagon is particularly important in stimulating glycogenolysis, gluconeogenesis, and ketogenesis.

-Glucagon's principal target tissue is the **liver**. Like insulin, glucagon is secreted first into the portal blood and is therefore anatomically well positioned to regulate hepatic metabolism.

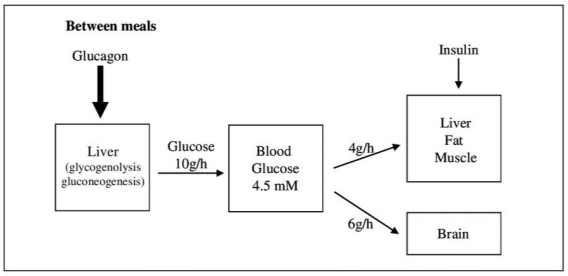
Glucagon doesn't act solely on the liver, but also has glycogenolytic action on cardiac and skeletal muscle and lipolytic action on adipose tissue, and it promotes the breakdown of protein by several tissues. However, these effects on protein tissue breakdown appear to be more prominent when tissues are exposed to pharmacological concentrations of glucagon. At more physiological concentration, the liver appears to be the major target tissue.

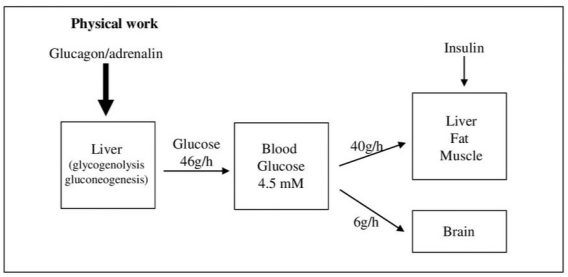
~~I'm sorry for the bad pictures but I did'nt find similar pictures in the internet or books.~~ لقيتهم في الديب ويب

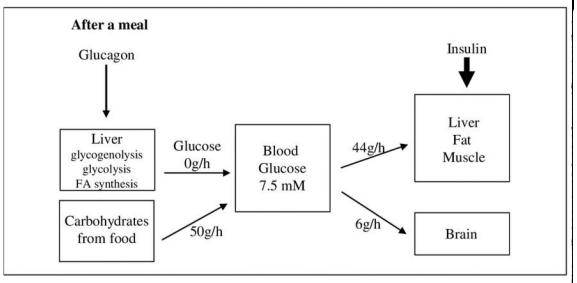
These are diagramatic representation of the patterns of glucagon and insulin release at rest (A), during exercise (B) and following a meal of carbohydrate (C) and the concequential changes in glucagon distribution.

You should distinguish the difference between the 3 states:

	Glucose	Insulin	Glucagon	Liver gives	Liver, fatm muscles cells take	Brain
At rest	Normal	Normal	Normal	10 g	4 g	6 g
During exercise	Normal	—	+	+ 46 g	+ 40 g	6 g Not affected
After a meal	+	++	–	— 0 g	+ 44 g	6 g Not affected







And that's the end of endocrine physiology

Good Luck