بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 22

Integration Of metabolism

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How Your Metabolism Works | Return2Health

Hormones and Metabolism

Insulin binds to RTK which upregulates GLUT-4 expression and glucose uptake into the cell.

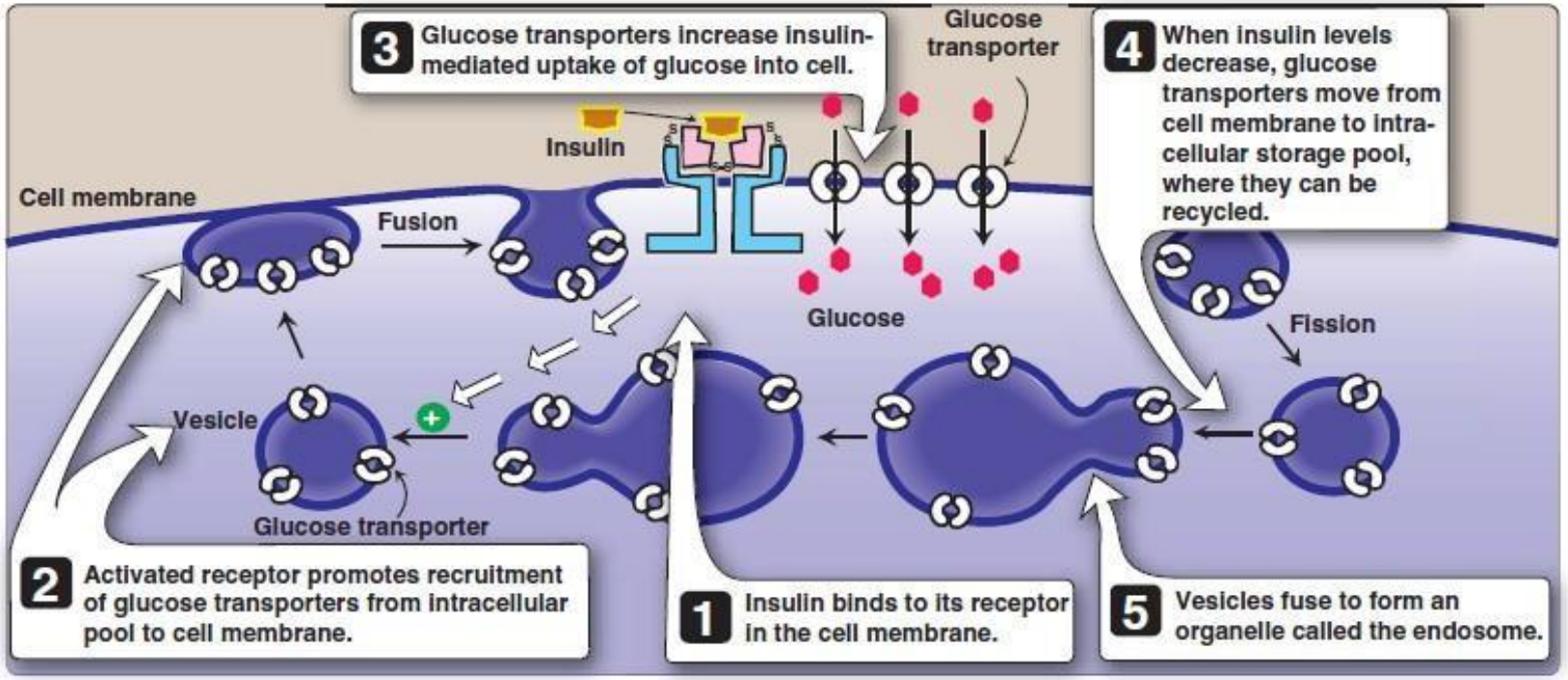


Figure 23.8
Insulin causes the recruitment of glucose transporters (GLUTs) from intracellular stores in skeletal and cardiac muscle and adipose tissue.

Carbohydrate metabolism

- ✓ Glucose storage mostly in three tissues: liver, muscle, and adipose tissue.
- ✓ ↑ glycogen synthesis in the liver and muscle.
- ✓ ↑ glucose uptake by increasing transporters in muscle and adipose tissue.
- ✓ ↓ glycogenolysis and gluconeogenesis in the liver & kidney cells.

Effects on protein synthesis

- ✓ ↑ entry of amino acids into cells and protein synthesis

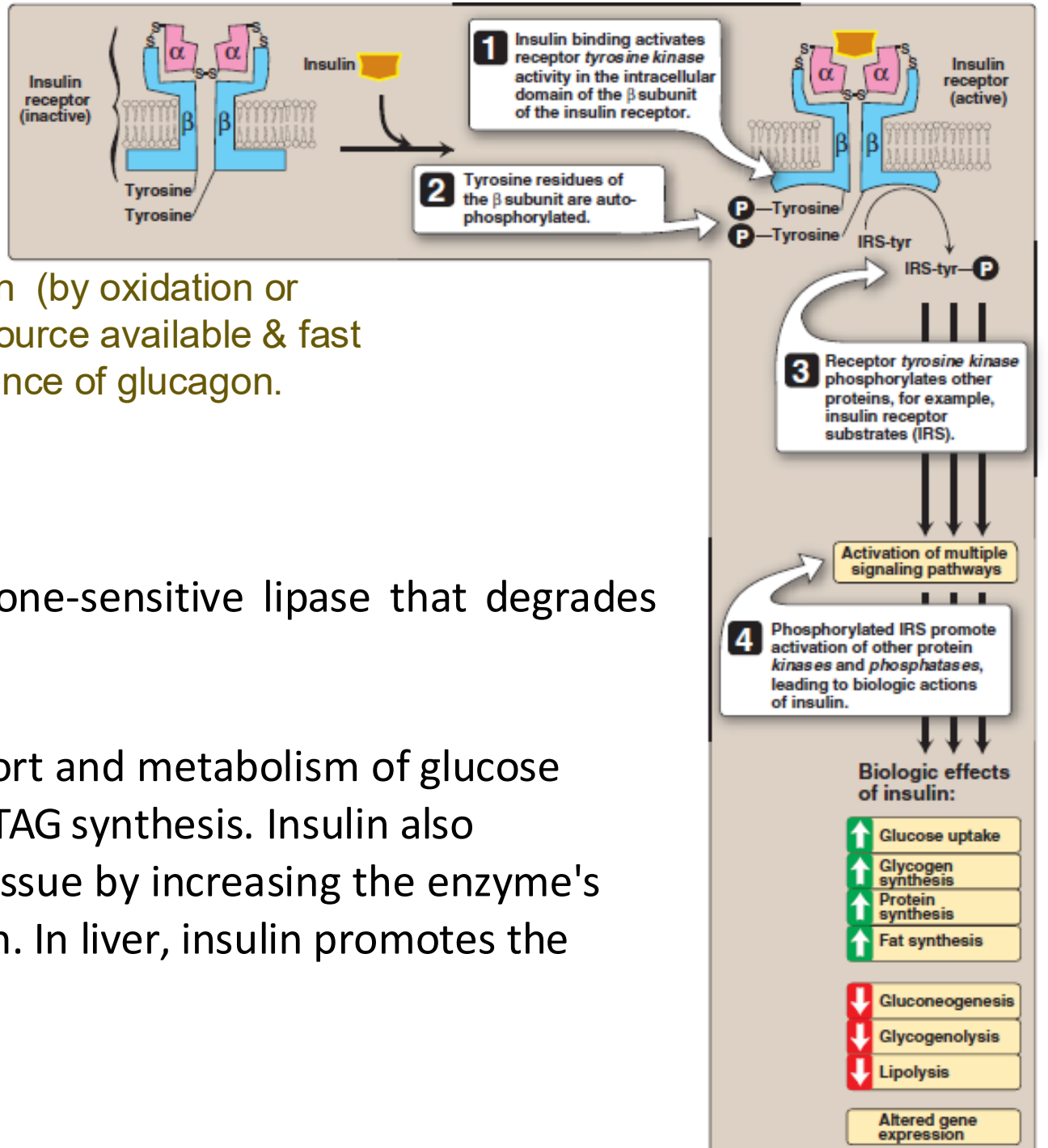
Insulin is generally active in the well-fed state; glucose concentration is also high in the well-fed state.
the signaling pathway of insulin when it binds to its receptor tyrosine kinase upregulates expression of GLUT-4 on the cell surface, increasing their number, allowing more entry of glucose into the cells. This signaling pathway of insulin also activates series of proteins and molecules that end up in activation of certain genes and certain enzymes and inactivation of other metabolic enzymes.
Carbohydrate metabolism:
Entry of glucose increases, this would activate glycolysis as a source of energy for the cell, this will also activate the storage of glucose in the form of glycogen, specifically in liver and muscle cells , glycogenolysis will be inhibited.

Insulin & Amino Acid Metabolism

In the well-fed state, Insulin will also allow entry of more amino acid into cells; protein synthesis is activated.

The process of protein synthesis is energy-consuming.(this is why it takes place in well fed state)

Metabolic effects of insulin



Lipid synthesis & storage increases, but lipid degradation (by oxidation or lipolysis) is inhibited because we have another energy source available & fast which is the glucose. Lipid degradation is active in presence of glucagon.

Effects on lipid metabolism

✓ ↓ release of fatty acids from adipose tissue.

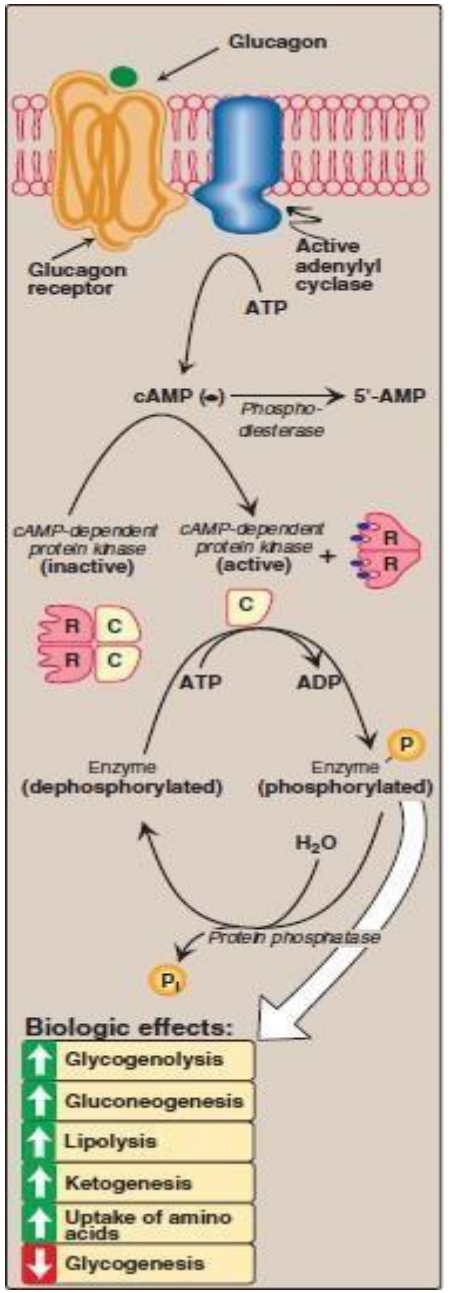
a. Decreased TAG degradation by inhibiting hormone-sensitive lipase that degrades triacylglycerol in adipose tissue.

b. Increased TAG synthesis by increasing the transport and metabolism of glucose into adipocytes, providing glycerol 3-phosphate for TAG synthesis. Insulin also increases the lipoprotein lipase activity of adipose tissue by increasing the enzyme's synthesis, thus providing fatty acids for esterification. In liver, insulin promotes the conversion of glucose to triacylglycerols.

Metabolic effects of glucagon

- ✓ Glucagon is a polypeptide (29 aa) hormone secreted by the α cells of the pancreatic islets of Langerhans.
- ✓ Glucagon, along with epinephrine, cortisol, and growth hormone (the "counter-regulatory hormones"), opposes many of the actions of insulin
- ✓ Glucagon receptors are found in hepatocytes but not on skeletal muscle.
- ✓ Glucagon acts to maintain blood glucose levels by activation of hepatic **glycogenolysis** and **gluconeogenesis**.
- ✓ Glucagon secretion is increased by:
  1. Low blood glucose. also fasting or starvation conditions.
  2. Amino acids derived from a meal containing protein.
  3. Epinephrine or norepinephrine.
- ✓ Glucagon secretion is inhibited by elevated blood glucose and by insulin.

Glucagon binds to a GPCR



Glycogen & Muscle Cells

While glycogen degradation is increased in hepatocytes under the influence of glucagon, it does **not** increase in muscle cells, even in fasting conditions. however, muscle cells have higher amounts of glycogen than hepatocytes, and this muscle glycogen is to be used only by muscle depending on the physical exercise the person is doing in the fasting state. Muscle glycogen is sustainable in the fasting state even during high physical activity. In liver, glycogen may be depleted and gluconeogenesis may be activated, Glycogenolysis is also activated in the hepatocytes to release glucose residues, these will **not** be used inside hepatocytes to generate energy but will be released to the blood stream, which will maintain blood glucose levels, also glucose will be delivered to tissues that depend on glucose exclusively as a source of energy (e.g. : brain, adrenal medulla, lens).

In fight or flight: the body needs energy in a quick manner; epinephrine and Norepinephrine will activate secretion of glucagon which activates glycogenolysis specifically in muscle for energy.
In stress: cortisol is the primary hormone in stress, needs to maintain blood sugar levels in a similar manner.

Metabolic effects of glucagon

1. Effects on carbohydrate metabolism: increase in the breakdown of liver (not muscle) glycogen and an increase in gluconeogenesis.

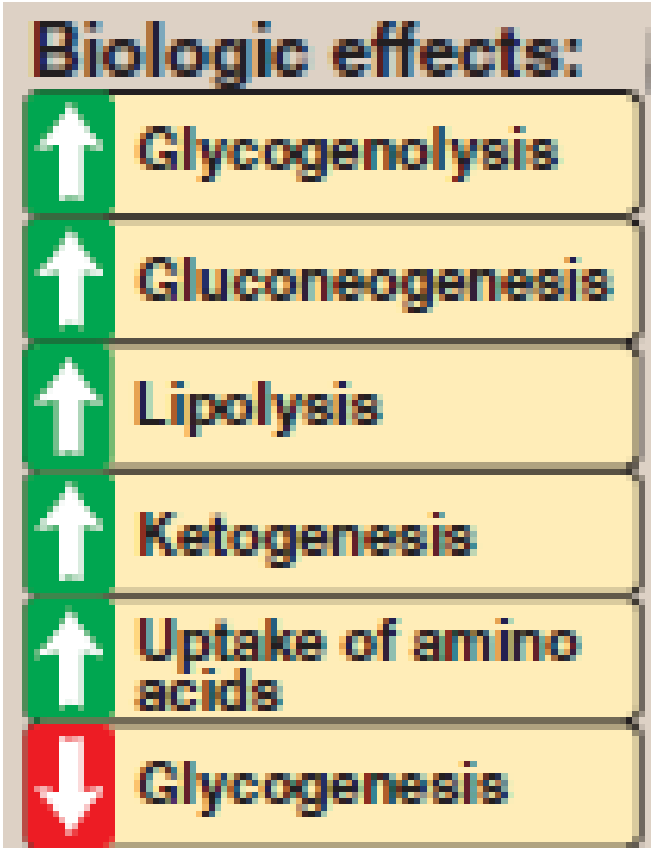
Breaking down muscle glycogen depend on the exercise, gluconeogenesis occurs mainly in hepatocytes spesifically in the first hours-days of fasting
With more contribution of the kidneys whenever fasting lasts more than weeks

2. Effects on lipid metabolism: Glucagon activates lipolysis in adipose.

The free fatty acids released are taken up by liver and oxidized to acetyl coenzyme A, which is used in ketone body synthesis.

HSL is sensitive to and activated by glucagon, leading to TAG hydrolysis.
Fate of:

A. **fatty acids-** energy production by beta-oxidation.
B. **glycerol-** gluconeogenesis in kidney and liver cells.

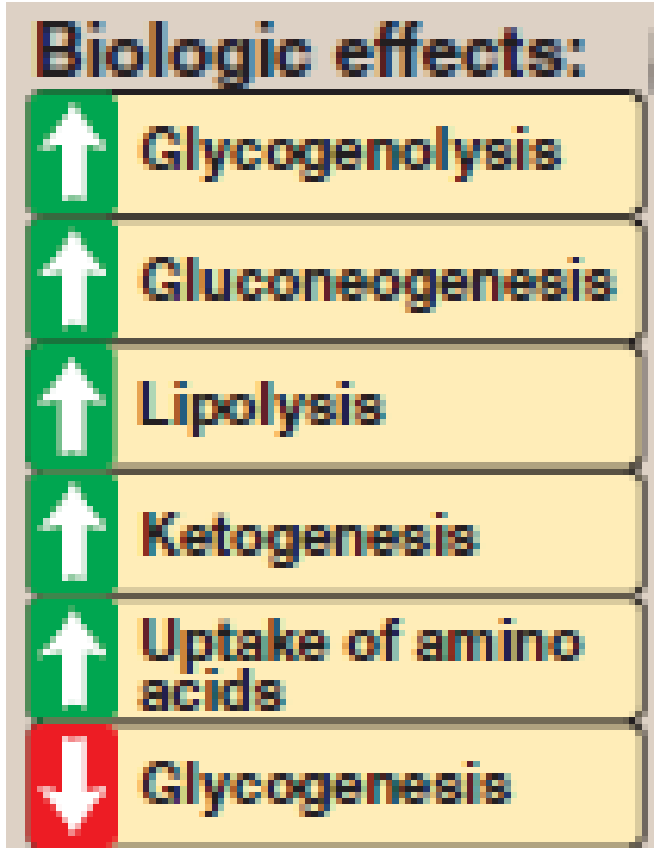


Increased [acetyl CoA]s are used for ketogenesis during fasting, acetyl CoA will not be used in TCA cycle in this case because it's restricted by the concentration Of oxaloacetate (which will be used in gluconeogenesis)

Metabolic effects of glucagon

3. Effects on protein metabolism: Glucagon increases uptake of amino acids by the liver, resulting in increased availability of carbon skeletons for gluconeogenesis, thus, plasma levels of amino acids are decreased.

Protein degradation is activated, muscle protein is broken down first (structural proteins) since they are relatively less important in function than enzymetic or transport proteins when the body prioritize protein degradation.



Insulin vs Glucagon

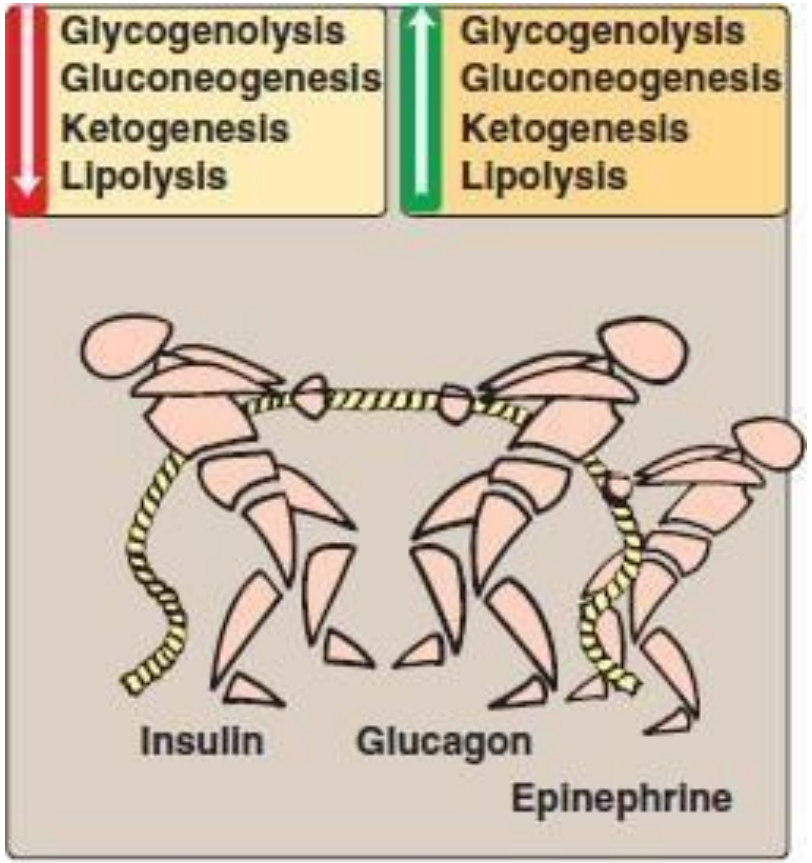


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

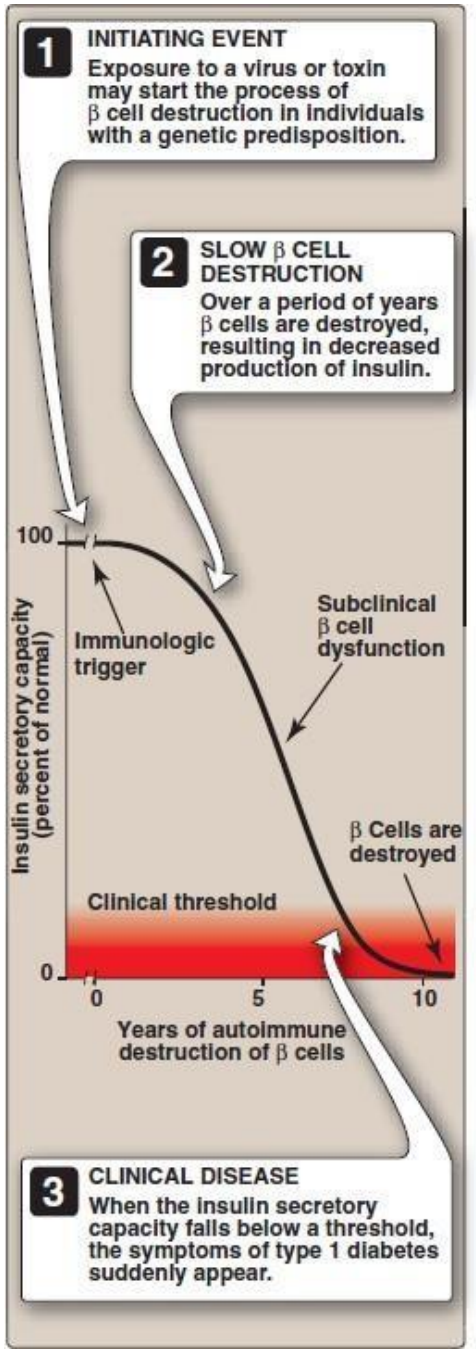
Diabetes and Metabolism

Type I Diabetes Mellitus (DM)

- Insulin deficiency

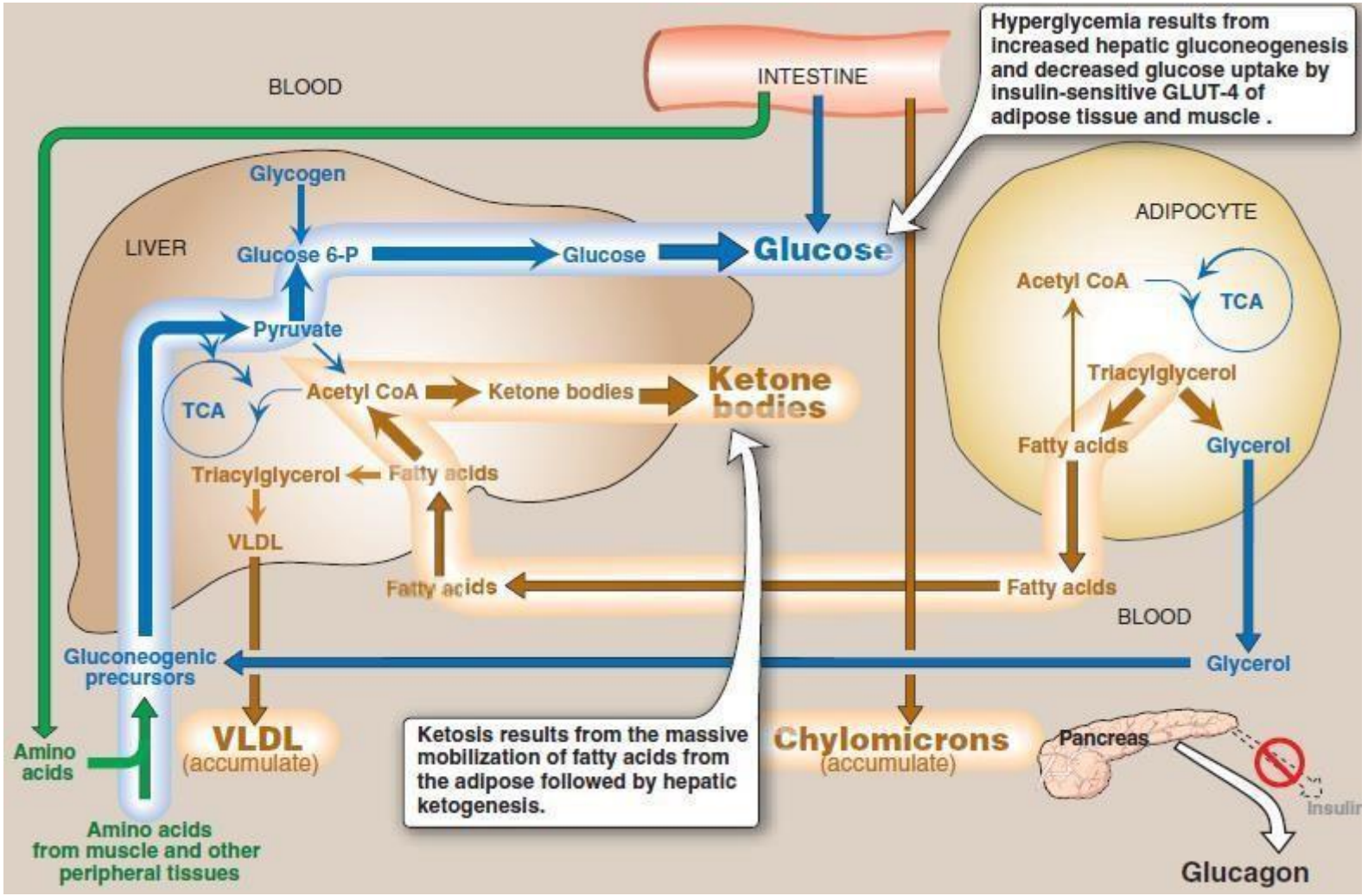
A juvenile disease, affects mainly children. It is caused by autoimmune destruction of beta cells in the pancreas over time, which are responsible for insulin secretion and production. It is a gradual process (usually takes years) and is subclinical up until a certain threshold is reached, then symptoms start to show.

Type I diabetes can also be caused by viruses or certain drugs.



Metabolic changes in type 1 DM

- The metabolic abnormalities result from an insulin deficiency
- Affects metabolism in three tissues: liver, muscle, and adipose tissue



Type I Diabetes

In type I diabetic patients there is high glucose concentration in the bloodstream, No or little insulin secretion will be stimulated Since there's no uptake of sugar (no GLUT 4), cells are in starvation conditions, this mimics fasting conditions & cells send signals that stimulate lipolysis in adipocytes, and TAGs are broken down to glycerol & fatty acids, LCFAs are tranported via albumin, SCFAs & MCFAs move by there own in bloodstream, as well as glycerol since it's polar. Fatty acids are up taken by cells that can utilize them as a source of energy and produce Acetyl CoA by Beta-oxidation, which will be used in Krebs cycle depending on OAA availability. The excess [acetyl CoA] in hepatocytes stimulates ketogenesis and the release of ketone bodies into the bloodstream. If ketone bodies in blood are released in very high amounts, it might lead to ketoacidosis. This explains strong acetone smell in these patients as a symptom of ketoacidosis.

glycogen degradation is stimulated in hepatocytes, Glycogen degradation → release of glucose in the bloodstream, which increases sugar blood levels even more. glycerol will be up taken by hepatocytes & kidney cells to activate Gluconeogenesis which will furthermore increase blood sugar levels.

Some FAs in addition to glycerol molecules will be phosphorylated to G3P by glycerol kinase for synthesis of triacylglycerol. Triacylglycerol will be packaged as VLDL in hepatocytes and released into bloodstream which will Cause accumulation of VLDL in the blood.

Chylomicrons will also accumulate in blood, because without insulin lipoprotein lipase (enzyme in endothelial cells that hydrolyses TAGs in chylomicrons leaving chylomicron remnants) will not be activated. This explains why diabetic patients have high lipid concentration in blood which may lead to atherosclerosis and then to high blood pressure.

Also break down of amino acid specifically in muscle cells, these amino acids will be uptaken by hepatocytes & kidney cells to activate gluconeogenesis.

Metabolic changes in type 1 DM

Ketoacidosis is More significant in Type I diabetes

- Elevated levels of blood glucose and ketones are the hallmarks of untreated type 1
- **Hyperglycemia** due to increased hepatic production of glucose, combined with diminished peripheral utilization (muscle and adipose have the insulin-sensitive GLUT-4)
- **Ketoacidosis** results from increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic fatty acid β-oxidation and synthesis of 3-hydroxybutyrate and acetoacetate
- **Hypertriacylglycerolemia:** excess fatty acids are converted to TAG, which is packaged and secreted in very-low-density lipoproteins (VLDL)
- ↑ Chylomicrons synthesis because lipoprotein degradation catalyzed by lipoprotein lipase in the capillary beds of muscle and adipose tissue is low in diabetics (synthesis of the enzyme is decreased when insulin levels are low)

Type II Diabetes Mellitus (DM)

- Most common (90%) More common in adults
- Develops gradually without obvious symptoms
- Polyuria and polydipsia and polyphagia 3 famous symptoms
- A combination of insulin resistance and dysfunctional β cells
- The metabolic alterations are milder than those for type 1, because insulin secretion in type 2, although not adequate, does restrain ketogenesis and blunts the development of diabetic ketoacidosis (DKA)
- Pathogenesis does not involve viruses or autoimmune antibodies.

Usually, insulin resistance precedes Type II diabetes because insulin resistance may cause dysfunction of Beta cells esp. when accompanied by obesity & uncontrolled blood sugar for long time.

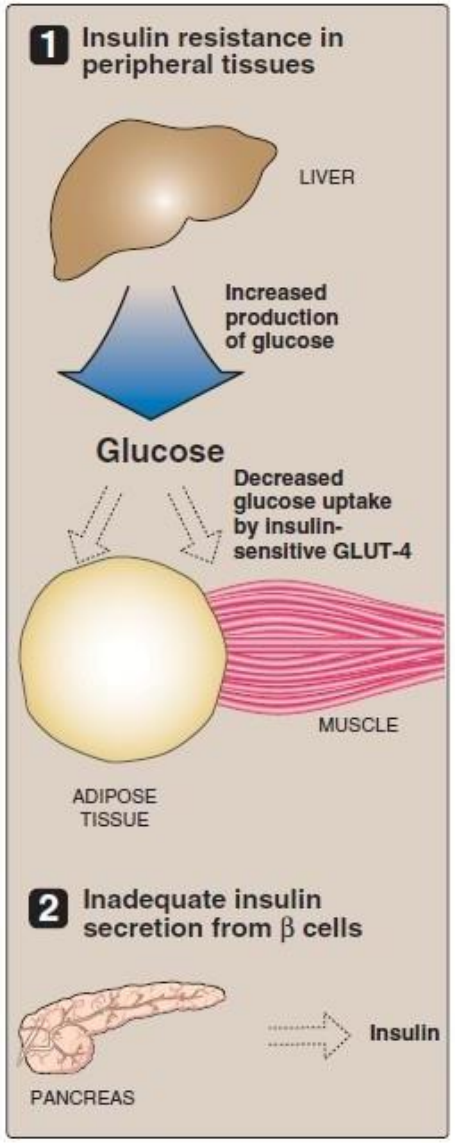


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes.

Insulin Resistance (IR)

Unlike type I Diabetes Here: LPL Is active & the pancreas Produces higher Amounts of Insulin to compensate This resistance

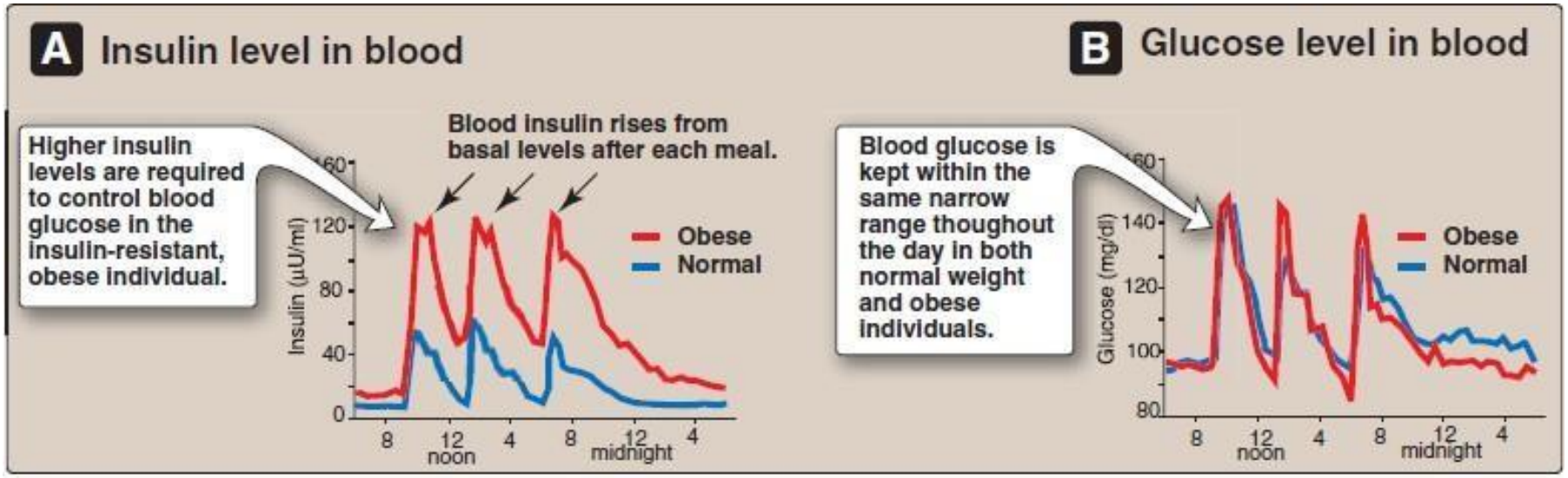


Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.

Because of insulin Resistance ; higher Amounts of insluin Are needed For the body To go back to fasting blood Sugar

- ✓ IR is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal (or elevated) circulating concentrations of insulin.
- ✓ IR is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.
- ✓ Obesity is the most common cause of IR.
- ✓ IR alone will not lead to type 2 diabetes.
- ✓ Type 2 diabetes develops in insulin-resistant individuals who also show impaired β-cell function.

Metabolic changes in type 2 DM

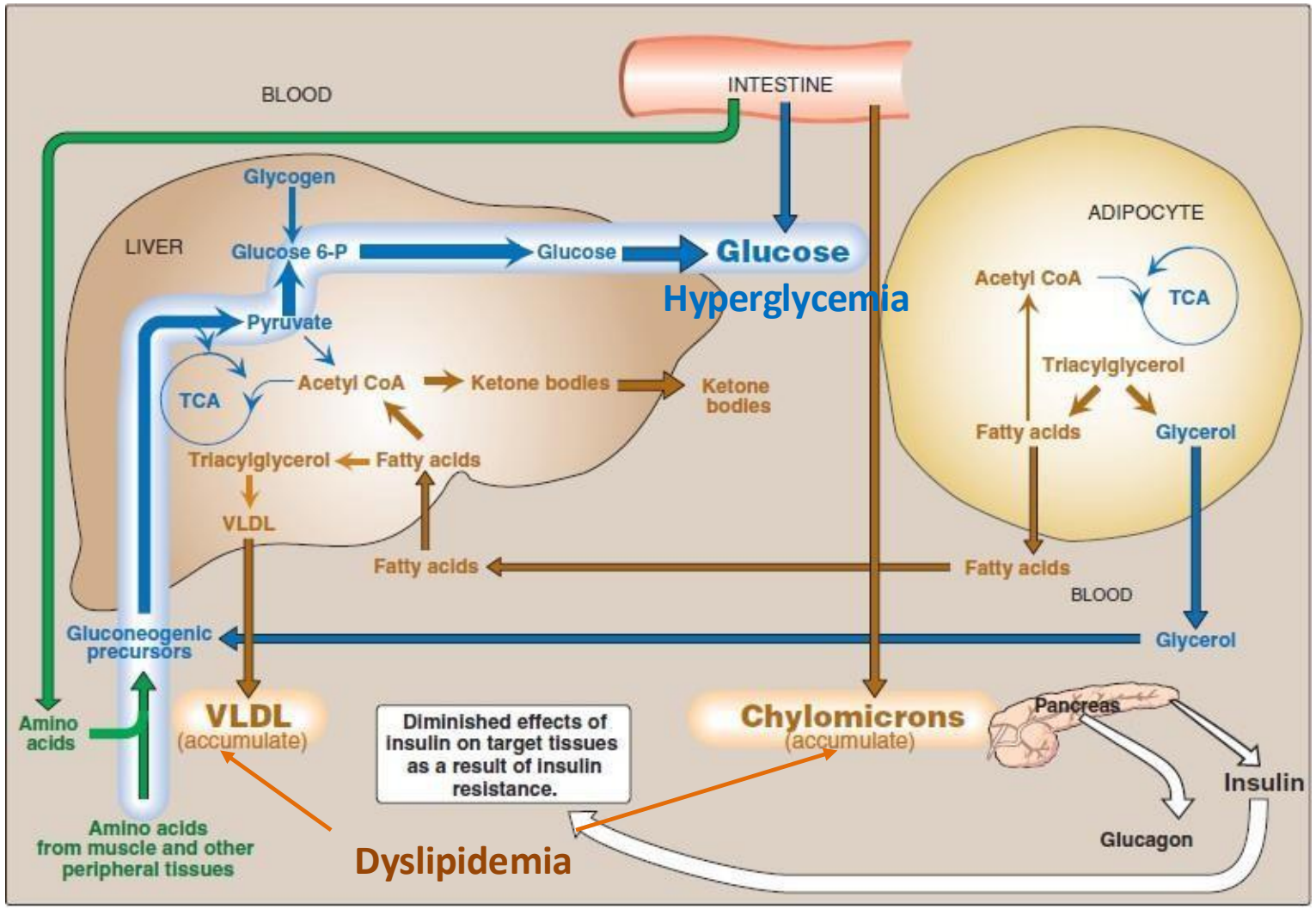


Figure 25.10
Intertissue relationships in type 2 diabetes.

Glucose hyperglycemia (because of insulin resistance) can be uncontrolled if the patient is not taking the medication or on a diet, which leads to type II diabetes. The cells in starvation conditions, because glucose is not sufficiently reuptaken from blood into cells. Cells depend on fatty acids, activation of lipolysis of TAGs in adipocytes, same pathways are activated here : gluconeogenesis, VLDL & Chylomicron accumulation and glycogenolysis*(please refer to the slides 32,33 for details)
, but to a lesser extent than Type I diabetes because glucose in Type II diabetes enter the cells in small amounts and used for energy.
Also ketone bodies here are produced in very low amounts or not even produced.

Metabolic changes in type 2 DM

1. Hyperglycemia Less hyperglycemia than that of diabetes type I, because insulin is still being secreted.

- Caused by increased hepatic production of glucose, combined with diminished peripheral use.
- **Ketosis is usually minimal or absent** in type 2 DM because the presence of insulin—even in the presence of IR— diminishes hepatic ketogenesis.

2. Dyslipidemia

- In the liver, fatty acids are converted to **triacylglycerols**, which are packaged and secreted in **VLDL**.
- ↑ **Chylomicrons** synthesis from dietary lipids by the intestinal mucosal cells because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low in diabetics, and the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia.
- **Low HDL** levels are also associated with type 2 diabetes.

Fasting and Metabolism

OVERVIEW OF FASTING

Fasting state: minimum 2 hours after consuming a meal

- Begins if no food is taken after the absorptive period.
- Result from an inability to obtain food, the desire to lose weight rapidly, or clinical situations in which an individual cannot eat, for example, because of trauma, surgery, cancer, or burns.
- In the absence of food, plasma levels of glucose, amino acids, and TAG fall, reducing insulin secretion and increasing glucagon release.
- The nutrient deprivation is a catabolic period characterized by degradation of TAG, glycogen, and protein.

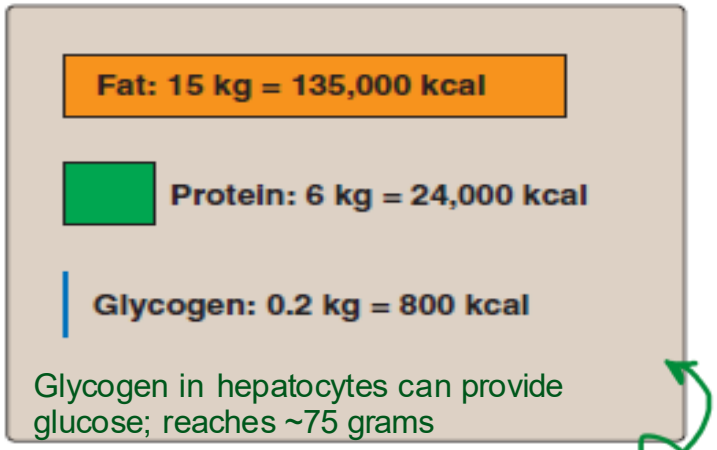


Figure 24.9
Metabolic fuels present in a 70-kg man at the beginning of a fast. Fat stores are sufficient to meet energy needs for about 3 months.

- Priorities:

1) to maintain adequate plasma levels of glucose to supply brain, RBCs, and other glucose-requiring tissues with glucose the need to mobilize fatty acids from adipose tissue, and the synthesis and release of ketone bodies from the liver, to supply energy to all other tissues.

- Although protein is an energy source, each protein also has another function, therefore, only ~1/3 of the body's protein can be used for energy production without fatally compromising vital functions. we start breaking down less important proteins

Enzyme changes in fasting

- The flow of intermediates through the pathways of energy metabolism is controlled by four mechanisms:

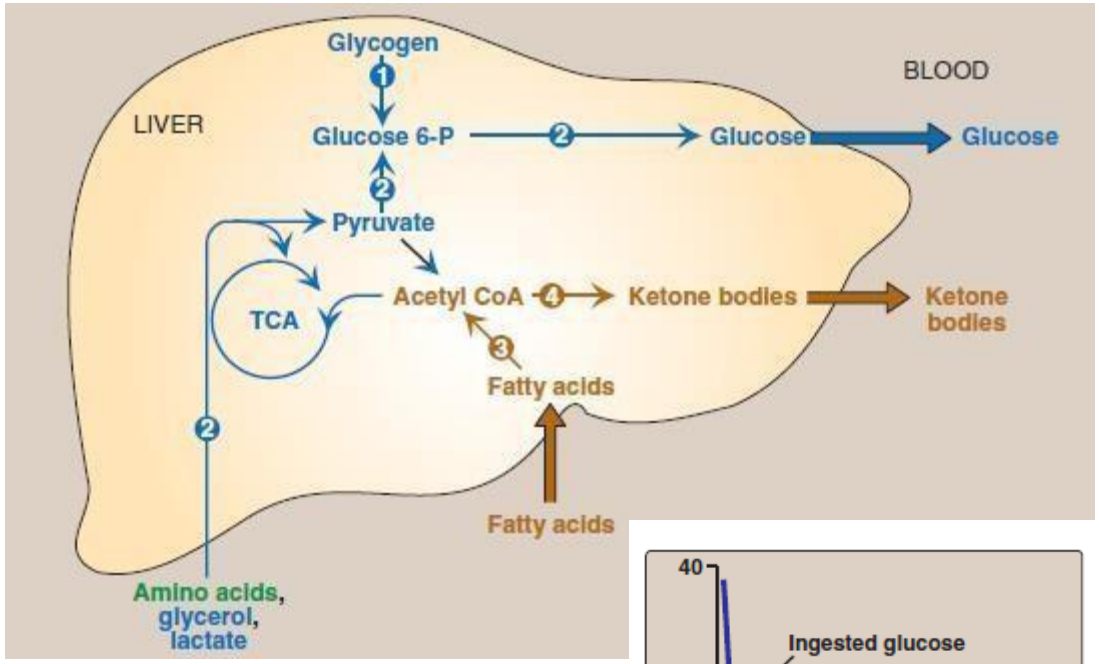
1) the availability of substrates Gluconeogenesis
2) allosteric regulation of enzymes
3) covalent modification of enzymes
4) induction-repression of enzyme synthesis. activation of signaling pathways by hormones eg: glucagon which activates certain transcription factors & gene expression of target genes

- The metabolic changes observed in fasting are generally opposite to those in the absorptive state

- In fasting, substrates are not provided by the diet but are available from the breakdown of stores and/or tissues.

LIVER IN FASTING

- The primary role of the liver during fasting is to maintain blood glucose through the synthesis and to distribute fuel molecules for use by other organs



- The liver first uses glycogen degradation and then gluconeogenesis to maintain blood glucose levels to sustain energy metabolism of the brain and other glucose-requiring tissues in the fasted (postabsorptive) state.

- Increased fatty acid oxidation as a major source of energy for liver

- Increased synthesis of ketone bodies especially 3- hydroxybutyrate

Ketogenesis is also active, because in fasting state Beta-oxidation of FAs is activated; part of Acetyl CoA that is produced is used in ketogenesis.

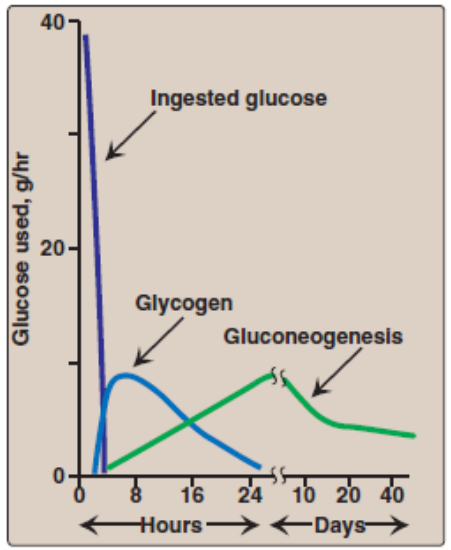
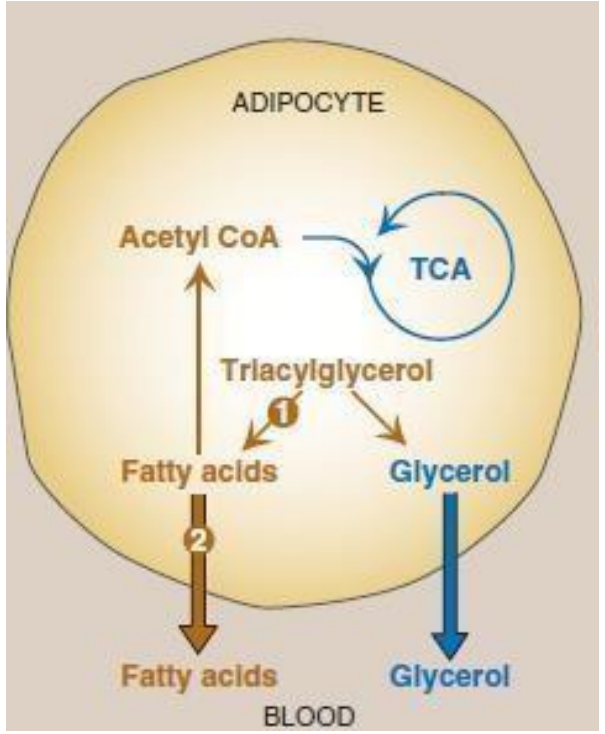


Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

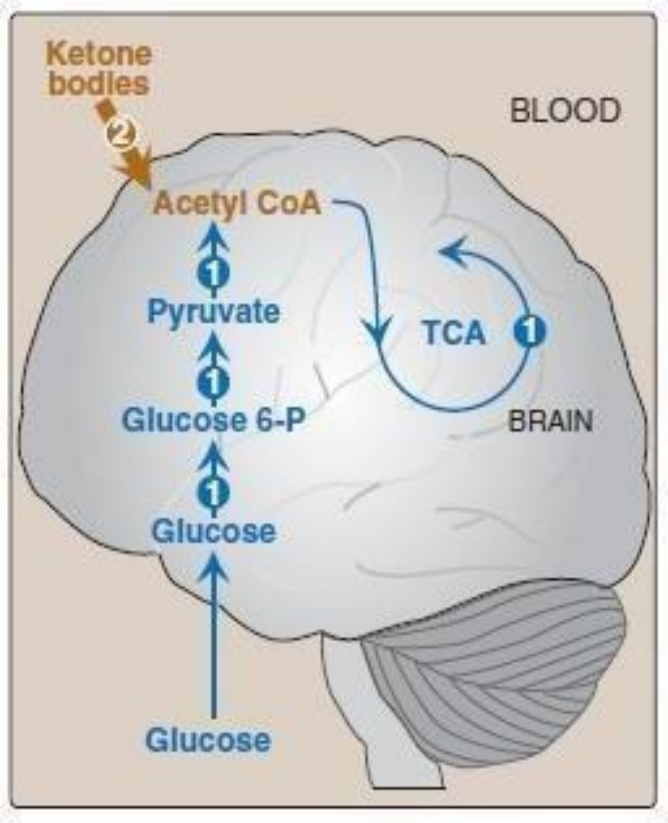
ADIPOSE TISSUE IN FASTING

Induced by glucagon and sometimes epinephrin



- Glucose transport by insulin-sensitive GLUT-4 into the adipocyte and its subsequent metabolism are depressed due to low insulin levels. This leads to a decrease in fatty acid and TAG synthesis.
- Increased degradation of TAG by hormone sensitive lipase
- Increased release of hydrolyzed fatty acids from stored TAG into the blood as albumin bound FA to be transported to a variety of tissues for use as fuel.
- The glycerol produced from TAG degradation is used as a gluconeogenic precursor by the liver.
- Decreased uptake of fatty acids since lipoprotein lipase activity of adipose tissue is low during fasting. Consequently, circulating TAG of lipoproteins is not available to adipose tissue.

BRAIN IN FASTING



- During the first days of fasting, the brain continues to use glucose exclusively as a fuel.
- Blood glucose is maintained by hepatic gluconeogenesis from glucogenic precursors, such as amino acids from proteolysis and glycerol from lipolysis.

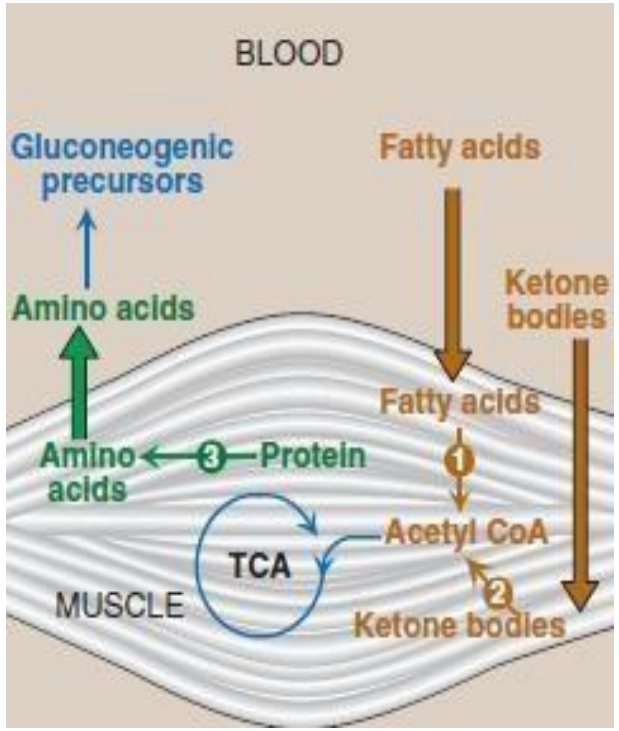
Ketone bodies can cross BBB and enter neurons where they will Be broken down into Acetyl CoA which will enter krebs cycle for energy

- In prolonged fasting (greater than 2–3 weeks), plasma ketone bodies reach significantly elevated levels, and replace glucose as the primary fuel for the brain reducing the need for protein catabolism for gluconeogenesis and sparing glucose and, thus, muscle protein.

Kidneys mainly use amino acids as precursors for gluconeogenesis, gluconeogenesis is a sustained source of glucose; but for prolonged fasting (weeks) the brain adapts to use ketone bodies: Acetoacetate & 3-hydroxybutarate.

RESTING SKELETAL MUSCLE IN FASTING

Remember there's no glucagon receptors in muscle cells.



- Resting muscle uses fatty acids as its major fuel source.
- Exercising muscle initially uses its glycogen stores as a source of energy.
- During intense exercise & fight or flight response, glucose 6-phosphate derived from glycogen is converted to lactate by anaerobic glycolysis
- As glycogen reserves are depleted, free fatty acids from TAG of adipose tissue become the dominant energy source.
- Glucose transport and metabolism are decreased due to low insulin
- During the first 2 weeks of fasting, muscle uses fatty acids from adipose tissue and ketone bodies from the liver as fuels.
- After about 3 weeks of fasting, muscle decreases its use of ketone bodies and oxidizes fatty acids almost exclusively.
- Rapid breakdown of muscle protein during the first few days of fasting to provide AAs (Ala, Gln) for gluconeogenesis in the liver.

KIDNEY IN LONG-TERM FASTING

Gln is used to transport NH3 to the hepatocytes

- Kidney expresses the enzymes of gluconeogenesis, including G-6- phosphatase, and in late fasting about 50% of gluconeogenesis occurs here.
- The Gln released from the muscle's metabolism of branched-chain amino acids is taken up by the kidney and acted upon by renal glutaminase and glutamate dehydrogenase, producing α-ketoglutarate that can be used as a substrate for gluconeogenesis
- Kidney also provides compensation for the acidosis that accompanies the increased production of ketone bodies
  By producing NH3 from Gln which is basic & reduces the acidosis
- NH3 produced from deamination picks up H+ from ketone body dissociation, and is excreted in the urine as NH_4^+, decreasing the acid load in the body.
- In long-term fasting, nitrogen disposal occurs in the form of ammonia rather than urea.

NH3 Reduction

Renal glutaminase in kidneys removes ammonia from Gln by deamination, producing glutamate, a-ketoglutarate is produced from glutamate by enzyme glutamate dehydrogenase.

Any amino acid that gives us pyruvate or any Krebs cycle intermediate (a- ketoglutarate in this case) is considered “glucogenic amino acid” : an amino acid that can be used in gluconeogenesis, so Gln is a gluconeogenic amino acid.

Increased levels of NH3 from amino acid degradation are highly toxic, in prolonged fasting the liver has high workload from gluconeogenesis & other active metabolic pathways all at the same time, hepatocytes are the most affected by NH3 toxicity. urea cycle consumes energy so its activity decreases.

Additional Resources:

رسالة من الفريق العلمي:

"Life is about accepting the challenges along the way, choosing to keep moving forward, and savoring the journey."

— **Roy T. Bennett, The Light in the Heart**

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			