Pancreatic hormones and glucose metabolism

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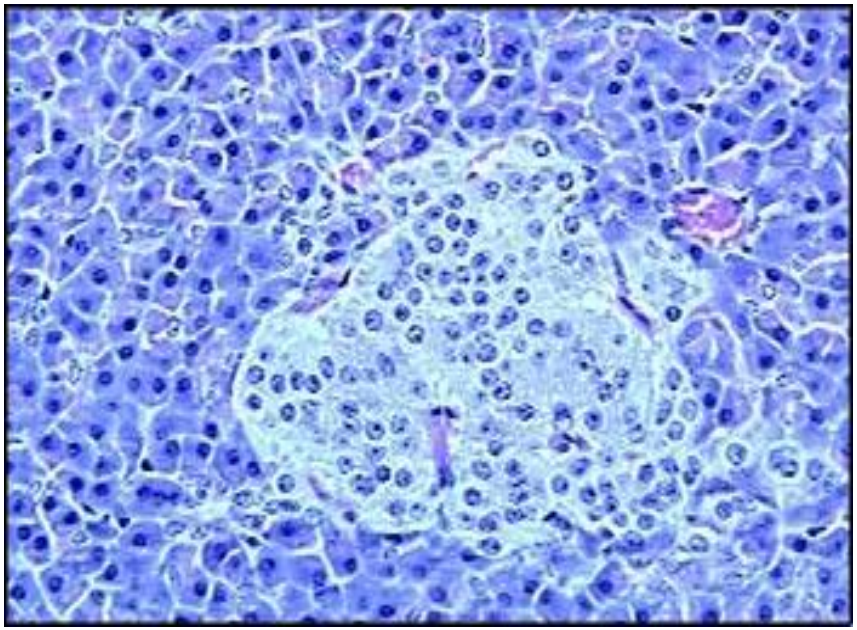
Hormones important for glucose metabolism

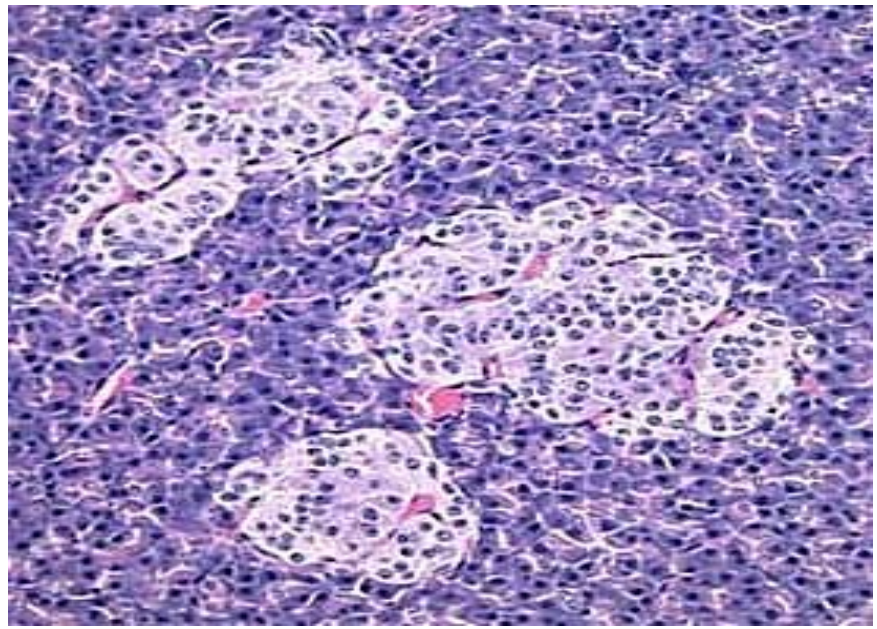
		Blood glucose
Pancreas	Insulin	↓
	Glucagon	↑
Adrenal	Cortisol	↑
	Epinephrine	↑
Pituitary	Growth hormone	↑

Structure of the pancreas

2 major types of tissues

1. acini- secretes digestive juices into the duodenum
2. The islets of Langerhans-secretes insulin and glucagon into blood





The human pancreas bears 1 to 2 million islets of Langerhands with 3 different types of cells

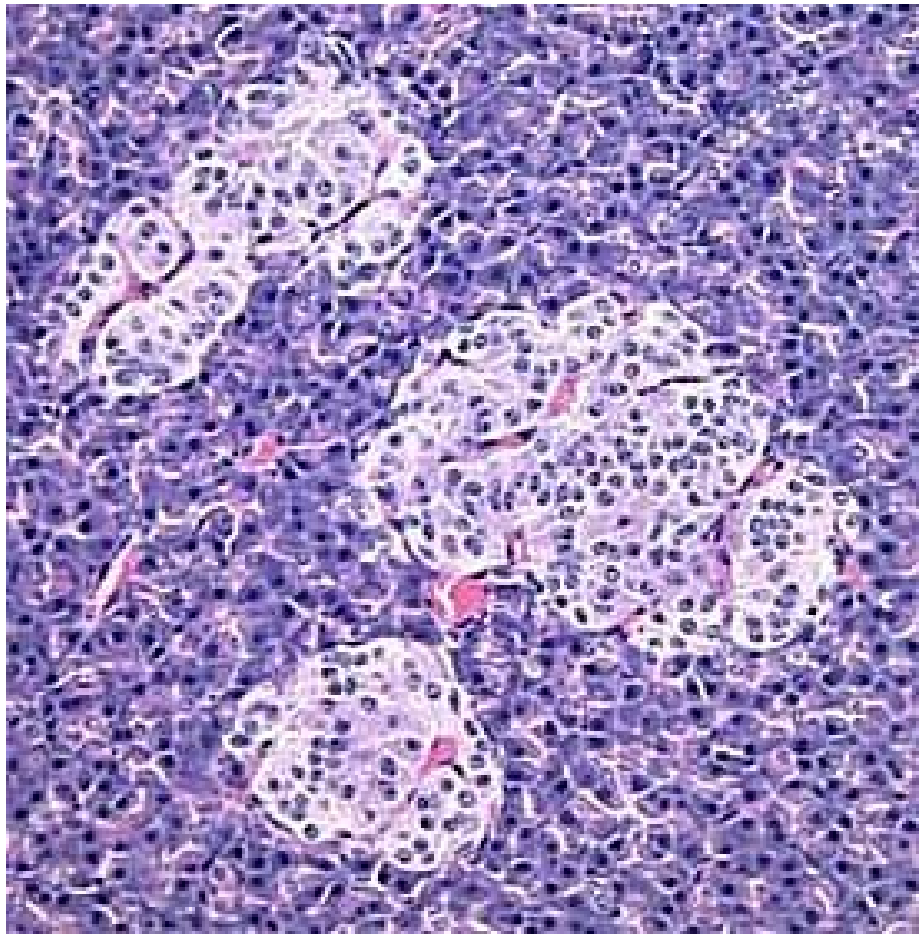
Alpha cells- 25% of total cells, secrete glucagon

Beta cells- 60% of total cells, secrete insulin and amylin

Delta cells- ~10% of total cells, secrete somatostatin

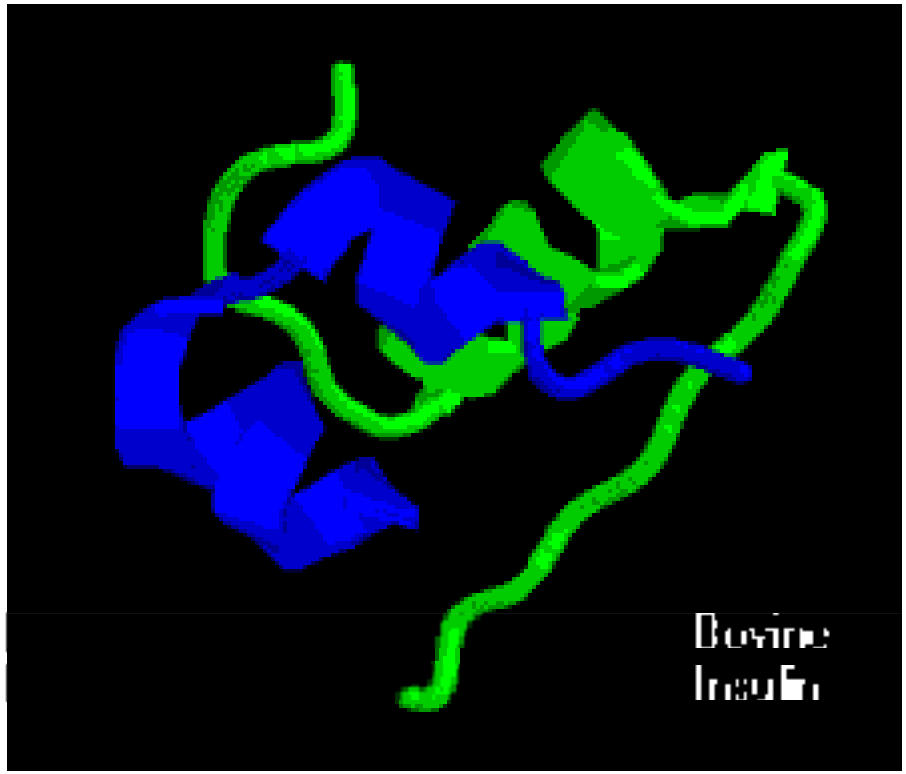
PP cells- secretes pancreatic polypeptide

- **Islets are richly vascularised**
- **Although islets comprise only 1-2% of the mass of the pancreas, they receive about 10 to 15% of the pancreatic blood flow**
- **They are innervated by parasympathetic and sympathetic neurons**
- **In addition to blood glucose changes, nervous signals also modulate secretion of insulin and glucagon.**



Structure of insulin

- **Small protein, with a molecular weight (about 6000 Da)**
- **2 chains (A- 21 a.a.; B- 30 a.a.)**
- **Amino acid sequence is highly conserved among vertebrates, many diabetic patients are treated with insulin extracted from pig and cow pancreases.**



- **Insulin and glucagon are critical participants in glucose homeostasis and serve as *acute regulators* of blood glucose concentration**

Physiological effects

1. **Carbohydrate Metabolism**

- **Insulin promotes muscle glucose uptake and metabolism**
- **Normal resting muscle membrane is not highly permeable to glucose, except when stimulated by insulin**
- **Insulin stimulates glycogen storage in muscle**
- **Insulin facilitates glucose transport through the muscle cell membrane**
- **Insulin promotes liver uptake, liver storage and use of glucose**
- **Insulin promotes conversion of excess glucose into fatty acids and inhibits gluconeogenesis in the liver**

Mechanism of increased glucose uptake and liver storage by insulin

1. Insulin inactivates liver phosphorylase, the enzyme that converts glycogen to glucose
2. Insulin enhanced uptake of glucose from the blood by increasing activity of an enzyme called glucokinase (to phosphorylates glucose after it diffuses into liver cells)
3. Insulin stimulates the activity of glycogen synthase which promotes glycogen synthesis

Net effect: To increase amount of glycogen in liver

Insulin-independent effect

- The brain cells normally use glucose for energy
- Therefore, the brain cells are permeable to glucose and can utilize glucose independently of the effect exerted by insulin

2. Fat metabolism

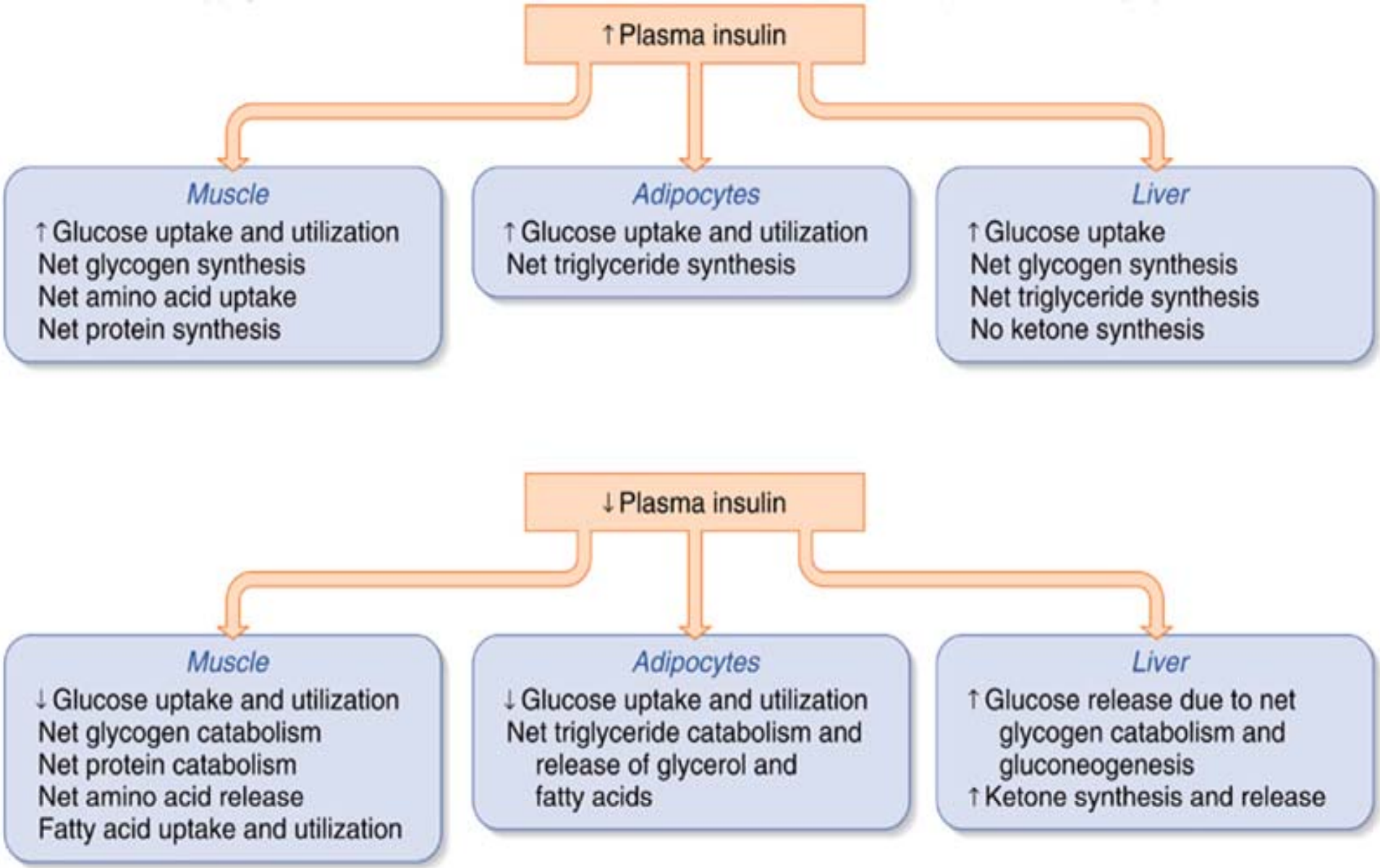
- Insulin promotes fat synthesis and storage in adipose tissue (fat-sparing effect)
- This is especially true when liver is saturated with glycogen (5-6% of total liver mass), additional glucose will be converted to fat (**glucose→pyruvate →acetyl coenzyme A →fatty acid**)
- Insulin inhibits lipase activity which causes hydrolysis of triglycerides
- Insulin also promotes glucose transport through the cell membrane into fat cells to form glycerol and small amount of fatty acid

3. Protein metabolism

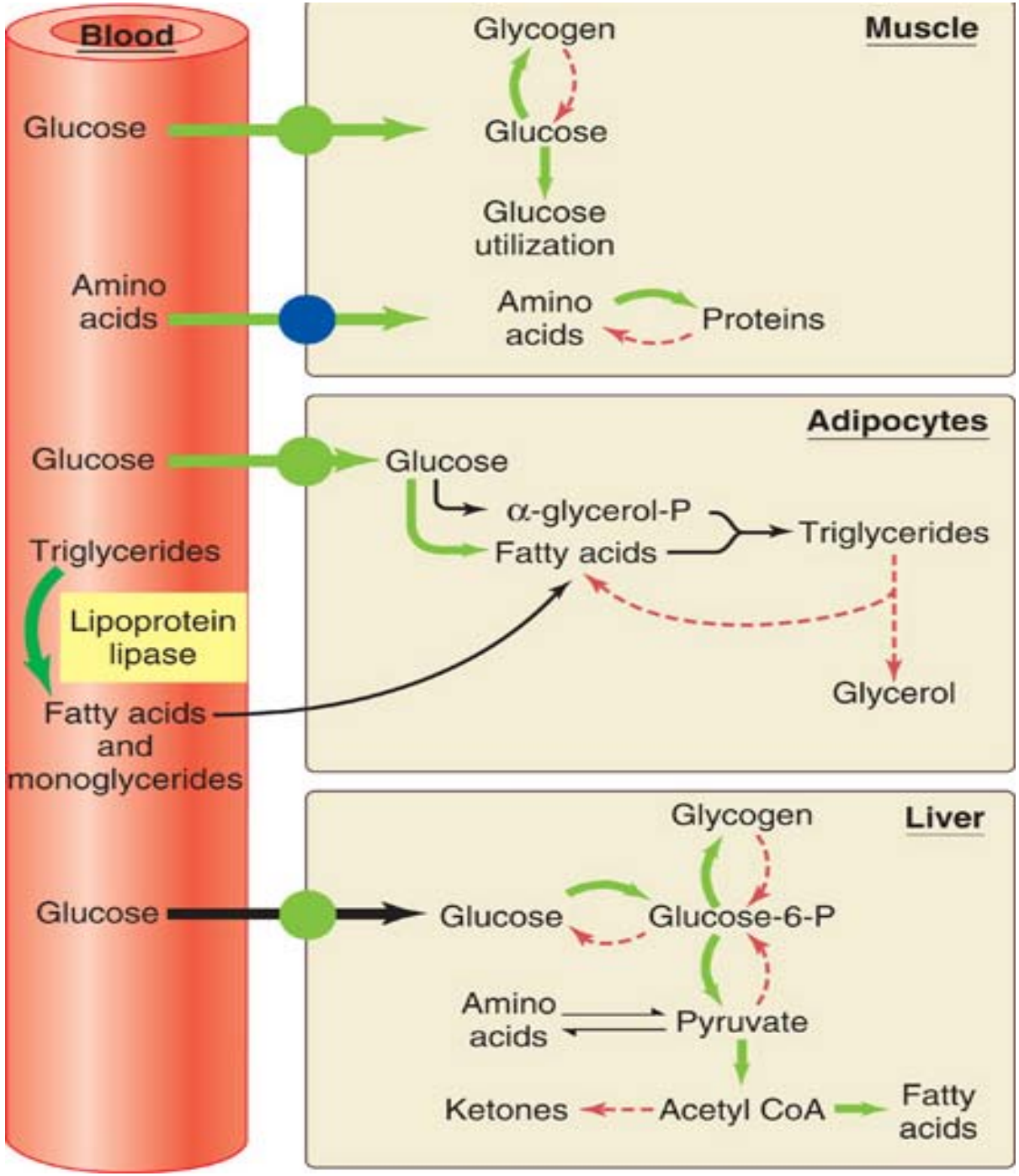
- Insulin promotes protein synthesis and storage
- Insulin stimulates uptake of amino acid into cells
- Insulin activates translation of mRNA and sometimes transcriptional rate and therefore making new proteins
- Insulin inhibits the catabolism of proteins and thus decreases the rate of amino acid releae into the blood from cells, esp the muscle cells
- In liver, insulin inhibits the rate of gluconeogenesis

Insulin lack causes

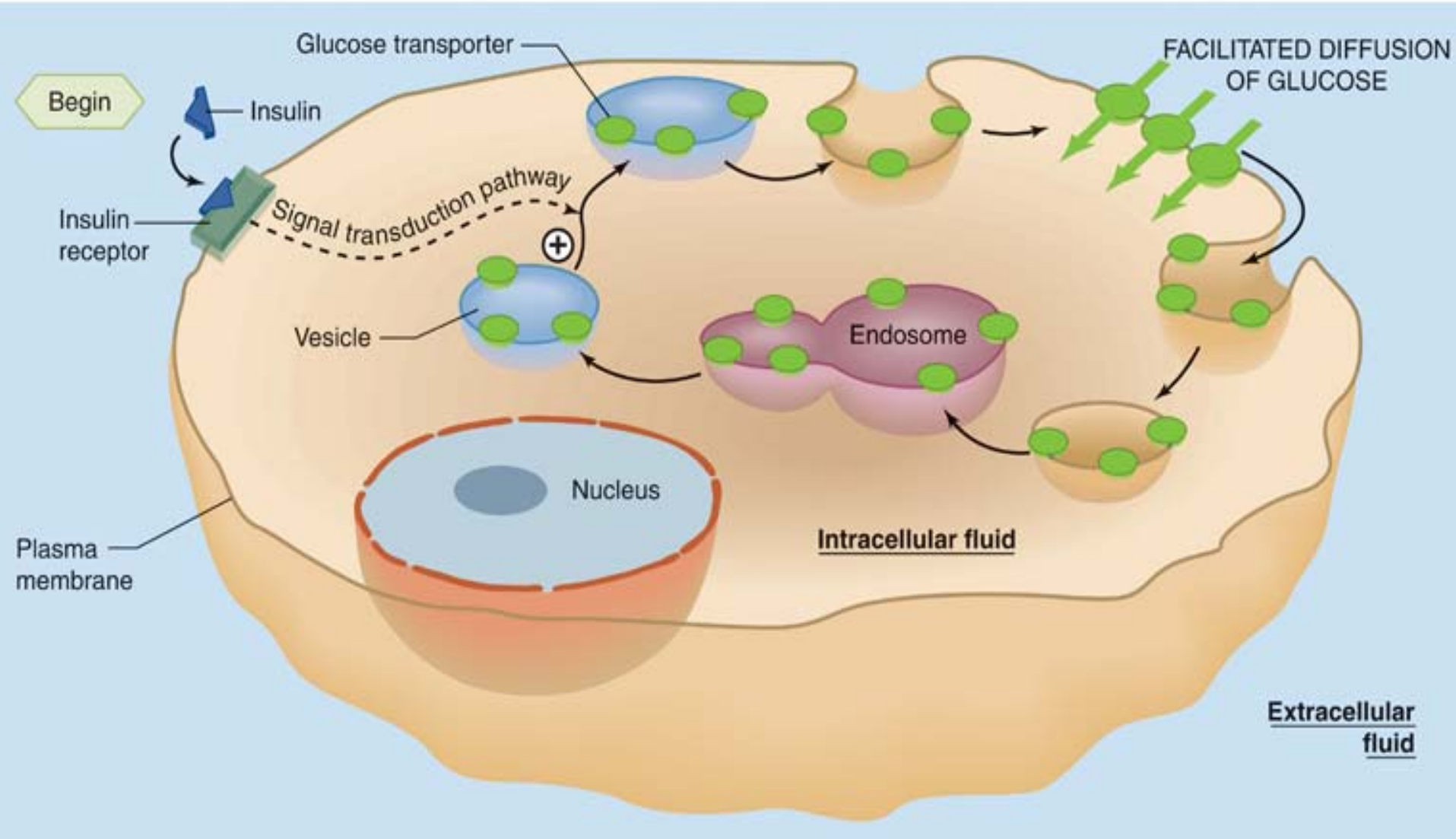
1. Increased plasma cholesterol and phospholipids concentrations (due to excess fatty acids)
2. Increased release of acetoacetic acid (ketone bodies) from fatty acid oxidation and leads to ketoacidosis
3. Increased protein breakdown (protein wasting) and increased plasma amino acids and therefore leads to enhanced urea excretion


↑ Plasma insulin
Muscle
↑ Glucose uptake and utilization
Net glycogen synthesis
Net amino acid uptake
Net protein synthesis
Adipocytes
↑ Glucose uptake and utilization
Net triglyceride synthesis
Liver
↑ Glucose uptake
Net glycogen synthesis
Net triglyceride synthesis
No ketone synthesis
↓ Plasma insulin
Muscle
↓ Glucose uptake and utilization
Net glycogen catabolism
Net protein catabolism
Net amino acid release
Fatty acid uptake and utilization
Adipocytes
↓ Glucose uptake and utilization
Net triglyceride catabolism and release of glycerol and fatty acids
Liver
↑ Glucose release due to net glycogen catabolism and gluconeogenesis
↑ Ketone synthesis and release

Major response of target cells to insulin



Stimulation of glucose transporter translocation by insulin in muscle and adipocyte



Regulation of insulin secretion.

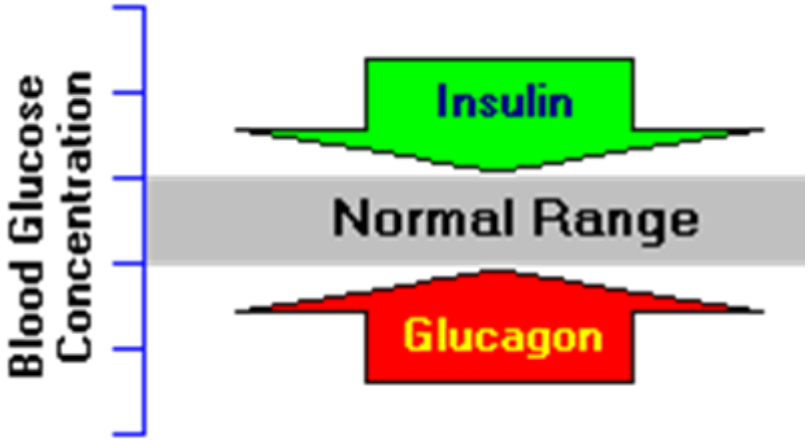
1. Negative feed-back by glucose.
   (glucose stimulates)
2. Amino acids. (proteins).
3. Free fatty acids
3. Hormones.
   GH, cortisol, adrenaline,
   glucagon
   GI hormones
4. Neural.
   parasympathetic (stimulates)
   sympathetic (inhibits)

Glucagon

- Linear peptide of 29 amino acids

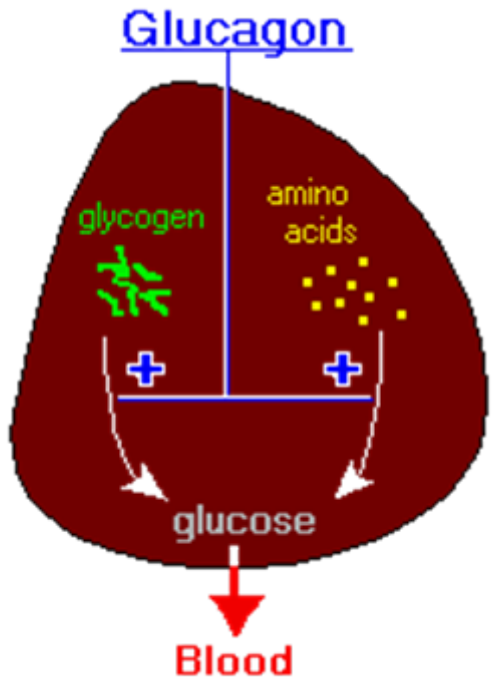
- Its primary sequence is almost perfectly conserved among vertebrates

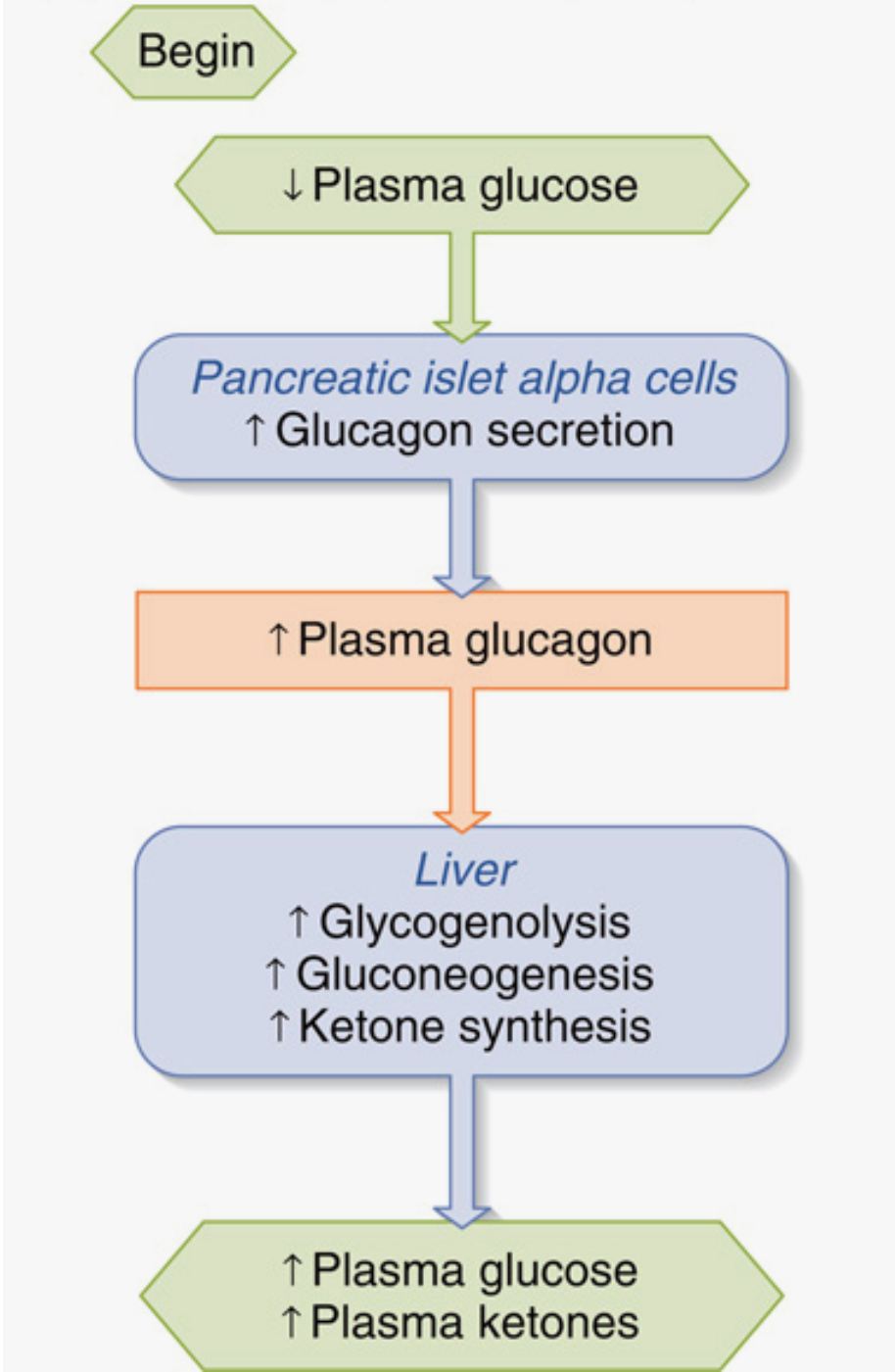
- The major effect of glucagon is to stimulate an increase in blood concentration of glucose

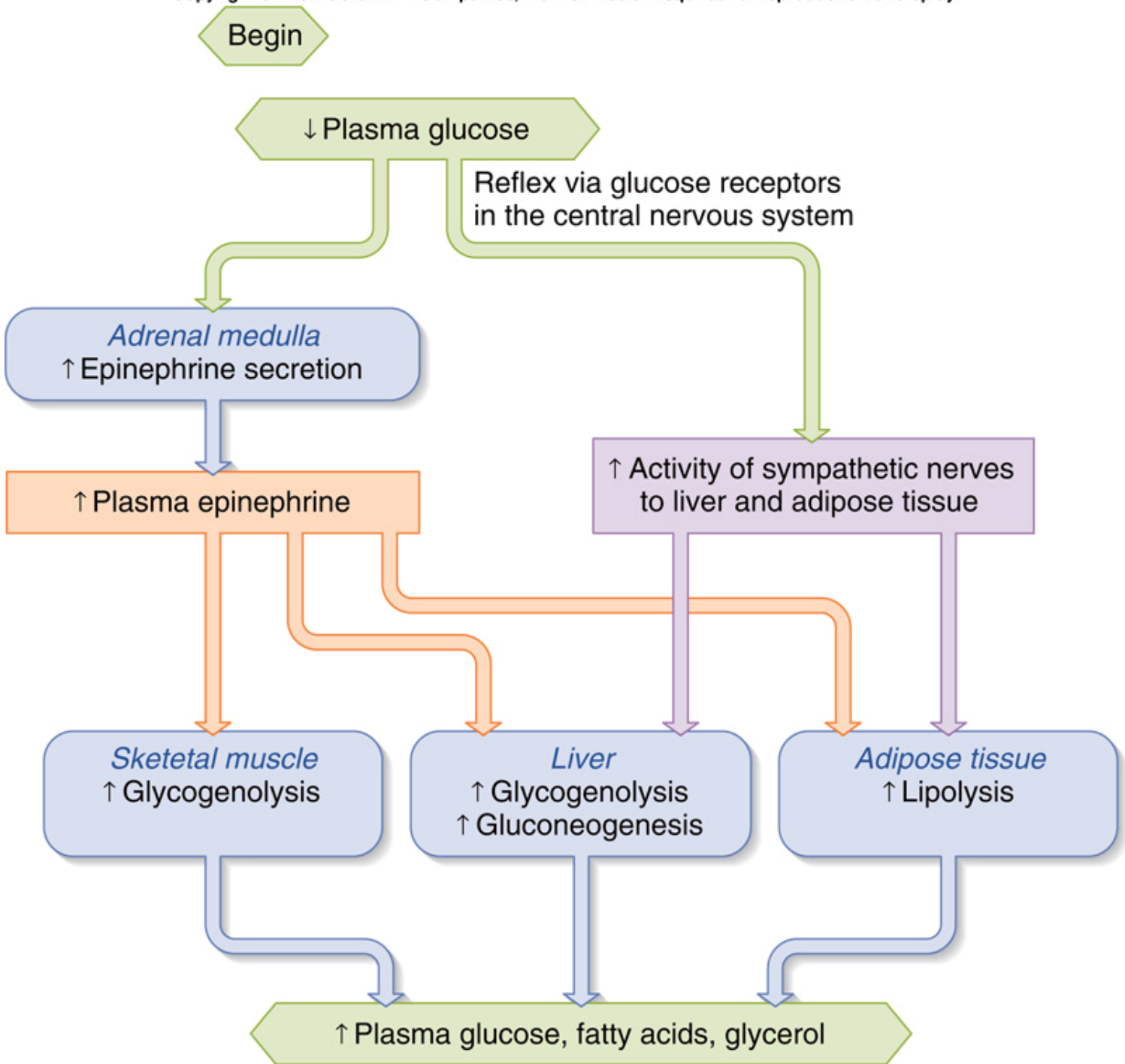


Physiological effects of glucagon.

1. glycogenolysis (liver).
2. gluconeogenesis (liver).
3. lipolysis (adipose tissue, minor)







Regulation of glucagon secretion.

1. **Negative feed-back.**
   (glucose suppresses)

2. ***2. Amino-acids (gluconeogenesis, e.g. after protein rich meals)**
   (prevent hypoglycaemia)

3. **Sympathetic nervous system stimulates.**

4. **Effect of insulin lack. (Insulin inhibits)**
5. **Exercise**

***Since high blood levels of amino acids also stimulate insulin release, this would be a situation in which both insulin and glucagon are active.**

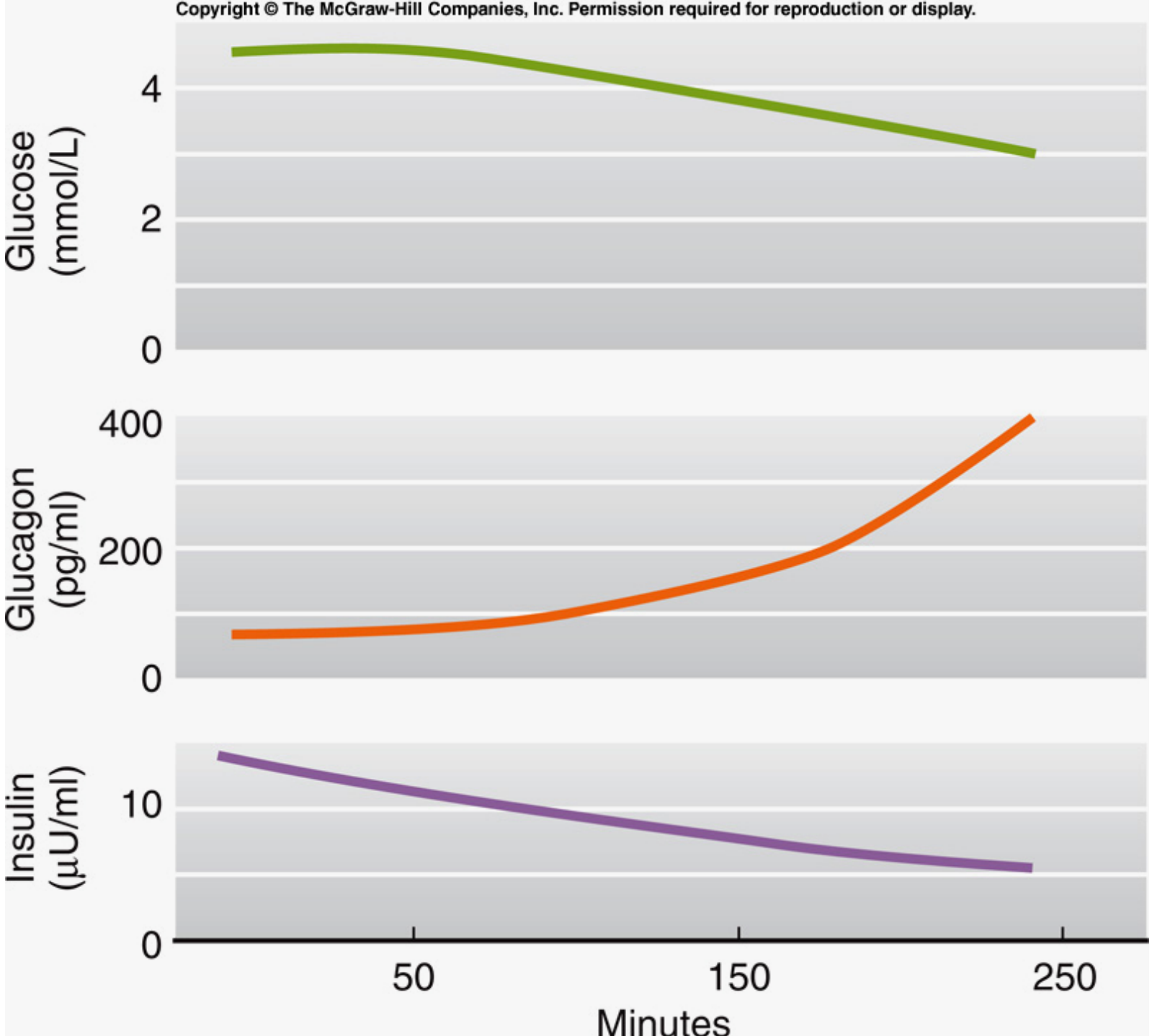
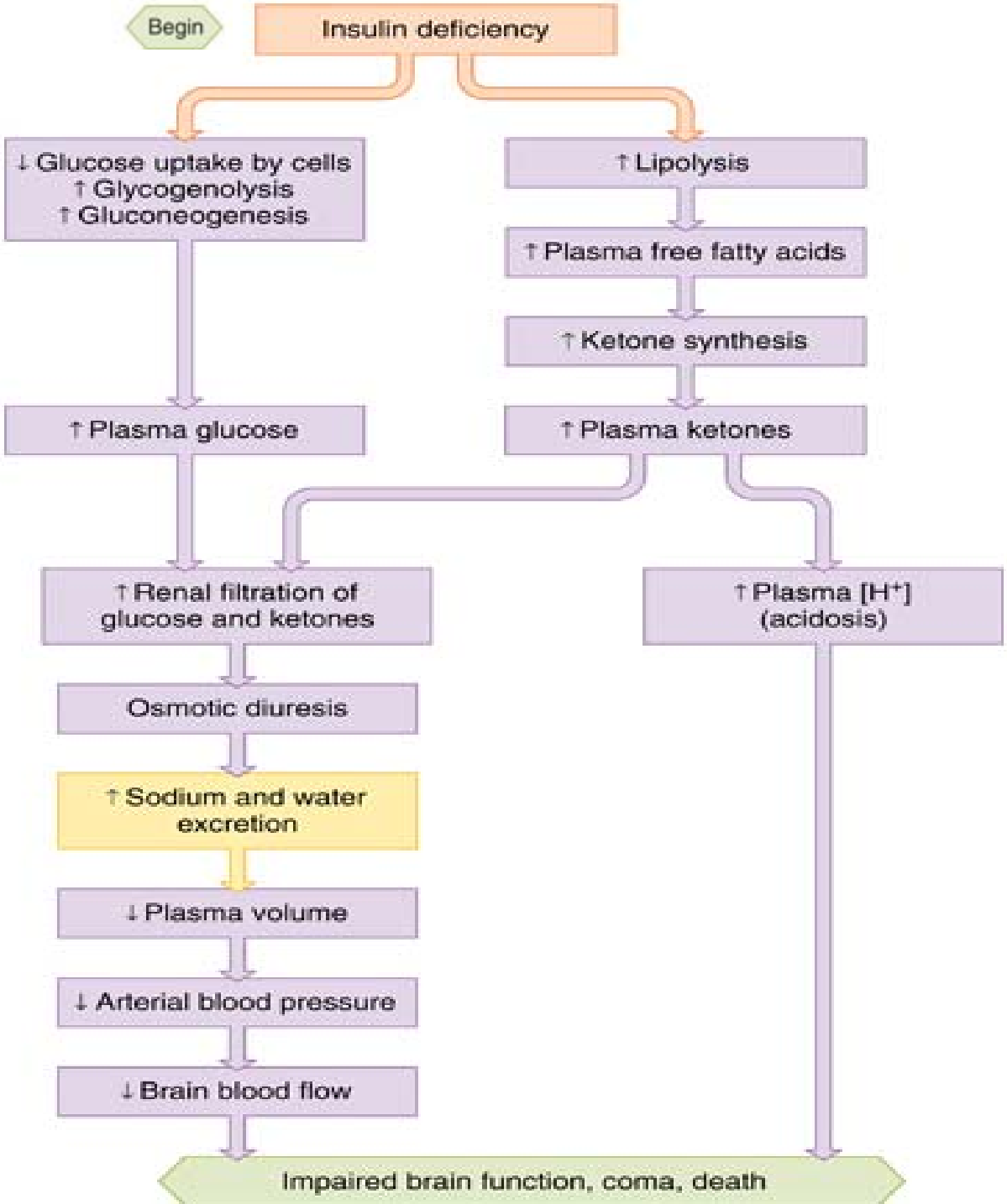


TABLE 16–4 *Summary of Glucose-Counterregulatory Controls**

	GLUCAGON	EPINEPHRINE	CORTISOL	GROWTH HORMONE
Glycogenolysis	✓	✓		
Gluconeogenesis	✓	✓	✓	✓
Lipolysis		✓	✓	✓
Inhibition of glucose uptake by muscle cells and adipose tissue cells			✓	✓


Begin
Insulin deficiency
↓ Glucose uptake by cells
↑ Glycogenolysis
↑ Gluconeogenesis
↑ Lipolysis
↑ Plasma free fatty acids
↑ Ketone synthesis
↑ Plasma glucose
↑ Plasma ketones
↑ Renal filtration of glucose and ketones
↑ Plasma [H+] (acidosis)
Osmotic diuresis
↑ Sodium and water excretion
↓ Plasma volume
↓ Arterial blood pressure
↓ Brain blood flow
Impaired brain function, coma, death

Insulin Deficiency

Two principal forms

1. **Type I or insulin-dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion**
2. **Type II or non-insulin-dependent diabetes mellitus, is caused by decreased sensitivity of target tissues to the metabolic effect of insulin (insulin resistance)**

Type I or insulin-dependent diabetes mellitus

- **Result of a deficiency of insulin.**
- **Onset is typically in childhood (at about 14 years of age in US)**
- **Due to destruction pancreatic B cells, most likely the result of autoimmunity or viral infections to one or more components of those cells.**
- **May have heredity tendency for beta cell degeneration even in the absence of viral infections or autoimmune disorders**

Type I diabetes

Can develop abruptly in a period of few days or weeks

1. blood glucose surge
2. Increased utilization of fats for energy and formation of cholesterol by the liver
3. Increased protein breakdown

Consequences

1. High levels of blood glucose (100mg/dl up to 300-1200mg/dl)
2. Loss of glucose in urine
3. Dehydration
4. Tissue injury due to chronic high glucose level (inadequate blood supply to the tissues leads to increased risk of heart attack, stroke, kidney disease, retinopathy and blindness, and ischemia of the limbs)
5. Metabolic acidosis (pH 7.4 $\rightarrow$pH 6.9) due to increased utilization of fat
6. Weight loss
7. Lack of energy

Physiological compensations for metabolic acidosis

1. In lungs, hyperventilation helps to remove excessive carbon dioxide (also at expense of some bicarbonate as well)
2. In kidneys, excretion of bicarbonate will be reduced together with increased production of new bicarbonate to be added back to the extracellular fluid

Type II or non-insulin-dependent diabetes mellitus

- Result of insulin resistance
- Target tissues fail to respond appropriately to insulin.
- The onset of this disease is in adulthood (after 30 years of age).
- Accounts for ~90% of all diabetic cases
- Is associated with increased plasma insulin concentration (hyperinsulinemia) which is a compensatory response by the pancreatic beta cells for reduced sensitivity of target cells to insulin
- The decrease in insulin sensitivity impairs carbohydrate utilization and storage and raises blood glucose level and therefore stimulating a compensatory increase in insulin secretion

- The culprit for Type II diabetes is obesity and excess weight gain
- Several studies have linked obesity with decreased insulin receptors esp. in the skeletal muscle, adipose tissue and liver
- However, most of the insulin resistance seems to be caused by abnormalities of the signaling pathway mediated by insulin

Insulin resistance

Forms part of the cascade of metabolic symptoms which have the following features

1. Obesity
2. Insulin resistance
3. Fasting hyperglycaemia
4. Increased blood triglycerides and decreased blood (high-density lipoprotein)cholesterol
5. Hypertension

Other factors that can cause insulin resistance and Type II diabetes

1. Cushing syndrome/acromegaly/steroid therapy have been suggested to decrease the sensitivity of certain tissues to the metabolic effects of insulin
2. Polycystic ovary syndrome (PCOS) increases ovarian androgen production and insulin resistance; insulin resistance and hyperinsulinemia appears to be found in ~80% of affected women

Clinical features of Type I and Type II diabetes

Feature	Type I	Type II
Age at onset	<20 years	>30 years
Body mass	Low to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, insulin

Diagnosis

1. Urinary glucose
2. Fasting blood glucose and insulin levels

   - normal level is 90mg/dl, upper limit of normal is 110mg/dl, anything above indicates DM or marked insulin resistance
   - In type I diabetes, **plasma insulin levels are low or undetectable** during fasting and sometimes even after a meal
   - in type II diabetes, plasma insulin may be **several fold higher in conc. than normal** and usually increases to greater extent after ingestion of glucose

Diagnosis

3. Glucose tolerance test

- When a normal fasting person ingests 1g of glucose (per kg body weight), the blood glucose level rises from about 90mg/dl to 120mg/dl to 140mg/dl and falls back to below normal in about 2 hours
- In persons with diabetes, the fasting blood glucose conc. is always above 110mg/dl and often above 140mg/dl
- With ingestion of glucose, diabetic people show a much greater increase in blood glucose level than normal people and it usually takes longer for the glucose level to fall back to normal (4-6 hours)
- Also, it fails to fall below the control level

Diagnosis

4. Acetone breath

- The presence of acetoacetic acid in the blood is greatly elevated in severe diabetes and they will be converted to acetone
- Acetone is volatile and vaporized into the expired air
- Ketoacids can also be determined in the urine by common lab test

Treatment

- In type I diabetes- insulin replacement therapy
- In type II diabetes- diet and exercise to reduce weight and to reverse insulin resistance; also exogenous insulin to regulate blood glucose

Hyperinsulinemia (excessive insulin secretion)

- Result of an insulin-secreting tumor.
- ~10-15% of these adenoma are malignant
- This condition is much less common than diabetes mellitus.
- Causes a precipitious drop in blood glucose
- The brain becomes starved for energy, leading to the syndrome of *insulin shock*, which is acutely life-threatening.
- Usually, ~1000g glucose has to be administered every 24 hours to prevent hypoglycemia in some patients

Glucagon deficiency or excess

- **Diseases associated with hypo- or hypersecretion of glucagon are rare.**
- **Cancers of alpha cells (glucagonomas) are one condition known to cause excessive glucagon secretion.**
- **These tumors typically lead to a wasting syndrome and, interestingly, rash and other skin lesions.**
- **Many diabetic patients with hyperglycemia also have elevated blood concentrations of glucagon, but glucagon secretion is normally suppressed by elevated levels of blood glucose.**