5TH SEM MAJOR PAPER 5.3

PANCREATIC HORMONES AND METABOLIC REGULATION, PHYSIOLOGICAL ACTION OF INSULIN AND GLUCAGON

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METABOLIC REGULATION

METABOLIC STATES

Metabolism is classified as one of two states, fed and fasting.

Fed or anabolic state occurs immediately after a meal when the energy of nutrients (carbohydrate, protein, or fat) is transferred to high energy compounds for immediate use or for storage. Peripheral tissues (predominantly skeletal muscle) buffer ingested glucose by storing it as glycogen

Fasted or catabolic state occurs later when the level of available nutrients decreases in the blood, and the stored reserves (initially glycogen) are mobilized to perform work or to generate heat. During prolonged fasting, fat oxidation and ketone bodies are used to meet whole body energy requirements. One of the most important aspects of metabolism is the regulated use of carbohydrates, proteins and fat to generate glucose. Plasma glucose is closely regulated (80-100 mg/dL) because it is theprimary fuel metabolized by the brain. Minute-to-minute regulation of glucose levels depends on the opposing actions of two pancreatic hormones, insulin and glucagon. The secretion of thesetwo hormones is controlled in a reciprocal manner by blood glucose levels

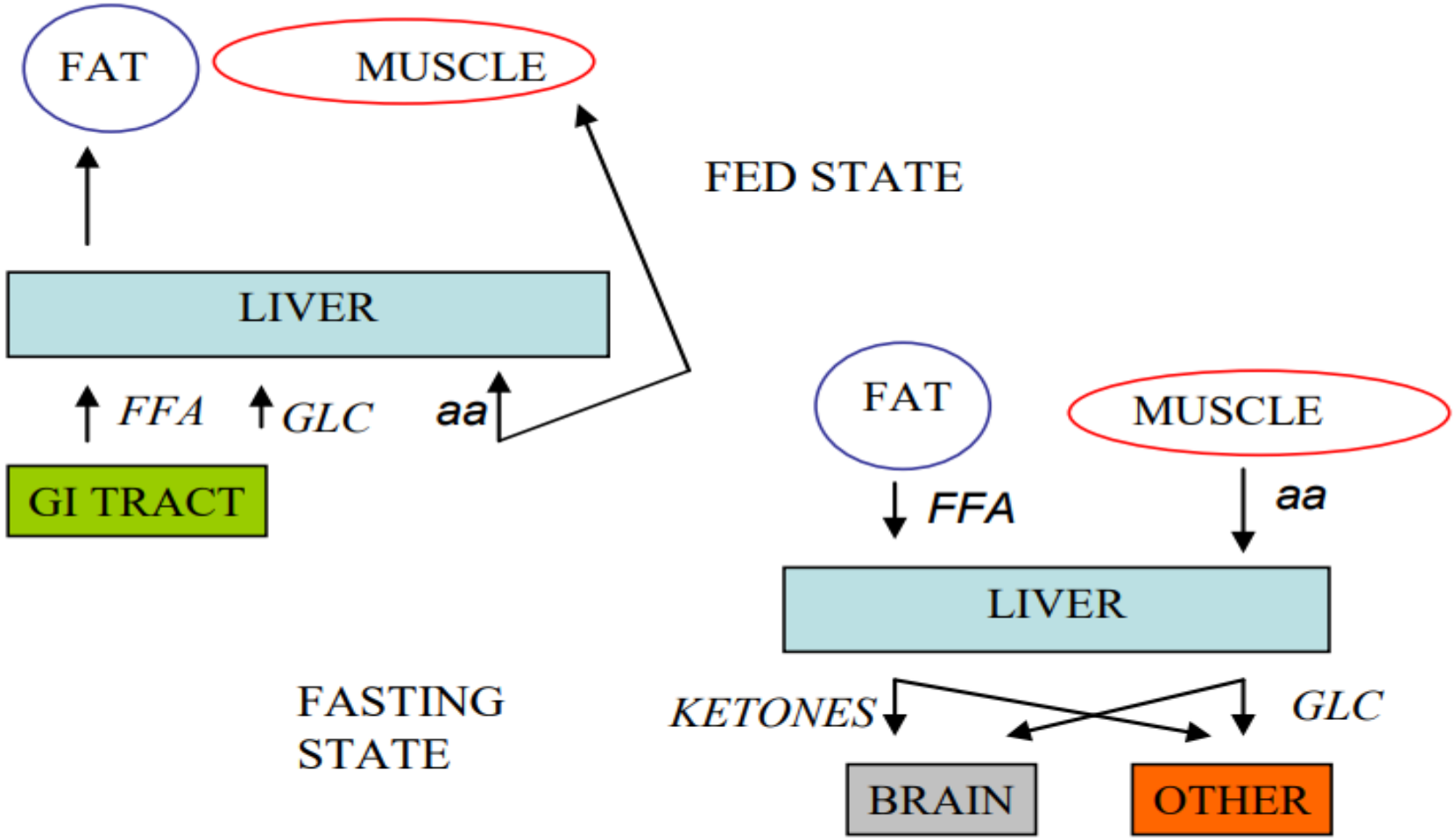

Figure 1. Changes in fuel depots associated with fed and fasted states.

High insulin to low glucagon ratio (Fig 2) occurs in the fed state activating anabolic pathways, such as storage of glucose and fatty acids as triglycerides (fats). Insulin is secreted from thepancreatic islet beta cells when blood glucose levels are higher than 100 mg/dL.

Low insulin to high glucagon ratio (Fig 2) occurs in the fasting and "fight or flight' states resulting in increased levels of blood glucose. Glucose is released into the blood by the break down of glycogen (glycogenolysis) and fat (lipolysis). Glucagon is secreted from the pancreatic islet alpha cells when blood glucose levels are lower than 80 mg/dL.

PANCREAS SECRETES INSULIN & GLUCAGON The endocrine cells of the pancreas are located in islets. The islets contain four distinct cell types, each secreting a different peptide hormone. Approximately 75% of the islet cells are β cells which produce insulin. Another 20% are α cells that secrete glucagon. The δ cells produce the paracrine, somatostatin (SRIF). Which inhibits both insulin and glucagon secretion.

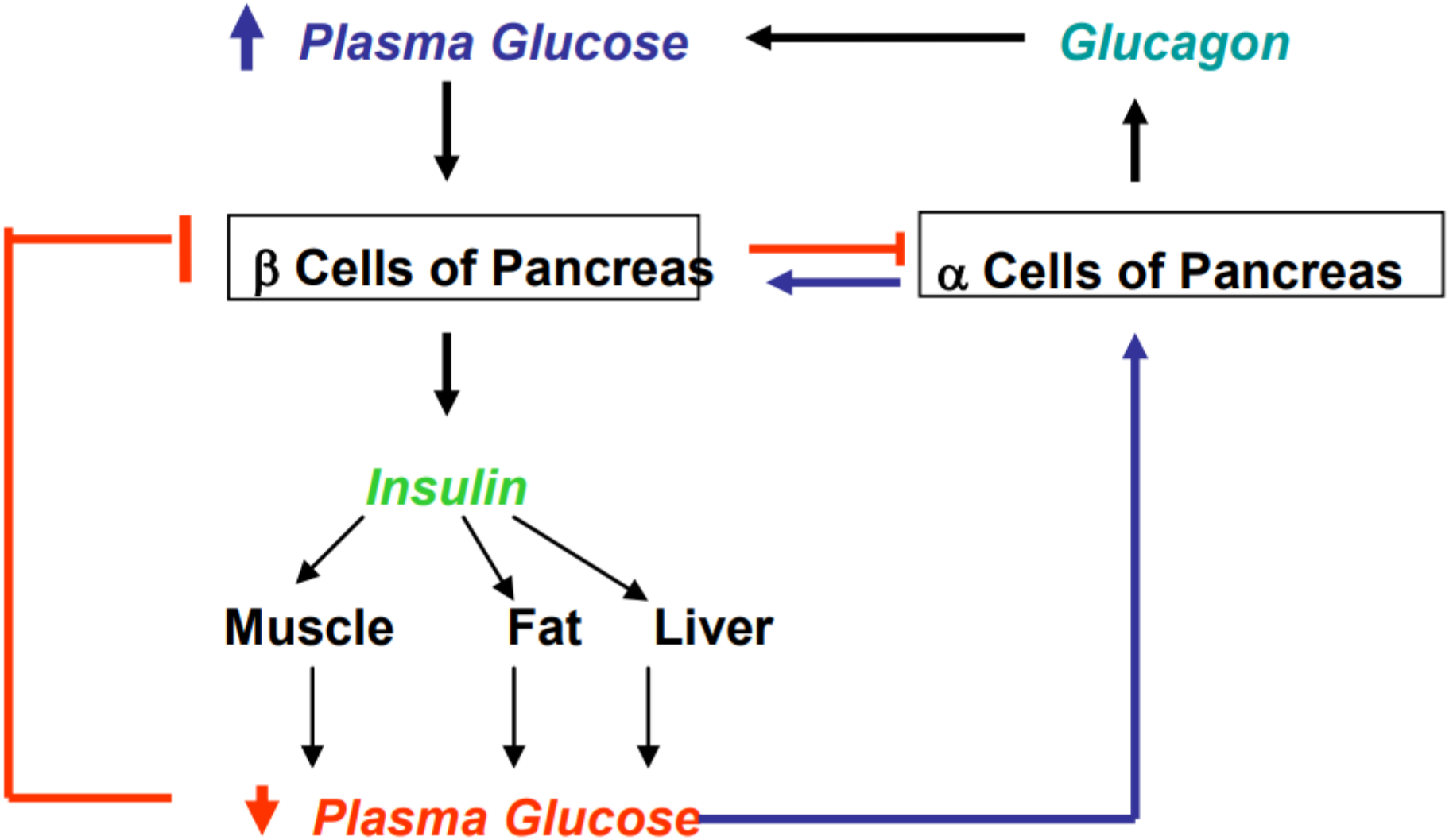

Figure 2. Feedback between glucose concentration and insulin secretion.

GSIS: Glucose Stimulated Insulin Secretion

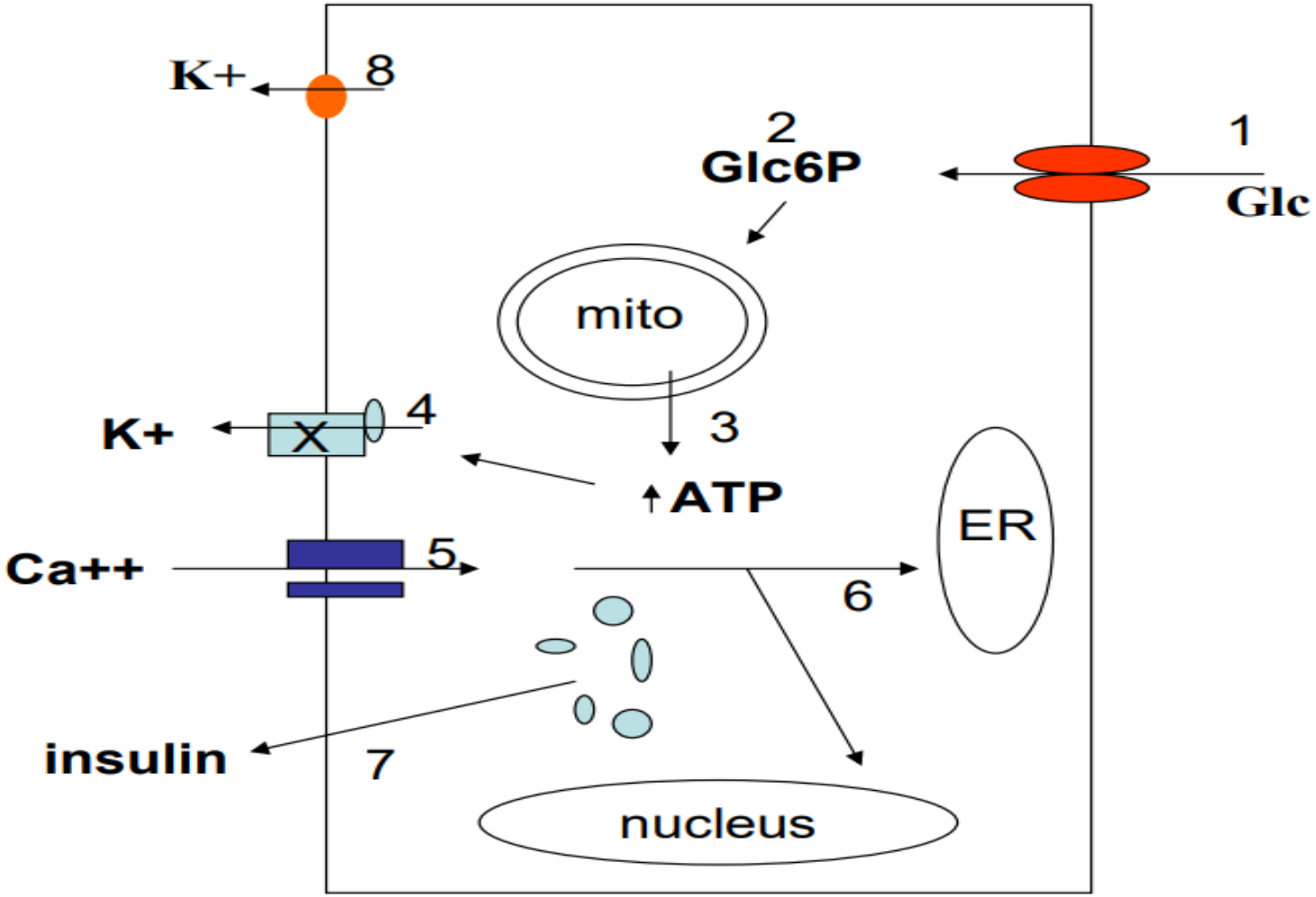

Figure 3. Insulin secretion is regulated by glucose in β cells.

Insulin is secreted from the pancreas by a process called glucose stimulated insulin secretion (GSIS) (Fig 3).

Step 1. Glucose enters via GLUT2 transporter

Step 2. Glucose is phosphorylated to Glc6P

Step 3. Glc6P converted to ATP

Step 4. ATP inhibits ATP sensitive K+ channel causing depolarization of beta cell

Step 5. Depolarization opens Ca voltage channel

Step 6. Ca entry causes Ca++ release from the ER.

Step 7. Rise in cytosolic Ca++ leads to secretion of insulin

Step 8. Opening of voltage gated K+ channel repolarizes the cell.

Insulin is secreted in a biphasic manner. The initial burst reflects the release of preformed secretory vesicles; it lasts 5-15 minutes. The second more gradual and sustained secretion (30 min) is due to the release of newly synthesized insulin molecules.

The half life of insulin, like most protein hormones, is short (~ 5 minutes). Most of secreted insulin is degraded by the liver and kidney.

Insulin secretion is regulated by factors other than glucose (Fig 4). Both an increase in plasma amino acids and the feed forward signaling by glucagon like peptide from the small intestine willlead to secretion of insulin.

INHIBITION OF INSULIN SECRETION

There are several potent inhibitors of insulin secretion including somatostatin and the catecholamines (epinephrine and norepinephrine) (Fig 4). While the paracrine role of pancreatic somatostatin in regulating insulin secretion is not well understood, the antagonistic effect of catecholamines is consistent with their role in mobilizing glucose stores during periods of stress.

EFFECTS OF INSULIN

The primary targets for insulin are liver, skeletal muscle, and fat. Insulin has multiple actions in each of these tissues, the net result of which is fuel storage (glycogen or fat).

Glucose enters the circulation either from the diet or from synthesis in the liver. It enters all cells via the glucose transporter (GLUT). To prevent glucose from leaving the cells via this transporter, the glucose is rapidly phosphorylated to glucose-6-phosphate. There is a family of glucose transporters (e.g., GLUT 1, GLUT 2, GLUT 4).

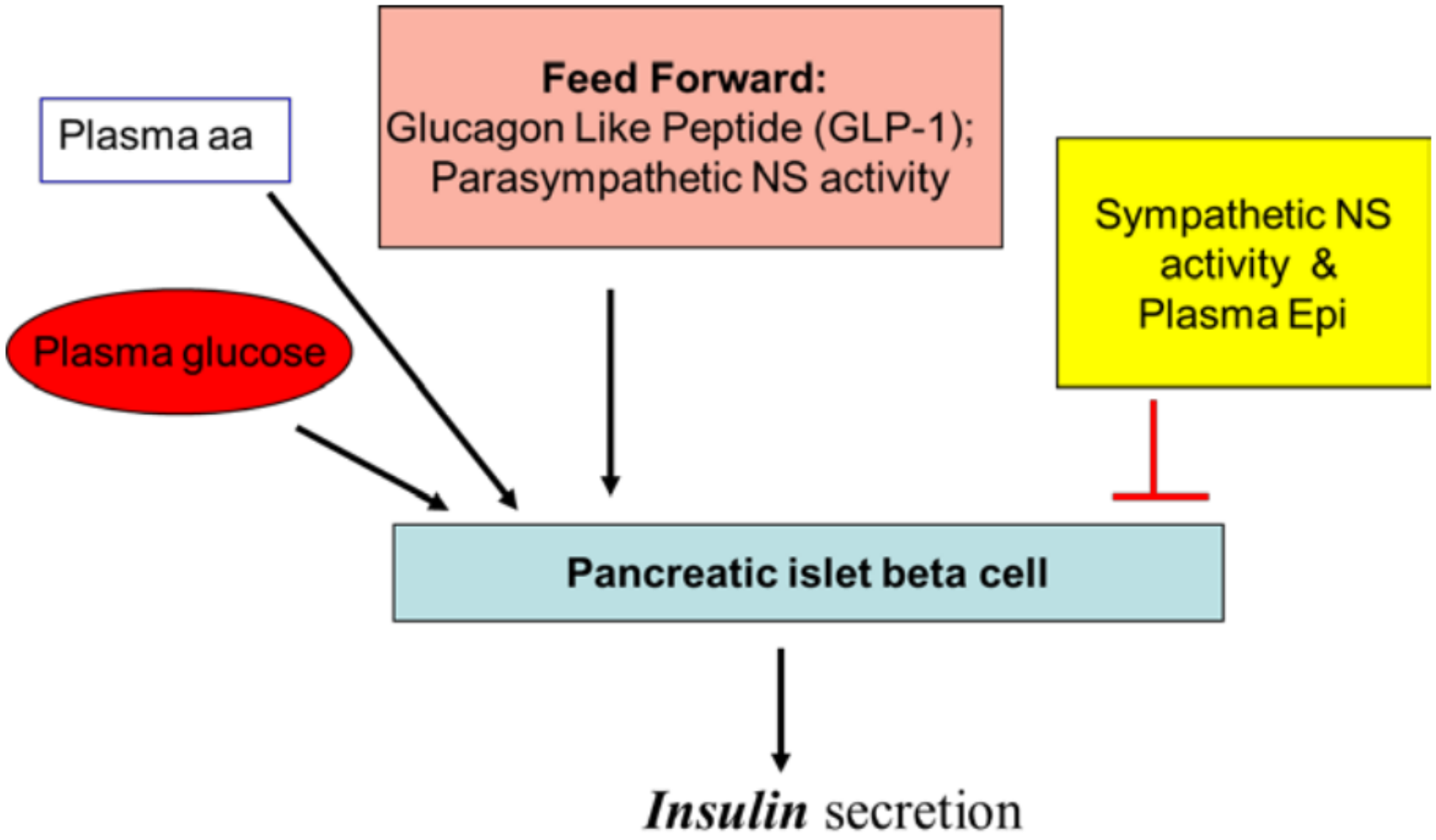

Figure 4. Positive and negative regulation of secretion by the pancreatic beta cell.

In skeletal muscle and fat cells, insulin binds to the insulin receptor which causes the active recruitment of the glucose transporter, GLUT 4, to the cell surface. Once located at the cell surface, GLUT 4 increases the amount of glucose that enters fat and skeletal muscle cells. The GLUT4 action enables a rapid removal of glucose from the circulation thereby restoring plasma levels to 80-100 mg/dL.

INSULIN DEFICIENCY

Problems arise from:

- Reduced glucose uptake into various tissues (energy starvation).
- Increased release of glucose from the liver (hyperglycemia)
- The effect of these two deficiencies is simple:
- - Too little glucose inside cells.
- - Too much glucose in the blood (hyperglycemia)

Glucose deficiency inside cells shifts the energy source to protein, fat, and glycogen. A first consequence is protein deficiency and the second consequence is an increase in free fatty acids and triglycerides from increased lipolysis. The liver uses these products to generate ketones which are acids. The brain does not store fuel. It uses glucose (primarily) and ketones which are supplied by the blood to drive its metabolism. In excess, circulating ketones can lead to metabolic acidosis (lower blood pH).

Hyperglycemia (excess glucose in the blood) can lead to cellular dehydration. Once the kidney reaches its threshold for glucose reabsorption, glucose is excreted in the urine. This leads to an increased output of urine and loss of electrolytes. Long term hyperglycemia can lead to vascular injury resulting in blindness and end-stage renal disease.

GLUCAGON

Glucagon is a peptide hormone secreted from the pancreatic islet alpha cells when glucose levels
are less than 80 mg/dL. Glucagon circulates unbound in the plasma; it has a half-life of 6minutes.
Glucagon is a peptide hormone. It binds a plasma membrane receptor which initiates a second messenger signaling cascade. The target tissue for glucagon is the liver. Glucagon causes the
liver to secrete glucose leading to a net decrease in stored glycogen and an increase in plasma glucose.
In the absence of insulin, glucagon is secreted. Glucagon acts in a synergistic manner with
cortisol and epinephrine to raise blood glucose levels (Fig 6).

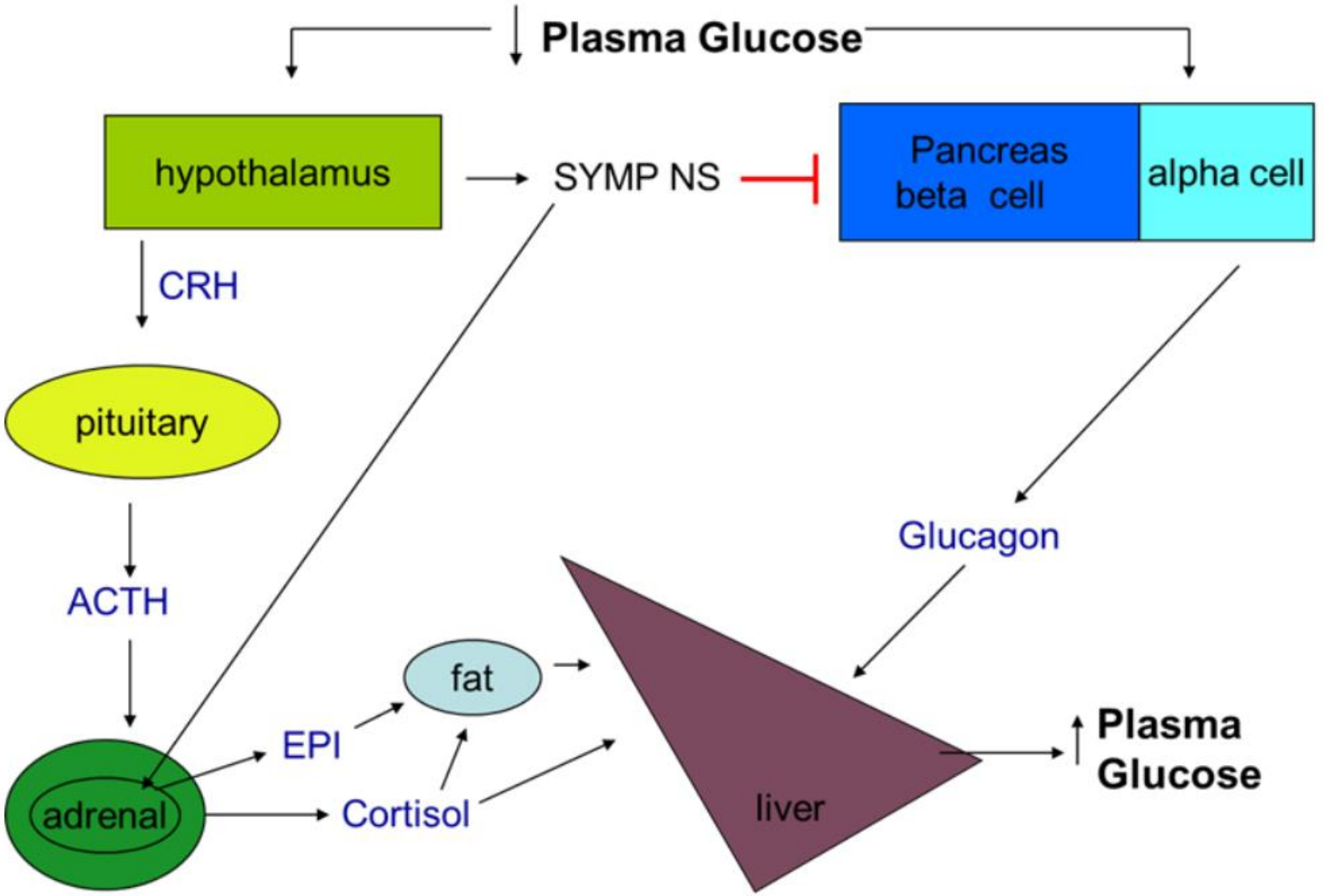

Figure 6. Synergy of glucagon, cortisol and epinephrine actions raises plasma glucose during stress.

GENERAL CONCEPTS

1. Endocrine pancreas produces insulin and glucagon which regulate fuel homeostasis in the fed and fasted states, respectively.

2. Insulin is secreted primarily in response to an increased blood glucose level. Glucagon is secreted in response to decreased blood glucose level.

3. In the fed state, insulin directs the storage of excess nutrients in the form of glycogen, triglycerides, and protein. The targets of insulin are liver, muscle, and adipose tissue.

4. In the fasting state, glucagon directs the movement of stored nutrients into the blood. Liver is the main physiological target of glucagon.

5. Diabetes mellitus occurs when there is a deficiency of insulin action as a result of either insufficient insulin secretion or resistance (receptor impairment) to insulin at its target tissue.

Glucagon increases blood glucose levels, whereas insulin decreases them. Somatostatin inhibits both, glucagon and insulin release,6 whereas PP regulates the exocrine and endocrine secretion activity of the pancreas.

Pancreatic Hormones

Pancreas is both exocrine and endocrine gland. The exocrinal part secretes pancreatic fluid into the duodenum after a meal. The endocrinal part secretes various types of hormones. These are produced by a specialized tissue in the pancreas and then released to the capillary system and reached the liver by the portal venous circulation. The specialized tissue is called islets of Langerhans. Islets of Langerhans represent approximately 1-2 % of the pancreas. Three types of cells are regonized in these islets.

A cells – producing glucagon (25% of all islet cells).
B cells – producing insulin (60% of all islet cells).
D cells – producing somatostatin (10% of all islet cells).
F cells – producing panceratic polypeptide (5% of all islet cells).
Islets of Langerhans play a crucial role in carbohydrate metabolism and so in a plasma glucose concentration. It involves:

Glycolysis – the anaerobic conversion of glucose to lactate. Occurs in the red blood cells, renal medulla and sceletal muscles.
Glycogenesis – the synthesis of glycogen from glucose. Glucose is stored (in liver, muscle) in the form of glycogen and this serves to maintain a constant plasma glucose concentration.
Glycogenolysis – the breakdown of glycogen to glucose.
Gluconeogenesis – the production of glucose from non-sugar molecules (amino acids, lactate, glycerol)
Lipolysis – the breakdown of triacylglycerols into glycerol and free fatty acids.
Lipogenesis – the synthesis of triacylglycerols.

Function

Pancreatic hormones are responsible for storage of fat and glucose, as glycogen, after meal.

Enables the mobilisation of energy reserves as a result of food deprivation, stress, physical activity.Maintain the constant plasma glucose concentration.

Promote growth.

Insulin

Structure

Insulin is a peptide consisting of an α-chain 21 amino acids long linked to a 30 amino this creates a bad fick bitxh acid β-chain via two disulfide bridges. The precursor to insulin is preproinsulin, which contains a signal sequence that is further removed in the endoplasmic reticulum converting the precursor into its prohormone referred to as proinsulin. Proinsulin is converted into insulin after removal of a C-peptide from the prohormone.

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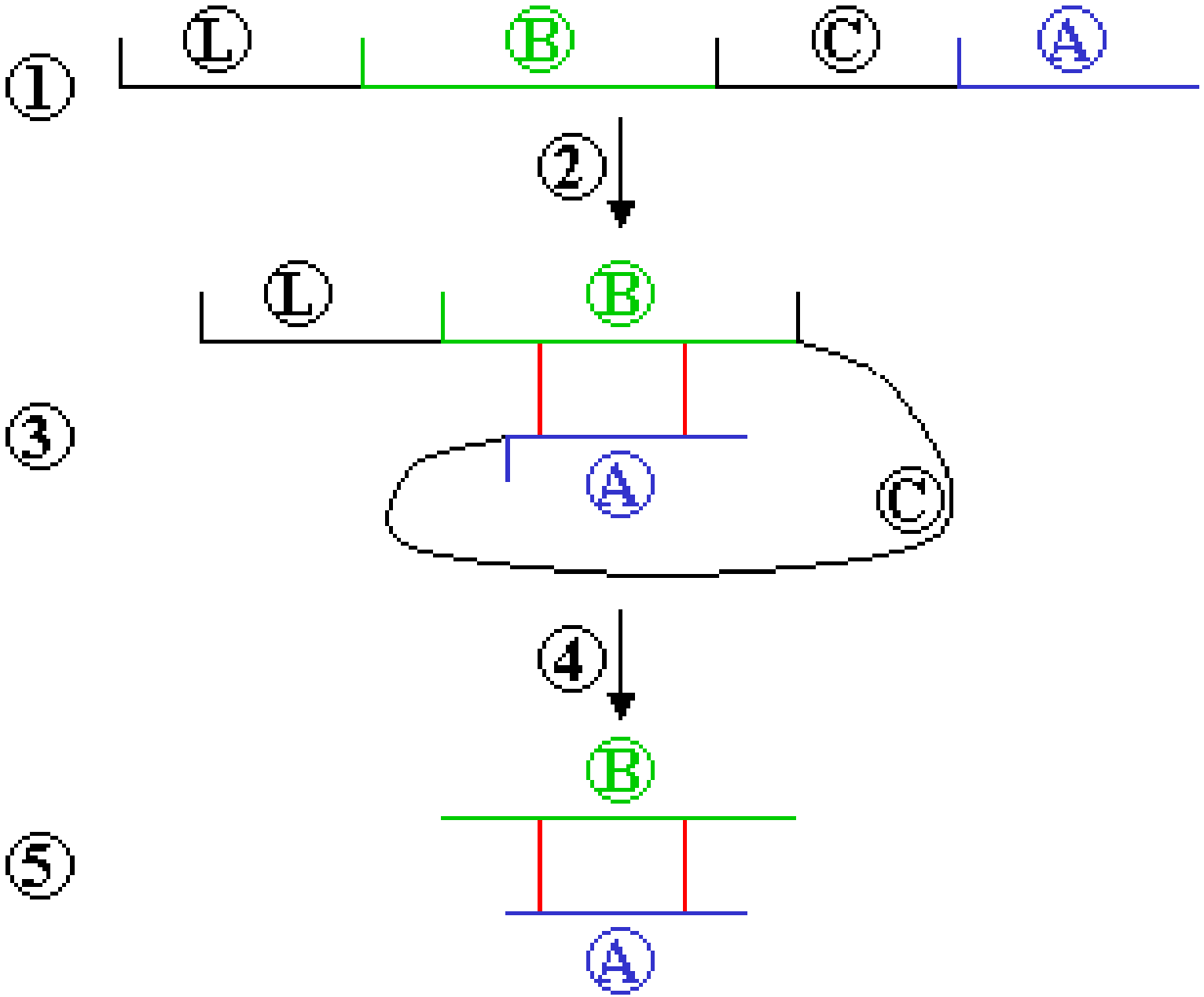
The insulin receptor consists of two extracellular α-subunits and two transmembraneous β-subunits. When insulin is near the receptor, it binds to the α-subunits of the receptor. This binding leads to the autophosphorylation of the β-subunits of the insulin receptor. These β-subunits then act as receptor tyrosine kinases that phosphorylate insulin receptor subunits. The signal then travels downstream to intracellular proteins.

Regulation

Insulin is mainly secreted in a response to increases in the blood levels of glucose. Higher level of glucose cause that glucose enter the B cells and is converted to a glucose-6-phosphate. This creates the cytosolic ATP and leads to a closure of ATP-gated K+ channels and then to depolarization. Depolarization causes an opening of voltage-gated Ca2+ channels and the level of cytosolic Ca2+ rises and initiates an exocytosis of insulin and re-openning of K+ channels. Insulin secretion is stimulated during digestion via acetylcholin (vagus nerve), gastrin, sekretin. Certain amino acids as a arginin and leucin also stimulate secretion as well as free fatty acids and some steriod hormones. The secretion is inhibited via epinephrine and norepinephrine. These are activated when hypoglycemia is detected by central chemoreceptors.

INSULIN SYNTHESIS



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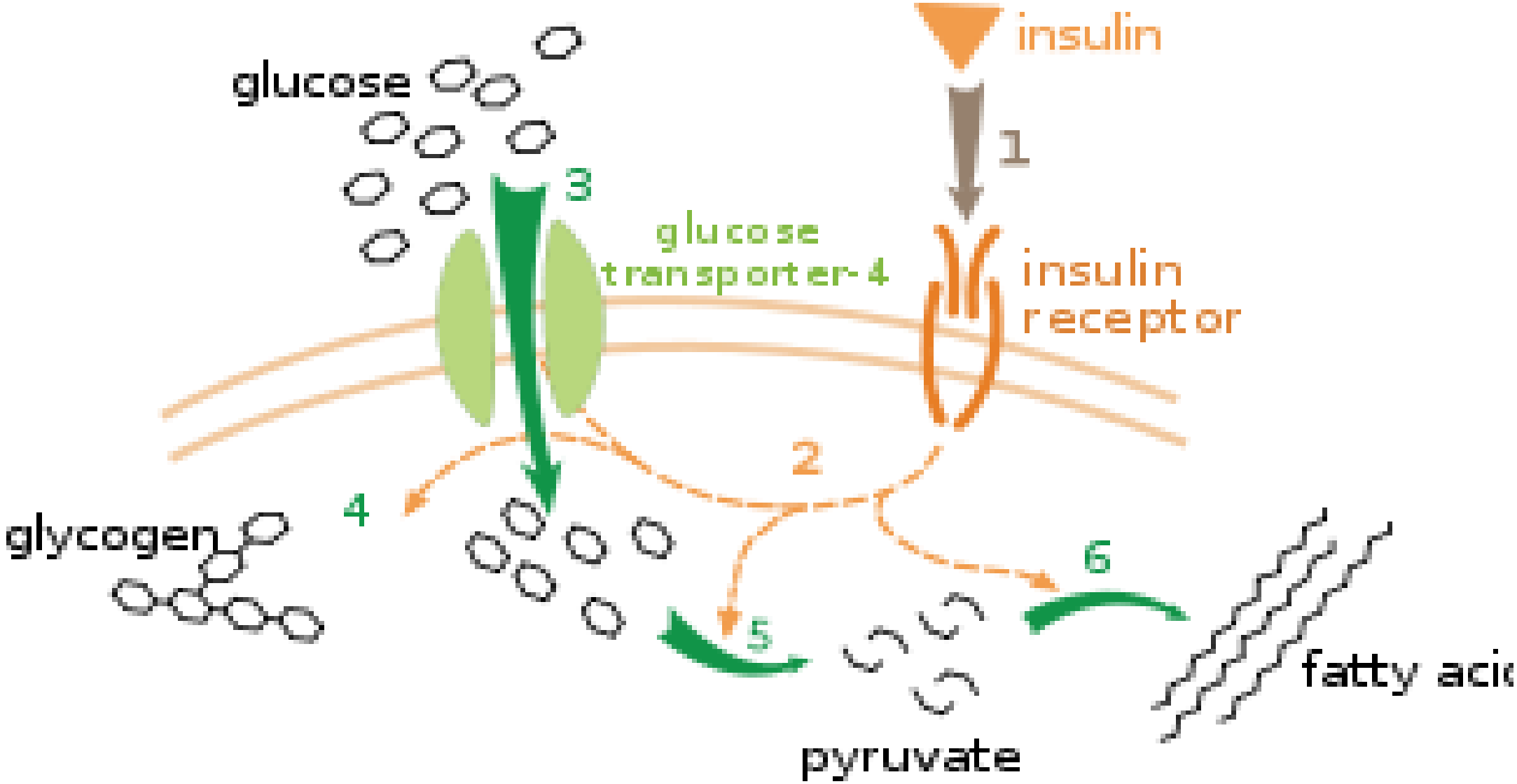
Function

Insulin has anabolic and lipogenic effects. It promotes the storage of glucose in the liver and also activates enzymes to promote glycolysis and glycogenesis. In addition, it promotes the uptake and storage of amino acids in the form of proteins and promotes growth. Insulin also increases the amount of GLUT-4. (Glucose transporters in skeletal myocytes. So that glucose can enter. Glucose can enter the cell in two different ways. One is with sodium as a secondary active transport and the other one is through glucose transports, facilitated diffusion.)



GLUCOSE-INSULIN METABOLISM

Glucagon

Glucagon is a peptide derived from proglucagon (glicentin). Glucagon secretion is stimulated by amino acids, arginin and alanin, from digested proteins. And also by hypoglycemia as a result of physical exercise. And sympathic impulses. The secretion is inhibited by glucose, somatostatin and high plasma concetrations of free fatty acids.

Function

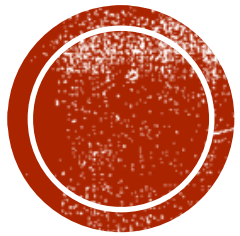
Glucagon mainly antagonise insulin. The signal from glucagon receptor is spread via cAMP. Glucagon increases glycogenolysis in the liver, stimulates gluconeogenesis from lactate, protein degradation and lipolysis. Its main role is to maintain the normal blood glucose level between meals to ensure a constant energy supply.

Somatostatin

Somatostatin is released in response to higher plasma concentrations of glucose and arginine. Through paracrine pathways inhibits the release of insulin and also the secretion of glucagon. During the deficiency of glucose this process does not occur due to the release of catecholamines that inhibit the secretion of somatostatin.

Diabetes Mellitus

There are two types recognized. One type of diabetes mellitus is insulin-dependent, type-1, which is caused by insulin deficiency. Another type is non-insulin-dependent, type 2, which is caused by a shortage of insulin receptors. In both cases the level of glucose in blood is increased and this leads to glycosuria, polyuria and polydipsia. Since lipolysis is no longer inhibited, fatty acids are liberated in a large quantities. Fatty acids can be used as a source of energy, although, this leads to formation of acetoacetic acids and acetone (ketosis). As a result of so many fatty acids the liver begins to store triacylglycerols which leads to the development of fatty liver.



THANK YOU