Disorders of carbohydrate metabolism

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INTRODUCTION:

The main function of glucose is as a major tissue energy source. Glucose is the only utilizable source of energy for some tissue ,for example erythrocytes (no have mitochondria) and central nervous system (this is because the brain cannot synthesize glucose, store glucose in significant amounts, metabolize substrates other than glucose and ketones

- plasma ketone concentration are usually very low and ketones are of little importance as an energy source under physiological conditions, and extract enough glucose from the extracellular fluid at low concentrations for its metabolic needs, because entry in to brain cells is not facilitated by insulin. The body's sources of glucose are dietary carbohydrate and endogenous (principally hepatic) production by glycogenolysis (release of glucose stored as glycogen) and gluconeogenesis (glucose synthesis from, e.g. lactate, glycerol and most amino acids).

- Blood glucose concentration depends on the relative rates of influx of glucose into the circulation and of its utilization. Following a meal, glucose is stored as glycogen, which is mobilized during fasting. Although the blood glucose concentration falls somewhat if fasting continues, and hepatic glycogen stores are used up after about 24 hours, adaptive changes lead to the attainment of a new steady state.

- After approximately 72 hours, blood glucose concentration stabilizes and can then remain constant for many days. The principal source of glucose becomes gluconeogenesis, from amino acids and glycerol, while ketones, derived from fat, become the major energy substrate.

- **Note:**
- Glycolysis pathways is employed by all tissues for the breakdown of glucose to provide energy (in the form of ATP) and intermediates for other metabolic pathways. Glycolysis is at the hub of carbohydrate metabolism because virtually all sugars whether arising from the diet or from catabolic reactions in the body- can ultimately be converted to glucose.

- Gluconeogenesis is formation of glucose from non carbohydrate molecules for example lactate, amino acids and glycerol. The integration of these various processes, and thus the control of blood glucose concentration, is achieved through the concerted action of various hormones: these are insulin and the 'counter regulatory' hormones, namely glucagon, cortisol, catecholamines and growth hormone. Physiologically, the two most important hormones in glucose homoeostasis are insulin and glucagon.

- Insulin is a 53 amino acid polypeptide, secreted by the B-cells of the pancreatic islets of Langerhans in response to a rise in blood glucose concentration. Insulin promotes the removal of glucose from the blood through stimulating the relocation of the insulin-sensitive GLUT-4 glucose transporter from the cytoplasm to cell membranes, particularly in adipose tissue and skeletal muscle.

- . Insulin also stimulates glucose uptake in the liver, but by a different mechanism: it induces the enzyme glucokinase, which phosphorylates glucose to form glucose 6-phosphate, a substrate for glycogen synthesis. This process maintains a low intracellular glucose concentration and thus a concentration gradient that facilitates glucose uptake. Insulin stimulates glycogen synthesis (and inhibits glycogenolysis) through interaction with an exquisitely coordinated control mechanism that is central to the regulation of blood glucose concentration. In summary, binding of insulin to its receptor leads to activation of protein phosphatase 1.

- This enzyme dephosphorylates both glycogen synthase (thereby activating it and promoting glycogen synthesis) and phosphorylase kinase (rendering it inactive and thus preventing the activation of glycogen phosphorylase, the key enzyme of glycogenolysis). As a result of these actions, in the fasting state, when insulin secretion is inhibited, hepatic glycogenolysis is stimulated and glucose is liberated into the blood. Insulin also exerts control over glycolysis and gluconeogenesis, stimulating the former and reciprocally inhibiting the latter, by stimulating the expression of phosphofructoldnase, pyruvate kinase and the enzyme responsible for the synthesis of the key allosteric modifier, fructose 2,6-bisphosphate (see Fig. I1.3).

Insulin is also important in the control of fat metabolism: it stimulates lipogenesis and inhibits lipolysis. It also stimulates amino acid uptake into cells and protein synthesis, and intracellular potassium uptake.

Clucagon is a 29 amino acid polypeptide secreted by the -cells of the pancreatic islets; its secretion is decreased by a rise in the blood glucose concentration. In general, its actions oppose those of insulin:

- it stimulates hepatic (though not muscle) glycogenolysis through activation of glycogen phosphorylase, gluconeogenesis, lipolysis and ketogenesis. The combined effects of insulin and glucagon are shown diagrammatically in Fig. 11.4. Disordered glucose homoeostasis can lead to hyperglycaemia (often to a degree diagnostic of diabetes) or to hypoglycaemia.

Hormones involved in glucose homoeostasis			
Hormone	**Principal actions**		
Insulin	Increases	cellular glucose uptake	M, A
		glycogen synthesis	L, M
		protein synthesis	*L, M*
		fatty acid and triglyceride synthesis	*L, A*
	Decreases	gluconeogenesis	L
		glycogenolysis	L, M
		ketogenesis	*L*
		lipolysis	*A*
		proteolysis	*M*
Glucagon	Increases	glycogenolysis	L
		gluconeogenesis	L
		ketogenesis	*L*
		lipolysis	*A*
Adrenaline	Increases	glycogenolysis	L, M
		lipolysis	*A*
Growth hormone	Increases	glycogenolysis	L
		lipolysis	*A*
Cortisol	Increases	gluconeogenesis	L
		glycogen synthesis	L
		proteolysis	*M*
	Decreases	tissue glucose utilization	L, M, A

Fig. 11.1 Hormones involved in glucose homoeostasis. Letters indicate sites of action: L = liver, M = skeletal muscle, A = adipose tissue. Normal type indicates actions directly affecting glucose; other effects are shown in italics.

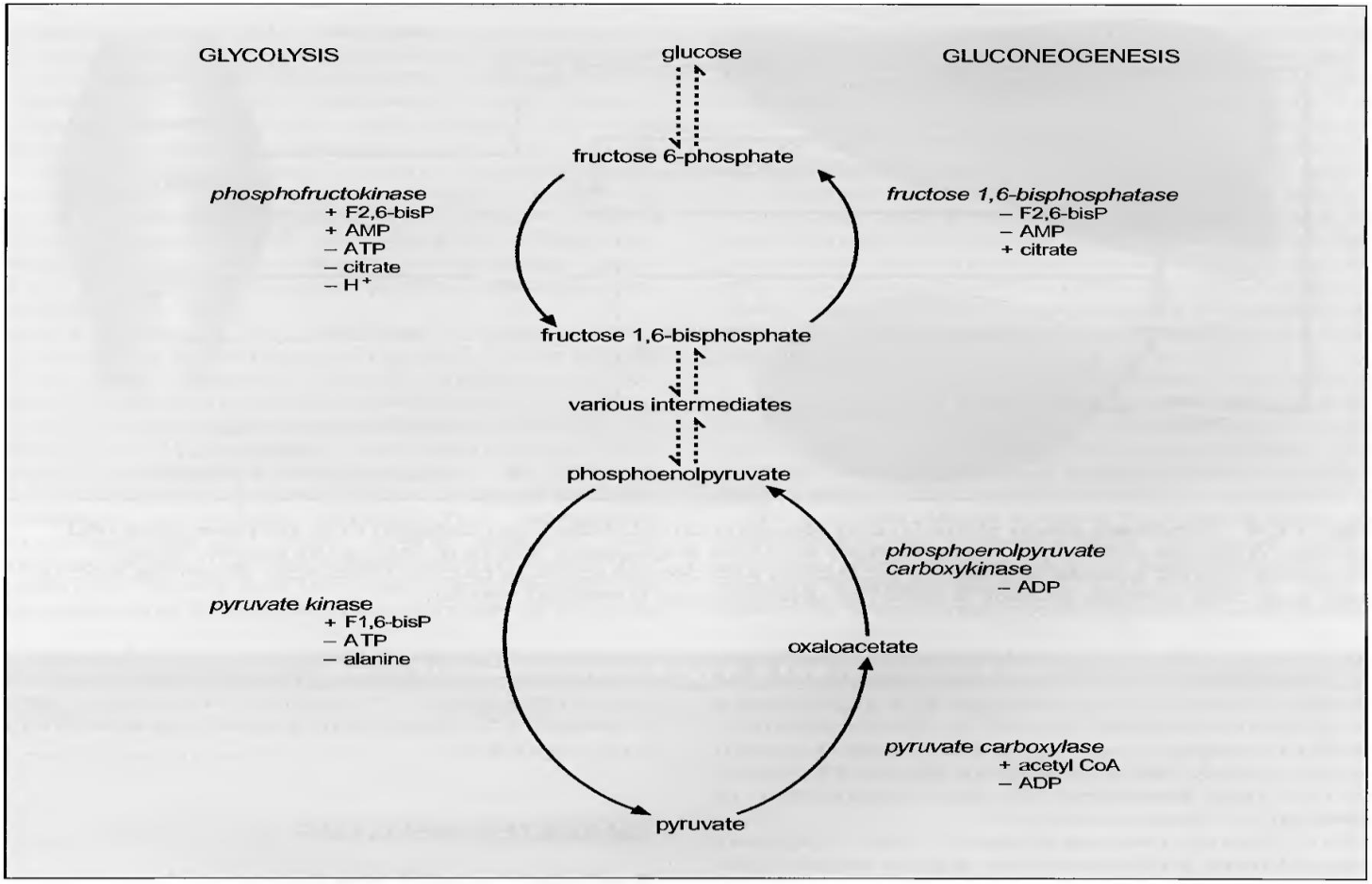

Fig. 11.3 Reciprocal control of glycolysis and gluconeogenesis in the liver. Insulin (released in the fed state) stimulates the expression of phosphofructokinase, pyruvate kinase and the enzyme responsible for the synthesis of fructose 2,6-bisphosphate (F2,6-bisP): glycolysis is promoted and gluconeogenesis is inhibited. Glucagon (released in the fasting state) inhibits expression of these enzymes and stimulates the production of phosphoenolpyruvate carboxykinase and fructose 1,6-bisphosphatase: gluconeogenesis is stimulated and glycolysis is inhibited.
The names of enzymes are given in italics. + Indicates substances that activate enzymes; – indicates substances that inhibit enzymes. ADP = Adenosine diphosphate; AMP = adenosine monophosphate; acetyl CoA = acetyl coenzyme A.

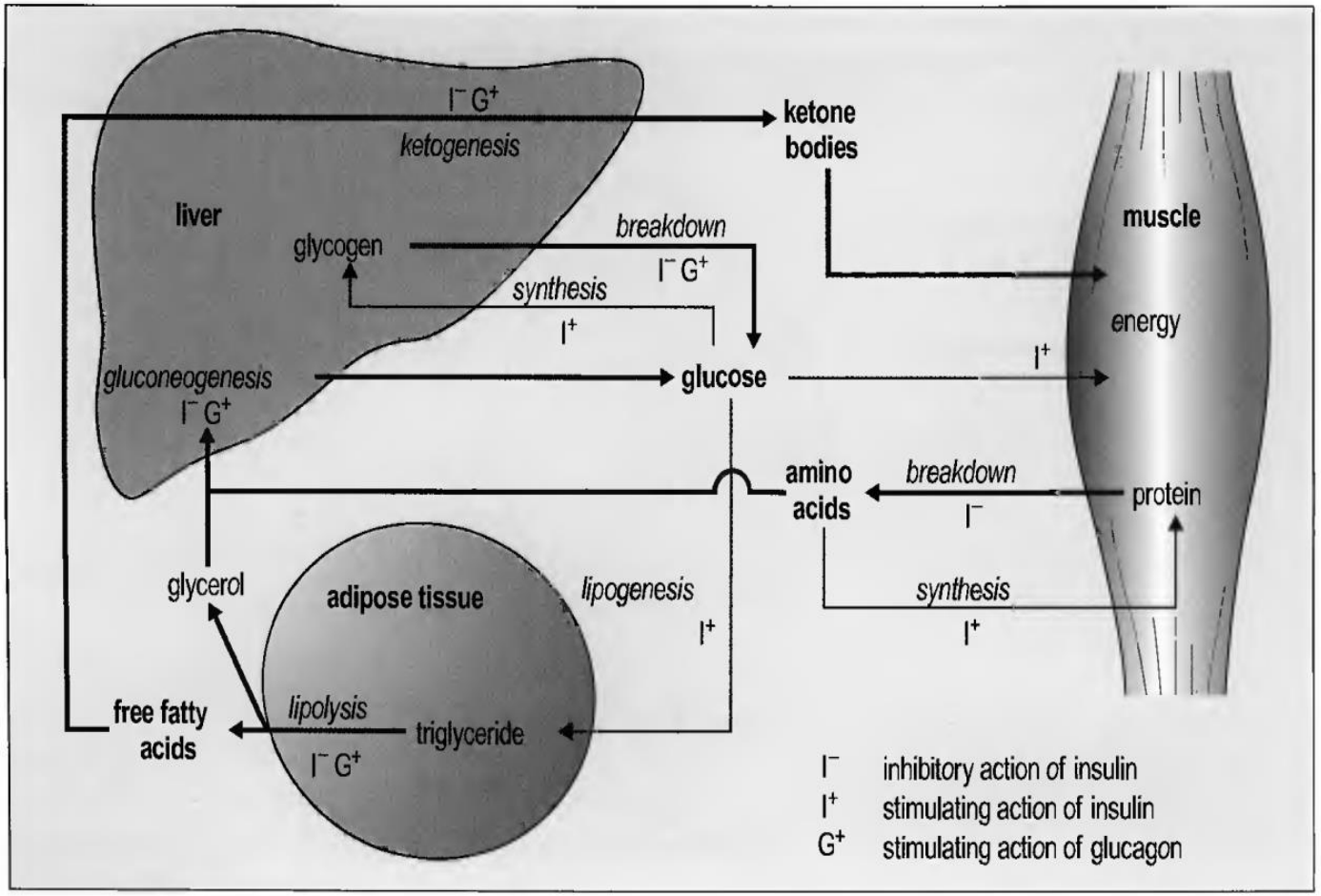

Fig. 11.4 Combined effects of insulin and glucagon on substrate flows between liver, adipose tissue and muscle. When the ratio of the concentrations of insulin to glucagon falls (e.g. during starvation), there is increased hepatic glucose and ketone production and decreased tissue glucose utilization. When the ratio is high (e.g. after a meal), glucose is stored as glycogen and converted into fat.

- **Diabetes Mellitus** :

Diabetes is not one disease, but rather is a heterogeneous group of syndromes characterized by an elevation of fasting blood glucose caused by a relative or absolute deficiency in insulin. Diabetes mellitus is the leading cause of adult blindness and amputation, and a major cause of renal failure, heart attacks, and strokes. Most cases of diabetes mellitus can be separated into two groups (Figure 25.1), **type 1** (formerly called **insulin-dependent diabetes mellitus)** and **type 2** (formerly called **non-insulin-dependent diabetes mellitus)**

- Approximately 30,000 newly-diagnosed cases of type 1 and 625,000 cases of type 2 diabetes mellitus are estimated to occur yearly in the United States. The incidence and prevalence of type 2 disease is increasing because of the aging of the United States population, and the increasing prevalence of obesity and sedentary lifestyles. This increase in children with type 2 diabetes is particularly disturbing.

	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	10 Million = 90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar coma
TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin

Figure 25.1
Comparison of type 1 and type 2 diabetes.

- **TYPE 1 DIABETES**:
Persons with type 1 diabetics constitute approximately ten percent of the ten million diabetics in the United States. The disease is characterized by an absolute deficiency of insulin caused by an autoimmune attack on the B cells of the pancreas. In type 1 diabetes, the islets of Langerhans become infiltrated with activated T lymphocytes, leading to a condition called insulitis.

- Over a period of years, this autoimmune attack leads to gradual depletion of the B cell population. However, symptoms appear abruptly when eighty to ninety percent of the B cells have been destroyed. At this point, the pancreas fails to respond adequately to ingestion of glucose, and insulin therapy is required to restore metabolic control and prevent life-threatening ketoacidosis. This destruction requires both a stimulus from the environment (such as a viral infection) and a genetic determinant that allows the B cells to be recognized as "non-self."

- **A. Diagnosis of type 1 diabetes**
- The onset of type 1 diabetes is typically during childhood or puberty, and symptoms develop rapidly. Patients with type 1 diabetes can usually be recognized by the abrupt appearance of **polyuria** (frequent urination), **polydipsia** (excessive thirst), and **polyphagia** (excessive hunger), often triggered by stress or an illness. These symptoms are usually accompanied by fatigue, weight loss, and weakness. The diagnosis is confirmed by a fasting blood glucose greater than 126 mg/dl commonly accompanied by ketoacidosis.

- **B. Metabolic changes in type 1 diabetes**
- The metabolic abnormalities of diabetes result from a deficiency of insulin and a relative excess of glucagon. These aberrant hormonal levels most profoundly affect metabolism in three tissues: liver, muscle, and adipose tissue (Figure 25.3).

- **Hyperglycemia and ketoacidosis**: Elevated levels of blood glucose and ketones are the hallmarks of untreated diabetes mellitus. Hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral use due to an inability of muscle and adipose cells to take up glucose (see Figure 25.3). Ketosis results from increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic synthesis of 3hydroxybutyrate and acetoacetate.

- Diabetic keotacidosis occurs in twenty-five to forty percent of those newly diagnosed with type 1 diabetes, and may recur if the patient becomes ill (most commonly with an infection) or does not comply with therapy. Ketoacidosis is treated by replacing fluid and electrolytes, followed by administration of low-dose insulin to gradually correct hyperglycemia without precipitating hypoglycemia.

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- **2.Hypertriacylglycerolemia:** Not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. These excess fatty acids are converted to triacylglycerol, which is packaged and secreted in **very-low-density lipoproteins (VLDL). Chylomicrons** are synthesized from dietary lipids by the intestinal mucosal cells following a meal . Because lipoprotein degradation catalyzed by *lipoprotein lipase* in adipose tissue is low in diabetics (synthesis of the enzyme is decreased when insulin levels are low), the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia (see Figure 25.3).

- **Hypoglycemia in type 1 diabetes:** One of the therapeutic goals of diabetes is to decrease blood glucose levels in an effort to minimize the development of the long-term complications of the disease .However, appropriate dosage is difficult to achieve in all patients, and hypoglycemia caused by excess insulin is the most common complication of insulin therapy, occurring in more than ninety percent of patients. The frequency of hypoglycemic episodes, coma, and seizures is particularly high with intensive treatment regimens designed to achieve tight control of blood glucose (Figure 25.5).

-).Recall that in normal individuals hypoglycemia triggers a compensatory secretion of counter regulatory hormones, most notably glucagon and epinephrine, which promote hepatic production of glucose. However, patients with type 1 diabetes also develop a deficiency of glucagon secretion. This defect occurs early in the disease and is almost universally present four years after diagnosis.These patients thus rely on epinephrine secretion to prevent severe hypoglycemia. However, as the disease progresses, type 1 diabetes patients show diabetic autonomic neuropathy and impaired ability to secrete epinephrine in response to hypoglycemia. The combined deficiency of glucagon and epinephrine secretion creates a condition sometimes called "hypoglycemia unawareness." Thus,patients with longstanding diabetes are particularly vulnerable to hypoglycemia.

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- Hypoglycemica can also be caused by strenuous exercise. Exercise promotes glucose uptake into muscle and decreases the need for exogenous insulin. Patients should, therefore, check blood glucose levels before or after intensive exercise to prevent or abort hypoglycemia.
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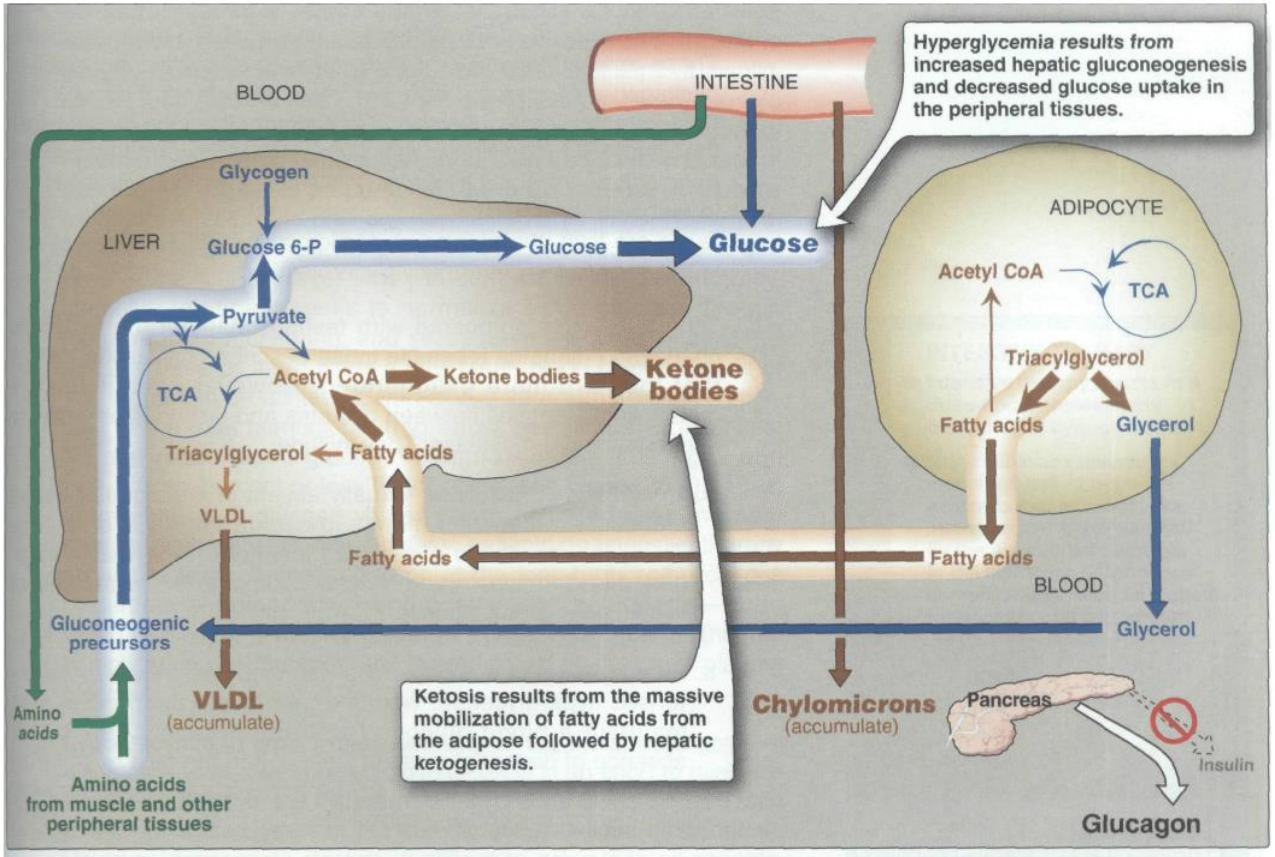

Figure 25.3
Intertissue relationships in type 1 diabetes.

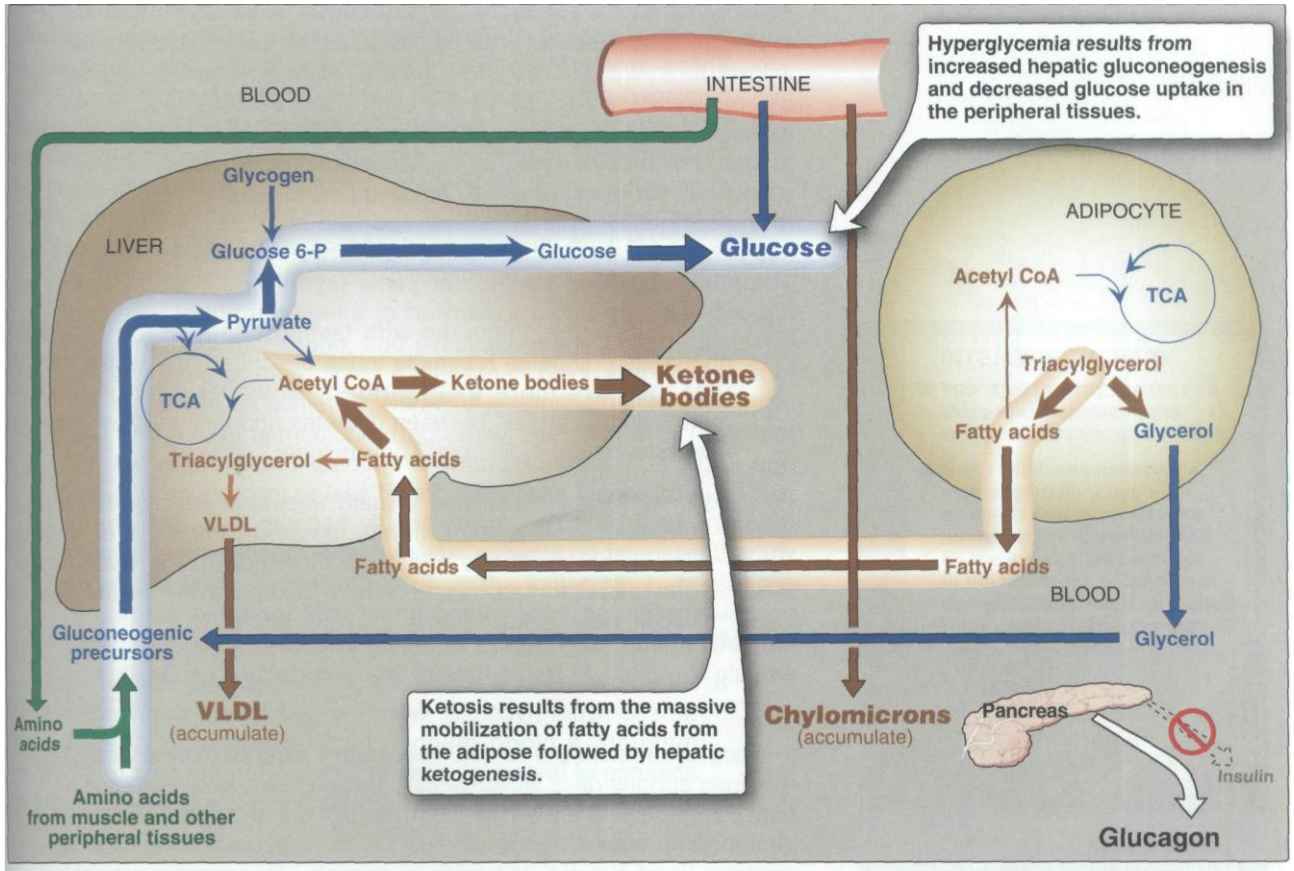

Figure 25.3
Intertissue relationships in type 1 diabetes.

TYPE 2 DIABETES: •

Type 2 diabetes is the most common form of the disease, afflicting approximately ninety percent of the diabetic population in the United States. Typically, type 2 diabetes develops gradually without obvious symptoms. The disease is often detected by routine screening tests. However, many individuals with type 2 diabetes have symptoms of polyuria and polydipsia of several weeks duration. Polyphagia may be present, but is less common.

- Patients with type 2 diabetes have a combination of insulin resistance and dysfunctional B cells (Figure 25.6). but do not require insulin to sustain life, although insulin may be required to control hyperglycemia in some patients. The metabolic alterations observed in type 2 diabetes are milder than those described for the insulin-dependent form of the disease, in part, because insulin secretion in type 2 diabetes—although not adequate—does restrain ketogenesis and blunts the development of diabetic ketoacidosis.

- Diagnosis is based most commonly on the presence of hyperglycemia-that is a blood glucose concentration of greater than 126 mg/dl The occurrence of the type 2 disease is almost completely determined by **genetic factors** (see Figure 25.1). For example, in virtually all monozygotic twinships, the disease develops in both individuals. The disease does not involve viruses or autoimmune antibodies.

- **A. Insulin resistance**
- Insulin resistance is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal circulating concentrations of insulin. For example, insulin resistance is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.

- **Insulin resistance and obesity:** Obesity is the most common cause of insulin resistance. Most people with obesity and insulin resistance do not become diabetic. In the absence of a defect in B-cell function, non-diabetic, obese individuals can compensate for insulin resistance with elevated levels of insulin. For example, Figure 25.7A shows that insulin secretion is two to three times higher in obese subjects than it is in lean individuals. This higher insulin concentration compensates for the diminished effect of the hormone (as a result of insulin resistance), and produces blood glucose levels similar to those observed in lean individuals .

- **2. Insulin resistance and type 2 diabetes:** Insulin resistance alone will not lead to type 2 diabetes. Rather, type 2 diabetes develops in insulin-resistant individuals who also show impaired B-cell function. Insulin resistance and subsequent development of type 2 diabetes is commonly observed in the elderly, and in individuals who are obese, physically inactive, or in women who are pregnant. These patients are unable to sufficiently compensate for insulin resistance with increased insulin release.

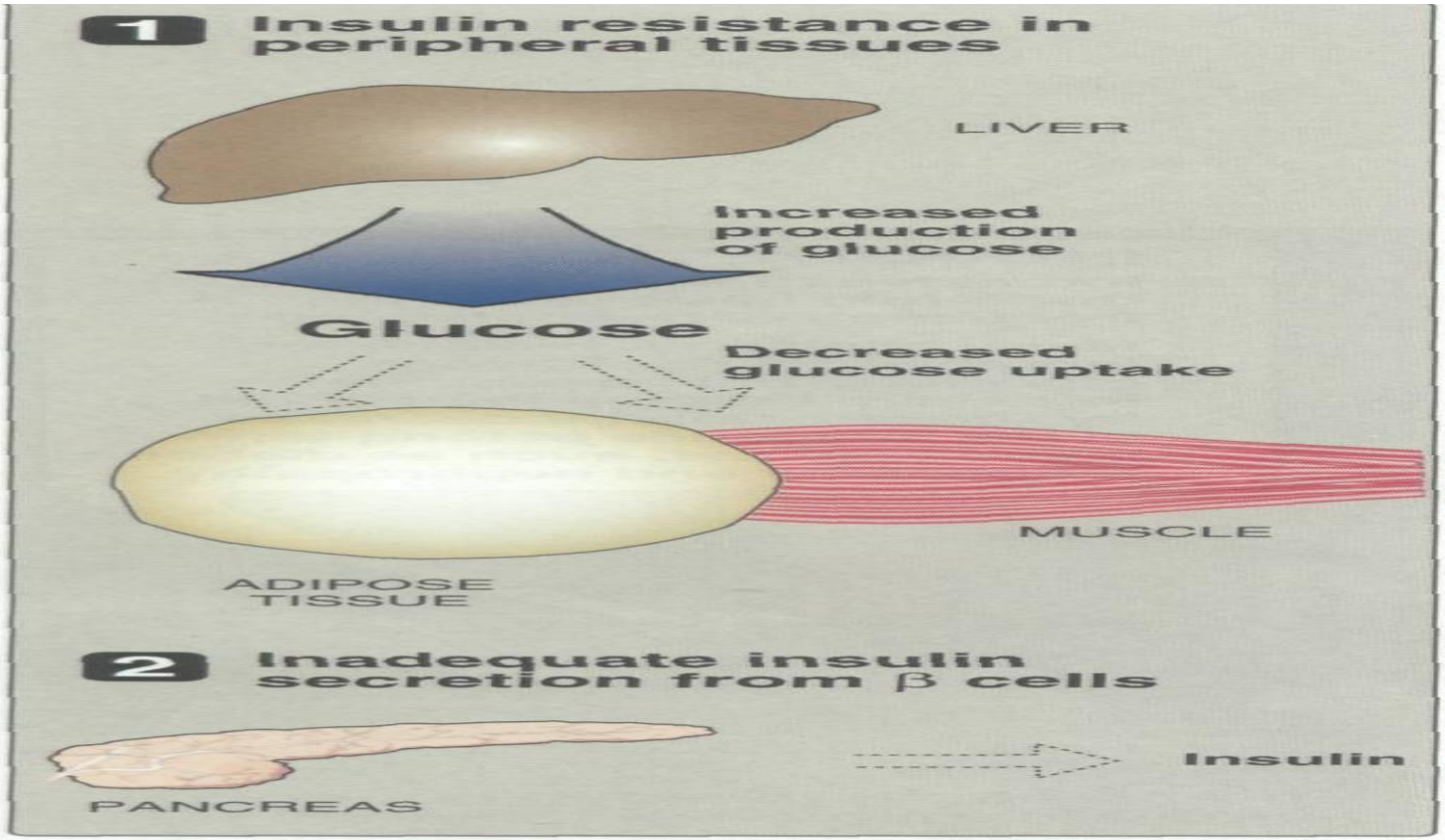

Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes.

- **C.Metabolic changes in type 2 diabetes**
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- The metabolic abnormalities of type 2 diabetes mellitus are the result of insulin resistance expressed primarily in liver, muscle, and adipose tissue .
- **Hyperglycemia:** Hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral use. Ketosis is usually minimal or absent in type 2 patients because the presence of insulin-even in the presence of insulin resistance-diminishes hepatic ketogenesis.

- **Hypertriacylglycerolemia: In** the liver, fatty acids are converted to triacylglycerols, which are packaged and secreted in VLDL. **Chylomicrons** are synthesized from dietary lipids by the intestinal mucosal cells following a meal . Because lipoprotein degradation catalyzed by *lipoprotein lipase* in adipose tissue is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia

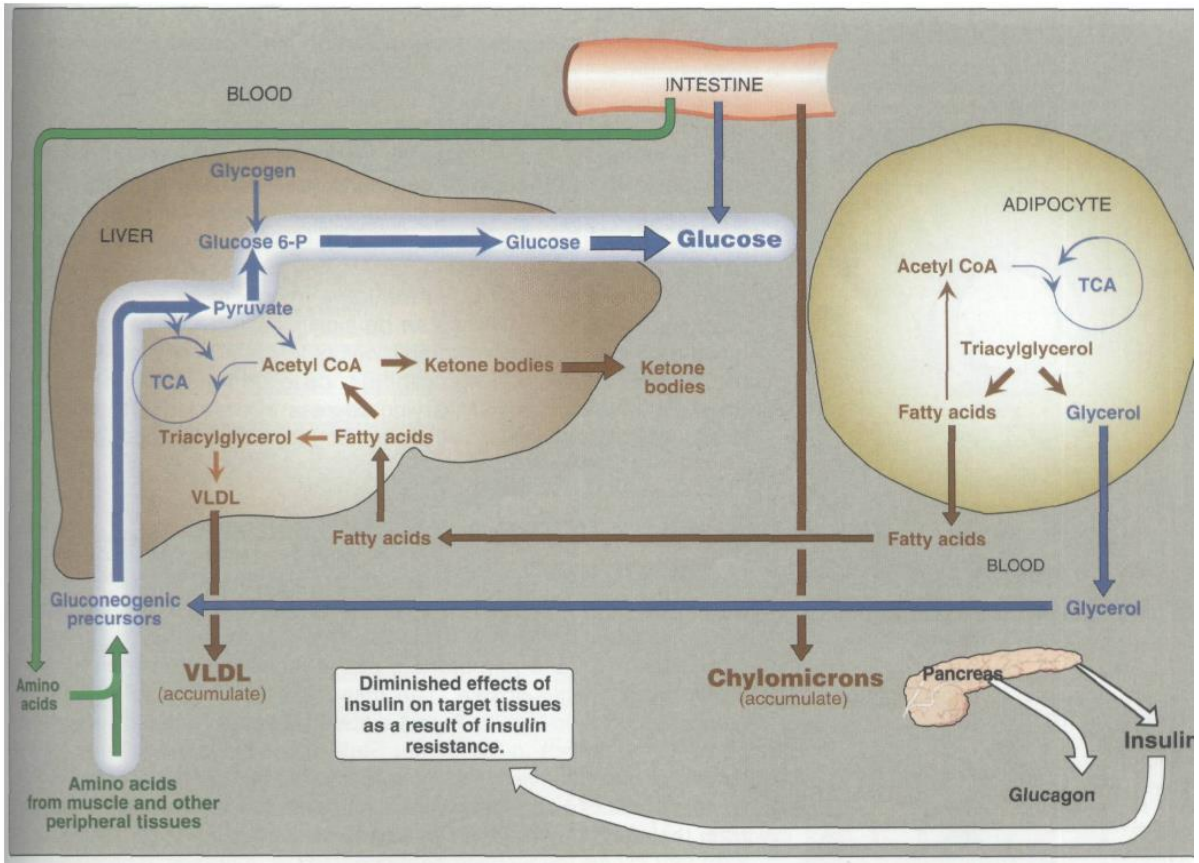

Figure 25.10
Intertissue relationships in type 2 diabetes.

- **D. Treatment of type 2 diabetes**
- The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits, and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modifications often correct the hyperglycemia of type 2 diabetes.
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- Thank you