# Clinical Chemistry

## CARBOHYDRATE METABOLISM & RELATED DISORDERS

- LECTURE- ONE

# CHO Metabolism & Related Disorders

## CHEMISTRY of CHO

- **The main monosaccharide hexoses are reducing sugars. Naturally occurring polysaccharides are long-chain carbohydrates composed of glucose subunits.**
- **_ *Starch*, found in plants, is a mixture of amylose (straight chains) and amylopectin (branched chains).**
- **_ *Glycogen*, found in animal tissue, is a highly branched polysaccharide.**

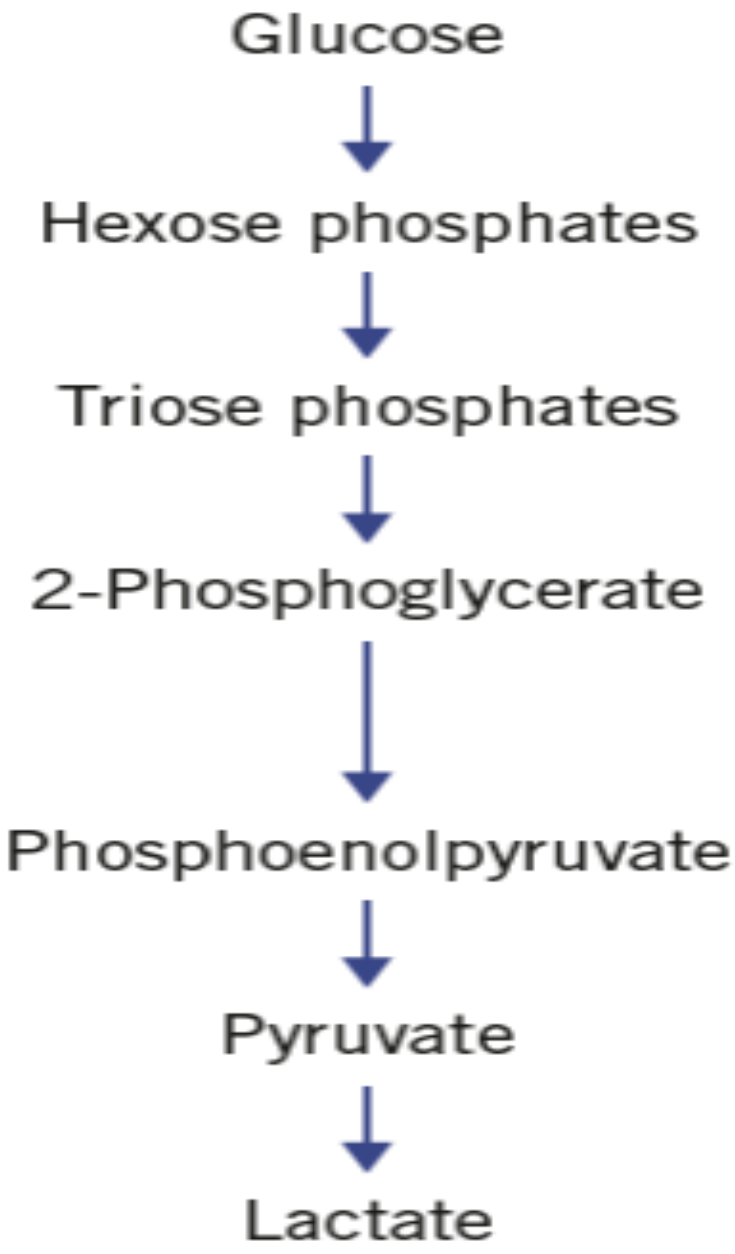


**Figure 12.1** Simplification of glycolysis pathways.

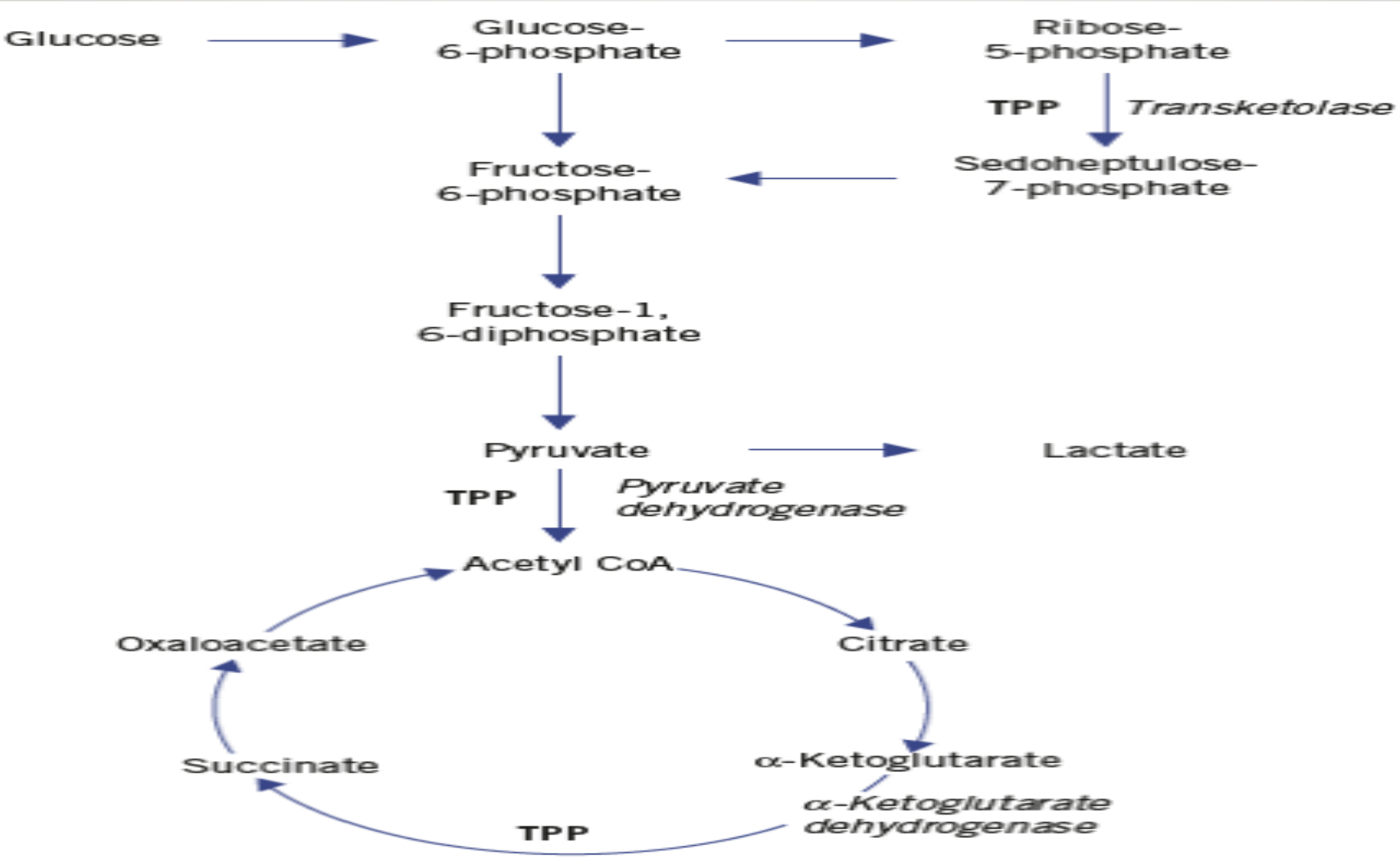


**Figure 12.2** Simplification of the tricarboxylic acid (Krebs) cycle. CoA, coenzyme A; TPP, thiamine pyrophosphate.

# Functions of Extracellular Glucose

**The main function of glucose is as a major tissue energy source. Liberated through the pathways of glycolysis , Krebs cycle [tricarboxylic acid (TCA)] and respiratory chain coupled –oxidative phosphorylation .**

**The brain is highly dependent upon the extracellular glucose concentration for its energy supply; indeed, hypoglycaemia is likely to impair cerebral function or even lead to irreversible neuronal damage. This is because the brain cannot:**

**_ Synthesize glucose,**

**_ Store glucose in significant amounts,**

**_ Metabolize substrates other than glucose and ketones**

**– Plasma ketone concentrations are usually very low and ketones are of little importance as an energy source under physiological conditions,**

**_ Extract enough glucose from the extracellular fluid (ECF) at low concentrations for its metabolic needs ,because entry into brain cells is not facilitated by insulin.**

# Control of Plasma Glucose Concentration

- Normally the plasma glucose concentration remains between about 4 mmol/L and 10 mmol/L, despite the intermittent load entering the body from the diet. The maintenance of plasma glucose concentrations below about 10 mmol/L minimizes loss from the body as well as providing the optimal supply to the tissues. Renal tubular cells reabsorb almost all the glucose filtered by the glomeruli, and urinary glucose concentration is normally too low to be detected by the usual tests.

# Hormones Concerned With Glucose Homeostasis

## *Insulin*

- **Insulin is the most important hormone controlling plasma glucose concentrations. A plasma glucose concentration of greater than about 5 mmol/L acting via the glucose transporter -2 stimulates insulin release from the pancreas β-cell. These cells produce proinsulin, which consists of**
- **51-amino-acid polypeptide insulin and a linking peptide (C-peptide,).**

Splitting of the peptide bonds by prohormone convertases releases (via intermediates ) equimolar amounts of insulin and C-peptide into the ECF.

Insulin binds to specific cell surface receptors on muscle and adipose tissue, thus enhancing the rate of glucose entry into these cells.

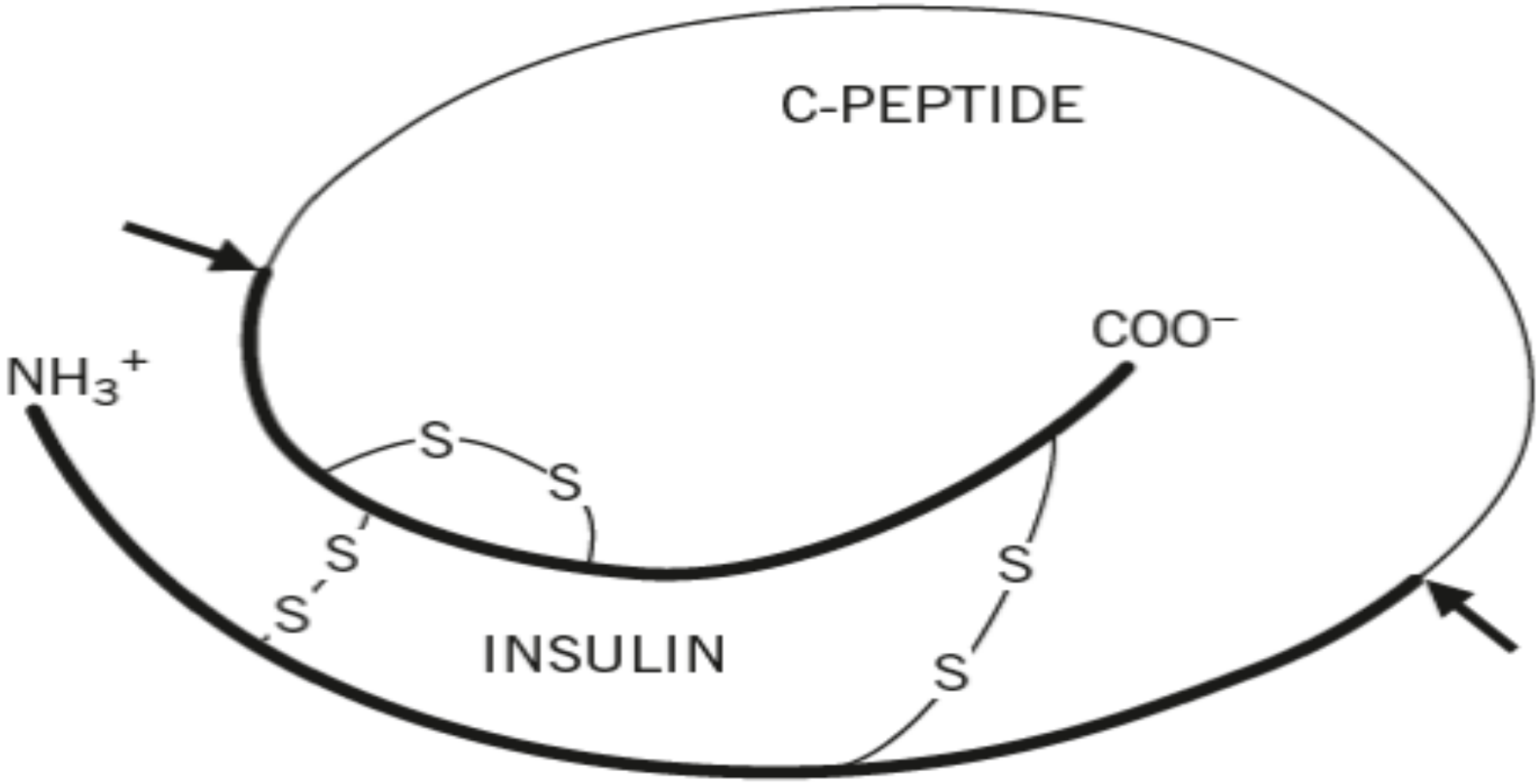


**Figure 12.3** Structure of proinsulin, indicating the cleavage sites at which insulin and C-peptide are produced.

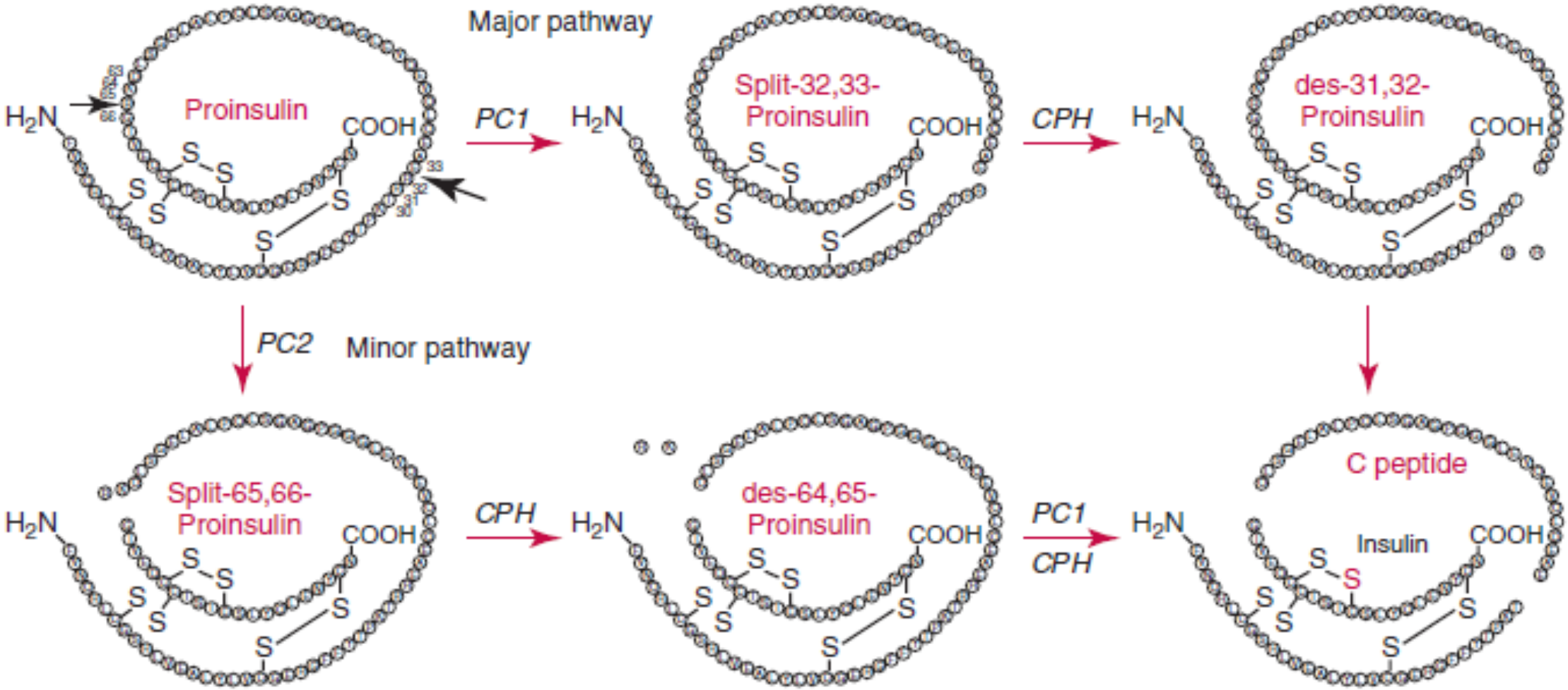


**Figure 46-3** **Processing of proinsulin. The enzymes prohormone convertase 1 and 2 (PC1 and PC2) act on proinsulin to form the appropriate split proinsulins. Carboxypeptidase-H (CPH) removes the two exposed basic amino acid residues *(circles)*.**

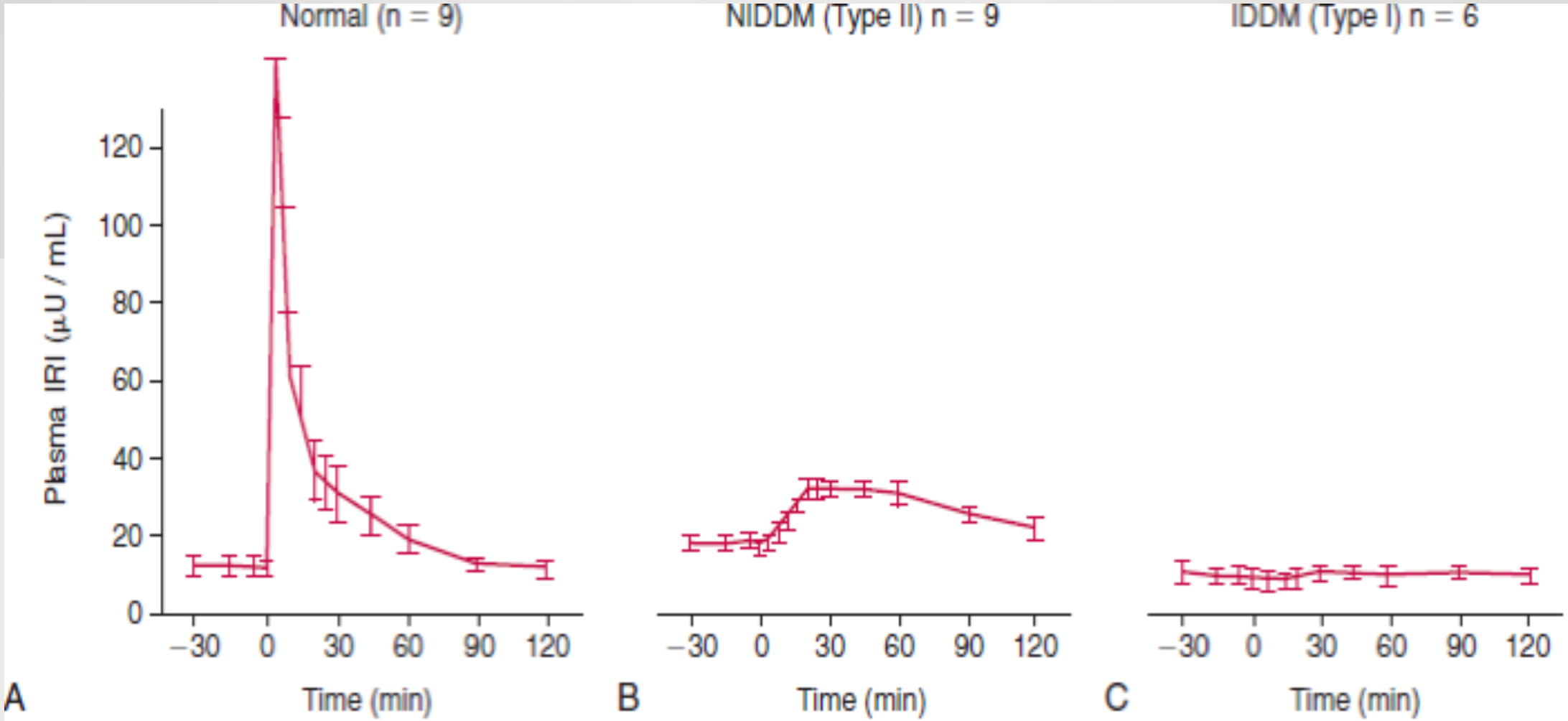


**Figure 46-4** **Response of plasma insulin to glucose stimulation. A 20 g glucose pulse is given intravenously at time 0. A, Healthy subjects. B, Patients with type 2 diabetes mellitus (NIDDM). C, Patients with type 1 diabetes mellitus (IDDM). *IRI,* Immunoreactive insulin. Values before time 0 represent baseline.** *(From Pfeifer MA, Halter JB, Porte D Jr. Insulin secretion in diabetes mellitus. Am J Med 1981;70:579-88.)*

-Insulin-induced activation of enzymes stimulates glucose incorporation into glycogen (glycogenesis) in liver and muscle .

-Insulin also inhibits the production of glucose (gluconeogenesis) from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis).

-The transport of glucose into liver cells is insulin independent but,

by reduction of the intracellular glucose concentration (due to metabolism), insulin does indirectly promote the passive diffusion of glucose into them

Insulin also directly increases the transport of amino acids, potassium and phosphate into cells, especially muscle; these processes are independent of glucose transport.

-In the longer term, insulin regulates growth and development and the expression of certain genes.

**Table 26.1. Physiologic Actions of Insulin and Insulin Counterregulatory Hormones**

| Hormone | Function | Major Metabolic Pathways Affected |
|---|---|---|
| Insulin | • Promotes fuel storage after a meal<br>• Promotes growth | • Stimulates glucose storage as glycogen (muscle and liver)<br>• Stimulates fatty acid synthesis and storage after a high-carbohydrate meal<br>• Stimulates amino acid uptake and protein synthesis |
| Glucagon | • Mobilizes fuels<br>• Maintains blood glucose levels during fasting | • Activates gluconeogenesis and glycogenolysis (liver) during fasting<br>• Activates fatty acid release from adipose tissue |
| Epinephrine | • Mobilizes fuels during acute stress | • Stimulates glucose production from glycogen (muscle and liver)<br>• Stimulates fatty acid release from adipose issue |
| Cortisol | • Provides for changing requirements over the long-term | • Stimulates amino acid mobilization from muscle protein<br>• Stimulates gluconeogenesis<br>• Stimulates fatty acid release from adipose issue |

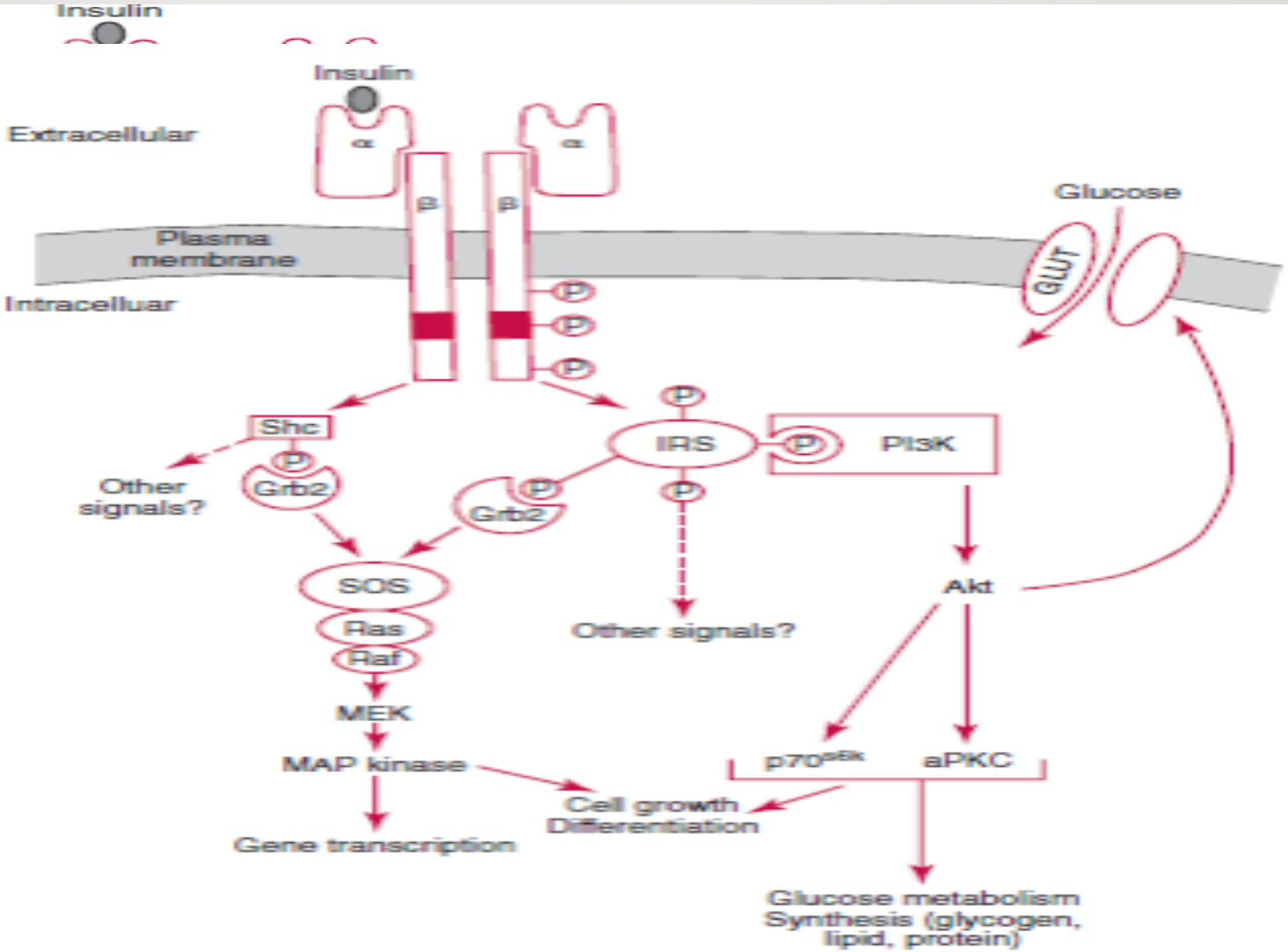


**Figure 46-5** **Mechanism of insulin action. Binding of insulin to the extracellular α-subunit of the insulin receptor induces autophosphorylation of the β-subunit of the receptor and phosphorylation of selected intracellular proteins, such as Shc and the insulin-receptor substrate (IRS) family. These latter phosphoproteins interact with other targets, thereby activating phosphorylation cascades, which result in glucose uptake (in adipose tissue and skeletal muscle), glucose metabolism, synthesis (of glycogen, lipid, and proteins), enhanced gene expression, cell growth, and**

# *Glucagon*

- **Glucagon is a single-chain polypeptide synthesized by the α-cells of the pancreatic islets.**
- **Its secretion is stimulated by hypoglycaemia.**
- **Glucagon enhances hepatic glycogenolysis (glycogen breakdown) and gluconeogenesis .**

- ***Other hormones***
- **When plasma insulin concentrations are low, for example during fasting, the hyperglycaemic actions of hormones, such as growth hormone (GH), glucocorticoids, adrenaline (epinephrine) and glucagon, become apparent, even if there is no increase in secretion rates**

Secretion of these so-called counter regulatory - hormones may increase during stress and in patients with acromegaly , Cushing's syndrome or in pheochromocytoma and thus oppose the normal action of insulin.

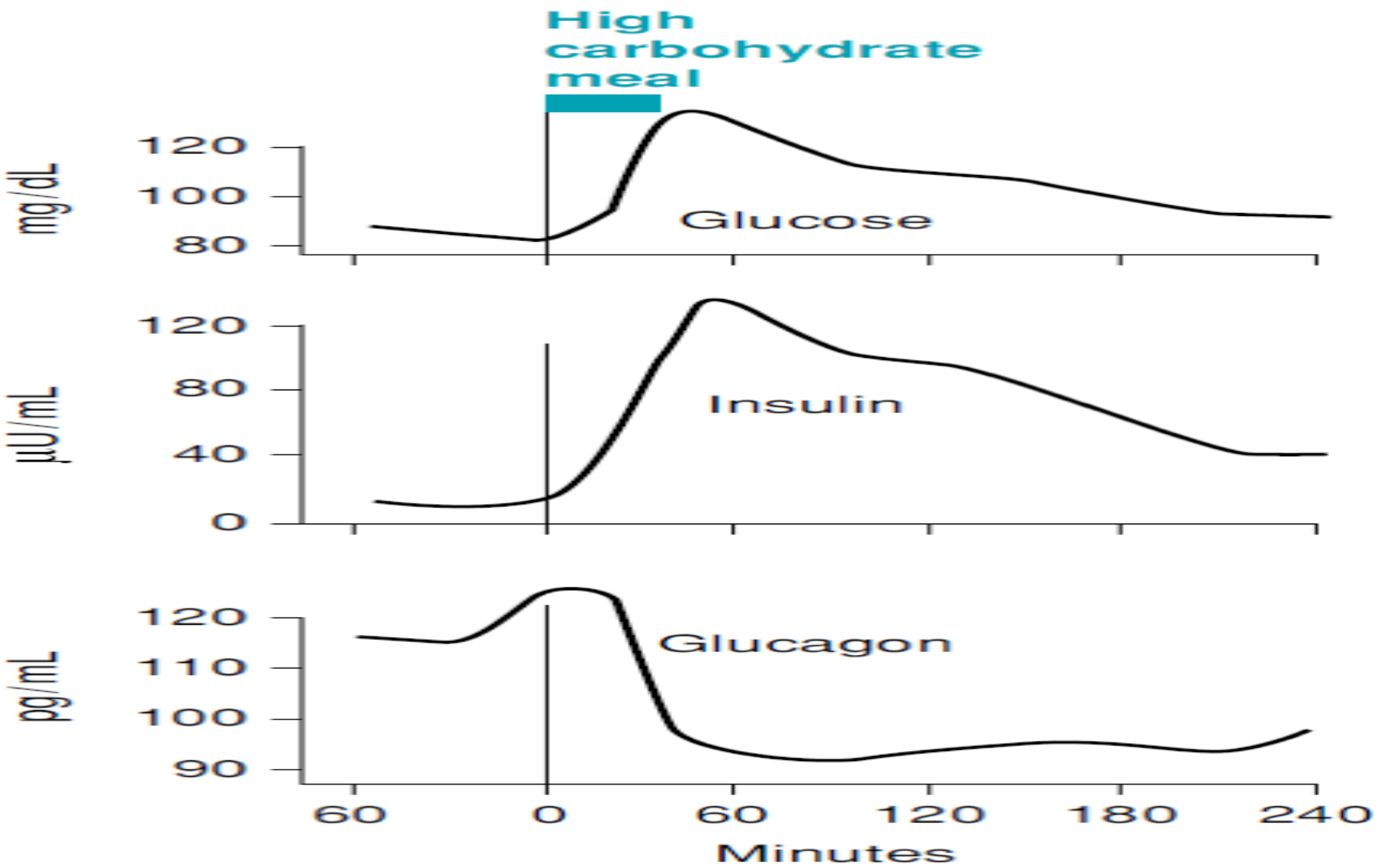


**Fig 26.8.** Blood glucose, insulin, and glucagon levels after a high-carbohydrate meal.

# Role of Liver in Glucose Metabolism

The liver is the most important organ maintaining a constant glucose supply for other tissues, including the brain.

It is also of importance in controlling the postprandial plasma glucose concentration.

Portal venous blood leaving the absorptive area of the intestinal wall reaches the liver first, and consequently the hepatic cells are in a key position to buffer the hyperglycaemic effect of a high-carbohydrate meal

**The entry of glucose into liver and cerebral cells is not directly affected by insulin,**

**But depends on the extracellular glucose concentration.**

- **The conversion of glucose to glucose-6-phosphate (G6P), the first step in glucose metabolism in all cells, is catalysed in the liver by the enzyme glucokinase,**

- **which has a low affinity for glucose compared with that of hexokinase, which is found in most other tissues.**

- **Glucokinase activity is induced by insulin.**

- **Therefore, hepatic cells extract proportionally less glucose during fasting, when glucose concentrations in portal venous plasma are low, than after carbohydrate ingestion**

**Conversion of intracellular glucose to G6P in adipose and muscle cells is catalysed by the enzyme hexokinase, which, because its affinity for glucose is greater than that of hepatic glucokinase, ensures that glucose enters the metabolic pathways in these tissues at lower extracellular concentrations than those in the liver.**

- This helps to maintain a fasting supply of glucose to vulnerable tissues such as the brain.

- The liver cells can store some of the excess glucose as glycogen.
- The rate of glycogen synthesis (glycogenesis) from G6P may be increased by insulin secreted in response to systemic hyperglycaemia.

The liver can convert some of the excess glucose to fatty acids, which are ultimately transported as TG in very low-density lipoprotein (VLDL) and stored in adipose tissue.

The liver contains the enzyme glucose-6-P

which by hydrolysing G6P derived from either glycogenolysis or gluconeogenesis,

Thereby releasing glucose and helps to maintain extracellular fasting concentrations.

*Hepatic glycogenolysis is stimulated by the hormone glucagon, secreted by the α-cells of the pancreas in response to a fall in the plasma glucose concentration,

and by catecholamines such as adrenaline or noradrenaline.

The liver modifies the potential hyperglycaemic effect of a high-carbohydrate meal by extracting relatively more glucose than in the fasting state from the portal plasma.

However, some glucose does pass through the liver and the rise in the systemic concentration stimulates the β-cells of the pancreas to secrete insulin.

**Insulin may further enhance hepatic and muscle glycogenesis.**

**Entry of glucose into adipose tissue and muscle cells, unlike that into liver and brain, is stimulated by insulin and, under physiological conditions, the plasma glucose concentration falls to near fasting levels.**

*The relatively high insulin activity after a meal also inhibits the breakdown of TG (lipolysis) and protein (proteolysis).

If there is relative or absolute insulin deficiency, as in diabetes mellitus, these actions are impaired.

## Other Organs

The renal cortex is the only other tissue capable of gluconeogenesis, and of converting G6P to glucose.

The gluconeogenic capacity of the kidney is particularly important in hydrogen ion homeostasis and during prolonged fasting.

Tissues, such as muscle, can store glycogen but, because they do not contain glucose-6-phosphatase, thus cannot release glucose from cells and so can only use it locally; this glycogen plays no part in maintaining the plasma glucose concentration.