

hypoglycemia, and both inhibit cellular utilization of glucose while promoting fat utilization. However, the effects of both of these hormones develop slowly, usually requiring many hours for maximal expression.

Epinephrine is especially important in increasing plasma glucose concentration during periods of stress when the sympathetic nervous system is excited. However, epinephrine acts differently from the other hormones in that it increases the plasma fatty acid concentration at the same time. The reasons for these effects are as follows: (1) epinephrine has the potent effect of causing glycogenolysis in the liver, thus releasing within minutes large quantities of glucose into the blood; (2) it also has a direct lipolytic effect on the adipose cells because it activates adipose tissue hormone-sensitive lipase, thus greatly enhancing the blood concentration of fatty acids as well. Quantitatively, the enhancement of fatty acids is far greater than the enhancement of blood glucose. Therefore, epinephrine especially enhances the utilization of fat in such stressful states as exercise, circulatory shock, and anxiety.

## Glucagon and Its Functions

Glucagon, a hormone secreted by the alpha cells of the islets of Langerhans when the blood glucose concentration falls, has several functions that are diametrically opposed to those of insulin. Most important of these functions is to increase the blood glucose concentration, an effect that is exactly the opposite that of insulin.

Like insulin, glucagon is a large polypeptide. It has a molecular weight of 3485 and is composed of a chain of 29 amino acids. On injection of purified glucagon into an animal, a profound *hyperglycemic* effect occurs. Only 1 µg/kg of glucagon can elevate the blood glucose concentration about 20 mg/100 ml of blood (a 25 per cent increase) in about 20 minutes. For this reason, glucagon is also called the *hyperglycemic hormone*.

### Effects on Glucose Metabolism

The major effects of glucagon on glucose metabolism are (1) breakdown of liver glycogen (*glycogenolysis*) and (2) increased *gluconeogenesis* in the liver. Both of these effects greatly enhance the availability of glucose to the other organs of the body.

**Glucagon Causes Glycogenolysis and Increased Blood Glucose Concentration.** The most dramatic effect of glucagon is its ability to cause glycogenolysis in the liver, which in turn increases the blood glucose concentration within minutes.

It does this by the following complex cascade of events:

1. Glucagon activates *adenylyl cyclase* in the hepatic cell membrane,
2. Which causes the formation of *cyclic adenosine monophosphate*,
3. Which activates *protein kinase regulator protein*,
4. Which activates *protein kinase*,
5. Which activates *phosphorylase b kinase*,
6. Which converts *phosphorylase b* into *phosphorylase a*,
7. Which promotes the degradation of glycogen into glucose-1-phosphate,
8. Which then is dephosphorylated; and the glucose is released from the liver cells.

This sequence of events is exceedingly important for several reasons. First, it is one of the most thoroughly studied of all the *second messenger* functions of cyclic adenosine monophosphate. Second, it demonstrates a cascade system in which *each succeeding product is produced in greater quantity than the preceding product*. Therefore, it represents a potent *amplifying mechanism*; this type of amplifying mechanism is widely used throughout the body for controlling many, if not most, cellular metabolic systems, often causing as much as a millionfold amplification in response. This explains how *only a few micrograms of glucagon can cause the blood glucose level to double or increase even more within a few minutes*.

Infusion of glucagon for about 4 hours can cause such intensive liver glycogenolysis that all the liver stores of glycogen become depleted.

**Glucagon Increases Gluconeogenesis.** Even after all the glycogen in the liver has been exhausted under the influence of glucagon, continued infusion of this hormone still causes continued hyperglycemia. This results from the effect of glucagon to increase the rate of amino acid uptake by the liver cells and then the conversion of many of the amino acids to glucose by gluconeogenesis. This is achieved by activating multiple enzymes that are required for amino acid transport and gluconeogenesis, especially activation of the enzyme system for converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis.

### Other Effects of Glucagon

Most other effects of glucagon occur only when its concentration rises well above the maximum normally found in the blood. Perhaps the most important effect is that glucagon *activates adipose cell lipase*, making increased quantities of fatty acids available to the energy systems of the body. Glucagon also inhibits the storage of triglycerides in the liver, which prevents the liver from removing fatty acids from the blood; this also helps make additional amounts of fatty acids available for the other tissues of the body.

Glucagon in very high concentrations also (1) enhances the strength of the heart; (2) increases blood flow in some tissues, especially the kidneys; (3) enhances bile secretion; and (4) inhibits gastric acid secretion. All these effects are probably of minimal importance in the normal function of the body.