Normal nutrient homeostasis depends on the balance between the effects of insulin and those of the so-called contrainsulin or counterregulatory hormones. These hormones include glucagon, epinephrine, growth hormone, and cortisol. Although thyroxine and triiodothyronine affect various aspects of metabolism, circulating thyroid hormone levels are not acutely affected by nutrient signals, and fluctuations in their daily secretion do not alter metabolic processes. For these reasons, thyroxine and triiodothyronine are not generally considered among the classical contrainsulin hormones. Regulating factors in addition to insulin and the contrainsulin hormones affect metabolic balance. These factors include various neurotransmitters (noradrenaline from sympathetic postganglionic neurons, acetylcholine from parasympathetic neurons and neuropeptides) and substrates including glucose. Detailed discussion of the latter regulatory factors is beyond the scope of this chapter. Their roles have been reviewed elsewhere.

**Glucagon**

Glucagon, a 29-amino-acid polypeptide with a molecular weight of 3485 daltons (Fig. 6.1), was discovered as a "contaminant" hyperglycemic factor in pancreatic extracts by Kimball and Murlin in 1923 and finally sequenced by Bromer et al. during the late 1950s. Studies of its mechanism during the 1960s by Sutherland et al. led to the discovery of the second messenger cyclic adenosine monophosphate (cAMP). Full appreciation of its importance for normal fuel homeostasis in humans and diabetes mellitus did not come until the 1970s when the availability of somatostatin, an inhibitor of glucagon secretion, permitted investigation of its lack under various experimental conditions.

**Biosynthesis**

Glucagon is secreted by $A$ cells of pancreatic islets. Normally, these cells constitute approximately 15–20% of the total islet cell mass. In most species $A$ cells are located at the periphery of islets juxtaposed to $B$ cells, which secrete insulin, and $D$ cells, which secrete somatostatin. Glucagon is synthesized initially as a large molecule of approximately 12,000 daltons. This peptide undergoes cleavage to a 9000-dalton molecule, which is cleaved to a 4900-dalton molecule that is finally cleaved to yield the 3485-dalton molecule. The whole process takes about 90 minutes. All of these peptides are immunoreactive, but only the 3485-dalton molecule is biologically active.

**Plasma Glucagon**

Values for plasma glucagon vary considerably from individual to individual. The main factors responsible are the specificity of the antiserum used in the immunoassay and the relative proportion of the total immunoreactivity accounted for by the 3485-dalton molecule. In the dog and humans the pancreas is not the sole source of glucagon. $A$ cells, similar to those in pancreatic islets, have been found in the stomach and in the small and large intestines. These cells contain a peptide that is immunologically and physicochemically similar or identical to pancreatic $A$ cell glucagon and that has a glucagon-like biological activity. These observations could explain the presence of circulating glucagon immunoreactivity following total pancreatectomy in humans and other species. The relative contribution of pancreatic and extrapancreatic $A$ cells to plasma glucagon and substrate homeostasis remains to be established. Control of extrapancreatic glucagon secretion seems to differ from that of pancreatic glucagon.

**normally in humans and most other mammalian species, arterial and peripheral venous plasma immunoreactive glucagon concentrations range between 35 and 200 pg/ml (1.0 x 10^-8 to 6.0 x 10^-8 M) after a 12- to 16-hour fast. Portal venous levels can average 1.5–3.0 times those present in arterial blood because of extraction of glucagon by the liver. As with other peptide hormones, circulating glucagon immunoreactivity is heterogeneous. By using chromatog-
of ions such as potassium, calcium, and magnesium. 42

or glucagon probably involves a cAMP-calcium inter-
lar calcium,41 and is influenced by the concentration
extracellular space. Like insulin secretion, secretion

gon is stored within

mentary calcium.41 and is influenced by the concentration

such as potassium, calcium, and magnesium.42

heterogeneity of plasma glucagon can compli-
icate the interpretation of in vivo studies of glucagon
secretion and metabolism. Changes in plasma gluca-

The pancreatic content of glucagon varies con-
siderably among species; the human pancreas con-
tains approximately 700-1000 μg of glucagon. Gluca-
gon is stored within A cells in distinctive granules and
is secreted by a process called emiocytosis,38 which
involves migration of secretory granules to the
periphery of cells, fusion of granules with the plasma
membrane, and extrusion of granule contents into the
extracellular space. Like insulin secretion, secretion
of glucagon probably involves a cAMP-calcium inter-
action,39,40 is dependent on the presence of extracellu-
ar calcium,41 and is influenced by the concentration
of ions such as potassium, calcium, and magnesium.42

In vivo secretion of glucagon is the net result of

In normal humans the metabolic clearance rate of

heterogeneity of circulating glucagon immunoreactivity is taken into
account. When portal venous and peripheral venous plasma is subjected to gel filtration, it seems that the
liver does not appreciably extract the biologically inac-
tive 9000- and more than 40,000-dalton plasma gluca-

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