with atrophic centers and central ulceration. They are often painful. Vitiligo occurs at increased frequency in individuals with type 1 DM. *Acanthosis nigricans* (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or localized *granuloma annulare* (erythematous plaques on the extremities or trunk) and *scleredema* (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population. *Lipoatrophy* and *lipohypertrophy* can occur at insulin injection sites but are now unusual with the use of human insulin.

# 420 Hypoglycemia

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Hypoglycemia is most commonly caused by drugs used to treat diabetes mellitus or by exposure to other drugs, including alcohol. However, a number of other disorders, including critical organ failure, sepsis and inanition, hormone deficiencies, non-β-cell tumors, insulinoma, and prior gastric surgery, can cause hypoglycemia (Table 420-1). Hypoglycemia is most convincingly documented by *Whipple's triad:* (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration measured with a precise method (not a glucose monitor), and (3) relief of symptoms after the plasma glucose level is raised. The lower limit of the fasting plasma glucose concentration is normally ~70 mg/dL (~3.9 mmol/L), but lower venous glucose levels occur normally, late after a meal, during pregnancy, and during prolonged fasting (>24 h). Hypoglycemia can cause serious morbidity; if severe and prolonged, it can be fatal. It should be considered in any patient with episodes of confusion, an altered level of consciousness, or a seizure.

**TABLE 420-1 CAUSES OF HYPOGLYCEMIA IN ADULTS**

| |
|---|
| **Ill or medicated individual** |
| 1. Drugs |
| Insulin or insulin secretagogue |
| Alcohol |
| Others |
| 2. Critical illness |
| Hepatic, renal or cardiac failure |
| Sepsis |
| Inanition |
| 3. Hormone deficiency |
| Cortisol |
| Glucagon and epinephrine (in insulin-deficient diabetes) |
| 4. Non–islet cell tumor |
| **Seemingly well individual** |
| 5. Endogenous hyperinsulinism |
| Insulinoma |
| Functional β-cell disorders (nesidioblastosis) |
| Noninsulinoma pancreatogenous hypoglycemia |
| Post–gastric bypass hypoglycemia |
| Insulin autoimmune hypoglycemia |
| Antibody to insulin |
| Antibody to insulin receptor |
| Insulin secretagogue |
| Other |
| 6. Accidental, surreptitious, or malicious hypoglycemia |

***Source:*** From PE Cryer et al: J Clin Endocrinol Metab 94:709, 2009. ©The Endocrine Society, 2009.

## SYSTEMIC GLUCOSE BALANCE AND GLUCOSE COUNTERREGULATION

Glucose is an obligate metabolic fuel for the brain under physiologic conditions. The brain cannot synthesize glucose or store more than a few minutes' supply as glycogen and therefore requires a continuous supply of glucose from the arterial circulation. As the arterial plasma glucose concentration falls below the physiologic range, blood-to-brain glucose transport becomes insufficient to support brain energy metabolism and function. However, redundant glucose counterregulatory mechanisms normally prevent or rapidly correct hypoglycemia.

Plasma glucose concentrations are normally maintained within a relatively narrow range—roughly 70–110 mg/dL (3.9–6.1 mmol/L) in the fasting state, with transient higher excursions after a meal—despite wide variations in exogenous glucose delivery from meals and in endogenous glucose utilization by, for example, exercising muscle. Between meals and during fasting, plasma glucose levels are maintained by endogenous glucose production, hepatic glycogenolysis, and hepatic (and renal) gluconeogenesis (Fig. 420-1). Although hepatic glycogen stores are usually sufficient to maintain plasma glucose levels for ~8 h, this period can be shorter if glucose demand is increased by exercise or if glycogen stores are depleted by illness or starvation.

Gluconeogenesis normally requires low insulin levels and the presence of anti-insulin (counterregulatory) hormones together with a coordinated supply of precursors from muscle and adipose tissue to the liver (and kidneys). Muscle provides lactate, pyruvate, alanine, glutamine, and other amino acids. Triglycerides in adipose tissue are broken down into fatty acids and glycerol, which is a gluconeogenic precursor. Fatty acids provide an alternative oxidative fuel to tissues other than the brain (which requires glucose).

Systemic glucose balance—maintenance of the normal plasma glucose concentration—is accomplished by a network of hormones, neural signals, and substrate effects that regulate endogenous glucose production and glucose utilization by tissues other than the brain (Chap. 417). Among the regulatory factors, insulin plays a dominant role (Table 420-2; Fig. 420-1). As plasma glucose levels decline within the physiologic range in the fasting state, pancreatic β-cell insulin secretion decreases, thereby increasing hepatic glycogenolysis and hepatic (and renal) gluconeogenesis. Low insulin levels also reduce glucose utilization in peripheral tissues, inducing lipolysis and proteolysis and consequently releasing gluconeogenic precursors. Thus, a decrease in insulin secretion is the first defense against hypoglycemia.

As plasma glucose levels decline just below the physiologic range, glucose counterregulatory (plasma glucose–raising) hormones are released (Table 420-2; Fig. 420-1). Among these, pancreatic α-cell glucagon, which stimulates hepatic glycogenolysis, plays a primary role. Glucagon is the second defense against hypoglycemia. Adrenomedullary epinephrine, which stimulates hepatic glycogenolysis and gluconeogenesis (and renal gluconeogenesis), is not normally critical. However, it becomes critical when glucagon is deficient. Epinephrine is the third defense against hypoglycemia. When hypoglycemia is prolonged beyond ~4 h, cortisol and growth hormone also support glucose production and restrict glucose utilization to a limited amount (~20% compared to epinephrine). Thus cortisol and growth hormone play no role in defense against acute hypoglycemia.

As plasma glucose levels fall further, symptoms prompt behavioral defense against hypoglycemia, including the ingestion of food (Table 420-2; Fig. 420-1). The normal glycemic thresholds for these responses to decreasing plasma glucose concentrations are shown in Table 420-2. However, these thresholds are dynamic. They shift to higher-than-normal glucose levels in people with poorly controlled diabetes, who can experience symptoms of hypoglycemia when their glucose levels decline toward the normal range (*pseudohypoglycemia*). On the other hand, thresholds shift to lower-than-normal glucose levels in people with recurrent hypoglycemia; e.g., patients with aggressively treated diabetes or an insulinoma have symptoms at glucose levels lower than those that cause symptoms in healthy individuals.

**Clinical Manifestations** Neuroglycopenic manifestations of hypoglycemia are the direct result of central nervous system glucose deprivation. These features include behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged,