Hypoglycemia commonly causes brain fuel deprivation, resulting in functional brain failure, which can be corrected by raising plasma glucose concentrations. Rarely, profound hypoglycemia causes brain death that is not the result of fuel deprivation per se. In this issue of the JCI, Suh and colleagues use cell culture and in vivo rodent studies of glucose deprivation and marked hypoglycemia and provide evidence that hypoglycemic brain neuronal death is in fact increased by neuronal NADPH oxidase activation during glucose reperfusion (see the related article beginning on page 910). This finding suggests that, at least in the setting of profound hypoglycemia, therapeutic hyperglycemia should be avoided.

Hypoglycemia, including iatrogenic hypoglycemia in people with diabetes, causes brain fuel deprivation that initially triggers a series of physiological and behavioral defenses but if unchecked results in functional brain failure that is typically corrected after the plasma glucose concentration is raised. Rarely, profound, and at least in primates prolonged, hypoglycemia causes brain death. Given the survival value of maintaining physiological plasma glucose concentrations, it is not surprising that mechanisms that normally very effectively prevent or rapidly correct symptomatic hypoglycemia have evolved (1). As a result, hypoglycemia is a distinctly uncommon clinical event except in people who use drugs that lower plasma glucose concentration (2). Although there are other drugs, and several relatively uncommon conditions, that cause hypoglycemia (2), in the vast majority of instances the offending drug is an insulin secretagogue or insulin used to treat diabetes mellitus (2, 3). As a result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations, hypoglycemia is the limiting factor in the glycemic management of diabetes (3). It causes recurrent morbidity in most people with type 1 diabetes mellitus (T1DM) and in many with advanced T2DM and is sometimes fatal. Furthermore, hypoglycemia, as well as prior exercise and sleep, further compromise glycemic defenses by causing hypoglycemia-associated autonomic failure and thus a vicious cycle of recurrent hypoglycemia. Finally, the barrier of hypoglycemia precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the long-term vascular benefits of glycemic control.

Functional brain failure
Recent interest in alternative brain fuels (including lactate derived from glucose largely within the brain; refs. 4–6) notwithstanding, glucose is an obligate metabolic fuel for the brain under physiological conditions (7). Because the brain cannot synthesize glucose or store substantial amounts as glycogen in astrocytes, the brain requires a virtually continuous supply of glucose from the circulation. Facilitated diffusion of glucose from the blood into the brain is a direct function of the arterial plasma glucose concentration. The rate of blood-to-brain glucose transport exceeds the rate of brain glucose metabolism at normal (or elevated) plasma glucose levels, but it falls and becomes limiting to brain glucose metabolism when arterial glucose concentrations fall to low levels (8). Thus, hypoglycemia causes brain fuel deprivation and, as a result, functional brain failure.

The sequence of responses to falling plasma glucose concentrations (1) is illustrated in Figure 1. Initially, declining plasma glucose levels activate defenses against hypoglycemia. Physiological defenses normally include decrements in pancreatic β-cell insulin secretion as glucose levels decline within the physiological postabsorptive plasma glucose concentration range (approximately 3.9–6.1 mmol/l [70–110 mg/dl]). The glycemic threshold for decreased insulin secretion is approximately 4.5 mmol/l (81 mg/dl). Increments in pancreatic β-cell glucagon and adrenomedullary epinephrine secretion (among other neuroendocrine responses) normally occur as glucose levels fall just below the physiological range (threshold equal to approximately 3.8 mmol/l [68 mg/dl]). If these defenses fail to abort the hypoglycemic episode, lower glucose levels trigger a more intense sympathoadrenal response that causes neurogenic (or autonomic) symptoms; neuroglycopenic symptoms occur at about the same glucose level (threshold equal to approximately 3.0 mmol/l [54 mg/dl]). The perception of symptoms, particularly neurogenic symptoms, prompts the behavioral defense, the ingestion of food. If all of these defenses fail, lower glucose levels cause overt functional brain failure that

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**Nonstandard abbreviations used:** T1DM, type 1 diabetes mellitus.

**Conflict of interest:** The author has served on advisory boards of Novo Nordisk Inc., Takeda Pharmaceuticals North America Inc., MannKind Corp., and Merck and Co. and as a consultant to TevelRx Inc., Amgen Inc., and Marcadia Biotech in recent years.

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can progress from measurable cognitive impairments (threshold equal to approximately 2.8 mmol/l [50 mg/dl]) to aberrant behaviors, seizure, and coma. Coma can occur at glucose levels in the range of 2.3–2.7 mmol/l (41–49 mg/dl) (9) as well as at lower glucose levels. All of these responses are typically corrected after the plasma glucose concentration is raised.

Episodes of hypoglycemia are a fact of life for most people with T1DM and many with advanced T2DM (3). In T1DM, plasma glucose concentrations may be less than 2.8 mmol/l (50 mg/dl) as much as 10% of the time; the average patient suffers two episodes of symptomatic hypoglycemia per week and one episode of severe, temporarily disabling hypoglycemia per year. Although iatrogenic deaths do result from the adverse effects of drug therapy (9, 10) (the mechanisms are unclear but could include cardiac arrhythmias), seemingly complete recovery from hypoglycemia-induced functional brain failure after the plasma glucose concentration is raised is the rule (3, 11). Permanent neurological damage is rare (11).

**Brain death**

Profound, prolonged hypoglycemia can cause brain death. In studies of insulin-induced hypoglycemia in monkeys, 5–6 hours of blood glucose concentrations of less than 1.1 mmol/l (20 mg/dl) were required for the regular production of neurological damage (12); the average blood glucose level was 0.7 mmol/l (13 mg/dl). Fortunately, hypoglycemia of that magnitude and duration occurs rarely in people with diabetes.

The mechanisms of the common, hypoglycemia-induced functional brain failure and of the rare, hypoglycemia-induced brain death that occurs at very low, and at lower glucose levels. All of these responses are typically corrected after the plasma glucose concentration is raised.

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