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 the 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 sympathetic 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

Nonstandard abbreviations used: T1DM, type 1 diabetes mellitus.

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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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cose reperfusion that was documented to cause detrimental effects. Superoxide pro-
duction, and presumably neuronal death, occurred as a result of hypoglycemia, but
these occurred to a greater extent with glucose reperfusion, less so when posthy-
poglycemic blood glucose concentrations were raised to the range of 1.0–2.0 mmol/l
(18–36 mg/dl) than when they were raised to the range of 5.0–10.0 mmol/l (90–180
mg/dl). Studies involving less profound hypoglycemia were not reported.

The distinction between the common hypoglycemia-induced functional brain
failure and the rare hypoglycemia-induced brain death drawn here is admittedly
arbitrary. Plasma glucose concentrations of less than 1.0 mmol/l (18 mg/dl) occur
occasionally in people with diabetes (9), and dying brain cells, presumably neurons,
have been reported following episodes of hypoglycemia at plasma glucose levels
of less than 1.0 mmol/l (18 mg/dl) (9) and dying brain cells, presumably neurons,
have been reported following episodes of hypoglycemia at plasma glucose levels
of 1.7–1.9 mmol/l (30–35 mg/dl) — but not following episodes of hypoglycemia
at plasma glucose levels of 2.5 mmol/l (45 mg/dl) — in rats (16). Thus, it could be
reasoned that these categories are not bina-
ry and that there is a continuous spectrum with increasing risk of neuronal death at progressively lower plasma glucose con-
centrations. Nonetheless, seemingly com-
plete recovery follows the vast majority of
episodes of clinical hypoglycemia.

The appropriate clinical extrapolation
of these data is not entirely clear. As
the authors point out (13), plasma glucose concentrations must be raised in hypoglycemic patients. In the common clinical
setting of hypoglycemia-induced func-
tional brain failure, plasma glucose levels
should be raised into the physiological
range promptly with the expectation that
recovery of brain function will follow. At
this point there is no clear evidence that
posttreatment hyperglycemia is detrimen-
tal to recovery, but there is no reason to
think it is beneficial in that setting. On
the other hand, undertreatment will delay
recovery. In the rare clinical setting of pro-
found, prolonged hypoglycemia, where the
risk of neuronal death is higher, the
data suggest that plasma glucose levels
should be raised cautiously with avoid-
ance of hyperglycemia (13–15). Nonethe-
less, it would seem reasonable to raise the
plasma glucose level into the physiologi-

cal range (e.g., > 3.9 mmol/l [70 mg/dl]) promptly. Clearly, additional studies of this important issue are needed.

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