Counterregulation to hypoglycaemia: physiology

S.A. Amiel

RD Lawrence Professor of Diabetic Medicine, King’s College, London, United Kingdom.
e-mail: stephanie.amiel@kcl.ac.uk

Maintenance of blood glucose concentrations is critical to normal function, as many tissues, not least the brain, use glucose as their preferred metabolic fuel. Glucose enters the circulation from the liver, which stores glucose as glycogen and can synthesise new glucose from other substrates, and from the diet. Glucose is consumed by tissue activity. The rates of endogenous glucose production and tissue glucose utilisation are tightly controlled in health by neuro-endocrine systems which are centrally coordinated. In health, extremes of hypo- or hyper-glycaemia do not occur.

As plasma glucose concentrations start to fall, for example in fasting or during exercise, the counterregulatory systems are activated. Pancreatic insulin secretion is reduced and pancreatic glucagon increased, so endogenous, particularly hepatic, glucose production is stimulated. The β cell responds not just to the glucose concentration, but also to the cessation of insulin secretion by neighbouring β cells. The glucagon response is diminished in the presence of sulphonylureas (which can maintain endogenous insulin secretion in the face of hypoglycaemia) [19, 27] and lost from patients with diabetes who have lost all endogenous insulin secretion. [4] Catecholamines and the sympathetic nervous system can work to correct hypoglycaemia if the pancreatic response is not enough and become critical in C-peptide deficient diabetic patients treated with insulin [4, 29]. In addition to increasing the drive on the pancreatic counterregulatory mechanisms, catecholamines increase endogenous glucose production by enhancing glyco- genolysis. Their peripheral actions on adipose tissue (lipolysis) provide fuel for gluconeogenesis, supporting endogenous glucose production and slowing peripheral tissue utilisation of glucose, both effects contributing to sustaining the blood glucose supply to the brain. Growth hormone and cortisol, which also cause peripheral insulin resistance and indirectly support gluconeogenesis, are important in the sustaining plasma glucose concentrations. Other counterregulatory responses include the enhancement of gastric emptying [18]. In health, the counterregulatory responses are initiated at slightly higher glucose levels than those associated with significant cognitive decline [24] — any upset of this protective hierarchy can lead to clinical problems such as hypoglycaemia unawareness and counterregulatory failure sometimes seen in diabetes [1]. It should be noted that recovery of cognitive function after induced hypoglycaemia is delayed beyond the restoration of the blood glucose concentrations or the time taken to lose the symptoms of hypoglycaemia or resolve the hormonal responses [11]. In general, hypoglycaemia severe enough to cause brain dysfunction occurs only in the presence of excess insulin (drug treatment for diabetes; tumours secreting insulin or insulin-like growth factors) and/or the deficiency of some or all of the counterregulatory responses. Although counterregulatory responses decline with age (being high in children [2] and delayed and reduced in the elderly [25]), there is no indication that hypoglycaemia becomes a clinical problem outside the settings of such pathology. The major determinant of the glucose level triggering a counterregulatory response appears to be the level of glucose to which the individual has been exposed in the recent past [16, 33].

Counterregulatory responses to hypoglycaemia are initiated by a fall in the metabolic rate of glucose sensing cells. We know this because infusions of non-glucose metabolic fuels such as lactate [23, 35] or 3-OH-butyrate1 can delay the onset and diminish the magnitude of the hormonal responses to experimentally induced hypoglycaemia — with a similar effect on cortical dysfunction. The favoured site for the main mammalian glucose sensor is in the brain, partly because teleologically it makes sense to place it in the tissue that is most dependent on a sustained supply of glucose in its circulation and partly because of classical observations of disturbed glucose regulation in animals with hypothalamic lesions (Claude Bernard’s “Piqûre diabetes”). More recently, a case report of the glycaemic effects of a sarcom lesion in the hypothalamus, with resolution of problematic hypoglycaemia after shrinkage of the lesion with steroid therapy, confirmed the importance of the hypothalamus in human glucose regulation [12]. Local infusion of glucoprivic agents into the hypothalamus of experimental animals can induce inappropriate counterregulation in non-hypoglycaemic animals [5] and the infusion of glucose or lactate6 into or around the ventromedial hypothalamus of rats diminishes the counterregulatory response to induced systemic hypoglycaemia.
Other animal work supports the presence of a further glucose sensor in the portal vein of the liver, and we have shown that oral glucose can diminish slightly the symptomatic and adrenergic responses to systemic hypoglycaemia in man. These data support the concept of a second glucose sensor in the portal vein monitoring the input of glucose from the gastrointestinal tract and influencing the centrally mediated stress response to hypoglycaemia. Studies of neuronal activation using c-fos activation show a network of neurones activated by glucoprivation. Neurones whose firing rates are controlled by high or low glucose converge on the ventromedial hypothalamus, which remains a major player in the control of responses to hypoglycaemia. Neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging are being used to identify regional brain activation in response to glucose ingestion and are potentially useful tools for investigating brain function and metabolism in hypoglycaemia in man.

Glucose sensing neurones may well use similar molecular mechanisms for sensing changes in blood glucose concentration as the pancreatic β-cell and appropriate glucose transporters, KATP channels and glucokinase have been identified in neurones. At least some aspects of counterregulation occur at higher glucose levels in patients with glucokinase mutations; in vitro, hyperglycaemia and sulphphonylureas, which mimic hyperglycaemia by stimulating insulin secretion from the pancreatic β-cell, enhance secretion of the inhibitory neurotransmitter GABA. It has been suggested that glucose sensing neurones respond to hypoglycaemia by de-repressing sympathetic centres, perhaps via diminished secretion of inhibitory neurotransmitters.

Our greater understanding of the mechanisms of normal glucose regulation should help us design strategies to help diabetic patients avoid problems with glucose regulation in response to their disease and its treatments.

REFERENCES


