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Nutrition of the brain: macronutrient supply

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GLUCOSE

It has long been accepted that the human brain uses glucose as its only metabolic fuel and, thus, is entirely dependent on glucose for its function. This is in spite of the fact that the brain contains many enzyme systems theoretically capable of metabolizing non-glucose substrates such as glycerol, fatty acids, lactate, ketones and amino acids. Nevertheless, it is true that the brain is the major consumer of glucose in the resting state and about 10% of the blood glucose is extracted by the brain. Of that glucose, over 90% is fully oxidized to CO_2 and water with the generation of high-energy phosphates. Perhaps about 5% of brain glucose is metabolized through the hexose monophosphate shunt and the remainder through glycolysis to lactate and pyruvate, and only a very small quantity is synthesized into glycogen. The glycogen stores of the brain are very small and do not provide a useful reservoir of glucose in times of glucose lack.

It is undoubtedly true that failure of the blood glucose supply to the brain produces significant loss of brain function (Amiel *et al.* 1991*b*). Indeed, the body is well designed to prevent such falls in glucose. If blood glucose does begin to fall, in response to prolonged starvation or extreme exercise or to insulin administration, a counter-regulatory response is initiated which acts both to restore blood glucose levels and produce a symptom complex that stimulates the subject to eat (Amiel, 1991). In terms of blood glucose restoration, the most important part of the endogenous response is probably the cessation of pancreatic insulin secretion and the stimulation of pancreatic glucagon. These hormone changes stimulate hepatic glucose production causing blood sugars to rise again. Almost equally effective and clinically very important is the stimulation of adrenaline secretion and of the sympathetic nervous system. Together with cortisol and growth hormone secretion, these responses not only stimulate and support hepatic glucose production, but also lower the rate at which peripheral tissue such as muscle and fat can take up glucose from the circulation. Furthermore, the adrenaline and sympathetic nervous system stimulation is associated with symptoms of anxiety, sweating, tremor and palpitations and hunger, stimulating eating, the most effective way of correcting the situation (Hepburn *et al.* 1991). Only if these mechanisms fail and/or blood glucose is forced below 3 mmol/l, do the higher cerebral functions of

psychomotor coordination and cognitive function become impaired (Widom & Simonson, 1990; Maran *et al.* 1993).

It is believed that cerebral metabolism is involved not just in cognitive processes but also in the recognition of developing hypoglycaemia and the initiation of much of the counter-regulatory response. Evidence for this theory comes from the selective catheterization experiments of Cherrington's group in Nashville (Biggers *et al.* 1989). They catheterized dogs in order to be able to perfuse separately the body and the brain. When the animals were rendered bodily hypoglycaemic but brain glucose levels were maintained, the hormonal and glucose kinetic responses of counter-regulation were virtually obliterated, suggesting that cerebral hypoglycaemia was necessary to initiate these protective responses. In studies in man, Nagy *et al.* (1992) have renovated an older procedure of measuring cerebral metabolism by measuring cerebral blood flow and substrate arterio–venous differences across the brain. They have been able to calculate rates of cerebral glucose metabolism across the whole brain and demonstrate quite clearly a decrement in cerebral blood glucose uptake in normal individuals at a blood glucose level of approximately 3·8 mmol/l, an arterial blood glucose around or slightly above that necessary to stimulate adrenergic counter-regulatory responses and certainly higher than that usually believed to be associated with cognitive dysfunction.

The rate-limiting step in cerebral glucose metabolism is cerebral glucose uptake. McCall *et al.* (1986) have demonstrated that the process can adapt itself to prevailing glucose levels. Acute hypoglycaemia produces no alteration in the rate at which brain tissue can extract glucose *in vitro*, but when the experiments are repeated after 4 d of moderate hypoglycaemia, rates of brain glucose extraction are significantly increased. The mechanism of adaptation is by means of an increase in the number of membrane glucose transporters.

Correlations can be made between humans and studies in animals. Some patients with insulin-dependent diabetes mellitus (particularly those with long-term disease and/or very tight metabolic control) exhibit a phenomenon now known as loss of awareness of hypoglycaemia. Underlying this is a failure to generate adrenergic and symptomatic counter-regulatory responses to hypoglycaemia until blood sugar has fallen much lower than the level that would normally be required (Amiel *et al.* 1988). For example, adrenaline responses to hypoglycaemia do not begin in such individuals until blood sugar has reached about 2·2 mmol/l, whereas in non-diabetic or less-well-controlled diabetic patients, such responses begin at a blood sugar level of 3·6 mmol/l. Since in all subjects cognitive function (measured by four-choice reaction time) begins to deteriorate at a mean blood glucose of about 2·8 mmol/l, in the hypoglycaemia-unaware patient cognitive function deteriorates at a higher blood glucose level (i.e. earlier) than that at which symptomatic responses occur. By the time glucose is low enough to generate responses that should produce symptoms, the patient may be too cognitively impaired to respond. Boyle's group (Nagy *et al.* 1993) have shown that in normal individuals a 2 d period of moderate insulin-induced hypoglycaemia results in a maintenance of blood glucose utilization rates during induced hypoglycaemia, until blood glucose reaches 2·5 mmol/l. In the hypoglycaemia-naive subjects, brain glucose utilization has fallen considerably by the time blood glucose is 3·6 mmol/l. While in this study, hypoglycaemia-naive subjects lost motor function when their blood glucose fell to 2·5 mmol/l, after 2 d of hypoglycaemia, these subjects were able to retain motor function in the face of a similar blood glucose level. However, intellectual function assessed by the

Stroop test, showed a similar deterioration on both occasions at 2·5 mmol/l. In the second study, this intellectual deterioration was occurring in the face of diminished symptoms and hormonal responses in a similar way to that seen in tightly controlled diabetic subjects. It is suggested that the lowering of glucose levels associated with symptom generation and hormone responses in the well-controlled and long-duration diabetic patients with loss of awareness of hypoglycaemia may be induced as an adaptation to recurrent quite mild hypoglycaemia in their daily lives. The danger lies in the apparent lack of a similar degree of adaptation of the cerebral cortex.

NON-GLUCOSE SUBSTRATES FOR CEREBRAL METABOLISM

Ketone bodies

The apparent adaptation to mild hypoglycaemia would suggest that both initiation of counter-regulatory responses and the deterioration of psychomotor coordination and cognitive function result from slowed rates of cerebral metabolism, rather than as a direct response to fluctuations in blood glucose levels. Given that the brain does have the enzyme capacity to metabolize other substrates, it is worth ascertaining whether such substrates can support brain metabolism and function if glucose is scarce. In a classic study of three obese individuals starved for many days, Owen et al. (1967) demonstrated that the human brain could become a net consumer of ketone bodies. Coupled with evidence of reduced responsiveness to hypoglycaemia (Drenick et al. 1972) and better preserved cerebral function after prolonged fasting in man, this led to the assumption that the brain could use ketones for metabolism and function, but only after a period of adaptation. Hawkins et al. (1971), however, were able to measure in animals similar cerebral net consumption of ketones during acute ketone infusion and suggested that a prolonged period of adaptation was not necessary. In man we have evidence to support this theory, in that infusion of 3-hydroxybutyrate during insulin-induced hypoglycaemia produced a marked diminution in adrenaline responses to the hypoglycaemia, suggesting that at least that part of the brain responsible for recognizing and initiating counter-regulation could support its metabolism with ketone bodies if they were present during times of glucose lack (Amiel et al. 1991a). However, obliterating the rise in ketone bodies (and non-esterified fatty acids) during hypoglcyaemia had no effect on counter-regulation in man, suggesting that other mechanisms were involved (Fanelli et al. 1993).

Lactate

Plasma lactate levels are known to rise during counter-regulatory response to hypo-glycaemia. The brain has the enzyme systems necessary to metabolize lactate and Avagaro et al. (1990) have studied substrate uptake and release across the brain of dogs, both normal and diabetic, including glucose, lactate and 3-hydroxybutyrate. During normoglycaemia, the brain is a net consumer of glucose and to a very small degree of 3-hydroxybutyrate and releases lactate as an endproduct of glycolysis in both normal and diabetic animals. However, during hypoglycaemia the brain of diabetic animals becomes a net consumer of substantial quantities of lactate and the authors suggested that in this circumstance, lactate might be the most important alternate fuel for cerebral metabolism and not, as previously supposed, ketone bodies. We have investigated, therefore, the effect of lactate infusion during induced hypoglycaemia in man, using a lactate dose that

produced a plasma lactate level of about 2·5 mmol/l, approximately equivalent to the sort of level seen in moderate exercise. Lactate infusion was associated with a marked diminution of counter-regulatory hormone responses and a lowering of the glucose level that initiated them (Maran *et al.* 1994). This response was similar to that seen in hypoglycaemia-unaware diabetic patients, but a marked contrast was seen in terms of cognitive dysfunction. Slowing and inaccuracy of the four-choice reaction time was seen at lower blood glucose levels during lactate infusion than in the absence of the additional metabolic fuel, suggesting that lactate was able to some extent to support cerebral glucose metabolism and maintain cognitive function during hypoglycaemia.

The future

The clinical implications of these findings are as yet uncertain, but have exciting potential. Recent evidence has confirmed that strict glycaemic control is beneficial to patients with diabetes in terms of reducing the risk of development of long-term complications of the disease such as blindness, nerve damage and renal disease (The Diabetes Control and Complications Trial Research Group, 1993). With currently available insulins, the major problem with attempts to achieve such chronic normo-glycaemia in people with insulin-dependent diabetes is a tendency to produce hypo-glycaemia intermittently and create a scenario of loss of awareness of hypoglycaemia and greater risk of severe episodes with clinically significant cognitive dysfunction. The possibility that therapeutic regimens might be designed to provide non-glucose fuels for cerebral metabolism during hypoglycaemia must be explored. To date, we and others have looked at ketone bodies and lactate, and the potential for other non-glucose substrates for cerebral metabolism is under active investigation.

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