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Cerebral ketone body metabolism

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Summary: Ketone bodies (KBs) are an important source of energy for the brain. During the neonatal period, they are also precursors for the synthesis of lipids (especially cholesterol) and amino acids. The rate of cerebral KB metabolism depends primarily on the concentration in blood; high concentrations occur during fasting and on a high-fat diet. Cerebral KB metabolism is also regulated by the permeability of the blood–brain barrier (BBB), which depends on the abundance of monocarboxylic acid transporters (MCT1). The BBB's permeability to KBs increases with fasting in humans. In rats, permeability increases during the suckling period, but human neonates have not been studied. Monocarboxylic acid transporters are also present in the plasma membranes of neurons and glia but their role in regulating KB metabolism is uncertain. Finally, the rate of cerebral KB metabolism depends on the activities of the relevant enzymes in brain. The activities vary with age in rats, but reliable results are not available for humans. Cerebral KB metabolism in humans differs from that in the rat in several respects. During fasting, for example, KBs supply more of the brain's energy in humans than in the rat. Conversely, KBs are probably used more extensively in the brain of suckling rats than in human neonates. These differences complicate the interpretation of rodent studies. Most patients with inborn errors of ketogenesis develop normally, suggesting that the only essential role for KBs is as an alternative fuel during illness or prolonged fasting. On the other hand, in HMG-CoA lyase deficiency, imaging generally shows asymptomatic white-matter abnormalities. The ability of KBs to act as an alternative fuel explains the effectiveness of the ketogenic diet in GLUT1 deficiency, but its effectiveness in epilepsy remains unexplained.

The term 'ketone body' (KB) refers to three compounds: acetoacetate, 3-hydroxybutyrate and acetone. Acetoacetate and 3-hydroxybutyrate can be interconverted in many tissues by 3-hydroxybutyrate dehydrogenase. Acetone is formed from acetoacetate by spontaneous decarboxylation and is generally considered of little metabolic significance. KBs are formed in the liver, predominantly from fatty acids, and can be used by many tissues. Cardiac muscle, for example, oxidizes KBs in

preference to fatty acids (which are themselves used in preference to carbohydrates) (Little et al 1970). The most significant feature of KB metabolism, however, is that KBs can be used by the brain. In this review, I will consider the roles and the regulation of cerebral KB metabolism and its clinical relevance. I will include studies in rodents because there have been many fewer human studies. There are, however, differences between the species in cerebral KB metabolism.

METABOLIC ROLES

A source of energy

KBs are an energy source for the brain at times of glucose shortage, such as prolonged fasting. In this respect, they differ from fatty acids. It is still uncertain why the brain does not oxidize fatty acids. Fatty acids cross the blood–brain barrier, using a specific carrier (Spector, 1988), and β-oxidation enzymes are expressed in brain (Reichmann et al 1988), though the activity of 3-ketoacyl-CoA thiolase (EC 2.3.1.16) may be low (Yang et al 1987). Whatever the reason, brain does not oxidize fatty acids and, instead, they are converted in the liver to KBs. KBs are the principal alternative to glucose as a fuel for the brain and they allow the brain access to the body's fat stores.

In the 1960s, cerebral KB uptake was studied in three human subjects fasted for 5–6 weeks for the treatment of obesity (Owen et al 1967). Calculations showed that their bodies' entire stores of carbohydrate and gluconeogenic precursors were insufficient to meet the brain's energy requirement for this duration. The cerebral vessels were catheterized and the blood flow and concentrations of metabolic fuels were measured. Glucose uptake was much lower than under basal conditions and KB uptake was sufficient to supply approaching 60% of the brain's energy requirement.

The proportion of the brain's energy requirement that can be supplied by KBs differs between species. Cerebral KB utilization in rats has been calculated either by measuring A-V concentration differences (Dahlquist and Persson, 1976) or by infusing radioactive 3-hydroxybutyrate and measuring incorporation into the brain (Cremer 1982; Hawkins et al 1986). In fasted adult rats, KBs supply much less of the brain's energy than in humans and they may provide as little as 3.2% of the brain's requirement (Hawkins et al 1986). In contrast, KB uptake could account for >30% of the brain's energy requirement in suckling rats (Cremer, 1982).

Substrates for anabolism

The second function of KBs in the brain is to provide substrates for the synthesis of various molecules. KBs are particularly important for the synthesis of lipids, such as cholesterol in myelin. Studies in 18-day-old rats found that KBs are incorporated into brain cholesterol and fatty acids much more readily than glucose is incorporated (Webber and Edmond 1977). Studies of cultured mouse astrocytes and neurons gave similar results (Lopes-Cardozo et al 1986). The preferential use of KBs for lipid synthesis probably occurs because they can be converted directly to acetoacetyl-CoA in the cytoplasm by acetoacetyl-CoA synthetase (EC 6.2.1.16, see Figure 1). Cytosolic acetoacetyl-CoA thiolase can then convert acetoacetyl-CoA to acetyl-CoA. Cytosolic

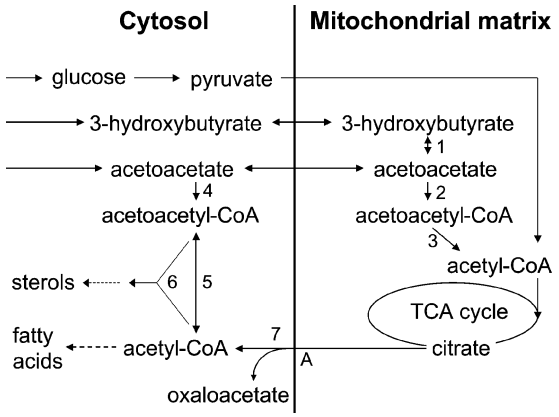

Figure 1 Simplified diagram showing pathways of cerebral ketone body metabolism compared with glucose. Enzymes: 1 = 3-hydroxybutyrate dehydrogenase; 2 = succinyl-CoA 3-oxoacid CoA transferase; 3 = mitochondrial acetoacetyl-CoA thiolase (also called β-ketothiolase and methylacetoacetyl-CoA thiolase); 4 = acetoacetyl-CoA synthetase; 5 = cytoplasmic acetoacetyl-CoA thiolase; 6 = cytoplasmic hydroxymethylglutaryl-CoA synthase; 7 = ATP-citrate lyase. A: Part of pyruvate/malate shuttle for transport of acetyl-CoA out of mitochondria

acetyl-CoA can be generated from glucose (via the tricarboxylic acid cycle and ATP-citrate lyase, Figure 1) but this is a less direct pathway due to the inability of acetyl-CoA to cross the mitochondrial inner membrane. KBs are incorporated into fatty acids in the brain but they are primarily used for cholesterol synthesis (Koper et al 1981). Acetoacetyl-CoA synthetase expression in human brain parallels that of HMG-CoA reductase (EC 1.1.1.34), providing further evidence for the importance of this pathway in sterol synthesis (Ohgami et al 2003). Although KBs are the preferred substrates for brain lipogenesis, they appear not to be essential. Thus, rats fed a hypoketogenic diet develop normally (Auestad et al 1990). Development is also normal in most human patients with defects of ketogenesis (Morris et al 1998; van der Knaap et al 1998), though imaging sometimes shows white-matter abnormalities (see Clinical Considerations below).

KBs can also be used for the synthesis of amino acids in the brain, as shown by studies of rat brains following the intravenous injection of labelled KBs. Indeed, in immature rats (up to the age of 15 days), KBs are more readily incorporated into cerebral amino acids than is glucose (DeVivo et al 1975). The effects of ketosis on glutamate and GABA metabolism are discussed later under Clinical Considerations, because they may explain the anticonvulsant effects of ketogenic diets.

REGULATION OF CEREBRAL KETONE BODY METABOLISM

Concentrations in blood

Blood concentration is the most significant factor affecting the rate of cerebral KB metabolism. Normally, blood KB concentrations are very low. The main

physiological causes of ketosis are fasting or a high-fat diet, such as that of mammals prior to weaning. The level of ketosis induced by these stimuli varies between species.

Humans can achieve very high circulating KB concentrations during prolonged fasting, as shown in Owen's study of three obese adults (Owen et al 1967). After fasting for 5–6 weeks, the mean total circulating KB concentration was 7.8 mmol/L (range 5.8–9.7). Even after shorter periods of fasting, impressive ketonaemia can be reached (e.g. total plasma KBs of 4.9 ± 0.4 mmol/L in 15 children starved for 30 h) (Haymond et al 1982). Rats cannot achieve such high concentrations but, after 4–5 days of fasting, the total circulating KB concentration is generally 3–4 mmol/L (Gjedde and Crone 1975; Hawkins et al 1971; Moore et al 1976).

In contrast, rats generally have higher circulating KB concentrations than humans during the suckling period. At this age, the level of ketosis primarily reflects the composition of the milk. Mature rat milk is high in fat and low in carbohydrate, compared with human milk (Table 1). Thus, suckling rats aged 1–20 days have total circulating KB concentrations approaching 1.5 mmol/L (Krebs et al 1971). In human neonates, typical total KB concentrations are 0.08–0.12 mmol/L after the first 3 days (Hawdon et al 1992). Higher values are seen on days 2 and 3 (mean 0.42 mmol/L in Hawdon's study) but this is not due to the composition of colostrum, which contains less fat than mature milk (Table 1).

Transport across the blood-brain barrier and into cells

Transport across the blood–brain barrier (BBB) is the second factor regulating KB utilization. The BBB is relatively impermeable to most hydrophilic substances, such as KBs, unless they are transported by a carrier protein. Studies in the 1970s showed that the BBB contains a transporter for short-chain monocarboxylic acids, such as KBs and lactate (Gjedde and Crone, 1975). All three KBs are transported but at different rates: acetoacetate uptake is twice that of 3-hydroxybutyrate at a given arterial concentration (Hawkins et al 1971). Uptake of acetone has also been demonstrated (Likhodii et al 2003), but the rate of transport has not been compared with those of the other two KBs. A family of proton-linked monocarboxylic acid transporters (MCTs) has now been identified; there are at least nine related genes in mammals (Halestrap and Price 1999). MCT1 is widely expressed and it has been demonstrated on the luminal and abluminal membranes of BBB endothelial cells in rodents (Gerhart et al 1997; Leino et al 1999; Pellerin et al, 1998) and in humans (Froberg et al 2001).

Studies of cerebral uptake showed that the BBB permeability to 3-hydroxybutyrate in rats increases by a factor of 7 during the suckling period and falls again after weaning (Gjedde and Crone 1975; Moore et al 1976). In adult rats, the BBB

Table 1 Composition of rat and human milk expressed as percentages of energy content

	Rat mature milk	*Human mature milk*	*Human colostrum*
Fat	69%	53%	41%
Carbohydrate	8%	39%	45%
Protein	23%	8%	14%
Reference	(Dymsza et al 1964)	(*McCance and Widdowson's The Composition of Foods*, 2004)	

permeability to KBs is never as high as in sucklings, but increased permeability can be induced by a high-fat diet or by prolonged fasting (Gjedde and Crone 1975; Moore et al 1976); short periods of fasting do not alter permeability (Hawkins et al 1971). Molecular studies have now confirmed that MCT1 expression in the BBB of rodents is much higher prior to weaning (Gerhart et al 1997; Pellerin et al 1998) — up to 25-fold higher than in adults (Leino et al 1999). Diet-induced ketosis can increase MCT1 expression 8-fold in the BBB of adult rats (Leino et al 2001). It is not yet known how MCT1 expression is regulated. It seems most likely that BBB expression is induced directly by prolonged high KB concentrations, but endocrine and developmental regulation are also possible.

Two studies have considered the effect of fasting on BBB permeability in humans. Starvation for 3.5 days appeared to increase the permeability to KBs, as measured by the 'intravenous double indicator method' (Hasselbalch et al 1995). The same conclusion was reached in a study using magnetic resonance spectroscopy to measure cerebral 3-hydroxybutyrate concentrations (Table 2). When plasma concentrations were raised acutely by an intravenous infusion of 3-hydroxybutyrate, cerebral concentrations showed a small rise (Pan et al 2001). When plasma concentrations were raised to a similar level by prolonged fasting, cerebral 3-hydroxybutyrate concentrations rose much higher (Pan et al 2000), implying that BBB permeability had increased.

The uptake of KBs by brain cells has been investigated using dissociated cells from rat brain (Tildon and Roeder 1988) and cultured rat astrocytes (Tildon et al 1994). The results suggest that KB entry occurs by two mechanisms: diffusion (at a moderately high rate) and a carrier-mediated process. MCTs have now been demonstrated on neurons and glia as well as in the BBB. Glial cells predominantly express MCT1, while neurons may express MCT1 or MCT2 (Pellerin et al 1998). The expression of MCTs on brain cells does not fall after weaning, in contrast to the BBB expression. This is probably because KB uptake is a minor role for MCTs on brain cells — their main function may be the shuttling of lactate from astrocytes to neurons (Pellerin et al 1998). Diet-induced ketosis is, however, said to increase MCT1 staining on neuropil, as well as on endothelial cells (Leino et al, 2001).

Activity of ketone body-metabolizing enzymes

In rat brain there are age-related changes in the three mitochondrial enzymes of KB utilization (3-hydroxybutyrate dehydrogenase (EC 1.1.1.30), succinyl-CoA 3-oxoacid

Table 2 Brain and plasma 3-hydroxybutyrate concentrations in adult human subjects during fasting or an intravenous infusion of 3-hydroxybutyrate

	Fasting		*Infusion of 3-hydroxybutyrate*
	48 h	72 h	
Cerebral 3-hydroxybutyrate	0.60 ± 0.26	0.98 ± 0.16	0.24 ± 0.04
Plasma 3-hydroxybutyrate	1.67 ± 0.34	3.15 ± 0.67	2.12 ± 0.30

Values are mean concentration (mmol/L) $\pm$ standard deviation for 5 subjects in fasting study and 6 subjects in infusion study (Pan et al 2000, 2001)

CoA transferase (EC 2.8.3.5) and mitochondrial acetoacetyl-CoA thiolase (EC 2.3.1.9), see Figure 1). For all three enzymes, activity is relatively low at birth but rises steadily through the suckling period to a maximum, about 5 times the initial activity, at the time of weaning (age 21 days). Subsequently, activities fall again to low values in adults (Middleton 1973; Page et al 1971). The changes in enzyme activity parallel the changes in BBB permeability to KBs and together they allow the brain to use the high levels of KBs circulating during the suckling period.

In adult rats, the mitochondrial enzymes of KB utilization do not increase in brain in response to a high-fat diet (Middleton 1973) or starvation (Williamson et al 1971). Blood KB concentrations and BBB permeability are thought to be the main factors limiting cerebral KB metabolism. In accordance with this, cerebral KB concentrations are generally low. For example, in rats fasted for 48 h, the mean brain 3-hydroxybutyrate concentration was 0.2 mmol/L with a mean blood concentration of 1.6 mmol/L (Hawkins et al 1971). Cerebral enzyme activity might, however, limit KB use during more prolonged fasting, when blood KB concentrations can reach >3 mmol/L and BBB transport increases (Gjedde and Crone 1975).

The cytoplasmic enzymes of KB metabolism (acetoacetyl-CoA synthetase and cytoplasmic acetoacetyl-CoA thiolase (EC 2.3.1.9) show different changes in cerebral activity with age. The activity of both enzymes is maximal at birth and gradually falls to 25–50% of the initial value in adult rats (Buckley and Williamson 1973; Middleton 1973). These cytoplasmic enzymes are used for the synthesis of lipids, particularly cholesterol (Figure 1). In the brain, the need for cholesterol is highest during myelination. This process is active at birth in the rat and decreases considerably by the age of 30 days, correlating with the changes in the cytoplasmic enzymes.

There have been few studies of the enzymes of KB metabolism in human brain. One study found low activities in fetal brain. 3-Hydroxybutyrate dehydrogenase and succinyl-CoA 3-oxoacid CoA transferase activities were similar from early childhood until adulthood. Total acetoacetyl-CoA thiolase was higher in older subjects (Page and Williamson 1971). The results may, however, have been affected by the delay in obtaining tissue *post mortem*.

In humans, fasting leads to higher cerebral KB concentrations than in rats. After fasting for 40 hours, the mean CSF 3-hydroxybutyrate concentration was 0.60 mmol/L in 58 boys aged 6–15 years (mean blood concentration 3.7 mmol/L) (Lamers et al 1987). Magnetic resonance spectroscopy showed similar or higher 3-hydroxybutyrate concentrations in brain when adults were fasted for 48–72 h (Table 2) (Pan et al 2000, 2001). Magnetic resonance spectroscopy has also demonstrated high brain 3-hydroxybutyrate concentrations in children on a ketogenic diet (Novotny and Rothman 1996). These high concentrations suggest that, in humans, cerebral enzyme activity may be a factor limiting KB metabolism.

REGIONAL VARIATION IN CEREBRAL KB METABOLISM

Suckling rats show relatively homogeneous KB uptake throughout the brain (Nehlig et al 1991), consistent with the importance of KB substrates at this age. In adult rats, however, KB uptake varies in different regions of the brain. After an intravenous

infusion of radioactive 3-hydroxybutyrate, autoradiography showed highest uptake in the cerebral cortex (especially the deep layers), the superior and inferior colliculi and regions that have no BBB, such as the pituitary and pineal glands (Hawkins et al 1986). Uptake was low in the corpus callosum and other white-matter structures, reflecting their low metabolic rate and capillary density. KB uptake was also low in central structures, such as the basal ganglia and midbrain (apart from the colliculi). The pattern of KB uptake resembles that of glucose uptake, but there are some interesting differences. Glucose uptake is higher in the superficial layers than the deep layers of the cortex (Hawkins and Biebuyck 1979). Glucose uptake is also high in the basal ganglia (Hawkins and Biebuyck 1979; Zeller et al 1997).

MCT1 expression in the brain resembles the pattern of KB uptake in some respects. There are differences, however, because MCT1 is found on glia and neurons as well as on BBB epithelial cells and because the pituitary and pineal have no BBB. In suckling mice, MCT1 expression, like KB uptake, is relatively uniform throughout the brain, though there is stronger expression in the cerebellum (Pellerin et al 1998). The similarity is expected because MCT1 is predominantly vascular at this age. In adult mice, MCT1 is expressed at high levels in the cortex, cerebellum, hippocampus and corpus striatum (Pellerin et al 1998). This distribution differs from KB uptake, as expected, because MCT1 is now predominantly glial (and neuronal) and KB transport is a minor role. Within the cerebral cortex, MCT1 expression and KB uptake are both low in layer I, but the significance of this is unclear.

In suckling rats, the mitochondrial enzymes of KB metabolism have relatively uniform activity throughout the brain. Enzyme activity is low in most regions of the adult rat brain. Studies of 3-hydroxybutyrate dehydrogenase have, however, shown higher activity in the cerebral cortex (Bilger and Nehlig 1992). This correlates with the ability of the adult cerebral cortex to take up KBs (Hawkins et al 1986).

CLINICAL CONSIDERATIONS

Myelination in disorders of ketogenesis

Knowledge of cerebral KB metabolism is relevant for inborn errors of KB metabolism and for use of the ketogenic diet. Given the importance of KBs as substrates for myelination, one might expect disorders of ketogenesis to be associated with cerebral white-matter abnormalities. Magnetic resonance imaging has, indeed, shown diffuse mildly increased signal in the white matter of patients with HMG-CoA lyase (EC 4.1.3.4) deficiency (McKusick 246450) (van der Knaap et al 1998). Superimposed on this are foci of more abnormal signal (Ozand et al 1991; van der Knaap et al 1998). In most cases, multiple lesions have been present, varying in size from a few millimetres to large confluent areas; as well as in the cerebral hemispheres, they have been reported in the internal capsule and brainstem but not in the corpus callosum or cerebellar white matter. Despite the imaging abnormalities, most patients have had no neurological problems and normal or slightly below average intelligence. The findings would be compatible with hypomyelination, caused by the lack of KB.

Use of ketogenic diets for epilepsy

It has long been recognized that fasting suppresses seizures in some patients, and in the early 1920s it was suggested that this might be due to ketonaemia. High-fat, low-carbohydrate 'ketogenic diets' are an effective treatment for many children with refractory epilepsy. In one study of 150 such children, 27% achieved >90% reduction in seizures (Freeman et al 1998). Ketogenic diets are less widely used in adults. This is sometimes justified on the basis that cerebral KB uptake is low in adult rats. In adult humans, however, the brain uses KB extensively during prolonged ketonaemia. The ketogenic diet certainly can be effective in adult patients if compliance is achieved (Sirven et al 1999).

It is still uncertain why the ketogenic diet improves epilepsy. Hypotheses can be classified into those suggesting a direct anticonvulsant effect of KBs, those suggesting that cerebral KB metabolism reduces neuronal excitability, and those suggesting less direct effects of the diet. Direct anticonvulsant effects have been demonstrated for acetone (Likhodii et al 2003). Acetone has less metabolic significance than the other KBs but it is transported across the BBB and raised brain levels have been demonstrated in patients on the ketogenic diet (Seymour et al 1999). Direct anticonvulsant actions have also been postulated for 3-hydroxybutyrate, which has structural similarities to GABA. One study of hippocampal brain slices found that 3-hydroxybutyrate enhanced GABA-mediated inhibitory postsynaptic potentials (Ge and Niesen 1998), but other studies found no such enhancement.

KBs are used by the brain for energy and for the synthesis of lipids and amino acids. KBs are an efficient energy source and it has been suggested that the ketogenic diet suppresses seizures by increasing cerebral energy reserves (DeVivo et al 1978). This hypothesis is somewhat paradoxical, as the primary factor in inducing ketosis is a lack of carbohydrate; seizures can be suppressed by starvation-induced ketosis, though one might not expect this to increase energy reserves. DeVivo and colleagues did, however, find a raised ATP:ADP ratio and increased creatine levels in rats on a ketogenic diet (DeVivo et al 1978). Moreover, ^{31}P magnetic resonance spectroscopy showed increased cerebral energy reserves in humans on a ketogenic diet for epilepsy (Pan et al 1999), though the change could have *resulted* from the improved seizure control rather than the other way round.

Given the importance of KBs in cerebral lipid synthesis, it is hardly surprising that ketogenic diets alter the levels of some lipids in rat brain. Different changes, however, are seen with versions of the diet that are equally effective in preventing seizures (Dell et al 2001). Changes in lipids are, therefore, probably not responsible for the anticonvulsant effects of the ketogenic diet.

KBs are also involved in cerebral amino acid synthesis and metabolism. In particular, KBs have effects on the neurotransmitters glutamate and GABA, which may affect neuronal excitability. KBs have been shown to shift the glutamate/aspartate equilibrium towards glutamate in synaptosomes, cultured astrocytes and intact mouse forebrain (Erecinska et al 1996; Yudkoff et al 1997, 2001). KB oxidation probably alters the equilibrium by depleting oxaloacetate, a substrate for the transamination (Figure 2); pyruvate carboxylase may be inhibited by KBs, exacerbating

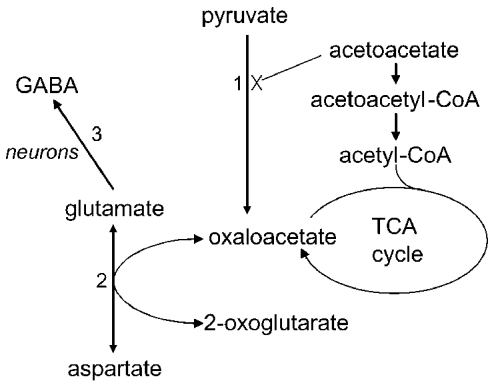

Figure 2 Simplified diagram showing some effects of ketone bodies on cerebral glutamate and GABA metabolism. Enzymes: 1 = pyruvate carboxylase; 2 = aspartate transaminase; 3 = glutamate decarboxylase

the oxaloacetate depletion (Hazen et al 1997). The increased concentration of glutamate relative to aspartate may prevent seizures by increasing GABA levels, since GABA is formed from glutamate in GABAergic neurons. High KB concentrations increased GABA concentrations in isolated synaptosomes (Erecinska et al 1996) and, to a lesser extent, in intact mouse forebrain (Yudkoff et al 2001).

Ketosis may also affect the transport of amino acids across the BBB. In mice, administration of a ketogenic diet led to increased blood leucine concentrations and increased uptake of leucine by the forebrain (Yudkoff et al 2001). Leucine crosses the BBB in exchange for glutamine, which is formed in astrocytes from glutamate. Increased leucine uptake will, therefore, *tend* to lower astrocyte glutamine concentrations. Astrocytes derive some of their glutamate from the synaptic cleft and ketosis may, therefore, minimize surges in intrasynaptic glutamate. Clearly, this might be relevant to the prevention of seizures.

Finally, the ketogenic diet might reduce neuronal excitability by changes less directly related to KBs. For example, the ketogenic diet has been shown to increase the level of uncoupling proteins in the hippocampus of rats; this may have neuroprotective effects by decreasing the production of reactive oxygen species (Sullivan et al 2004). Changes in pH, hormones and hydration have also been proposed as mechanisms of action for the ketogenic diet but none of these seems likely. In rats, the diet does not alter cerebral pH (Al Mudallal et al 1996). Ketosis is associated with low insulin concentrations, whereas high insulin concentrations may protect against seizures (Uysal et al 1996). Children on ketogenic diets readily become dehydrated and mild dehydration may reduce neuronal excitability (Rosen and Andrew 1991), but the diet is equally effective if normal hydration is maintained.

Use of ketogenic diets for inherited disorders

The ketogenic diet is also useful in a few inherited disorders. Some patients with pyruvate dehydrogenase (EC 1.2.4.1) deficiency (McKusick 300502) improve with

this treatment (Falk et al 1976; Wijburg et al 1992). Pyruvate dehydrogenase deficiency impairs carbohydrate oxidation but does not interfere with KB use by the brain (or other organs). Unfortunately, most patients with pyruvate dehydrogenase deficiency are profoundly handicapped and remain so despite this treatment.

The ketogenic diet is more useful in GLUT1 deficiency (McKusick 138140). GLUT1 is the glucose transporter found in the BBB. Patients with GLUT1 deficiency present with developmental delay, seizures and a complex movement disorder, associated with low CSF glucose concentrations (De Vivo et al 1991). Treatment with a ketogenic diet consistently leads to resolution of seizures in these patients (Klepper and Voit 2002). They also improve in other respects, indicating that ketosis is providing an alternative fuel for the brain, rather than just having an antiepileptic effect. In rats, the ketogenic diet leads to a modest increase in GLUT1 numbers (Leino et al 2001), which might also contribute to the improvement in patients with GLUT1 deficiency. As mentioned above, rat brain shows different distributions of glucose and KB uptake (Hawkins and Biebuyck 1979). This might be expected to impair the effectiveness of the ketogenic diet in GLUT1 deficiency. There are, however, always residual GLUT1 transporters in this disorder, which is associated with haploinsufficiency (Seidner et al 1998). KB uptake will complement the glucose uptake by residual GLUT1 transporters.

CONCLUSIONS

The roles and regulation of cerebral KB metabolism were largely established by studies 20–30 years ago. We continue to regard KBs primarily as a fuel for the brain in the newborn period and during fasting. KBs are also used as substrates for anabolism, especially lipid synthesis; experience with hypoketotic subjects suggests that this role is not essential, but some uncertainty remains. Blood concentrations and BBB transport are still considered the major determinants of cerebral KB metabolism. More recently, the monocarboxylate transporter genes have been identified and magnetic resonance spectroscopy has allowed cerebral KB concentrations to be measured in humans. We still do not know, however, the mechanism by which ketosis leads to increased MCT1 abundance in the BBB; neither are we sure of the importance of MCT1 and MCT2 on neurons and glia in controlling KB metabolism. Clinicians have learnt more about inborn errors of ketogenesis and GLUT1 deficiency has provided a new indication for the ketogenic diet. The biggest surprise, however, is that we still do not know the mechanism of action of the ketogenic diet in epilepsy.

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