

REVIEW

Clinical review: Ketones and brain injury

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Abstract

Although much feared by clinicians, the ability to produce ketones has allowed humans to withstand prolonged periods of starvation. At such times, ketones can supply up to 50% of basal energy requirements. More interesting, however, is the fact that ketones can provide as much as 70% of the brain's energy needs, more efficiently than glucose. Studies suggest that during times of acute brain injury, cerebral uptake of ketones increases significantly. Researchers have thus attempted to attenuate the effects of cerebral injury by administering ketones exogenously. Hypertonic saline is commonly utilized for management of intracranial hypertension following cerebral injury. A solution containing both hypertonic saline and ketones may prove ideal for managing the dual problems of refractory intracranial hypertension and low cerebral energy levels. The purpose of the present review is to explore the physiology of ketone body utilization by the brain in health and in a variety of neurological conditions, and to discuss the potential for ketone supplementation as a therapeutic option in traumatic brain injury.

Introduction

Ketogenesis is the process by which ketone bodies (KB), during times of starvation, are produced via fatty acid metabolism. Although much feared by physicians, mild ketosis can have therapeutic potential in a variety of disparate disease states. The principle ketones include acetoacetate (AcAc), β -hydroxybutyrate (BHB) and acetone. In times of starvation and low insulin levels, ketones supply up to 50% of basal energy requirements for most tissues, and up to 70% for the brain. Although glucose is the main metabolic substrate for neurons, ketones are capable of fulfilling the energy requirements of the brain.

The purpose of the present review is to explore the physiology of ketone body utilization by the brain in health and a variety of neurological conditions, and to discuss the potential for ketone supplementation as a therapeutic option in traumatic brain injury (TBI).

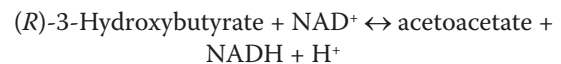
Ketones, metabolism and the brain

Ketone metabolism

Ketones are by-products of fat metabolism and are produced in hepatic mitochondria [1]. More specifically, the three KB are: AcAc – if not oxidized to form usable energy, this is the source of the two other KB; acetone – not an energy source, but instead exhaled or excreted as waste; and BHB – not technically a ketone, but reversibly produced from AcAc.

The precursor for the synthesis of ketones is acetyl coenzyme A (acetyl CoA), which is formed by β -oxidation of free fatty acids in the liver. The two important determinants of ketogenesis are the availability of acetyl CoA and the mobilization of fatty acids liberated from white adipose tissue during fasting or catecholaminergic stress [2,3].

AcAc is the central ketone body. AcAc is reduced to BHB by β -hydroxybutyrate dehydrogenase (BHD) in a NADH-requiring reversible reaction [3]:



The extent of this reaction depends on the state of the cellular pool of NAD^+ [4]. When highly reduced, most or all ketones will be in the form of BHB. The ratio of BHB to AcAc reflects the redox state within the mitochondrial matrix [5]. BHB is nonvolatile and is chemically stable. This ketone body's only metabolic fate is interconversion with AcAc. Once synthesized, ketones diffuse into the circulation.

Fate of circulating ketones

Plasma concentrations of circulating KB range from <0.1 mM/l in the postprandial state to as much as 6 mM/l during fasting, with levels reaching 25 mM/l in diabetic ketoacidosis [6-8]. Under normal dietary conditions, ketogenesis from fatty acids is at very low levels. This is attributable to the relatively high blood levels of the

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ketogenesis-inhibiting hormone insulin, and low blood levels of ketogenesis-promoting hormones, glucagon and cortisol [2]. One of the prerequisites for ketogenesis is therefore low levels of circulating insulin, as seen during starvation and diabetic ketoacidosis

The fate of circulating KB is to be taken up by extra-hepatic tissues, although 10 to 20% may be lost in the urine [8,9]. KB provide an energy source for several tissues including the brain, skeletal muscle, myocardium and liver, although the heart and kidney have the greatest capacity for utilization [10]. The rate of utilization appears to be a function of the circulating plasma levels [11-13].

Ketones and critical illness

The major illness associated by intensive care physicians with ketosis is diabetic ketoacidosis. Outside diabetic ketoacidosis, ketone measurement is not routinely performed and has been largely used as a research tool to quantify cellular redox status. The arterial ketone body ratio (AKBR) is utilized to reflect the mitochondrial redox status of hepatic cells and may reflect cellular energy status in a number of conditions including hemorrhage, hypoxia, sepsis and hepatic resection [14]. The AKBR (ratio of AcAc to BHB) reflects the cellular NAD⁺/NADH ratio, which cannot be measured directly and is linked to the phosphorylation potential of the cell (see equation above). In critically ill patients, the entry of acetyl CoA into the tricarboxylic acid cycle is limited. Acetyl CoA consequently combines with another molecule of acetyl CoA to form acetoacetic acid, which in turn is converted to BHB leading to an altered NAD⁺/NADH ratio and a decreased AKBR [14,15]. A reduced AKBR is therefore a sign of an inefficient tricarboxylic acid cycle. The AKBR has also been used as an indirect marker of the hepatocellular functional status as the predominant site of metabolism of the ketones is in the liver.

Not surprisingly, metabolic failure at the cellular level is associated with worse clinical outcomes. A low AKBR is associated with poor outcomes in both animal and human models of illness. Yassen and colleagues measured the AKBR in 20 critically ill patients [15]. They demonstrated a progressive decrease in those patients with septic shock who died. In a study of critically ill heart failure patients, Limuro and colleagues noted a survival of only 15% of patients with AKBR <0.7 [16]. Dresing and colleagues found the AKBR to be significantly lower in nonsurvivors than survivors in 30 polytrauma patients (0.6 vs. 1.3; $P = 0.001$) [17]. Levy and colleagues, however, failed to find a difference in AKBR levels between survivors and nonsurvivors in their cohort of septic patients [18]. In conjunction with the lactate:pyruvate ratio, the AKBR may provide further insight into the cellular redox potential of critically ill patients.

Ketones and the brain

Glucose is the major fuel for the brain in humans on a balanced diet. More recently it was proposed that other substances such as lactate and pyruvate may be utilized by neurons to sustain their activity [19]. Furthermore, during times of starvation, the brain has the capacity to adapt to the use of ketones as its major energy source (and in the metabolic disease diabetes mellitus). In longstanding starvation, ketones can provide 60 to 70% of the energy needs of the brain [20]. The 1.5 kg human brain utilizes 100 to 150 g glucose per day and 20% of the total body oxygen consumption at rest [7]. Protein catabolism can supply somewhere between 17 and 32 g glucose per day, well below the minimum daily cerebral glucose requirements [21]. In fact, to supply sufficient glucose to support brain metabolic requirements from protein alone would lead to death in about 10 days instead of the 57 to 73 days [22]. Moreover in subjects undergoing total starvation for 30 days, the decrease in hunger coincides with the elevation of blood ketones to 7 mM/l. During periods of ongoing starvation, an average-size person produces about 150 g KB per day [23]. One should note, however, that ketones are incapable of maintaining or restoring normal cerebral function in the complete absence of glucose.

Astrocytes may play a significant role in the regulation of brain energy metabolism [24]. Reports suggest that astrocytes can produce KB from fatty acids and leucine and are involved with other pathways of lipid metabolism, such as lipid synthesis and lipoprotein secretion [25-28]. Furthermore, it appears that the production of lactate and KB by astrocytes may increase secondary to neurotransmitters released during enhance synaptic activity [29,30].

Although the implications of ketone body production by astrocytes are still unclear, the fact that astrocytes outnumber neurons approximately 9:1 and occupy at least 50% of the cerebral volume suggests this constitutes a quantitatively important pathway in the brain [31].

Regulation of cerebral ketone uptake

As previously noted, humans can achieve very high circulating KB concentrations during prolonged fasting, up to 9 mM/l (range 5.8 to 9.7 mM/l) [20]. The plasma concentration of KB is a significant factor affecting the rate of cerebral uptake. The blood-brain barrier (BBB) is relatively impermeable to most hydrophilic substances, such as KB, unless they are transported by a carrier protein. A family of proteins involved in the transport of monocarboxylic acids such as lactic acid and pyruvate across cellular membranes, called monocarboxylic acid transporters (MCT1 and MCT2), are thought to play an integral role.

It is not yet understood how MCTs are regulated. KB are transported at different rates, with the uptake of

AcAc being twice that of BHB at a given arterial concentration [12]. Furthermore, prolonged fasting appears to increase the BBB uptake of ketones, with some researchers demonstrating an eightfold increase in the expression of MCT1 [32]. Similarly, Hasselbalch and colleagues reported a 13-fold increase in cerebral uptake of BHB in humans following several days of fasting [33]. In contrast, rapidly increasing plasma ketone concentrations do not lead to such a significant increase in cerebral ketone uptake. Pan and colleagues noted a much smaller increase in cerebral ketone concentrations following a rapid intravenous infusion of BHB as compared with prolonged fasting, implying that MCT upregulation is partly dependent on the length of exposure to increased plasma ketone levels [34,35].

Once across the BBB, KB enter brain cells to support cellular energy requirements. Studies of the uptake of KB by brain cells suggest entry occurs by two mechanisms: diffusion and a carrier-mediated process. MCTs have been demonstrated on neurons and glial cells although their role here appears less significant as compared with that on the BBB. The impact of mitochondrial enzyme activity involved in ketone metabolism is less clear. Certainly, mitochondrial enzymes can be upregulated by increased levels of BHB, as has been demonstrated following exposure to ketones through starvation or a prolonged high-fat diet [12,36-39]. In summary, therefore, a prolonged high blood ketone concentration leads to an increased rate of cerebral ketone uptake and metabolism.

Regional variation in ketone body metabolism

Data for the regional variation in ketone body metabolism are based largely on animal studies. Hawkins and colleagues and Morris noted that KB uptake varies from one brain region to another [40,41]. Following an intravenous administration of radioactive BHB to adult rats, uptake was greatest in the cerebral cortex (deep layers), in the superior and inferior colliculi, and in regions where the BBB is absent [40,41]. Areas with a low metabolic rate such as the corpus callosum and other white-matter structures demonstrated greatly reduced uptake. Interestingly, the pattern of KB uptake resembled that of glucose, except in the superficial layers of the cortex where glucose uptake was higher [42]. Similarly, MCT1 expression in the brain may resemble the pattern of KB uptake with some exceptions as MCT1 is found on glia and neurons as well as on BBB epithelial cells and because the pituitary and pineal have no BBB.

Neuroprotective effects of ketones

Neuroprotection is the mechanisms and strategies that, once implemented, may lead to salvage, recovery or regeneration of the nervous system. Ketones may have a

neuroprotective effect (see Figure 1). Ketones represent an alternative fuel for both the normal and the injured brain [43].

Firstly, BHB is more energy efficient than glucose and can stimulate mitochondrial biogenesis via the upregulation of genes encoding energy metabolism and mitochondrial enzymes [44]. There is a marked increase in the free energy of ATP hydrolysis, as demonstrated by a 25% increase in hydrolytic work of isolated rat perfused heart preparations when exposed to KB [45]. Also, ketones increase the intermediary metabolites delivered to the citric acid cycle with a 16-fold elevation in acetyl CoA content.

Secondly, ketones protect against glutamate-mediated apoptosis and necrosis through the attenuation of the formation of reactive oxidant species. Ketones can oxidize coenzyme Q, thus decreasing mitochondrial free radical formation. Additionally, the reduction of NAD favors reduction of glutathione, which ultimately favors destruction of hydrogen peroxide by glutathione peroxidase reaction [46,47].

Thirdly, ketones enhance the conversion of glutamate to GABA with the subsequent enhancement of GABA-mediated inhibition [48,49]. Cerebral ketone uptake also increases cerebral blood flow [50].

Fourthly, cell death from apoptosis is attenuated by ketone ingestion [48]. Mechanisms include reductions in activation of caspase-3, increases in calbindin and prevention of accumulation of the protein clusterin.

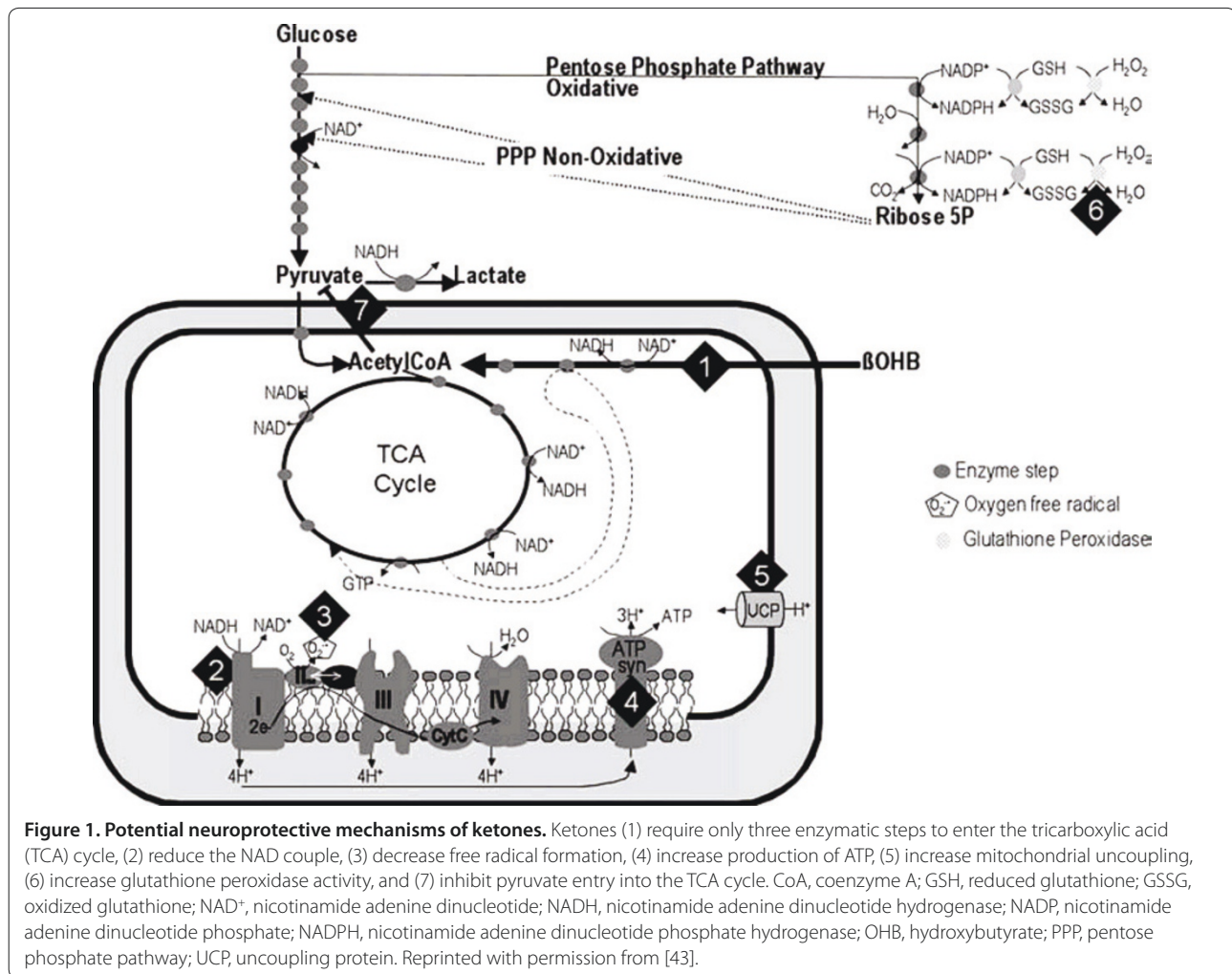
Lastly, cerebral ketone metabolism alters cerebral blood flow [50]. Hasselbalch and colleagues demonstrated a 39% increase in cerebral blood flow following an infusion of sodium BHB.

Current state of research – changes in ketone metabolism during brain injury

Models of injury – animal studies

Adaptive changes to cerebral ketone metabolism during development and starvation are well documented. However, there is evidence that other conditions including TBI, ischemia, hemorrhagic shock and hypoxia induce rapid changes in both vascular and cellular transporters that favor ketone uptake and metabolism. In addition, ketone-metabolizing enzymes demonstrate the ability to change in response to neuropathologic conditions. Collectively, these adaptations suggest that the brain may be more receptive to ketone metabolism under neuropathic conditions.

Researchers have demonstrated an increase in MCT1 and MCT2 expression following cerebral injury [51]. Similarly, ketone-metabolizing enzyme expression also appears to alter. Utilization of BHB in the brain is contingent on its conversion to AcAc by BHD, which is scarce in the adult brain, especially in the basal ganglia.



Studies confirm a significant increase in BHD activity following cerebral insult [52].

The brain's ability to utilize exogenous KB is altered. At times of oxidative stress, the ability of the brain to use glucose as a substrate for metabolic activity may become compromised. Certainly, hyperglycemia has been repeatedly shown to be deleterious to the injured brain [53]. During these times, an exogenous supply of ketones may force the brain to shift its reliance from glucose to ketones, thus taking advantage of improved transport and cellular metabolism. This shift can be advantageous in both acute brain injury models (glutamate excitotoxicity, hypoxia/ischemia, TBI) and neurodegenerative conditions (Parkinson's disease, Alzheimer's disease).

Extensive research has been performed using the glutamate-induced injury model, the cerebral hypoxia model and the ischemic injury model. Glutamate neurotoxicity is implicated in a number of neurodegenerative disorders associated with brain ischemia, hypoglycemia and cerebral trauma. During injury, glutamate and

aspartate are released through the reverse action of their transport systems or via enhanced exocytotic release. This in turn leads to excitotoxicity and the production of reactive oxidant species. Administration of ketones appears to limit the extent of damage [54-58]. For example, Massieu and colleagues demonstrated that AcAc effectively protects against glutamate neurotoxicity both *in vivo* and *in vitro* in rats chronically treated with a glycolysis inhibitor [55].

Hypoxic/ischemic injury leads to a decrease in oxidative metabolism by reducing oxygen availability [59,60]. Ketone administration ameliorates many of the sequelae of this process, including lactate generation, free radical damage and apoptotic cascade activation [61,62]. Suzuki and colleagues demonstrated that BHB prolonged the survival time in rat models of hypoxia, anoxia and global ischemia [63]. They further showed that BHB reduced infarct size after middle cerebral artery occlusion, irrespective of whether BHB administration was delayed.

Table 1. Animal and basic science studies on effects of ketone administration on brain injury

Mechanism of injury	Reference	Ketone source	Study	Outcome
Glutamate-induced injury	Massieu and colleagues [55]	i.v.	AcAc infusion for 14 days in adult rodent model prior to and during glutamate-induced injury	Decreased neuronal damage, decreased lesion volume and increased cellular ATP levels
	Noh and colleagues [57,58]	p.o.	21-day-old mice fed ketogenic diet prior to kainic-induced neuronal damage	Preservation of neurons in hippocampus by inhibiting caspase-3-mediated apoptosis
	Mejia-Toiber and colleagues [56]	<i>In vivo</i>	BHB applied before glutamate-induced neurotoxicity	BHB reduces injury and lipoperoxidation
	Maalouf and colleagues [54]	<i>In vivo</i>	Addition of BHB to <i>in vitro</i> model of glutamate neurotoxicity	Reduction in free radical formation and enhanced mitochondrial respiration
Cerebral hypoxia	Puchowicz and colleagues [60]	p.o.	Rats fed ketogenic diet 3 weeks prior to hypoxic injury	Decreased cerebral lactate and increased tolerance of hypoxia
	Masuda and colleagues [59]	<i>In vivo</i>	Rat neurons exposed to hypoxia following treatment with BHB	Decreased cell death and number of apoptotic cells with maintenance of mitochondrial membrane
Cerebral ischemia	Suzuki and colleagues [70]	i.v.	Rats infused with BHB 3 to 6 hours after bilateral carotid artery occlusion	Decreased cerebral edema and sodium content and increased ATP levels
	Suzuki and colleagues [63]	i.v.	BHB infusions following occlusion of the middle cerebral artery	50% reduction in cerebral infarct volume
	Marie and colleagues [69]	Fasted	Adult rats fasted for 24 hours before four-vessel occlusion	Decreased mortality, post-traumatic seizures and brain lactate
	Go and colleagues [68]	Fasted	Starvation-induced ketosis followed by carotid occlusion	Fasting protected rats from brain infarction
Traumatic brain injury	Prins and colleagues [65]	i.v.	BHB infusion following TBI in adult rats	Increase in serum BHB and cerebral BHB and improved cortical ATP levels
	Prins and colleagues [64]	p.o.	Rats with TBI fed ketogenic diet	50% reduction in cortical contusion volume
	Biros and Nordness [67]	p.o.	Rats of differing ages fed ketogenic diet following TBI	Younger rats demonstrated larger reduction in contusion volume
	Hu and colleagues [61,62]	p.o.	Rats fed ketogenic diet prior to TBI	Reduced brain edema and cellular apoptosis in rats fed ketone diet

AcAc, acetoacetate; BHB, β -hydroxybutyrate; *In vivo*, *in vivo* experiment; i.v., intravenous; p.o., per orally; TBI, traumatic brain injury.

More recently, TBI models have been developed [64,65]. TBI is associated with impaired cerebral energy production with prolonged glucose metabolic depression and reduction of ATP. Cerebral injury is further exacerbated by free radical production, and activation of poly-ADP-ribose polymerase via DNA damage [66]. As such, under these conditions of impaired glycolytic metabolism, shifting the brain toward ketone metabolism may limit the extent of cerebral injury [63,67-70] (see Table 1). Much of this work is attributable to Prins and colleagues, who demonstrated that administration of intravenous BHB after TBI in adult rats led to an increase in uptake of BHB and alleviated the decrease in ATP after injury. In a subsequent study they found that a ketogenic diet was effective in reducing the cortical contusion volume in a rat model of TBI [64,65].

Neurodegenerative conditions may also benefit from ketone administration as there is evidence of altered cerebral metabolism. Studies of Parkinson's disease and Alzheimer's disease confirm the encouraging effects of

ketones. Mechanisms are complex but include decreasing free radical production and providing acetyl CoA for energy production [45,52,71-74]. Other conditions that may be responsive to ketones include amyotrophic lateral sclerosis and certain brain tumors.

Models of injury – human research

Mild ketosis is induced in humans by either fasting or the consumption of a high-fat, low-carbohydrate diet. Most studies in humans have delivered ketones via the enteral route [75]. In adults, achieving blood levels of 5 to 7 mM/l total KB requires the production or intake of about 150 g per day [23]. This level, however, is subject to the influences of glucose, insulin, cortisol and catecholamines. To achieve a therapeutic response in refractory epilepsy, it has been suggested that the level of blood ketone should be above 4 mM/l [76].

Salts of KB can be produced. Several authors (see below) have administered sodium AcAc or sodium BHB successfully with few side effects. A new formulation

called KTX 0101 consists of a combination of NaCl and BHB, although relevant concentrations are not described [77]. The main issues related to intravenous administration of ketone solutions include volume loading, sodium loading and the potential for significant metabolic alkalosis. These issues will depend on the relevant concentrations of anions and cations in the mixture and on the osmolality.

There is a paucity of research examining the effects of ketone administration in humans. Interpretation of results is further complicated by variable routes of administration, concentrations and age variability of research subjects. For instance, research on the effects of intravenous ketone preparations are confined almost exclusively to adults, whereas dietary studies include a large number of children. As far as we are aware, only two clinical studies examining the neuroprotective effects of KB in humans have been undertaken. The first by Ritter and colleagues examined the effects of a ketogenic diet on biochemical markers of metabolism in head-injury patients but did not include clinical outcomes [78]. The second study, reported by Smith and colleagues, has never been published but the authors reported on the use of a sodium BHB solution for neuroprotection during cardiac surgery [77]. The bulk of the research has taken place using the rodent model.

Some general statements, however, can be made. Studies have demonstrated that ketones can be given enterally or intravenously with minimal side effects; that utilization of KB increases with rising blood concentrations, with a plateau at approximately 128 g/24 hours; that hyperketotic states are associated with improved glucose control; that increased plasma levels lead to an increase in cerebral uptake; and that ketogenic diets may lead to improved cognitive function in patients with chronic dementia (see Table 2). Well-designed outcome studies, however, are lacking [34,35,77-85].

Adverse effects of ketones

There are minimal data on the adverse effects of ketone administration, much of which are based on chronic intake via the enteral route rather than the parenteral route. In the acute setting, effects of parenteral formulations on the pH, sodium level, lipids and glucose are likely to dominate; for example, intravenous formulations would theoretically be alkalinizing, depending on the ketone concentration. This was confirmed by Hiraide and colleagues, who noted a significant increase in pH and sodium concentrations following the intravenous administration of a 20% solution of sodium BHB to severe trauma patients [81]. Also of potential concern is the reduction in glucose cerebral metabolism and the increase in cerebral blood flow demonstrated by Hasselbalch and colleagues during administration of intravenous BHB

[50]. The long-term consequences of these changes are not yet known.

Some side effects are predictable following enteral administration, such as dehydration and hypoglycemia. Other side effects are less common and present following prolonged use, including growth retardation, obesity, nutrient deficiency, decreased bone density, hepatic failure, and immune dysfunction. Freeman and colleagues reported a significant rise in mean blood cholesterol to over 250 mg/dl following prolonged intake of a ketogenic diet [86]. This effect in turn may be atherogenic, leading to lipid deposition in blood vessels. In addition there are reports of dilated cardiomyopathy in patients on the ketogenic diet, possibly as a consequence of the toxic effects of elevated plasma free fatty acids. Finally, an increased incidence in nephrolithiasis in patients on the ketogenic diet as well as increases in serum uric acid secondary have been reported [66,87].

Potential clinical applications for ketone solutions – traumatic brain injury

TBI is a major cause of mortality and morbidity in young adults [88]. Cerebral edema and subsequent intracranial hypertension is an important factor influencing patient outcome, and, despite considerable research, has proven difficult to manage. Over the past 30 years, osmotherapy has become an important tool in the management of intracranial hypertension after TBI [88]. Various substances, including urea, glycerol, sorbitol and mannitol, have been utilized [89,90]. More recently, hypertonic saline (HTS) has proven useful in controlling intracranial pressure (ICP).

HTS has been extensively studied in animal and human models of TBI [91-94]. These experiments suggest that small-volume resuscitation with HTS solution may be beneficial for increasing cerebral perfusion pressure and cerebral blood flow and for decreasing ICP while maintaining hemodynamic stability following TBI. Animal studies comparing HTS and mannitol suggest that HTS is more effective in reducing ICP and has a longer duration of action [95,96]. In humans, HTS appears effective for reducing ICP in cases of refractory intracranial hypertension following TBI. Several studies have confirmed a significant decrease in ICP correlated with an increasing serum osmolality [97-99].

In the past, researchers have combined hypertonic sodium with a variety of anions including acetate and lactate [100,101]. Acetate, a source of hydrogen ion acceptors, is an alternate source of bicarbonate by metabolic conversion in the liver. Acetate is a myocardial depressant, however, and can lead to hypotension in susceptible individuals. Hypertonic sodium/lactate solutions have also been investigated. Whilst HTS/lactate is generally considered safe and may provide cerebral nutrition, there

Table 2. Human studies investigating effects of exogenous ketone administration

Pathophysiological endpoint	Reference	Study	Outcome
Metabolic effects	Owen and colleagues [83]	Effect of ketones on insulin and free fatty acid release. Sodium AcAc given as i.v. infusion 1 mmol/kg over 2 hours to 12 normal adults after overnight fast	AcAc levels 4.74 mmol/l after 30 minutes. Utilization of ketones increased with rising blood concentrations to a maximum of 13 g/24 hours. Glucose remained normal
	Miles and colleagues [82]	Evaluation of protein-sparing effects of i.v. infusion of NaBHB in six healthy adults	Ketone levels reached 2.33 mmol/l. No protein sparing, significant alkalosis
	Hiraide and colleagues [81]	Twenty patients following severe trauma: 11 patients received i.v. 20% solution NaBHB at 25 μmol/kg/minute for 3 hours, and nine patients received sodium lactate	Ketone levels reached 1.5 mmol/l. Alanine release decreased in ketone group, suggesting a suppression of post-traumatic protein catabolism. Significant increase in sodium and pH
	Dashti and colleagues [80]	64 healthy obese adults with and without diabetes fed ketogenic diet for 56 weeks	Body mass index, glucose, total and low-density lipoprotein cholesterol decreased significantly whereas high-density lipoprotein increased
Central nervous system effects	Pan and colleagues [35]	Six healthy adults infused with NaBHB at a bolus rate of 80 μmol/kg/minute, then 20 μmol/kg/minute for 75 minutes. BHB brain levels measured by MRI	BHB blood levels reached 2.12 mmol/l. BHB brain levels increased to 0.24 mmol/l. Levels lower than noted in fasted individuals suggesting differences in brain transport of ketones in fasted state
	Pan and colleagues [34]	Five healthy adults. Ketones measured in brain using MRI in nonfasted state and after 2 and 3 days of fast	Plasma and brain BHB levels correlated well, with brain BHB ranging from 0.05 mmol/l in nonfasted state to 0.98 mmol/l after 3 days of fasting
	Blomqvist and colleagues [79]	Six healthy and six diabetic patients received infusion of BHB at 3 to 6 mg/kg/minute for 60 minutes followed by bolus of B-[¹¹ C]HB. PET scan was performed	Utilization rate of ketones increase proportionally with plasma concentrations. Rate-limiting step for ketone body utilization is transport into the brain
	Hasselbalch and colleagues [85]	Permeability of blood-brain barrier to BHB was assessed following a 3.5-day fast	Increase cerebral ketone influx during starvation determined by amount of ketone present in blood
	Ritter and colleagues [78]	Twenty head-injured patients assigned to conventional or ketogenic diet for 2 weeks	Group receiving a ketogenic diet demonstrated improved glucose control with higher ketone levels. Cerebral lactate was similar
	Smith and colleagues [77]	NaBHB i.v. solution known as KTX 0101 for neuroprotection post CABG. Details of study protocol not available	Phase Ia study not published
	Hasselbalch and colleagues [50]	Eight healthy adults received i.v. infusion of NaBHB at 4 to 5 mg/kg/minute for 3 hours. Cerebral blood flow measured using Kety-Schmidt technique	Increased cerebral uptake of ketones was counterbalanced by reduction in glucose metabolism. Cerebral metabolic rate was unchanged, but cerebral blood flow increased
	Reger and colleagues [84]	Twenty adults with Alzheimer's disease were randomized to receive a MCT diet or placebo on two occasions	On cognitive testing, MCT treatment facilitated performance for ε4-negative but not ε4-positive subjects. Also greater improvement with MCT treatment relative to placebo

AcAc, acetoacetate; B-[¹¹C]HB, R-β-[1-¹¹C]hydroxybutyrate; BHB, β-hydroxybutyrate; CABG, coronary artery bypass graft; i.v., intravenous; MCT, medium chain triglycerides; MRI, magnetic resonance imaging; NaBHB, sodium β-hydroxybutyrate; PET, positron emission tomography.

are limited animal data suggesting that fluids containing lactate may be associated with significant toxic effects [102]. Further research is required to clarify these issues.

There is therefore a need for a solution able to address two fundamental problems related to TBI; namely, refractory intracerebral hypertension and low cerebral energy levels. This requirement could theoretically be accomplished by incorporating ketones into a hypertonic solution such as HTS. There are, however, a number of challenges associated with the development of new parenteral solutions.

Firstly, the impact of the constituents on individual metabolism needs to be evaluated. The hypertonicity induced by 3% NaCl is well documented and desirable. The target sodium level is not known, however, and various authors have reported levels as high as 185 mmol/l. Secondly, although the long-term metabolic effects of ketone administration are described, little information exists on the acute changes induced by intravenous infusions. For example, the entry of ketones into cerebrospinal fluid is partly concentration dependent and therefore a certain serum level (possibly above

4 mM/l) is required for maximum utilization. What then is the effect of high ketone concentration on blood pH? Such a solution would be expected to be alkalinizing, but this will be altered by the rate of metabolism. Thirdly, which ketone should be incorporated, AcAc or BHB? Both ketones have been administered to humans in the past without ill effects. Fourthly, should cerebrospinal fluid or plasma levels be utilized to guide therapy? Lastly, ketones are expensive to produce, so can a commercially viable solution be developed?

Conclusion

There is both theoretical and clinical evidence that administering ketones to patients with cerebral injury may provide significant benefit. Furthermore, combining ketones with HTS may provide the added advantage of ICP control with improved cerebral metabolism. There are, however, a number of outstanding questions requiring further consideration. These questions include dosing, timing, and the route and duration of administration. Further research is necessary to clarify these issues and to determine whether an HTS ketone solution could be employed in the management of acute brain injury.

Abbreviations

AcAc, acetoacetate; acetyl CoA, coenzyme A; AKBR, arterial ketone body ratio; BBB, blood-brain barrier; BHB, β -hydroxybutyrate; BHD, β -hydroxybutyrate dehydrogenase; GABA, γ -aminobutyric acid; HTS, hypertonic saline; ICP, intracranial pressure; KB, ketone bodies; MCT, monocarboxylic acid transporter; NAD⁺, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogenase; TBI, traumatic brain injury.

Competing interests

The authors declare that they have no competing interests.

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