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Ketogenic regimens for acute neurotraumatic events

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Abstract

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CRediT authorship contribution statement
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CYF: Conceptualization, Investigation, Methodology, Writing/ original draft, writing/ review and editing, Visualization
JL: Investigation, Writing/ original draft
EDW: Investigation, Writing/ original draft
OS: Investigation, Writing/ original draft, Visualization
KLK: Investigation, Writing/ original draft
WTP: Investigation, Writing/ original draft
NA: Investigation, Writing/ original draft
WT: Investigation, Methodology, Writing/ original draft, writing/ review and editing

Dietary modification would be the most translatable, cost-efficient, and, likely, the safest approach available that can reduce the reliance on pharmaceutical treatments for treating acute or chronic neurological disorders. A wide variety of evidence suggests that the ketogenic diet (KD) could have beneficial effects in acute traumatic events, such as spinal cord injury and traumatic brain injury. Review of existing human and animal studies revealed that KD can improve motor neuro-recovery, gray matter sparing, pain thresholds, and neuroinflammation and decrease depression. Although the exact mechanism by which the KD provides neuroprotection is not fully understood, its effects on cellular energetics, mitochondria function and inflammation are likely to have a role.

Keywords

Ketogenic diet; ketone esters; spinal cord injury; traumatic brain injury; neurotrauma

Introduction

Within the last two decades, considerable progress has been made in understanding the role of modified nutrient diets in disease. Dietary modification, although more mundane than stem cell-based techniques and advanced genetic manipulations, would be the most translatable, cost-efficient, and, likely, the safest approach available for treating neurological disorders. In addition, diet is something patients can exert control over; therefore, it is an appealing tool for replacing pharmacological interventions. Although the effects of diet on physical function and pathology have been explored in many neurodegenerative disorders, including multiple sclerosis (MS) [1,2], Alzheimer's disease [3], Parkinson's disease [3,4] and traumatic brain injury (TBI) [5], a review of the evidence regarding the effect of modified diets in spinal cord injury (SCI) has not yet been conducted. In light of the patho-mechanistic overlaps of TBI and SCI, we focus here on both acute neurotraumatic events (ATE). ATE refer to injuries that involve the nerves, brain, or spine. This includes head injuries such as TBI and injuries to the spinal cord or nerves at the end of the spinal canal, i.e. cauda equina. TBIs can have long-lasting effects, including cognitive impairment, and SCI often causes permanent loss of strength, sensation, and function below the site of the injury. After the initial trauma of SCI and TBI, cell death and tissue loss continue for several weeks—a window in which one could effectively intervene with neuroprotective strategies [6]. During this time, an escalating cycle of metabolic cellular dysfunction, inflammation, oxidative damage, and neuronal apoptosis leads to progressive degeneration in the brain and spinal cord [5,7,8]. Notably, substantial evidence now suggests that dietary modifications can decrease the pathophysiology related to oxidative stress, neuroinflammation, and mitochondrial dysfunction commonly observed after SCI and TBI. Therefore, reducing these pathologies may improve neurological repair, growth, and function.

Interest in the potential benefits of administering a ketogenic diet (KD) for the treatment of ATE has surged recently. The classical KDs are high in fat (66% w/w) and adequate in protein (<20% w/w), while very low in carbohydrates (<3% w/w), although the exact ratio of fat to protein and carbohydrates often varies. On a KD diet, energy is largely derived from long-chain fatty acids. These fats are converted in the liver to the ketones, β-hydroxybutyrate (βHB), aceto-acetate, and acetone, which provide brain cells (neurons and astrocytes) with

an energy source that is more efficient than glucose [9,10]. Alternative ketogenic regimens have also been developed involving the medium-chain triglyceride (MCT) KD [11] and oral supplementation with ketone esters (KE) [12]. With the MCT KD, fats are provided through triglycerides comprising of about 60% octanoic acid and 40% decanoic acid. MCTs are metabolized more rapidly than long-chain fatty acids and thus, generate ketones more efficiently. Therefore, only 45% of the dietary energy must come from fats, which allows more carbohydrates and proteins to be included. KE are effective in combinations with an even further relaxed standard diet [13,14]. Both classical KDs and MCT KDs provide neuroprotection [12,13] via mechanisms that are only partially understood, including the regulation of cellular energetics, mitochondrial function, and antioxidant, anti-excitotoxicity, and anti-inflammatory factors (Figure 1).

To include all relevant animal and human interventional studies, we performed literature searches using combinations of terms related to the diet (“ketogenic” OR “ketone*, “hydroxybutyrate”) and neurological disorders (“spinal cord injury*”, “traumatic brain injury*”) in the respective Medical Subject Headings of the PubMed database in June 2020. To review the evidence of underlying neuroprotective mechanisms from animal studies, we also included “hydroxybutyrate” and “aceto-acetate” in our search terms and added searches in MEDLINE and Google Scholar. Additionally, we searched the reference lists of the included studies and relevant reviews. The number of papers identified, and the final number of papers deemed eligible after reviewing the titles, abstracts, and/or full-text manuscripts are included in Table 1. We considered clinical articles to be eligible if the research: 1) included adult human participants with SCI or TBI, or 2) evaluated the effects of a ketosis-inducing agent on health outcomes. We also reviewed all preclinical studies that explored potential mechanisms of actions of ketones and ketogenic regimens, and here present a current understanding of the effects of KD on neurological function in people with ATE.

Mechanisms of KD action

A growing number of mechanisms have been proposed to explain the beneficial effects of the KD after neurotrauma. In this section we briefly discuss what we know, to date, from studies using animal and cell models.

Ketones provide an alternative source of energy in the brain.—Low intake of carbohydrates through a KD or fasting typically causes hepatic ketogenesis, fueled by the beta-oxidation of fatty acids, which increases blood levels of βHB, aceto-acetate, and acetone [9]. These ketone bodies enter the brain via monocarboxylate transporters [15] and are subsequently broken down to acetyl-CoA, which can enter the tricarboxylic acid cycle (TCA). Glucose is the primary source of energy in the brain; however, up to 60% of the energy demands of the brain can be met by ketone metabolism [9,10]. Thus, a KD can provide an important alternative source of energy when pyruvate dehydrogenase activity is low [16], as occurs after SCI or TBI, where due to an increase in reactive oxygen species (ROS), key mitochondrial enzymes undergo oxidative damage and start to malfunction [17–19].

Ketones improve mitochondrial bioenergetics and prevent oxidative stress.—Oxidative stress and damage occur after SCI or TBI [20]. Ketones can reduce ROS production and improve mitochondrial bioenergetics by increasing nicotinamide adenine dinucleotide + hydrogen (NADH) oxidation [21]; activating mitochondrial uncoupling proteins [22,23]; increasing the expression of antioxidant enzymes, including NAD(P)H dehydrogenase [quinone] 1 (*NQO1*) and superoxide dismutase 1 and 2 (SOD1/2); ameliorating complex II/III activity [24]; and improving mitochondrial biogenesis, possibly through the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)/ sirtuin-3 (SIRT3)/ mitochondrial uncoupling protein 2 (UCP-2) axis [25]. After SCI, D-βHB improved mitochondrial respiration, as evidenced by normalized ATP production and less free radical production [26]. In addition, adherence to a KD increases mitochondrial glutathione levels in rodent hippocampus, and improves the overall mitochondrial redox status and protection against oxidative stress [27]. This could be mediated by the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) which increases antioxidant gene expression [28], and has been shown to be upregulated in nuclear fractions of brain tissue from KD-fed rats [29], as well as after TBI [30,31]. Nrf2 expression was also upregulated four weeks after SCI in rats switched to a KD four hours after injury [32]. At concentrations that occur with KD administration (EC_{50} 2.5–5 mM), βHB is also a direct endogenous inhibitor of class I histone deacetylases (HDACs) [33]. After 24 hours of fasting, murine kidneys had increased acetylation at the *Foxo3a* and metallothionein 2 (*Mt2*) promoters due to HDAC1 inhibition by βHB. Both genes protect against oxidative stress; in particular, Foxo3a increases the expression of the mitochondrial antioxidants manganese superoxide dismutase (MnSOD) and catalase [33]. This mechanism has recently been identified in the injured spinal cord as well, either with KD treatment initiated 2 weeks prior to injury [34,35] or with application of D-βHB via osmotic pumps at six hours after injury, which also increased the expression of SOD2, catalase, and Foxo3a [26] in a mouse model of SCI.

Ketones reduce inflammation.—βHB inhibits the nucleotide-binding oligomerization domain (NOD) - like receptor protein 3 (NLRP3) inflammasome, a multi-protein complex involved in caspase 1 activation and cleavage of pro-IL1β and pro-IL18. This was shown in multiple *in vitro* and *in vivo* scenarios of NLRP3 activation including a mouse model of peritonitis and intraperitoneal administration of βHB [36]. The NLRP3 inflammasome is also activated in the spinal cord after injury [37]; continuous subcutaneous βHB delivery via osmotic minipumps, starting six hours after SCI, mitigated NLRP3 activation after two weeks of treatment [26]. Moreover, βHB is the only known endogenous ligand of the hydroxycarboxylic acid (HCA2) receptor (aka GPR109A, PUMA-G, or niacin receptor), activating it at concentrations that are easily reached with KD administration or fasting (EC_{50} 0.7 mM) [38]. HCA2 receptor activation dampens inflammation [39,40] and prevents the production of pro-inflammatory enzymes, nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and cytokines (TNF-α, IL-1β, and IL-6) [41]. In rats, normalization of increased inflammatory factors in the blood, including myeloperoxidase, TNF-α, IL-1β, and IFN-γ, was observed at four weeks after SCI with KD treatment [32]. However, a causal link to functional improvement remains to be shown.

Animal studies of KD in SCI

Intermittent fasting (food withdrawal every other day) improved outcomes after acute cervical and thoracic SCI [42,43], providing the rationale to test KD in a cervical hemicontusive SCI model in adult rats [44]. Initiating a KD four hours after injury and maintaining it for 12 weeks led to improvement in two different reaching tests (tests used to evaluate manual dexterity and motor function), and histological evidence of gray matter sparing in this model. These findings were independently confirmed in the same model [32]. Supplementation with exogenous ketones (sodium salt) for the first three days of a KD similarly improved reaching and usage of the forepaw during vertical exploration in rats [45]. Sparing of corticospinal axons could be a plausible explanation for the improved distal limb function [45]. Of mechanistic interest, administration of just the ketone D-βHB via osmotic pump at six hours after a T9 thoracic contusion injury in mice improved the open field locomotor scores and improved pain thresholds [26], underlining the importance of this ketone.

Animal studies of KD in TBI

KD initiated before or after cortical impact TBI improved recovery in young (35-45 days old) but not older rodents (65-75 days old) [5,46]. KD started after the first of three mild TBIs, modelling repeated concussions every 24 hours, improved motor recovery (beam balance) seven days after injury [47]. In 47-day-old rats, KD initiated before mild TBI improved behavioral outcomes on the beam walk, increased exploration in the open field test, and improved neuroprotection [48]. Post-injury treatment with a KD reduced depressive-like behavior and was also neuroprotective. Key differences between young and old brains include temporal differences in energy depletion after TBI and higher blood ketone levels in the young rats [46]. Of mechanistic interest, intravenous infusion of βHB after a lateral fluid percussion TBI in female rats reduced the injury-induced increase in blood-brain barrier permeability and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) mRNA levels [49]. However, increased blood-brain barrier permeability was also observed in non-injured animals given βHB, which is troubling and needs further research.

Human studies of KD in SCI

In a small randomized clinical trial to assess the safety of a KD initiated within 72 hours in people with acute SCI (n=4, KD group; n=3, control group), KD was well tolerated, improved upper extremity motor scores, and reduced serum levels of neuroinflammatory protein, fibrinogen, and increased serum levels of an anti-inflammatory lysophospholipid, lysoPC 16:0 [50]. The KD administered provided approximately 72% of the total energy as fat, 25% as protein, and 3% as carbohydrate during enteral feeding and provided approximately 65% of the total energy as fat, 27% as protein, and 8% as carbohydrate and fiber during solid feeding.

Human studies of KD in TBI

Adult humans appear to be more responsive to KD therapies than rodents are and can use ketones to fuel up to 60% of their metabolic requirements, compared with 25% in rats

[5,9,51]. A recent study reported that brain uptake of ketones increased 13-fold in adult humans versus 5-fold in adult rats after TBI. Therefore, it is possible that KD therapy will prove more effective for TBI in adult humans than the rodent data suggest.

In a prospective interventional phase 2 trial of ventilated critically ill patients with acute brain injury (3 with stroke, 2 with subarachnoid hemorrhage, and 15 with TBI) administered a KD (8.3% protein, 3.1% carbohydrate, and 88.7% fat) over a six-day period, plasma βHB and aceto-acetate levels increased [52]. KD was well tolerated, safely administered, and did not impact cerebral hemodynamics. In addition, Bernini et al. examined cerebral ketone metabolism by measuring brain interstitial tissue aceto-acetate and βHB along with glucose, glutamate, pyruvate, lactate via cerebral microdialysis in 34 patients with TBI [53]. In all, 24 patients received standard enteral nutrition (25% protein, 43% carbohydrate, 30% lipids, and MCT 6.5 g/1000 Kcal) and 10 patients received MCT-enriched enteral formula (25% protein, 36% carbohydrate, 39% lipids, and MCT 23 g/1000 Kcal). Blood ketone levels correlated with brain ketone levels and higher brain ketone levels correlated with brain lactate, pyruvate and glutamate levels but not brain glucose levels. Fasting vs. stable nutrition state was associated with a decrease of brain ketone and blood ketone concentration. Continuous feeding with MCT-enriched diet did not increase the blood ketone concentration and provided a modest increase in blood and brain concentrations of free medium-chain fatty acids.

Conclusion

KD works by multiple mechanisms from mitochondrial function, inhibition of inflammation, and anti-oxidation. Our review of the existing literature has revealed that KD regimens can improve motor recovery, gray matter sparing, and pain thresholds in rats and neurorecovery and inflammation in humans with SCI. In addition, KD therapy can improve motor recovery and neuroprotection and decrease depression in rats with TBI. In addition, KD is shown to be safe for patients with SCI and TBI; however, most of this evidence is collected mainly from animal and small clinical studies and adherence may be a challenge in adopting KD to achieve health-promoting properties. Although development of a KD may be more difficult than other controlled feeding study menus due to the need of creating multiple menus that comply with the human KD protocols (~75-80% total energy as fat, ~20% as protein, and 5% as net-carbohydrate), it is not expected to use KD long-term, i.e. more than 6-12 weeks, in the neurotrauma setting. Patients and their caregivers should be informed of these challenges. Ultimately, an improved understanding of the potential therapeutic effects of KD in preventing or reversing neurological pathology and improving function will be invaluable for patients seeking self-efficacy in improving independence and clinicians seeking to provide evidence-based recommendations for patients and caregivers, as well as for guiding the direction of future research.

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List of Abbreviations

ATE	Acute Traumatic Events
ATP	Adenosine Triphosphate
COX2	Cyclooxygenase-2
Foxo3a	Forkhead box O3
HCA2	Hydroxy-carboxylic Acid Receptor 2
HDAC	Histone Deacetylase
IFN-γ	Interferon-gamma
IL-13	Interleukin-13
IL-18	Interleukin-18
IL-6	Interleukin-6
iNOS2	Nitric Oxide Synthase
KD	Ketogenic Diet
KE	Ketone Esters
LysoPC 16:0	1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine
MCT	Medium-chain Triglyceride
MnSOD	Manganese Superoxide Dismutase
Mt2	Metallothionein 2
NADH	Nicotinamide Adenine Dinucleotide+Hydrogen
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NLRP3	NLR family pyrin domain containing 3
NQO1	NAD(P)H Quinone Dehydrogenase 1
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
PGC1α	Peroxisome proliferator-activated receptor Gamma Coactivator 1-alpha
SCI	Spinal Cord Injury

SIRT3	Sirtuin (Silent mating type Information Regulation 2 homolog) 3
SOD	Superoxide?? Dismutase
TBI	Traumatic Brain Injury
TCA	Tricarboxylic Acid
TNFα	Tumor Necrosis Factor-alpha
UCP2	Mitochondrial Uncoupling Protein 2
βHB	β-Hydroxybutyrate

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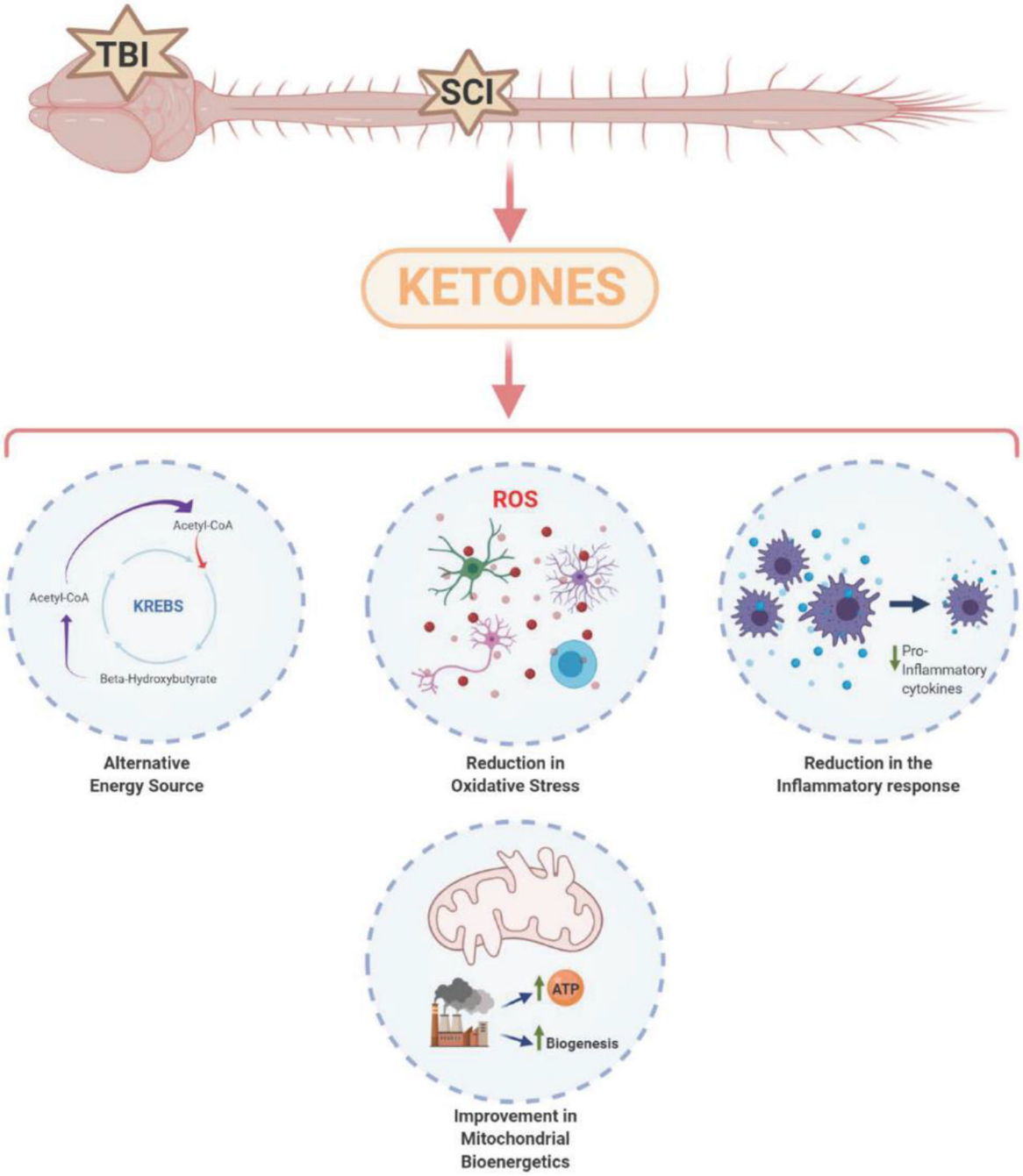

Figure 1.

Potential mechanisms of actions of ketones and ketogenic regimens after spinal cord injury and traumatic brain injury. 1) Ketones provide an alternative energy source to glucose, which might contribute to overcome the energy deficit seen during trauma. 2) Ketones can reduce free radical production and oxidative stress by improving mitochondrial function and increasing antioxidant enzymes. 3) Ketones may improve mitochondrial function and volume. 4) Ketones have been shown to reduce inflammatory response by reducing

infiltrating macrophages and lowering the pro-inflammatory cytokine production. Figure is created with BioRender.com.

Table 1.

Summary of the literature search conducted for each neurological condition of interest.

Neurological condition	Total number of studies screened	Total number of studies included in the review
SCI	133	1 (human), 11 (animal)
TBI	157	2 (human), 9 (animal)
Neuroprotective mechanism of βHB or acetoacetae	27	27

A literature search was conducted in the PubMed, MEDLINE, and Google Scholar databases on June 24, 2020. Eligible studies must 1) have utilized a ketosis-inducing agent (diet or supplementation) or 2) be clinical trials with adult humans or animal studies.