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Neuroketotherapeutics: A Modern Review of a Century-Old Therapy

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Abstract

Neuroketotherapeutics represent a class of bioenergetic medicine therapies that feature the induction of ketosis. These therapies include medium-chain triglyceride supplements, ketone esters, fasting, strenuous exercise, the modified Atkins diet, and the classic ketogenic diet. Extended experience reveals persons with epilepsy, especially pediatric epilepsy, benefit from ketogenic diets although the mechanisms that underlie its effects remain unclear. Data indicate ketotherapeutics enhance mitochondrial respiration, promote neuronal long-term potentiation, increase BDNF expression, increase GPR signaling, attenuate oxidative stress, reduce inflammation, and alter protein post-translational modifications via lysine acetylation and β-hydroxybutyrylation. These properties have further downstream implications involving Akt, PLCγ, CREB, Sirtuin, and mTORC pathways. Further studies of neuroketotherapeutics will enhance our understanding of ketone body molecular biology, and reveal novel central nervous system therapeutic applications.

Keywords: Ketone bodies; Ketogenic Diet; β-hydroxybutyrate; bioenergetics; Alzheimer's disease; mitochondria

Abbreviations: 2-DG, 2-deoxy-D-glucose; Aβ, amyloid-β; Acetyl-CoA, acetyl-coenzyme A; ADP, adenosine diphosphate; Akt, protein kinase B; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMP, adenosine monophosphate; APP, amyloid precursor protein; ANLS, astrocyte-neuron lactate shuttle; ATP, adenosine triphosphate; BDNF, brain derived neurotrophic factor; BHB, β-hydroxybutyrate; BHD1, β-hydroxybutyrate dehydrogenase 1; cAMP, cyclic AMP; CNS, central nervous system; CREB, cAMP response element-binding protein; CREM, cAMP response element modulatory protein; CTE, chronic traumatic

encephalopathy; DAG, diacylglycerol; EAE, experimental autoimmune encephalomyelitis; ETC, electron transport chain; $FADH_2$, flavin adenine dinucleotide; FDG-PET, fluorodeoxyglucose positron emission tomography; FFA3, free fatty acid receptor 3; FTD, frontotemporal dementia; GABA, γ-aminobutyric acid; GCL, glutamate cysteine ligase; GPR, G-coupled protein receptor; GSH, glutathione; GSK-3β, glycogen synthase kinase-3β; HCA2, hydrocarboxylic acid receptor 2; HD, Huntington's disease; HDAC, histone deacetylase; HMG-CoA, β-hydroxy-β-methylglutaryl-coenzyme A; H_2O_2, hydrogen peroxide; IP3, inositol 1,4,5-triphosphate; KAT, lysine acetyl-transferase; K_{ATP}, ATP-sensitive potassium channels; KD, ketogenic diet; KE, ketone ester; Kir, potassium inward rectifier channel; K_V, voltage sensitive potassium channel; LTP, long term potentiation; MAPK, mitogen activated protein kinase; MCAO, middle cerebral artery occlusion; MCT, medium chain triglyceride; MnSOD, manganese superoxide dismutase; MPP^+, 1-methyl-4-phenylpyridinium; MS, multiple sclerosis; mTORC, mammalian target of rapamycin complex; NADH, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light chain-enhancer of activated B cells; NG1, neuregulin 1; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NP-3, 3-nitroproprionic acid; Nrf2, nuclear factor erythroid 2-related factor; OXCT1, 3-oxoacid coenzyme A transferase 1; PD, Parkinson's disease; PKC, protein kinase C; PLCβ, phospholipase-C β; PLCγ, phospholipase-C γ; PPARγ, peroxisome proliferator activated receptor-γ; PTM, post-translational modification; RONS, reactive oxygen nitrogen species; SCOT, succinyl-coenzyme A:3-ketoacid transferase; Sirt, Sirtuin; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; TBI, traumatic brain injury; TCA, tricarboxylic acid; TDP-43, transactive response DNA binding protein 43 kDa; TSC, tuberous sclerosis; UCP, uncoupling protein; UPDRS, unified Parkinson's disease rating scale; VMH, ventromedial hypothalamus

1. Introduction

Ketogenic therapies include any intervention that intentionally shifts the body into a state of ketone body production. Termed ketogenesis or ketosis, achieving a state of heightened ketone production has been used to treat epilepsy for nearly a century. The efficacy of ketogenic therapies to improve functional outcomes in epilepsy have increased interest in their translational potential to treat other neurologic disorders, including Alzheimer's disease (AD) and stroke rehabilitation.

Ketogenesis can be achieved through multiple strategies including caloric restriction, administering medium chain triglycerides (MCT), strenuous exercise, and ketogenic diets (KD) which primarily feature fats and minimize carbohydrates (Gano et al., 2014). These generally well-tolerated interventions produce limited adverse effects. Ketotherapeutics still meet a considerable amount of scrutiny based on the association of ketones with the pathologic state of ketoacidosis, a complication of type I diabetes. It is important to recognize that these interventions produce a mild ketonemia, to about 5 mM, whereas ketoacidosis occurs when blood ketones enter a range of 10-25 mM. Ketoacidosis has not been found to manifest within the central nervous system microenvironment (Al-Mudallal et al., 1996).

While ketones can confer neurologic benefits, the mechanisms that underlie these benefits remain elusive. Here, we review the history of ketotherapeutics, potential mechanisms for their effects, and their therapeutic potential.

2. History of Ketotherapeutics

Ketogenic medicine perhaps dates back to ancient Greece. Most of the earliest writings on epilepsy were collected in *On the Sacred Disease*, part of the Hippocratic collection of works (Temkin, 1994; Wheless, 2008). This text illustrates that due to fears of demonic forces, society ostracized community members that suffered from fits, which today we understand to be epileptic seizures. Forced to fend for their meals in the wilderness, and being unequipped to

accomplish this task, these persons would struggle to obtain adequate caloric intake. Interestingly, after undergoing forced prolonged fasts they experienced reduced seizure frequency and severity.

The Book of Matthew from the New Testament provides a similar account. In one passage, a father requested help from Jesus and his apostles in curing his son of fits. They advised him to pray and have the child fast, which resulted in the child's recovery. The lower register of Raphael's *The Transfiguration* depicts this story. This painting possibly represents the earliest graphical depiction of bioenergetic medicine in the historical record, even if that was not the intended purpose of the work.

Fasting therapies were more formally adopted for the treatment of epilepsy in 1911 by the French physicians Guelpa and Marie (Guelpa, 1911). Similar revivals were spearheaded in the United States by the physician Hugh Conklin and fitness celebrity Bernarr Macfadden (Wheless, 2008). H. Rawle Geyelin, an endocrinologist, was the first to report cognitive improvements occurred in patients adhering to fasting regimens (Geyelin, 1921). In the same year, fasting and low carbohydrate/high fat diets were found to increase levels of the ketone bodies β-hydroxybutyrate and acetoacetate in normal, healthy subjects and were suggested to mediate neurologic benefits in children (Wilder, 1921; Woodyatt, 1921). Later investigations into the efficacy of KDs to treat epilepsy in adults demonstrated seizures were completely controlled or improved in 56 of 100 patients (Barborka, 1928).

The KD remained a popular epilepsy treatment until the 1980's, although its use gradually diminished with the advent of pharmaceutical therapies such as diphenylhydantoin, phenobarbital, and valproic acid. The KD enjoyed a resurgence in popularity following release of a made-for-TV movie, *First Do No Harm,* in 1997 and national media coverage on a television news program, *Dateline*, in 2000 (Wheless, 2008).

Increased popularity has expanded the number of ketogenic-related therapies. An increasing number of reports note the impact of ketotherapeutics on clinical phenotypes, cell physiology, and molecular physiology.

3. Molecular and Biochemical Ketone Biology

3.1. Ketogenesis

In mammals, ketosis results following prolonged periods of profound, reduced dietary intake. In this state, carbohydrate intake is low which results in decreased serum insulin and increased serum glucagon (Apfelbaum et al., 1972). This hormonal shift promotes hepatic glycogenolysis and gluconeogenesis to maintain euglycemia (Garber et al., 1974; Rui, 2014). A decline in insulin also promotes increased white adipose tissue lipolysis, which increases fatty acid circulation and β-oxidation (Vazquez-Vela et al., 2008).

Avid fatty acid β-oxidation occurs in liver mitochondria, where it generates increased levels of acetyl-CoA as shown in **Figure 1** (Drysdale and Lardy, 1953; Randle et al., 1963). Once the added acetyl-CoA surpasses the ability of the tricarboxylic acid (TCA) cycle to degrade it, it diverts to other needs such as cholesterol synthesis or ketogenesis (Baird et al., 1972; Garber et al., 1974). With ketogenesis, two molecules of acetyl-CoA are joined by thiolase to generate acetoacetyl-CoA (Middleton, 1972). A third molecule of acetyl-CoA is then added to produce β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) in a reaction mediated by HMG-CoA synthase (Hegardt, 1999). This HMG-CoA synthase-catalyzed reaction represents the rate-limiting step of the ketogenesis pathway. HMG-CoA lyase then liberates a two-carbon group to produce one molecule each of acetyl-CoA and acetoacetate **(Figure 2)**. Acetoacetate, therefore, represents, the first ketone body produced in the pathway (Puisac et al., 2012). Acetoacetate is further reduced by a molecule of NADH in a reaction mediated by β-hydroxybutyrate dehydrogenase 1 (BHD1) (Lehninger et al., 1960). This step produces the most abundant ketone found in circulation, β-hydroxybutyrate **(Figure 2)**.

Deficiencies in HMG-CoA lyase prevent ketogenesis, and following periods of fasting HMG-CoA lyase deficiency produces the pathologic state of hypoketotic hypoglycemia. Interestingly, this condition also commonly associates with seizures (Fernandes et al., 2013; Fernandes et al., 2015).

Of minor note, a small portion of acetoacetate undergoes non-enzymatic decarboxylation to form acetone (Kalapos, 2003) **(Figure 2)**. Acetone, while toxic in large concentrations, undergoes liver conversion via the methylglyoxal pathway. As acetone is highly volatile, when acetone production rates exceed conversion rates it is readily excreted by the pulmonary system. As a result, it does not reach appreciable levels under states of fasting or nutritional ketosis.

The net reaction is the synthesis of the two primary ketone bodies, β-hydroxybutyrate and acetoacetate, from two molecules of acetyl-CoA and the oxidation of one molecule of nicotinamide adenine dinucleotide (NADH). While the liver is certainly the primary organ for total body ketogenesis, though, other sites also produce ketone bodies. Increasing evidence reveals astrocytes perform ketogenesis when treated with medium chain triglycerides *in vitro*, which could play a role in regulating food intake (Le Foll et al., 2015a; Le Foll et al., 2014, 2015b; Le Foll and Levin, 2016). Ketones produced by astrocytes in response to increased dietary fat mediate this feedback by acting on ventromedial hypothalamic (VMH) neurons (Le Foll et al., 2014) that monitor nutrient status, including levels of glucose, lactate, and fatty acids.

Guzman and Blazquez proposed astrocyte-generated ketone bodies transfer to neurons (Guzman and Blazquez, 2001). Astrocytes are already known to perform a similar function, called the astrocyte-neuron lactate shuttle (ANLS), in which glucose is processed to lactate that then undergoes neuron consumption (Dienel, 2013). The possibility of an astrocyte-neuron ketone shuttle is certainly intriguing and underscores the need to investigate how metabolites influence distinct cell populations in the brain.

3.2. Ketolysis

Once produced by the liver, monocarboxylic acid transporters mediate the export of ketone bodies to the blood. This renders them available for extrahepatic catabolism and energy production (Hugo et al., 2012). The brain, heart, and muscle utilize ketone bodies (Fukao et al., 1997). Upon crossing the blood brain barrier, ketones are transported across cell plasma membranes via MCTs 1 and 2 in astrocytes and neurons, respectively (Vijay and Morris, 2014). Ketones are subsequently trafficked through the cytoplasm to the mitochondria, which serves as the primary site of ketone catabolism. Ketone catabolism largely features the reverse reactions that occur in ketogenesis, although specific parts of these opposing cycles are unique (Fukao et al., 1997).

The first step of ketone body catabolism is the oxidation of β-hydroxybutyrate to acetoacetate, with the concurrent reduction of NAD^+ to produce NADH **(Figure 1)**. BDH1 mediates this reaction. Acetoacetate is then converted to acetoacetyl-CoA by succinyl-CoA:3-ketoacid transferase (SCOT), also known as 3-oxoacid CoA-transferase 1 (OXCT1). As the name of this enzyme suggests, a CoA group is requisitioned from succinyl-CoA, thereby generating a molecule of succinate. The liver, which lacks SCOT, cannot consume ketones and this ensures its role as an exclusive ketone body producer. Lastly, acetoacetyl-CoA undergoes processing to two molecules of acetyl-CoA, which can then enter the tricarboxylic acid (TCA) cycle.

Ketones, upon contributing carbon to the TCA cycle, influence cell physiology in a number of ways. Forward progression through the TCA cycle generates the high-energy electron carriers NADH and flavin adenine dinucleotide ($FADH_2$), which serve as substrates for the electron transport chain (ETC) and are necessary for the production of ATP from ADP in oxidative phosphorylation. This allows for a greater degree of nervous system bioenergetic plasticity, as it reduces glucose dependence and shifts the cell towards aerobic respiration. Indeed, ketone bodies have been shown to reduce glycolysis flux (LaManna et al., 2009). This

likely occurs as part of a glycolysis negative feedback effect that arises due to increased NADH production.

Additionally, by supplying carbon to the TCA cycle ketone bodies increase TCA cycle anaplerosis (Owen et al., 2002). This in turn affects neurotransmitter levels as several TCA cycle intermediates serve as substrates for neurotransmitter synthesis. For example, α-ketoglutarate can exit the TCA cycle and undergo conversion to the major excitatory neurotransmitter, glutamate, or undergo decarboxylation to form an inhibitory neurotransmitter, γ-amino butyric acid (GABA). Acetyl-CoA itself combines with choline in the mitochondrial matrix to synthesize acetylcholine. Introducing ketone bodies to the nervous system not only effects bioenergetics, but also neurotransmitter levels.

3.3. Ketone bodies and mitochondrial function

How ketones influence mitochondrial efficiency is worth considering. In one study, supplementing the diet of C57BL/6J mice with a β-hydroxybutyrate-(R)-1,3-butanediol monoester ketone ester (KE) for 1 month was sufficient to induce ketonemia. The mice demonstrated increased expression of electron transport chain proteins, uncoupling protein (UCP) 1, and mitochondrial biogenesis signaling pathways in brown adipose tissue (Srivastava et al., 2012). Increased UCP expression in turn has multiple effects on mitochondrial physiology. First, in brown fat it increases heat production by shifting electron transfer energy away from ATP production. Second, increasing proton leak into the matrix can attenuate the generation of reactive oxygen nitrogen species (RONS) by helping to avoid matrix hyperpolarization. Data suggest that even a modest increase in proton leak can reduce hydrogen peroxide (H_2O_2) generation by as much as 70% (Echtay, 2007; Hansford et al., 1997; Votyakova and Reynolds, 2001).

A similar study examined the effects of a KE on the expression of brain UCP 4 and UCP 5 in Wistar rats. Brains of KE-supplemented rats exhibited a 1.5 fold increase in these UCPs (Kashiwaya et al., 2010). This is consistent with a prior study that reported caloric restriction

increased rat brain UCP 4 expression, with neurons and astrocytes exhibiting the greatest and least expression of UCP4 respectively (Liu et al., 2006). A KD additionally upregulated UCP 2 and 4 expression in the brains and in particular the hippocampal dentate gyri of C3HeB/FeJ mice (Sullivan et al., 2004). Upregulation of UCP 4 and 5 *in vitro* protected against the complex I inhibitor 1-methyl-4-phenylpyridinium (MPP^+), and the complex II inhibitor 3-nitroproprionic acid (3-NP) (Chu et al., 2009; Ho et al., 2006; Kwok et al., 2010; Ramsden et al., 2012; Wei et al., 2009). It appears that UCP-mediated neuroprotection requires signaling through the NF-κB pathway, and increased ATP production through increased complex II flux (Ho et al., 2012a; Ho et al., 2012b).

Ketotherapeutic-induced RONS attenuation extends beyond the upregulation of UCPs. Maintaining rats on a KD for 3 weeks increased levels of glutathione (GSH), a free radical scavenger. This increase was associated with an increase in glutamate cysteine ligase (GCL), the rate-limiting enzyme in GSH synthesis (Jarrett et al., 2008). It appears that KD-related increases in oxidative stress infrastructures are activated by initial increases in RONS, which induce oxidative stress response pathways through activation of its master regulator, nuclear factor erythroid 2-related factor (Nrf2) (Milder et al., 2010).

In rats, a KD increased brain expression of genes that accommodate oxidative phosphorylation and the TCA cycle including cytochrome c, isocitrate dehydrogenase, malate dehydrogenase, and subunits of succinate dehydrogenase, ATP synthase, cytochrome oxidase, and NADH dehydrogenase. This was associated with an electron microscopy-demonstrated rise in the number of hippocampal dentate gyrus mitochondria (Bough et al., 2006). It was unclear from this study, though, whether augmented mitochondrial mass was due to enhanced mitochondrial biogenesis, reduced mitophagy, or a combination of both.

3.4. Ketone bodies and post-translational protein modification

Increasing evidence suggests ketone bodies influence cell physiology independently, or at least indirectly, of their bioenergetic effects. Specifically, metabolites produced during ketone

catabolism influence intracellular signaling by inducing changes in protein post-translational modifications (PTMs) (Newman and Verdin, 2014a, b).

This phenomenon was initially considered after it was recognized that butyrate, a short chain fatty acid whose structure differs from a ketone body only by the absence of a beta carbon hydroxyl group, affects histone acetylation (Stilling et al., 2016). In HEK293 cells and rodent kidney, increasing β-hydroxybutyrate levels inhibits histone deacetylases (HDACs) 1, 3, and 4 and consequently increases acetylation of key histone residues. This acetylation enhances FOXO3A-mediated gene transcription. A subset of the effected genes includes those responsible for mitigating oxidative stress such as manganese superoxide dismutase (MnSOD) and catalase (Shimazu et al., 2013). Similarly, *in vitro* exposure to β-hydroxybutyrate promotes activity of the EP300 family of lysine acetyltransferases (KATs) (Marosi et al., 2016). Since ketones appear to modulate a number of enzymes that control the cycling of protein acetylation in the cytoplasm and nucleus, it is likely that ketones alter other compartments in a similar manner. Ketones could influence activity of Sirtuin 3, the major mitochondrial deacetylase, especially considering their recognized trafficking into the mitochondrial matrix (Rardin et al., 2013).

Another exciting recent development in the area of ketone body-PTM relationships is the discovery that β-hydroxybutyrate itself can modify lysine residues (Xie et al., 2016). β-hydroxybutyrylation of histone lysines produces gene expression changes that recapitulate those of histone acetylation. TCA intermediates generated during ketone body metabolism-associated reactions may additionally function as epigenetic modifiers. In particular, changes in protein succinylation that arise through the actions of α-ketoglutarate dehydrogenase, or other succinylation enzymes under ketotic conditions, are suspected (Gibson et al., 2015).

3.5. Ketone bodies as extracellular signaling ligands

In addition to its ability to influence intracellular signaling, β-hydroxybutyrate may also function as an extracellular receptor ligand. It has been demonstrated to have agonistic effects

on hydrocarboxylic acid receptor 2 (HCA2), otherwise known as the niacin receptor or G-Coupled Protein Receptor (GPR) 109A (Rahman et al., 2014). β-hydroxybutyrate is able to activate HCA2 with an EC_{50} near 700 μM, well below the approximately 5 mM concentrations observed in nutritional ketosis. HCA2 expression primarily occurs on the surface of cells derived from monocytes, including macrophages and microglia. Functioning as an inhibitory GPR, HCA2 activation suppresses cAMP levels, which ultimately reduces the production of pro-inflammatory cytokines. This suggests ketogenic therapies can produce a beneficial anti-inflammatory effect, a prediction that has been experimentally verified (Selfridge et al., 2015). Other authors provide a more comprehensive review of the effects of HCA2 activation (Offermanns and Schwaninger, 2015).

Outside of the CNS, β-hydroxybutyrate has ligand effects on GPR41, also known as free fatty acid receptor 3 (FFA3). GPR41 is a Gi/o receptor previously shown to respond to the short chain fatty acid butyrate (Stilling et al., 2016; Won et al., 2013). Its expression is primarily restricted to sympathetic chain ganglia. Upon exposure to β-hydroxybutyrate, GPR41 suppresses the activity of the sympathetic nervous system through the Gβγ-PLCβ-MAPK signaling pathway (Kimura et al., 2011). Through this mechanism, ketones are able to modulate body energy expenditure and metabolic homeostasis.

3.6. Ketone bodies and activation of signaling pathways

Exogenous administration of ketones and ketones produced through vigorous exercise increase the expression of brain derived neurotrophic factor (BDNF) (Marosi et al., 2016; Sleiman et al., 2016; Swerdlow, 2014). BDNF acts as a ligand for TrkB family nerve growth factor (NGF) receptors, and exhibits weak agonistic effects on the p75 receptor. Upon binding TrkB, BDNF activates protein kinase B (Akt), phospholipase C gamma (PLCγ), and cAMP response element binding protein (CREB) signaling pathways (Baydyuk and Xu, 2014). Interestingly, BDNF expression increases following histone deacetylase inhibition in cortical neurons (Koppel and Timmusk, 2013). The deacetylase inhibition properties of ketones may in

fact induce BDNF expression. The extent to which ketosis activates such pathways remains relatively understudied, and investigations into these interactions could potentially explain some ketotherapeutic effects.

Akt regulates cell growth through its downstream targets tuberous sclerosis (TSC) 1, TSC2, and mammalian target of rapamycin complex (mTORC) 1. It also enhances cell survival by inhibiting Bad, a pro-apoptotic factor. Akt interacts with the GABA receptor, ataxin-1, and the huntingtin protein (Manning and Cantley, 2007). Akt levels are typically low in the adult brain, but expression increases following injury in some models (Owada et al., 1997). Akt is protective in the setting of reduced trophic support, exposure to reactive oxygen species, and DNA damage (Chong et al., 2002, 2003; Chong et al., 2005; Henry et al., 2001; Kang et al., 2003; Matsuzaki et al., 1999).

PLCγ activation by BDNF signaling generates inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 and DAG, respectively, mobilize internal calcium stores and activate protein kinase C (PKC). Activation of these pathways has multiple effects including modulation of cell proliferation, migration, neurite outgrowth, synaptic plasticity, and survival. PLCγ expression primarily occurs in the cortex and hippocampus (Jang et al., 2013; Suh et al., 2008). PLCγ regulates N-methyl-D-aspartate (NMDA) receptor biology through neuregulin 1 (NRG1) (Gu et al., 2005). PLCγ facilitates hippocampal long-term potentiation (LTP), a process that facilitates the acquisition and storage of information at the synapse (Kandel, 2001; Minichiello et al., 2002). Given the role of PLCγ in cell survival and molecular mechanisms of learning, activation of PLCγ by ketone-induced BDNF signaling represents an intriguing potential mediator of ketotherapeutic effects.

CREB, typically activated by increases in cytosolic calcium or cAMP, has a recognized role in the regulation of circadian rhythms and memory formation (Silva et al., 1998). Disruption of CREB signaling pathways induces neurodegeneration of the hippocampus and dorsolateral striatum in mice lacking the related protein cAMP response element modulatory protein (CREM)

(Mantamadiotis et al., 2002). Certain CREB isoforms are critical in learning and memory processes (Silva et al., 1998). For instance, on food preference tasks mice lacking CREBα show competent immediate memory but reduced memory at 24 hours (Kogan et al., 1997). Ketone-mediated modulation of CREB activity through BDNF could have important translational potential in age-related dementias.

It was recently demonstrated that BDNF also induces the expression of inhibin β-A by modifying nuclear responses to synaptic NMDA-associated calcium currents. Inhibin β-A subsequently inhibits extrasynaptic NMDA receptor-mediated calcium currents that can inhibit mitochondrial function and induce glutamate excitotoxicity-related cell death (Lau et al., 2015). Exploiting the protective effects of inhibin β-A could conceivably benefit conditions or diseases that feature reduced BDNF signaling.

4. Relevance to Development and Neurologic Disease

4.1. Ketones in Development

Ketone bodies play a critical role during normal brain development (Cotter et al., 2011; Cunnane et al., 2016). Oxidation of ketones by the brain begins during fetal development (Adam et al., 1975). Mammalian neonates are largely reliant on maternal breast milk as their primary nutrition source. Maternal milk is rich in dietary fats and has a high ketogenic ratio due to its abundance of medium chain fatty acids (Breckenridge and Kuksis, 1967; Hilditch, 1944; Insull and Ahrens, 1959; Nehlig, 1999). Unlike adult ketosis, neonatal ketosis occurs independently of whether or not the infant is in a fed state (Lindblad et al., 1977). Despite the fact that long chain fatty acids do not freely diffuse into the brain, a robust amount of neonate brain energy production relies on ketone metabolism (Nehlig and Pereira de Vasconcelos, 1993). Blocking ketogenesis enhances seizure severity in rat pups (Minlebaev and Khazipov, 2011).

The importance of ketones to the developing brain extend well beyond their role in bioenergetics. Ketones serve as the primary substrate for lipid synthesis during periods of rapid brain growth (Cunnane and Crawford, 2003; Freemantle et al., 2006). Indeed, neonatal

ketogenesis appears so essential to development that even the neonatal intestine is capable of ketogenesis (Bekesi and Williamson, 1990).

4.2. Epilepsy

Epilepsy involves the aberrant, synchronous depolarization of neurons in the central nervous system. It generally manifests as paroxysmal disruptions of awareness, consciousness, and motor activity. Epilepsy affects 1% of the United States population and up to as many as 50 million people globally (Hirtz et al., 2007; Kobau et al., 2008; McNally and Hartman, 2012). As described previously, epilepsy represents the first condition that intentionally utilized ketotherapeutics. A modern randomized clinical trial in humans demonstrated that the KD was able to reduce seizures in 75% of pediatric epileptics over a three-month period (Neal et al., 2008). Despite their modern use extending back by as much as a century, its therapeutic mechanism remains a matter of much debate.

Anticonvulsant properties of acetoacetate were first demonstrated in rabbits administered thujone to produce seizures (Keith, 1935). Given that glutamate excitotoxicity represents one possible cause of neuronal damage from seizures, efforts were made to investigate whether ketotherapeutics worked by attenuating neuronal excitation by modulating neurotransmitter balance or release. There is some evidence to suggest that ketotherapies increase GABA. In rats, acetoacetate and β-hydroxybutyrate increased the accumulation of GABA in rat presynaptic vesicles (Erecinska et al., 1996). Magnetic resonance spectroscopy of humans maintained on a KD also showed increased brain GABA levels (Wang et al., 2003). Further, ketotic rats exhibit lower levels of glutamate in neurons but stable amounts of GABA. Since GABA is synthesized from glutamate, this indicates a greater proportion of glutamate may be converted to GABA, and thereby shift the total balance of these neurotransmitters towards inhibition (Melo et al., 2006).

Reducing glutamate release could also potentially reduce seizure-associated glutamate excitotoxicity. Acetoacetate reversibly inhibits glutamate release in mouse hippocampal slices

and cultured rat neurons at high concentrations of 10 mM (Juge et al., 2010). Others have noted this effect may not have physiologic relevance as extracellular levels of β-hydroxybutyrate in the hippocampal microenvironment were determined to be between 40-50 μM following three weeks of KD (McNally and Hartman, 2012; Samala et al., 2011). In light of this, the role of ketotherapeutics in modulating neurotransmitter balance remains speculative.

Ketotherapeutics may modulate neuronal excitability independent of influencing neurotransmitter levels. As previously discussed, following their entry into the TCA cycle ketones enhance the production of ATP. ATP levels could influence the activity of membrane ion pumps and thus alter neuron membrane potential. In this regard, ATP-sensitive potassium (K_{ATP}) channels are of particular interest given their recognized activation upon changes in the ATP/ADP ratio, and their effects on membrane polarization. Tanner et al. demonstrated that β-hydroxybutyrate enhances K_{ATP} channel opening in cultured mouse hippocampal neurons (Tanner et al., 2011). Cultured GABAergic substantia nigra pars reticulata (SNpr) neurons exhibited reduced firing rates in the presence of either acetoacetate or β-hydroxybutyrate. However, this effect disappeared following knockout of the potassium inward rectifier channel Kir6.2 or in the presence of the K_{ATP} channel inhibitor tolbutamide (Deransart et al., 2003). Consequently, it is possible that neuroprotection from seizure events could be mediated through reduced cell firing rates that result from changes in neuron membrane potential, and not the suppression or alteration of total neurotransmitter concentrations.

Voltage sensitive potassium channel Kv1.1 knockout mice maintained on a KD exhibited increased nuclear localization of the peroxisome proliferator activated receptor-γ 2 (PPARγ2) splice variant. This was associated with a 70% reduction in seizure frequency. The PPARγ antagonist GW9662 eliminated this benefit. Further, the anti-seizure effects of the KD were mimicked in Kv1.1 KO mice when administered the PPARγ agonist pioglitazone (Simeone et al., 2017). Modulation of PPARγ activity presents an attractive and readily available target for novel epilepsy therapeutics.

4.3. Alzheimer's Disease

AD is the most common form of dementia and involves progressive neurodegeneration that causes impaired memory and a reduced ability to perform activities of daily living. Theories vary regarding the underlying etiology of the overall disease process, but glucose hypometabolism, mitochondrial dysfunction, extracellular amyloid-β (Aβ) plaque accumulation, and intracellular tau protein neurofibrillary tangles are recognized biochemical and histological hallmarks (Swerdlow, 2011, 2012a, b).

Emerging evidence suggests defects in mitochondrial function and a consequential decline in respiratory chain function alter amyloid precursor protein (APP) processing to favor the production of the pathogenic Aβ fragment (Wilkins and Swerdlow, 2016). Several groups have shown that both APP and Aβ co-localize with mitochondria, suggesting the possibility that mitochondrial function and APP biology interact (Devi et al., 2006; Hansson Petersen et al., 2008). Ketone bodies block mitochondrial amyloid entry and improve cognition (Yin et al., 2016). This ability would predictably ameliorate Aβ-mediated suppression of respiratory chain function and could perhaps to some rescue the bioenergetic hypometabolism observed in AD brains (Swerdlow, 2012c). Alternatively, improving mitochondrial performance outright could reduce the production of Aβ and increase the production of soluble APPα, a molecule with trophic properties capable of binding the BDNF receptor p75 to promote neurite growth (Hasebe et al., 2013).

Fluorodeoxyglucose positron emission tomography (FDG-PET) studies find asymptomatic individuals with an increased AD risk show less prefrontal cortex, posterior cingulate, entorhinal cortex, and hippocampal glucose uptake than normal-risk individuals (de Leon et al., 2001; Ishii et al., 1997; Mosconi et al., 2011; Mosconi et al., 2008a; Mosconi et al., 2008b; Mosconi et al., 2009; Mosconi et al., 2008c; O'Dwyer et al., 2011; Reiman et al., 2004; Rosenbloom et al., 2011; Spulber et al., 2010; Villain et al., 2010; Vlassenko et al., 2010). This reduction associates with the downregulation of the glucose transporter GLUT1 in the AD brain

(Winkler et al., 2015). Further, increasing evidence suggests that increased insulin resistance contributes to the development of sporadic AD (de la Monte, 2009).

Clinical studies suggest ketogenic therapies may benefit AD patients. Medium chain triglyceride and ketone ester supplements raised plasma ketone levels and improved cognition in AD subjects (Henderson, 2008; Newport et al., 2015; Reger et al., 2004). This is in agreement with epidemiological studies that report positive associations between ketotherapeutic use and reduced AD risk (Henderson, 2008; Morris, 2005).

Preclinical studies performed using the triple transgenic mouse model of AD demonstrated reduced pathology following the administration of the ketogenic modulator 2-deoxy-D-glucose (2-DG), which inhibits glycolysis and increases cell reliance on respiratory chain oxidative phosphorylation (Yao et al., 2011a; Yao et al., 2011b). Further, PET studies using radiolabeled acetoacetate and β-hydroxybutyrate demonstrated single compartment kinetics of brain ketone body utilization, matching levels and uptake over a large range of concentrations (Blomqvist et al., 2002; Blomqvist et al., 1995). Importantly, brain uptake of acetoacetate did not significantly differ either globally or regionally in early stage AD patient brains, as compared to age-matched controls (Castellano et al., 2015). Of note, increased astrocyte metabolism appeared to mitigate Aβ-related impairment of memory function in day old chicks, which implies bioenergetic benefits require astrocyte function (Gibbs et al., 2009). It remains unclear if the brain's capacity to utilize ketones in general declines with age.

Catabolism of white matter lipids, with the purpose of providing substrate for astrocytic ketogenesis, may occur in the aging female brain (Klosinski et al., 2015). This could mitigate neurocognitive decline by compensating metabolism defects with ketolysis (Bartzokis et al., 2004a; Bartzokis et al., 2004b; Brinton, 2008; Carmichael et al., 2010; Kuczynski et al., 2010). While ketone compensation may delay the onset of clinical symptoms, this process could lead to white matter demyelination and its associated clinical consequences (Morris, 2005). It would be interesting to know if providing increased dietary fats sustains ketogenesis and reduces

white matter scavenging in the aged brain, thereby extending the window of ketone compensation and delaying the onset of AD symptoms. In support of this possibility, rats fed a high-fat diet rich in lipoic acid reportedly improved their performance on a novel object recognition task (Rodriguez-Perdigon et al., 2016).

4.4. Stroke

Stroke typically refers to an acute interruption of blood flow to a region of the brain that results in cell injury and cell death. Stroke carries significant morbidity and societal impact, and it is currently the fourth leading cause of death in the United States (Ovbiagele and Nguyen-Huynh, 2011). The majority of approved therapies to prevent and treat stroke focus on the prevention and dissolution of blood clots to maintain patent blood vessels. Therapeutics that can improve biochemical plasticity and confer resistance to the sequelae of ischemia could provide a strategy for reducing injury during and improving rehabilitation after stroke.

Supplying an oxidative phosphorylation-promoting intermediate would seem unlikely to enhance energy production within the ischemic core of an infarct. However, as discussed the physiologic role of ketones extend far beyond their direct role in bioenergetic pathways. Providing ketone bodies to the penumbra, the region of brain tissue lying directly adjacent to the ischemic core, may spare glucose for the core, thereby helping to sustain energy production in the absence of molecular oxygen (Gibson et al., 2012).

Preclinical studies in mice demonstrated that the KD and BHB reduce total infarct volume induced by permanent middle cerebral artery occlusion (MCAO) (Puchowicz et al., 2008; Rahman et al., 2014). Interestingly, this effect does not occur in HCA2 knockout mice, which suggests this benefit may rely on anti-inflammation signaling pathways. A similar phenomenon was reported in rodent models of ischemic stroke treated with BHB, which led to reductions in infarct volume, reduced brain edema, and improvements in motor function (Suzuki et al., 2002; Suzuki et al., 2001). This study did not determine, though, whether HCA2 signaling mediated these effects.

4.5. Traumatic Brain Injury

Epidemiologic studies link traumatic brain injury (TBI) to AD, PD, ALS and the recently described condition of chronic traumatic encephalopathy (CTE) (Bruce et al., 2015). Current therapies for TBI primarily consist of behavioral therapy and the pharmaceutical treatment of associated symptoms such as depression. We need therapies that can enhance TBI recovery, or can precondition high-risk individuals towards lesser injuries.

In rats, post-TBI administration of β-hydroxybutyrate reduced contusion volume in an age-dependent manner (Prins et al., 2005; Prins and Matsumoto, 2014). This associated with a reversal of injury-related ATP reduction (Prins et al., 2004). Recently, activation of the Akt/GSK-3β/β-catenin signaling pathway was found to enhance neuron survival in a TBI rat model (Zhao et al., 2012a). Ketone activation of Akt signaling, therefore, could offer a potential strategy for preserving neuron integrity.

It is important to note a study reported β-hydroxybutyrate increased blood-brain barrier permeability in a TBI rat model (Orhan et al., 2016). This may contribute to increased inflammation due to the exposure of brain parenchyma to pro-inflammatory blood components. The cost-benefit utility of ketotherapeutics in TBI, therefore, requires careful consideration.

4.6. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disorder that features the demise of upper and lower motor neurons (Ji et al., 2017). Disease progression manifests as progressive muscle weakness and paralysis. Once respiratory muscle involvement occurs, ventilation compromise ensues and ultimately the disease concludes in death. As is the case with AD, the majority of ALS cases are sporadic but a subset of familial cases arise from autosomal dominant mutations. One well-studied causal mutation occurs in the gene that encodes superoxide dismutase 1 (SOD1). Two ketogenic therapy studies, which evaluated a KD and an MCT, reported improved motor performance in SOD1-G93A transgenic mice. In both studies, ketotherapeutics reduced the loss of lower motor

neurons in the spinal cord ventral horn. However, neither study appeared to benefit survival outcomes (Zhao et al., 2012b; Zhao et al., 2006).

Another common feature of the disease, one that it shares with frontotemporal dementia (FTD), is a cytoplasmic accumulation of the ubiquitinated nuclear protein transactive response DNA-binding protein 43 (TDP-43). Recent studies demonstrate the toxic mechanism of TDP-43 requires its localization to mitochondria, where it reduces the expression of mitochondrial DNA-encoded proteins (Wang et al., 2016). As ketone bodies seem able to modify mitochondria-Aβ interactions, it would be interesting to see whether they similarly affect mitochondria-TDP43 interactions.

4.7. Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that presents with involuntary choreiform movements, impaired cognition, and psychiatric symptoms. It effects 5 to 8 people per 100,000 in Europe and North America. Disease pathogenesis involves trinucleotide repeat expansion of CAG residues in the *huntingtin* gene. The resulting polyglutamine-expanded protein undergoes errors in protein folding and toxic accumulation that ultimately leads to impaired neuron function and cell death. It primarily affects structures in the basal ganglia, which manifests grossly as caudate atrophy (Ross and Tabrizi, 2011).

Lim et al. provided initial support for the therapeutic potential of ketone bodies in HD. The investigators administered subcutaneous BHB to 3-nitroproprionic acid (3-NP) toxin and R6/2 genetic mouse models of HD. BHB attenuated motor dysfunction in both models. BHB-treated R6/2 mice also saw an extension of lifespan, as well as increased striatal histone acetylation (Lim et al., 2011). Further investigation in PC12 cells demonstrated the increase in histone acetylation occurred independent of mitochondrial function or HDAC inhibition. Additional testing of ketogenic therapies in HD appears warranted.

4.8. Parkinson's Disease

Parkinson's disease (PD) affects between 100 to 200 people per 100,000 over the age of 40, and its incidence increases with age. Disease pathogenesis involves a progressive neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The loss of these neurons manifests as progressive bradykinesia, tremors, and rigidity. Late stages of disease often feature increasing cognitive dysfunction and dementia (Kalia and Lang, 2015).

Preclinical studies in the MPTP mouse model show that infusing BHB or a KD reduces dopaminergic neuron degeneration, improves motor deficits, reduces microglial activation, and reduces expression of pro-inflammatory cytokines (Tieu et al., 2003; Yang and Cheng, 2010). Similarly, a KD reduces dopamine neuron loss in the 6-hydroxydopamine PD rat model (Cheng et al., 2009).

In a five participant pilot study of PD patients, a 28-day KD improved unified Parkinson's disease rating scale (UPDRS) scores. The small size of this study and the lack of a control group, though, precludes conclusive inferences (Vanitallie et al., 2005).

4.9. Multiple Sclerosis

Multiple sclerosis (MS) features an autoimmune-associated demyelination of CNS axons. It most often presents in a relapsing-remitting fashion that can include varying involvement of optic, sensory, motor, or coordination systems. After trauma, MS is the next most common CNS-related cause of young adult permanent disability (Noseworthy et al., 2000; Ramagopalan and Sadovnick, 2011).

Preclinical data from the mouse experimental autoimmune encephalomyelitis (EAE) multiple sclerosis model indicate a KD improves outcomes. In their 2012 study, Kim et al. demonstrated a KD reduced brain inflammation, mitigated motor disability, preserved CA1 long-term potentiation, and improved spatial learning and memory as assessed by the Morris water maze. The KD also induced a reduction in reactive oxygen species in conjunction with reduced pro-inflammatory cytokines (Kim et al., 2012). The anti-inflammatory properties of the KD are in

line with suggested benefits as discussed previously. It would be interesting to know if the HCA2 pathway modulates these effects.

5. Conclusions

Fatty acid β-oxidation by hepatocytes and astrocytes generates the primary ketone bodies, β-hydroxybutyrate and acetoacetate. These ketones are taken up and catabolized by neurons, and help produce energy via oxidative phosphorylation. Recent work suggests that ketone bodies or interventions that serve to produce or introduce ketone bodies provide neurologic benefits that extend beyond their direct role in bioenergetic fluxes. Specifically, ketones affect protein post-translational modifications, attenuate RONS production, increase anti-oxidant stress response pathway expression, modulate GPR and BDNF signaling pathways, contribute to anaplerosis, and exhibit anti-inflammatory effects **(Figure 3)**.

Ketotherapeutic approaches, therefore, may influence the nervous system through a variety of mechanisms. Their potential for treating a variety of neurologic conditions warrants consideration. It is further worth considering whether ketotherapeutics can promote healthy aging, an effect that could consequently delay the development or onset of age-dependent neurologic diseases.

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Figure Legends

Figure 1. Ketogenesis and Ketolysis. Hepatic mitochondria serve as the primary site for the production of serum ketone bodies. Acetyl-CoA generated from acyl-CoA β-oxidation is converted to HMG-CoA by the rate-limiting enzyme HMGCS2. HMG-CoA is further processed to the primary ketone bodies acetoacetate and β-hydroxybutyrate, which are released into the circulation via the monocarboxylate transporters (MCTs) 1 and 2. Ketone bodies enter the CNS via MCTs and are oxidized to acetyl-CoA through a series of reactions that require SCOT. Acetyl-CoA undergoes terminal oxidation through the TCA cycle to generate the high-energy electron carriers NADH and $FADH_2$. Electrons enter the respiratory chain, leading to the generation of ATP through ATP synthase.

Figure 2. Chemical Structures of Biologically Relevant Ketone Bodies. The physiologically relevant ketone bodies in order of decreasing serum concentrations are β-hydroxybutyrate (A), acetoacetate (B), and acetone (C). Acetone is highly volatile and is readily excreted via the pulmonary system or converted to lactate by the liver.

Figure 3. Pleiotropic Effects and Hypothesized Benefits of Ketotherapeutics. Multiple ketotherapeutics produce an increase in serum ketone bodies. Ketone bodies increase oxidative metabolism, reduce oxidative stress, alter epigenetic protein post-translational modifications, increase BDNF signaling, and signal through GPRs in various model systems. Many of these effects require further study to determine the underlying mechanism of action and ultimate therapeutic value. Observed and predicted effects are indicated with solid and dashed lines respectively.

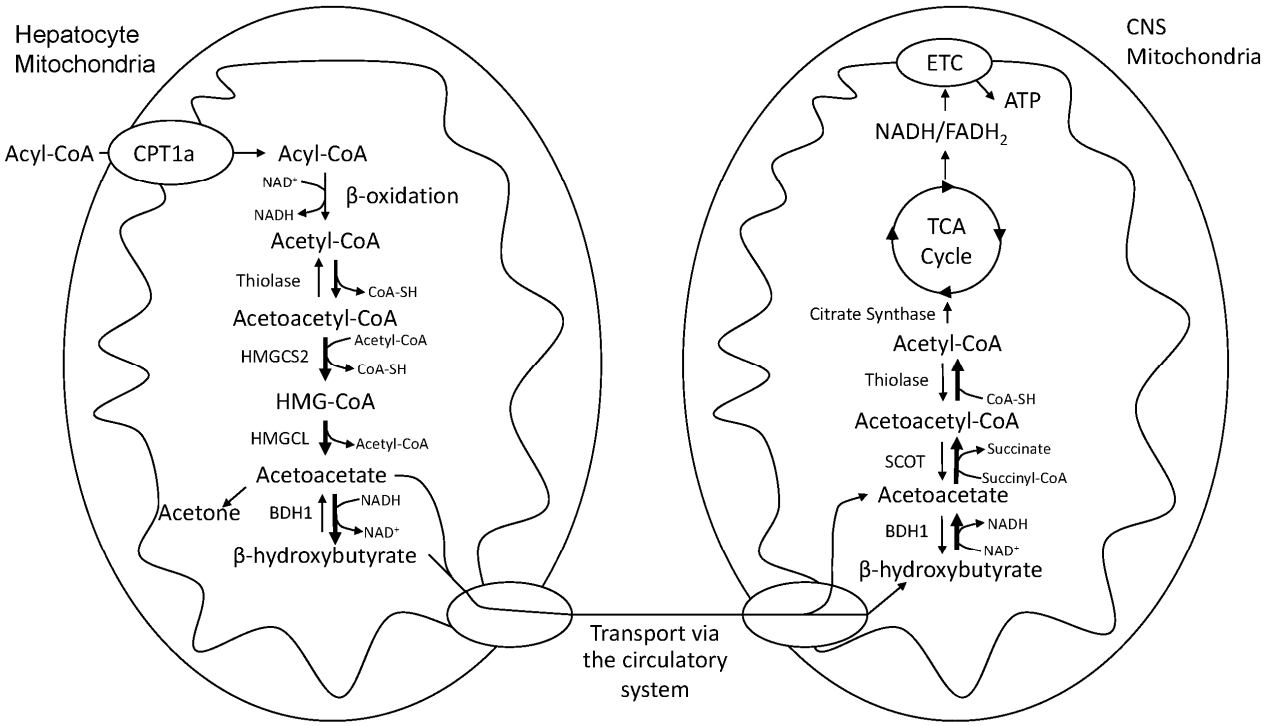
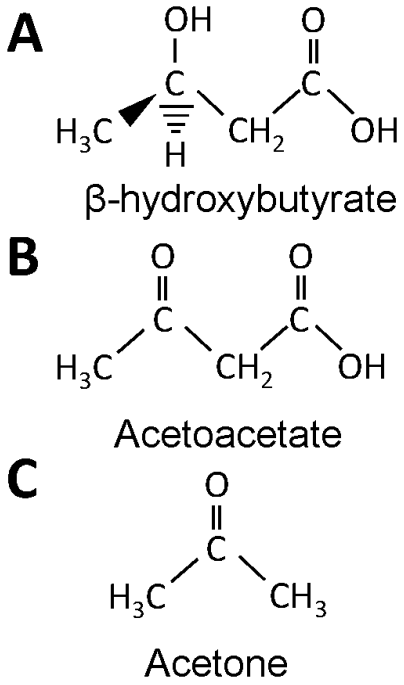

Hepatocyte
Mitochondria
Acyl-CoA
CPT1a
Acyl-CoA
NAD+
NADH
β-oxidation
Acetyl-CoA
Thiolase
CoA-SH
Acetoacetyl-CoA
HMGCS2
Acetyl-CoA
CoA-SH
HMG-CoA
HMGCL
Acetyl-CoA
Acetoacetate
Acetone
BDH1
NADH
NAD+
β-hydroxybutyrate
Transport via
the circulatory
system
CNS
Mitochondria
ETC
ATP
NADH/FADH2
TCA
Cycle
Citrate Synthase
Acetyl-CoA
Thiolase
CoA-SH
Acetoacetyl-CoA
SCOT
Succinate
Succinyl-CoA
Acetoacetate
BDH1
NADH
NAD+
β-hydroxybutyrate

Figure 1


A
OH
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β-hydroxybutyrate
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Acetone

Figure 2

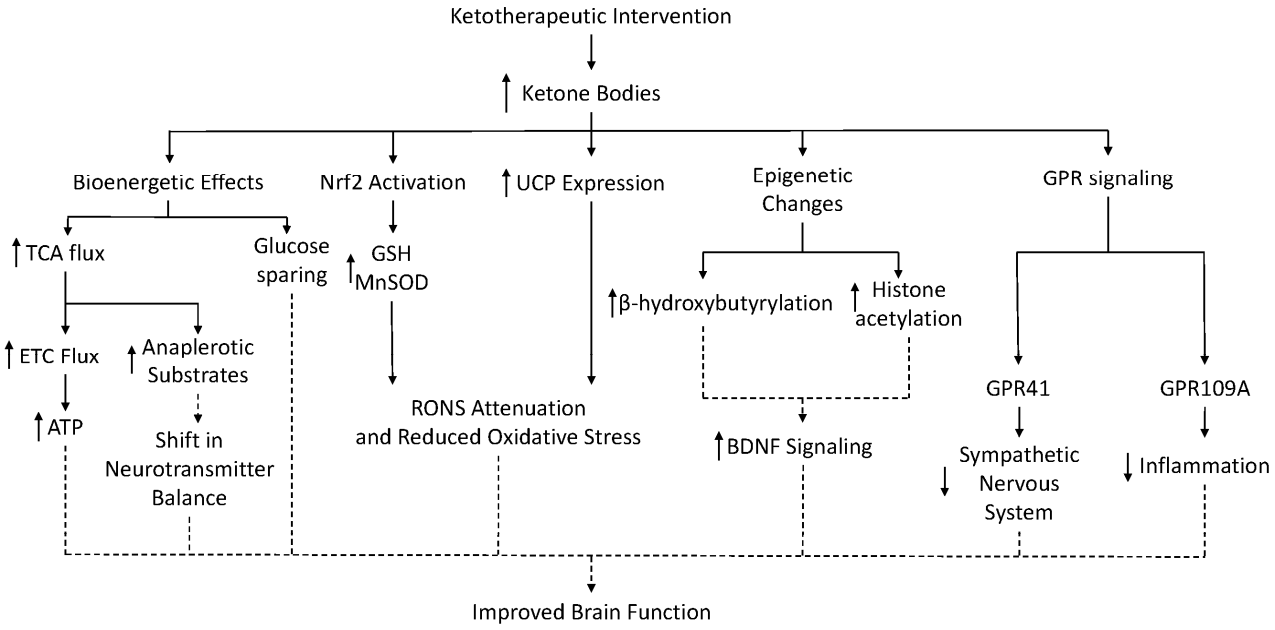
Ketotherapeutic Intervention
Ketone Bodies
Bioenergetic Effects
Nrf2 Activation
UCP Expression
Epigenetic Changes
GPR signaling
TCA flux
Glucose sparing
GSH
MnSOD
β-hydroxybutyrylation
Histone acetylation
ETC Flux
Anaplerotic Substrates
ATP
Shift in Neurotransmitter Balance
RONS Attenuation and Reduced Oxidative Stress
BDNF Signaling
GPR41
GPR109A
Sympathetic Nervous System
Inflammation
Improved Brain Function

Figure 3