Role of ketone bodies in diabetes-induced dementia: sirtuins, insulin resistance, synaptic plasticity, mitochondrial dysfunction, and neurotransmitter

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Patients with type 2 diabetes can have several neuropathologies, such as memory deficits. Recent studies have focused on the association between metabolic imbalance and neuropathological problems, and the associated molecular pathology. Diabetes triggers neuroinflammation, impaired synaptic plasticity, mitochondrial dysfunction, and insulin resistance in the brain. Glucose is a main energy substrate for neurons, but under certain conditions, such as fasting and starvation, ketone bodies can be used as an energy fuel for these cells. Recent evidence has shed new light on the role of ketone bodies in regulating several anti-inflammation cellular pathways and improving glucose metabolism, insulin action, and synaptic plasticity, thereby being neuroprotective. However, very high amount of ketone bodies can be toxic for the brain, such as in ketoacidosis, a dangerous complication that may occur in type 1 diabetes mellitus or alcoholism. Recent findings regarding the relationship between ketone bodies and neuropathogenesis in dementia are reviewed in this article. They suggest that the adequately low amount of ketone bodies can be a potential energy source for the treatment of diabetes-induced dementia neuropathology, considering the multifaceted effects of the ketone bodies in the central nervous system. This review can provide useful information for establishing the therapeutic guidelines of a ketogenic diet for diabetes-induced dementia.

INTRODUCTION

The prevalence of type 2 diabetes is markedly increasing all over the world; subsequently, many researchers have investigated various pathological problems caused by type 2 diabetes.[1] Among diverse pathological changes, recent studies have highlighted the strong association between severe neuropathology and the onset of diabetes.[2,3] Results of several epidemiologic studies suggested a positive correlation between the progression of diabetes and severity of memory loss, such as mild cognitive impairment and dementia.[2-4] Elevated glucose levels and insulin resistance in blood serum are reported to be critical risk factors for dementia onset.[5-7] Furthermore, researchers have reported that the brains of patients with type 2 diabetes have more brain

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atrophy, less brain volume, and impaired synaptic connectivity compared with normal brains.[8,9] Given these data, many researchers are focusing on various pathological mechanisms in diabetes-induced dementia.

Glucose is well known as a main fuel in the brain; it supports the survival of various brain cells.[10,11] However, during nutrient deprivation, after exercise, and during low-carbohydrate states, ketone bodies are used as an alternative energy source in the brain as well as in the rest of the body.[12–14] In systemic metabolism processes, ketone bodies are associated with major metabolic pathways, including fatty acid β-oxidation, the tricarboxylic acid cycle, and gluconeogenesis.[15] In the body, fatty acids undergo fatty β-oxidation after food ingestion and subsequently are converted to a acetyl coenzyme A in liver and also ketone bodies.[14]

Ketone bodies contribute to the elevation of antioxidant responses by regulating NAD and NAD+/NADH–coupled reactions and glutathione activity through complex pathways.[16] Ketosis—the increased but low levels of ketone bodies in blood, which is naturally produced in the fasted state or the low-carbohydrate state—is emerging as a therapeutic approach in various diseases.[17] In particular, many researchers have suggested that ketosis could treat several neurologic disorders, including epilepsy, Parkinson's disease, stroke, and dementia.[17–20] Several studies have demonstrated that ketone bodies, ketone esters, and β-hydroxybutyrate administration provide neuroprotective effects in diverse neurologic disorders.[16,21–23] However, increased levels of ketone bodies are not always beneficial for neuronal metabolism, because very high levels of ketone bodies, such as in ketoacidosis, a dangerous complication that may occur in type 1 diabetes mellitus and alcoholism, can be toxic for the brain.[24,25]

In this review, we summarize recently reported evidence, from many viewpoints, on the beneficial roles of ketone bodies in diabetes-induced dementia. More studies are needed into the role of ketone bodies in various neurologic pathologies.

CURRENT STATUS OF KNOWLEDGE ON BRAIN ENERGY METABOLISM

Brain energy metabolism is different from systemic body energy metabolism and is affected by the endocrine regulation of appetite and reward.[26] The brain requires continuous provision of energy in the form of adenosine triphosphate (ATP), made by glucose oxidative reactions in mitochondria.[26] Glucose is used as the main fuel in the brain, and glucose uptake supports the survival of various brain cells, including brain endothelial cells, neuron, astrocytes, and microglia.[10,11] ATP, the main form of energy in brain metabolism, is used by ion channel kinases such as Na^+/K^+–ATPase and Ca^{2+}-ATPase,[27,28] and is the neurotransmitter produced from the mitochondria of neurons and glia through the tricarboxylic acid cycle.[29,30] Briefly, excitatory neurons consume approximately 85% of ATP in the brain, whereas inhibitory neurons consume approximately 15% of remaining ATP.[31,32] ATP produced from glucose metabolism contributes to synaptic transmission in neurons and glia, leading to a stable neural network.[32,33]
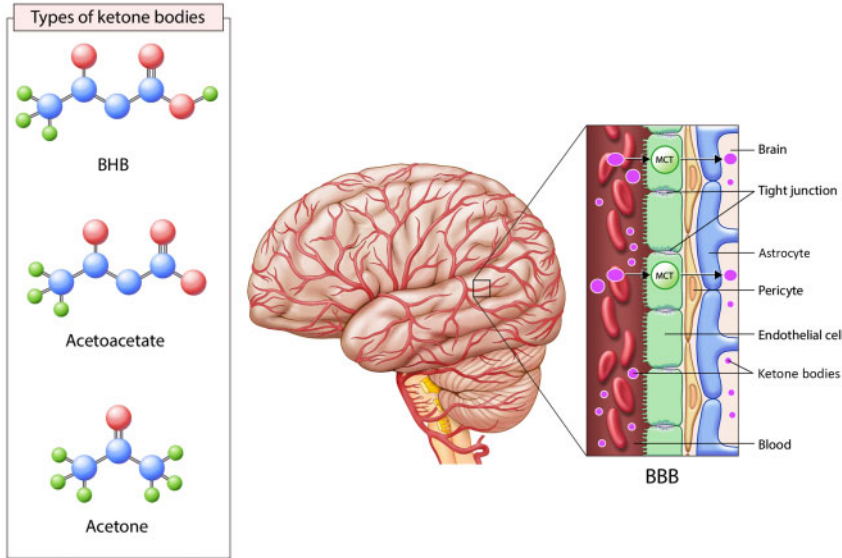
Recent studies demonstrated that impaired brain glucose metabolism leads to neurologic disorders, including Alzheimer's disease (AD), and Parkinson's disease.[31,34,35] Authors of previous studies have mentioned that γ-aminobutyric acid (GABA)ergic inhibitory interneurons are more sensitive to energy deprivation than are other neurons in brain regions related to memory function.[27,36] In 1 study, authors reported that the increase of glucose uptake in neurons by glucose transporter 1 promotes energy metabolism in cortical and hippocampal neurons and enhances memory function.[37] In the brain, poor glucose metabolism results in impaired ion transport, impaired vesicle recycling, and impaired synaptic plasticity.[36,38] Considering these previous findings, brain energy metabolism supplies nutrients and oxygen to neurons and glia and so contributes to brain function. Therefore, the regulation of brain energy metabolism may be a therapeutic issue to cure neurological pathology.

In the 1920s, the ketogenic diet (KD), a low-carbohydrate diet consisting initially of <20% of daily energy intake derived from carbohydrates, was developed to cure patients with epilepsy, and many researchers are continuing to gain pharmacological insights from it.[19] Ketone bodies generated in the liver provide an alternative energy source during a fasting and starving state.[39] In a starving state, fatty acid is converted to ketone bodies in astrocytes; subsequently, these ketone bodies enter a neuron to be used as a fuel (Figure 1[24] Achanta et al 2017).

Ketones known as β-hydroxybutyrate and acetoacetate (AcAc) are the major alternative fuels in the brain if blood glucose levels decrease due to food starvation[15,40] (Figures 1[24] Achanta et al 2017 and 2[14,41]). β-Hydroxybutyrate metabolism boosts ATP generation in comparison with glucose metabolism in the brain.[42]

Ketone bodies can cross the blood-brain barrier, and administration of a KD leads to increased concentration of the amino acid leucine in the brain[43] (Figure 1A[24] Achanta et al 2017). A KD also increases AcAc levels in the blood[44] and induces various cellular responses.[24] Ketone bodies are associated with diverse metabolic pathways, such as fatty acid β-oxidation, the tricarboxylic acid cycle, and gluconeogenesis,[45] and

A Ketone bodies cross BBB and enter brain

Types of ketone bodies

BHB

Acetoacetate

Acetone

Brain
Tight junction
Astrocyte
Pericyte
Endothelial cell
Ketone bodies
Blood

BBB

B Ketone body metabolism in neuron

Glucose ← Glycogen

Pyruvate

Fatty Acid

Ketone bodies

Acetoacetate

Acetyl-CoA

Ketone bodies (BHB)

GABA Glutamine ← Glutamine
Citrate
Oxaloacetate Glutamate Glutamate

α-Ketoglutarate

Malate

Succinate

Cerebral blood flow

Neuron Astrocyte Blood Vessel
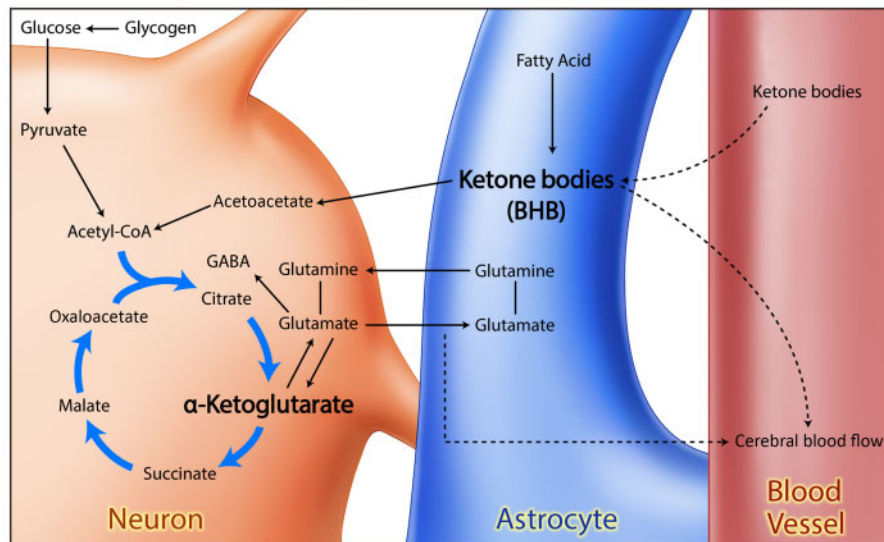
1. Brain energy metabolism and ketone body

Figure 1 **Brain energy metabolism and ketone bodies**. (A) Ketone bodies cross the BBB and enter the brain. There are several types of ketone bodies, including BHB, acetoacetate, and acetone. These ketone bodies could cross the BBB and subsequently enter the brain. (B) Ketone body metabolism in a neuron. After food ingestion, glucose changes into pyruvate, which, in turn, is metabolized to acetyl-coenzyme A, which circulates in the citric acid cycle. During fasting, fatty acids change into ketone bodies through *β*-oxidation. *α*-Ketoglutarate could change into glutamate, converting to glutamine and GABA neurotransmitters.[78] *Abbreviations*: BBB, blood-brain barrier; BHB, *β*-hydroxybutyrate; MCT, monocarboxylate transporter.

tend to be the critical energy fuel for extrahepatic tissues, such as brain, under several physiological conditions, including fasting, low-carbohydrate diets, hypoglycemia, and pregnancy.[14]

Ketone bodies in blood vessels enter neurons and are converted to AcAc, and they lead to GABA secretion in neurons through the citrate cycle (Figure 1B[24] Achanta et al 2017).

In the central nervous system (CNS), neurons can use ketone bodies as a fuel source, and this ketogenic metabolism in the brain is linked to cognitive function[46] as well as imbalanced glucose metabolism.[47] The ketone bodies AcAc and *β*-hydroxybutyrate are used as the main energy source in the brain during ketosis[48] (Figure 2[14,41]). Another study demonstrated that a KD has similar effects as calorie restriction in improving the

metabolic state in humans.[49] And in another study, researchers found that a KD enhanced neurovascular function against metabolic imbalance and promoted specific intestinal microbiota patterns.[50]

Authors of a positron emission tomography study reported that the absence of ketogenic intervention resulted in normal brain ketone uptake in mild AD.[51] Furthermore, KD results in a reduction in brain glucose uptake because ketone bodies are the favored fuel in the brain, compared with glucose.[52]

Ketone bodies from liver and blood could enter neurons and subsequently activate an increase in brain-derived neurotrophic factor production, which is involved in the improvement of mitochondrial biogenesis and synaptic plasticity (Figure 2[14,41]). Several studies have indicated that ketosis caused by a low-calorie diet enhances synaptic plasticity[53] and improves cognitive function.[54,55] Recent studies have also demonstrated that the administration of ketone bodies reduced neuronal cell damage, improved cognitive dysfunction and anxiety in an AD mouse model,[56] and protected against memory loss in patients with mild cognitive impairment[57,58] and AD.[44] Furthermore, in a recent clinical study, authors reported that brain ketone metabolism is involved in the severity of mild cognitive impairment and dementia, compared with healthy study subjects.[51] Ketone bodies have therapeutic effects in the treatment of neuropathology in diverse neurologic diseases, including epilepsy, AD,[59] Parkinson's disease,[60] autism,[40] brain tumor,[61] and stroke.[62]

Reviewing previous studies, we have identified the effects of ketone bodies in diabetes-induced dementia. In this review, we provide evidence on the potency of the KD for diabetes-induced dementia.

DIABETES-INDUCED DEMENTIA AND KETONE BODIES

Ketone bodies activate sirtuins in diabetes-induced dementia

Results of recent studies indicate impaired metabolic status, such as type 2 diabetes, aggravates learning and memory function[63] and is accompanied by severe neuroinflammation,[64] impaired synaptic plasticity,[65] increased toxic amyloid β (Aβ) aggregation, increased τ phosphorylation,[65] and abnormal mitochondrial
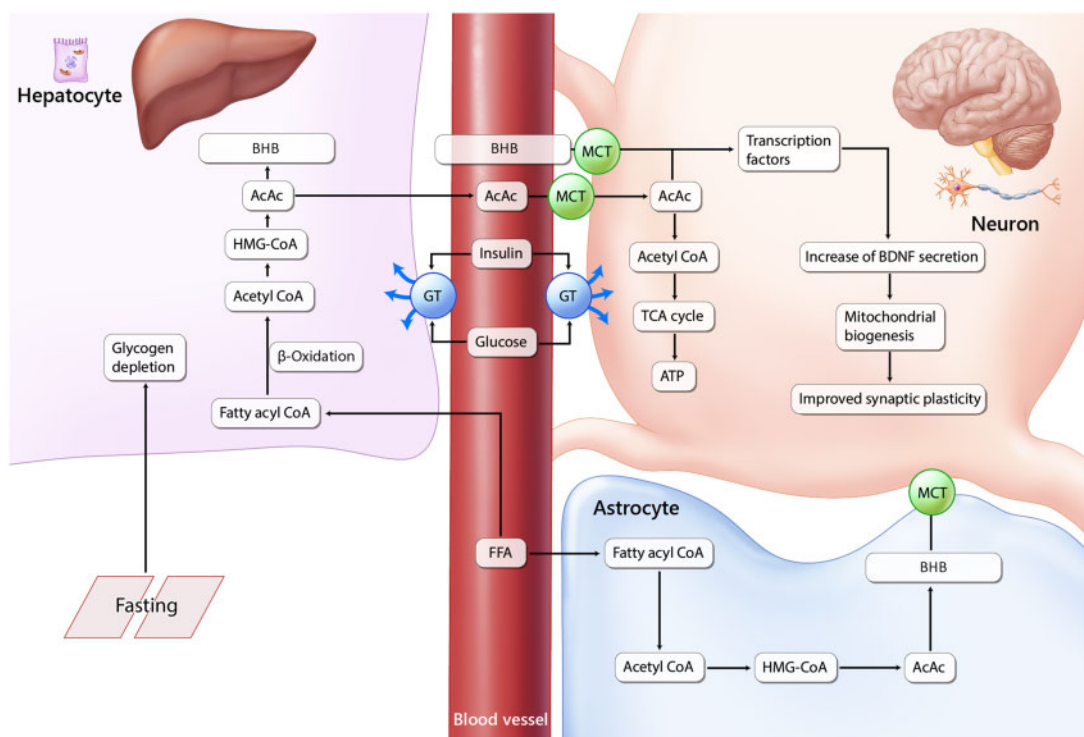
2. Ketone body in liver-brain axis

Figure 2 **Ketone bodies in liver-brain axis**. Ketone body BHB made by the liver could cross the blood-brain barrier (BBB) and contribute to the brain function. This liver-brain axis is the typical pathway of BHB and acetoacetate (AcAc) from liver and brain. During fasting, fatty acid changes into BHB through acetyl coenzyme-A. BHB and AcAc cross the BBB and enter neurons through an MCT channel. Next, BHB and AcAc contribute to the secretion of BDNF and the improvement of synapse plasticity.[14,41] *Abbreviations*: ATP, adenosine triphosphate; BHB, *β*-hydroxybutyrate; BDNF, brain-derived neurotrophic factor; CoA, coenzyme A; FFA, free fatty acid; GT, glucose transporter; HMG, 3-hydroxy-3-methylglutaryl; MCT, monocarboxylate transporter; TCA, the citric acid [cycle].

function.[66] These poor metabolic statuses damage neuronal cell function and boost rapid memory loss, ultimately triggering the onset of neurodegenerative diseases.[67]

Sirtuins (SIRTs) are NAD^+-dependent enzymes that affect multiple cellular responses such as energy metabolism, mitochondrial function, and the antioxidant redox pathway.[68] SIRTs mediate calorie restriction effects such as cell survival activation by regulating NAD^+ enzymes and through the 5′ AMP–activated protein kinase and mammalian target of rapamycin (mTOR) pathways.[69,70] SIRTs also could promote oxidative phosphorylation, deacetylation of transcription factors, anti-inflammatory responses, cell survival, and DNA repair, and inhibit glycolysis against oxidative stress.[71,72]

In particular, SIRT1 is required for cognition and the maintenance of neuronal plasticity,[73] and has been used for epilepsy.[74] SIRT6 and SIRT7 are strongly involved in DNA repair and antiaging responses.[75] SIRT3 and SIRT5 are major controllers of energy metabolism in mitochondria and regulate the acetylation and succinylation states of various energy enzymes.[76]

Ketones control the acetylation of proteins and increase histone deacetylation of the *SIRT1* gene in neurons[77] (Figure 3A[78]). The activation of the *SIRT1* gene caused by ketone bodies in the brain leads to the activation of uncoupling protein (UCP)2, UCP4, and UCP5 expression in the hippocampus[79,80] (Figure 3A[78]). Ultimately, the induced expression of UCPs by ketone bodies is linked to the activation of *SIRT1* in the brain.[81] SIRT1 results in increased insulin secretion through the repression of UCP2.[82] In addition, ketosis promotes macroautophagy through *SIRT1* activation in the cells.[83] Furthermore, the elevation of SIRT protein concentration by a KD reduces the production of reactive oxygen species (ROS) and DNA damage[84,85] caused by fasting, and activates mitochondrial function, and inhibits the activation of poly[ADP-ribose] polymerase 1 as a DNA damage index[86,87] caused by fasting (Figure 3A[78]). In the AD brain, SIRT3 attenuates the accumulation of Aβ and contributes to the improvement of neuronal hypometabolism.[88] SIRT3 is an important activator for oxidative phosphorylation[89] and promotes energy metabolism by increasing mitochondrial biogenesis.[90] The KD was found to exert neuroprotective effects by mediating SIRT3 in mouse model of stroke.[91] The KD could enhance SIRT3 activation and subsequently lead to the increase of ATP production in mitochondria[92] (Figure 3A[78]). Several studies have reported that a KD could induce *SIRT3* gene activation and subsequently protect neurons against brain damage.[91,93] Notably, *SIRT1* is strongly associated with cognitive performance[94] in metabolic-imbalance

conditions such as diabetes.[95] SIRT1 binds with deacetylated p53, inhibits the activation of the p53 pathway, and reduces the downstream target genes of p53[96] in the hippocampus[97] and cortex,[98] leading to memory dysfunction.

Moreover, SIRT1 regulates inflammatory pathway nuclear factor-$\kappa\beta$[99] and τ phosphorylation-related extracellular signal-regulated kinase signaling[100]; neuronal survival related to the forkhead box subgroup O pathway,[101]; energy metabolism–related peroxisome proliferator–activated receptor γ and its transcriptional coactivator PPARγ coactivator 1-α [102]; and neurite outgrowth involved in the mTOR/p70S6 kinase pathway[103] under normal and metabolic-imbalance conditions (Figure 3A[78]). These modulations of SIRT1 prove that it can ameliorate cognitive decline under metabolic-imbalance conditions.[104,105]

Several studies have demonstrated that SIRT1 increases the activation of glycogen synthesis kinase 3 β[98] and increases memory function, such as long-term potentiation, through glycogen synthesis kinase 3 β signaling.[106] In previous studies, researchers have mentioned that the inhibition of SIRT1 aggravates the progress of type 2 diabetes and insulin resistance.[107,108] Furthermore, SIRT1 promotes neurite outgrowth and improves insulin sensitivity in neurons through the PI3K/Akt signaling pathway.[109] In recent studies, authors have reported that SIRT1 and SIRT3 enhance mitochondrial dysfunction through the 5′ AMP–activated protein kinase–PPARγ coactivator 1-α pathway,[110,111] and ultimately improve cognitive dysfunction in a high-fat diet–induced metabolically imbalanced brain[66] (Figure 3A[78]). Some researchers have suggested that a KD reduces the activation of mTORC1 in the hippocampus by attenuating the phosphorylation of ribosomal protein S6.[112] The activation of SIRT1 by ketone bodies in neurons leads to the reduction of mTOR expression and reduces the activation of mTORC1 complex in neurons.[103]

To sum up, a KD could ameliorate cognitive decline in diabetes-induced dementia by activating *SIRT* genes, given that diabetes induces learning dysfunction and memory loss.[63]

Ketone bodies attenuate insulin resistance and oxidative stress in diabetes-induced dementia

In a recent study, researchers demonstrated that brain insulin resistance could damage hippocampal synaptic plasticity and decrease cognitive decline.[113] Insulin plays complex roles in the CNS, including feeding control, neurogenesis, neuronal survival, brain aging, and memory function.[114,115] Insulin receptors are expressed
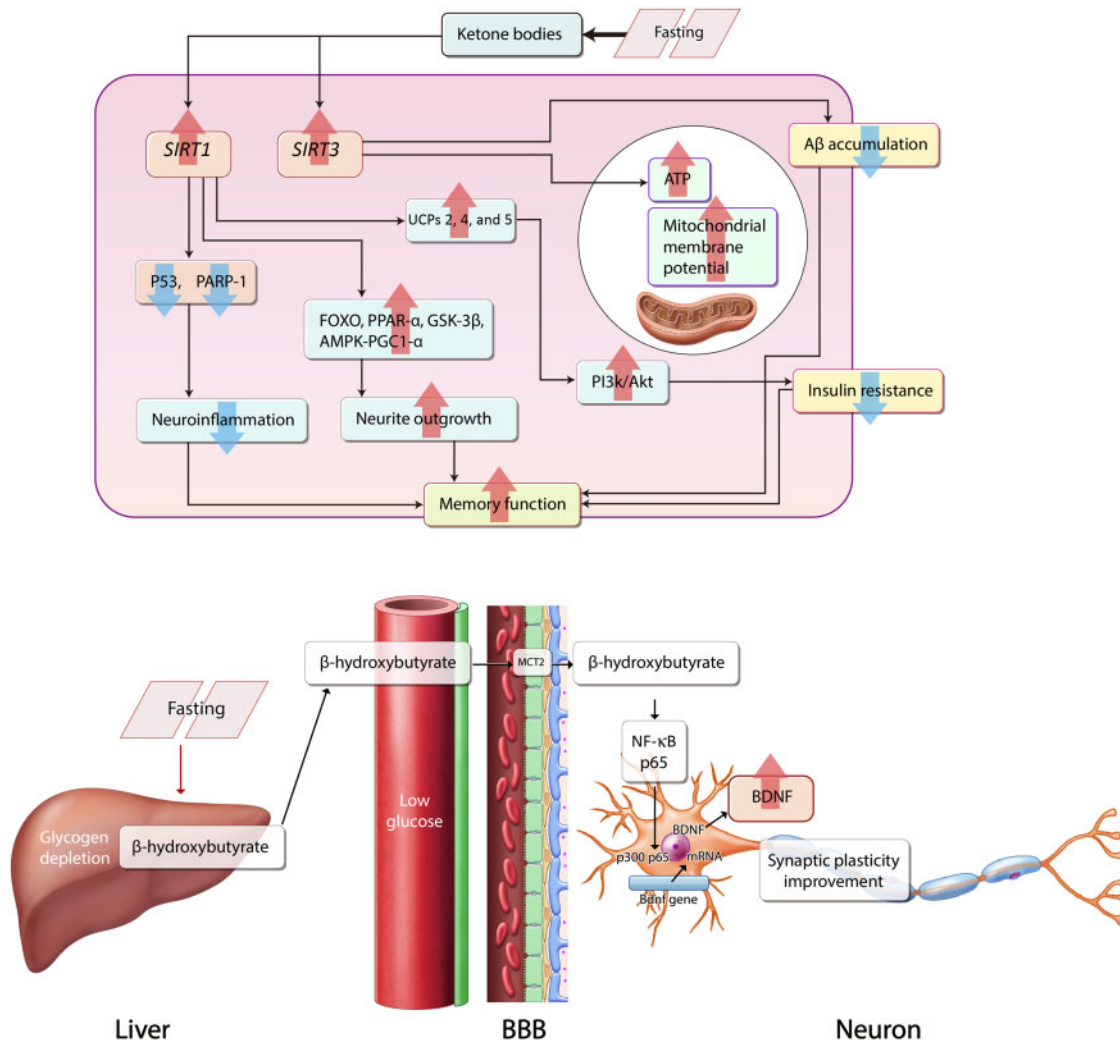
Figure 3 **Ketone bodies in a neuron**. (A) In a fasting state, ketone bodies increase SIRT1 activation, which reduces neuroinflammation through *P53* signaling and poly[ADP-ribose] polymerase 1 (PARP-1); increases FOXO, PPAR-α, GSK-2β, and AMPK-PGC1-α signaling; and UCP2, UCP4, and UCP5 activation, leading to the improvement of memory function. Also, ketone bodies activate SIRT3, which increases ATP production in mitochondria and reduces the accumulation of Aβ in the neuron, leading to the improvement of memory function. (B) *β*-Hydroxybutrate in hepatocyte cross the BBB and enter a neuron through MCT2. Subsequently, *β*-hydroxybutrate regulates NF-κB signaling and boosts the production of brain-derived neurotrophic factor in neuron, involving synaptic plasticity improvement.[78] *Abbreviations*: Aβ, amyloid *β*; ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; MCT2, human monocarboxylate transporter 2; UCP, uncoupling protein.

in memory function–related brain regions including the cortex and hippocampus.[116]

Insulin resistance is the impairment of insulin action and is found in diverse neurodegenerative diseases such as AD and Parkinson's disease and contributes to abnormal neural function, synaptic dysfunction, and cell death.[34,117,118] Many researchers have highlighted the importance of insulin resistance, because insulin resistance leads to metabolic syndromes such as diabetes and also triggers neurodegenerative diseases such as dementia.[119] Brain insulin resistance aggravated toxic Aβ

production and τ hyperphosphorylation in several studies.[120–123] Some authors reported that insulin administration could improve memory deficits in normal and AD mouse models.[124,125]

Ketogenesis is inhibited by insulin and stimulated by insulin deficiency.[126] Low levels of ketone bodies are linked to obesity and insulin-resistance status.[127,128] Some researchers demonstrated that ketone bodies could improve insulin sensitivity and so attenuate insulin resistance.[127–129] However, other in vitro studies showed that prolonged exposure to ketone bodies

altered insulin action, and thus ketone bodies could play a role in the development of insulin resistance.[130,131]

Clinically, the KD has already been used to treat insulin resistance in patients with type 2 diabetes.[132] Given that improvement of brain insulin resistance enhances memory function in the diabetic brain,[133] the modulation of ketone bodies may a good option for the treatment of diabetes-induced dementia by increasing brain insulin sensitivity. In addition, results of some studies suggested a KD reduces the generation of ROS[79,134] against oxidative stress and attenuates DNA methylation[135] involving antioxidant responses. Ketone bodies cross the blood-brain barrier by binding monocarboxylic acid transporters and enter neurons to reduce oxidative stress.[134,136] In 1 study, a KD decreased the secretion of proapoptotic mediators in an animal model of neurodegenerative disease.[137] Furthermore, previous studies have provided significant evidence that ketone bodies have neuroprotective effects against oxidative stress and metabolic-imbalance stress in brain cells.[134,138]

Collectively, ketone bodies could protect neuronal damage by inhibiting DNA breakdown, the apoptotic signal pathway, and the production of ROS in the brain of patients with diabetes, suggesting that diabetes-induced dementia is associated with neuronal damage, neuroinflammation, and excessive ROS production under oxidative stress conditions.[139,140]

Ketone bodies improve synaptic dysfunction and the imbalance of secretion of neurotransmitters in diabetes-induced dementia

Diabetes-related conditions such as hyperglycemia lead to a reduction in neurotransmitters, including GABA and glutamate, in the brain of animals with diabetes.[141] The abnormal reduction of cholinergic transmission was observed in STZ-induced diabetes in animal brain hippocampus in 1 study[142] as was a decrease in N-methyl D-aspartate receptors[143]; subsequently, the reduction of N-methyl D-aspartate receptors results in the decrease of long-term potentiation and postsynaptic density proteins.[143]

Dopamine is associated with cognition, feeding behavior, and emotion,[144] and dopamine receptors are decreased in the type 2 diabetes brain.[145,146] Serotonin, known as the 5-HT neurotransmitter, is associated with feeding behavior, sleep, and learning, and could regulate the secretion of insulin, neuronal cell regeneration, and synaptic plasticity.[147,148] In the brains of patients with type 2 diabetes and obesity, the activity of 5-HT signaling is commonly observed and triggers insulin resistance.[149] Glucagon-like peptide 1, a hormone

associated with glucose metabolism, improves neuronal cell survival, synaptic plasticity, and neurogenesis, and inhibits insulin resistance and neuroinflammation in the brain under oxidative stress.[150–154]

The KD invokes acidosis and ultimately contributes to changes in neurotransmitter receptors and ion channel opening.[155] Previous research has shown that a KD could increase the levels of the inhibitory neurotransmitter GABA[156] and the excitatory neurotransmitter glutamate[157] (Figure 1B[78] Marosi et al. 2016). In addition, a KD could result in a change in the level of monoamine neurotransmitters such as serotonin and dopamine,[158] which are related to depression and anxiety symptoms.[159] β-Hydroxybutyrate, a ketone body, could increase the level of brain-derived neurotrophic factor, which is involved in neuronal cell survival and antiapoptosis pathways[160] (Figures 2[14,41] and 3B[78]). Furthermore, a KD could boost the level of ATP and the activation of synaptic receptors.[161]

On the basis of this evidence, ketone bodies could regulate the secretion of neurotransmitters such as GABA, glutamate, serotonin, dopamine, and brain-derived neurotrophic factor involved in neurologic pathology.

Thus, a KD may be beneficial for improving the progress of neurologic pathology in diabetes-induced dementia through the modulation of neurotransmitter production.

Ketone bodies ameliorate mitochondrial dysfunction in diabetes-induced dementia

The mitochondrion is a central organelle for neurotransmission, synaptic plasticity, and energy homeostasis of neurons and glia.[162] Mitochondria take charge of the maintenance of cellular Ca^{2+} homeostasis, a required response in normal neuronal functioning.[163]

Excessive Ca^{2+} uptake into mitochondria occurs with the increase of ROS production and suppresses the synthesis of ATP, boosting the release of cytochrome c and increasing mitochondrial membrane potential.[164] Inappropriate mitochondrial permeability transition results in mitochondrial swelling and apoptosis of related proteins in mitochondria.[165] Mitochondrial dysfunction leads to impaired energy homeostasis and is highly correlated with the onset of neuronal degeneration.[166,167] Poor mitochondrial function is linked to neuronal death and neurodegenerative disease onset.[168] Metabolic imbalance conditions such as diabetes aggravate glucose use and lead to mitochondrial dysfunction, ultimately contributing to neuropathologic problems.[167,169] Suppression of energy production caused by mitochondrial dysfunction also damages insulin action in cells.[170] Cells of the CNS require a high amount of

ATP for neuronal transmission of electrical impulses; therefore, impaired mitochondrial function results in neurodegeneration and loss.[169] Previous studies have demonstrated that diabetes conditions lead to abnormal mitochondrial structure and elevated levels of oxidative phosphorylation, which are associated with high production of ROS.[171–173] Authors of other studies mentioned that mitochondrial dysfunction could result in a high level of interaction between Aβ and Aβ-binding dehydrogenase,[174,175] ultimately leading to cognitive impairment.[176] Impaired mitochondrial function was found both in diabetes and dementia in 1 study, and it also acted as a bridge regulator between diabetic pathology and neuropathology.[177] Considering these findings, diabetic conditions appear to lead to mitochondrial dysfunction in CNS cells and subsequently influence neuropathology, such as memory loss, in dementia.

A KD containing a high amount of fat and a low amount of carbohydrates has benefit in the treatment of neurologic diseases, including epilepsy.[178] β-Hydroxybutyrate can pass the blood-brain barrier through specific monocarboxylate transporters and move from the systemic circulation into the brain.[179,180] The KD and β-hydroxybutyrate boost mitochondrial density and mitochondrial function in neuronal processes in the hippocampus, the cognition-related region of the brain[17] (Figure 3A[78]). UCPs regulate the production of ROS and mitochondrial membrane potential in mitochondria, and some isoforms have a neuroprotective effect in CNS diseases.[181,182] The KD could increase the level of UCPs and ultimately attenuate secretion of ROS in hippocampal neurons[79] (Figure 3A[78]).

Furthermore, a KD regulates the deacetylation of various mitochondrial proteins, increases mitochondrial mass, and promotes mitochondrial function[76,91,183] (Figure 3A[78]). Mitochondrial biogenesis is affected by mitochondrial SIRTs[111] and PGC-1α.[110] A KD could ameliorate mitochondrial function under normal conditions as well as metabolically imbalanced conditions, such as increased free fatty acid levels and insulin resistance.[184–186]

In summary, on the basis of data from previous studies, a KD could enhance mitochondrial function in CNS cells, including the improvement of mitochondrial mass, density, and biogenesis, and the appropriate regulation of mitochondrial membrane potentiation. Thus, a KD may lead to improvements in cognitive function in diabetes-induced dementia.

Ketone bodies attenuate amyloid β aggregation in diabetes-induced dementia

Studies have focused on the relationship between the high risk of AD and diabetes pathologies.[119,187] Findings from 1 study suggested that diabetes leads to neuropathologic problems including severe Aβ toxicity,

as well as brain insulin resistance, mitochondrial dysfunction, and neuroinflammation.[188] In the brain, Aβ oligomers promote insulin resistance in hippocampal neurons in the diabetic brain, ultimately leading to memory loss.[189] Another study demonstrated that metabolic imbalance exacerbated AD pathogenesis, including memory deficit and neuroinflammation.[190] Administration of antidiabetic drugs resulted in the improvement of memory function in patients with AD and in a mouse model of AD.[191,192] In another study, high-fat diet–induced diabetic conditions increased Aβ deposition in APP/PS1xdb/db mice, compared with APP/PS1 knockout mice.[193] β-Hydroxybutyrate attenuates Aβ toxicity in SH-SY5Y neuronal cells through the inhibition of histone deacetylase.[194] In 1 study, researchers suggested that β-hydroxybutyrate could be considered an endogenous histone deacetylase inhibitor.[195] Researchers identified that ketone body administration could reduce toxic Aβ deposition and improve memory function in an APP swe/PS1dE9 transgenic AD mouse model.[20] In addition, β-hydroxybutyrate could upregulate the expression of tropomyosin receptor kinase A, affecting neuroprotective pathways and cholinergic neuronal function.[194,196] In some studies, authors reported that a KD inhibited the accumulation and total level of Aβ[197] and also inhibited the entrance of Aβ from the peripheral circulation system into the brain, resulting in improved cognitive function[20] (Figure 3A[78]).

Considering these findings, ketone bodies could attenuate toxic Aβ deposition and reduce the entrance of Aβ into the brain, ultimately contributing to the improvement of cognitive function.

CONCLUSIONS

Herein, we summarized recently reported evidence regarding the neuronal protective effects of ketone bodies in diabetes-induced dementia. Positive roles of ketone bodies include activating SIRTs in neurons associated with neuronal cell survival signaling, promoting insulin sensitivity, and protecting neuronal cells against oxidative stress damage. Moreover, ketone bodies ameliorate normal neurotransmitter secretion and enhance synaptic function. Ketone bodies also promote mitochondrial biogenesis and membrane potential. Furthermore, ketone bodies suppress toxic Aβ deposition in the brain. Given these findings, ketone bodies could improve neuropathogenesis such as memory decline in diabetes-induced dementia.

Taken together, this review on the neuroprotective properties of ketone bodies at low levels may provide useful information for establishing the appropriate clinical approach for use of a KD for diabetes-induced

dementia. More studies are needed to elucidate the exact mechanisms of the neuroprotective role of ketone bodies at low levels, which reverse to neurotoxic at high levels, and to understand the roles and specific modulation pathway of ketone bodies for the treatment of diabetes-induced dementia.

Acknowledgments

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