Review

An insight into the importance of B vitamins and melatonin in the prevention of diabetes through modulation of the brain energy metabolism- a comprehensive review

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Running title: Melatonin and B-vitamins in brain metabolism and diabetes

Received: March 31, 2023; Accepted: September 22, 2023

ABSTRACT

Energy metabolism is the biochemical pathway of converting macronutrients (carbohydrates, protein, and fat) to cellular energy for the maintenance of cell homeostasis. The brain is an organ that consumes unproportional energy compared to its size. Glucose (glycogen, in storage form of glucose) is the principal source of brain energy. Impairment in brain energy metabolism results in neuronal loss and subsequent neurodegenerative diseases including AD, PD, amyotrophic lateral sclerosis, Huntington's disease, etc. However, metabolic disorders such as chronic hyperglycemia, and insulin resistance are also linked with neuronal activity. Dysregulation in neuronal transmission is associated with oxidative stress and brain insulin resistance. Diabetes *mellitus* jeopardizes brain function through various mechanisms including glucose toxicity, BBB damage, neuroinflammation, and gliosis. B vitamins as antioxidants and neuroprotective agents, can improve brain glucose metabolism. Melatonin is a potent free radical scavenger and it can also modulate cellular cytokine levels and prevent insulin resistance. The neuroprotective and antihyperglycemic effects of melatonin improve the brain's antioxidant defense system, decrease brain NOS activity, and prevent glucose toxicity. Hence this review suggests a therapeutic use of a combination of melatonin and B vitamins to improve brain functioning disrupted by diabetes.

Key words: Brain, energy metabolism, glucose toxicity, diabetes, B vitamins, melatonin

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1. INTRODUCTION

Metabolism is a biochemical process of converting nutrients (carbohydrates, fatty acids, and amino acids) to energy on a cellular level, involving several enzyme-dependent pathways essential for maintaining energy homeostasis and macromolecular synthesis in humans (1). The mammalian brain depends on glucose as its principal source of energy. The brain consumes 25% of the body's energy for the restoration of the membrane gradient potential, intracellular

signaling, neurotransmitter recovery, and dendritic-axonal transport (2). Adult brain neurons have the major energy requirement (3) and thus need a continuous supply of blood glucose. The production of ATP by glucose metabolism powers brain function (4). On the other hand, glycogen is the storage form of glucose in the brain, mainly located in astrocytes (5). Glucose is partially metabolized to lactate in astrocytes, which is then released into the extracellular environment and acquired by neurons (6). Other brain cells, such as glial and ependymal cells, require high energy to carry out their specific functions through glycolysis and activating glycogenolysis (5). Thus, the continuous circulation of glucose and oxygen to brain cells is necessary for brain metabolism (6). In specific conditions, such as starvation and diabetes, scarcity of carbohydrates leads to increased ketone body (acetoacetic acid, β-hydroxybutyric acid, and acetone) production, brain can tolerate ketone body as an alternative energy source (7). Interruption in energy metabolism will result in impaired neuronal transmission followed by neuronal loss. The dysregulation of neuronal transmission is often associated with oxidative stress (8). Neurons communicate among different regions of the brain and the peripheral nervous system via electrical impulses and chemical signals. Therefore, metabolic impairment in neurons lead to different neurodegenerative disorders, including Alzheimer's disease (AD) (9), Huntington's disease (10), amyotrophic lateral sclerosis, and Parkinson's disease (11).

Moreover, metabolic disorders such as chronic hyperglycemia, microvascular complications, and insulin resistance also influence brain function (12–14). Numerous animal diabetic models indicate that glucose toxicity and resistant insulin signaling deteriorate brain functioning by modulating energy metabolism, synaptic plasticity, learning, and memory function resulting in poor cognitive behaviour, AD, and vascular dementia (12, 15). Oxidative stress in the peripheral tissues is responsible to induce insulin resistance (16). The brain is very susceptible to oxidative damage because of the high oxygen consumption rate, high lipid content, and a relative deficiency in antioxidant enzymes compared to other tissues. Reactive oxygen species (ROS) play a role in many neurodegenerative diseases, including diabetes, because neuronal cells are particularly vulnerable to oxidative assaults (17, 18). Diabetes affects brain function through various pathways, including glucose toxicity, BBB impairments, vascular damage, mitochondrial dysfunction, oxidative stress, brain insulin resistance, synaptic failure, neuroinflammation, and gliosis (19). The long-term effects of diabetes on the brain are manifested at the structural, neurophysiological, and neuropsychological levels (20).

Potent antioxidants in the diet may prevent diabetes-induced brain impairment and cellular oxidative damage. Vitamins and melatonin can both prevent oxidative stress and maintain redox equilibrium (21). Tan *et al*. (22) referred melatonin as an antioxidant vitamin. In spite of being generated endogenously, a substantial level of melatonin is present in foodstuffs including rice, wheat, seeds, fruits and vegetables. The bioavailability of dietary melatonin is also high. Melatonin and vitamins both are derived from plants but also frequently obtained from consumption of animal products of meat, dairy and eggs.

Vitamins are classic antioxidants prone to a deficit in infants and older adults. Prolonged deficiency of these micronutrients leads to malnutrition and several health complications (23). Among all, the B vitamins are a family of eight water-soluble vitamins acting as co-enzymes in diverse catabolic and anabolic reactions, that are critically related to cellular activities. Their cumulative impacts are particularly pervasive in many aspects of brain function, including energy production, DNA/RNA synthesis/repair, genomic and non-genomic methylation, and the production of several neurochemicals and signalling molecules (24). The B vitamins are synthesized in plants' chloroplast, mitochondria, and cytosol, except for vitamin B_{12}, which is synthesized by bacteria (25). B vitamins along with their other roles in general metabolic function have a great impact on brain function as they perform potential action in homocysteine metabolism. Increased levels of homocysteine in plasma are considered a predisposing factor to cardiovascular disease (26), AD and other dementias (27). Deficiencies in the key vitamins

involved in the conversion of homocysteine to methionine including folate, vitamin $B_{6,}$ and vitamin B_{12} are implicated as the underlying cause of developing neurodegenerative diseases (28).

Melatonin (N-acetyl-5-methoxytryptamine), an indoleamine, is synthesized in the pinealocyte from tryptophan and released into the peripheral system and cerebrospinal fluid (CSF) (29). Melatonin exerts its effect in both centrally and peripherally, and the binding sites of melatonin are present in different areas of the brain, including the hypothalamus, pars tuberalis, as well as in the immune cells, gonads, kidneys, and heart (29). Melatonin has both receptor-mediated and non-receptor-mediated actions. The non-receptor-mediated action explicates melatonin's amphipathic properties, meaning it can easily cross the cell and nuclear membrane of the brain and other body tissues (30). The antioxidant function of melatonin against the different models of oxidative stress is also receptor-independent action (31). Therefore, the blood-brain barrier (BBB) is easily crossed by melatonin due to its amphiphilicity (32). Then, the choroid plexus enables it to permeate the central nervous system (CNS) and cerebrospinal fluid (CSF) (33). Various regions of the CNS, including the cerebellum, olfactory bulb, prefrontal cortex, hippocampus, and striatum, express the rate-limiting enzyme of melatonin biosynthesis, that is arylalkylamine N-acetyltransferase (AANAT) (34, 35). In the CNS, melatonin degrades into N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), which is then deformylated to N^1-acetyl-5-methoxykynuramine (AMK) (36). AFMK and AMK still have cell-protective activity, including protective effects in mitochondria (37). Many studies have documented the potent antioxidant, anti-inflammatory, and neuroprotective effects of melatonin (38), and its analgesic actions in the peripheral neurodegenerative disorders (39). It reduces hyperglycemia by protecting the β cells of the pancreas (40). In this review, we summarize the action of melatonin and the B vitamins in the prevention of the impaired brain metabolism caused by hyperglycemia.

2. BRAIN AND ITS METABOLISM

Brain uses glucose as the main source of energy supply. In humans, brain only 2% of body weight, but consuming 20% of the total energy obtained from glucose (5.6 mg of glucose per 100 g of human brain tissue every minute) (41). The blood glucose can cross the BBB through its specific carrier and be stored as glycogen (6). Major brain operations like learning and memory consolidation depend critically on brain glycogen metabolism (42). Therefore, brain glycogen has been regarded as an emergency glucose reserve (43). In addition, during period of stress like hypoglycemia and ischemia, astrocyte and neurons are vitally dependent on glycogen storage with the process of glycogenolysis to provide glucose (44–46).

2.1. The overview of glucose metabolic pathways in the brain.

Glycogen synthesis and breakdown are intricate processes involving multiple enzymes and are precisely regulated by phosphorylation and dephosphorylation (47). Three enzymes located in the brain are critically involved in glycogen metabolisms, such as glycogen synthase (GS), glycogen phosphorylase (GP), and phosphorylase kinase (PK) (48). The brain isoform of GP is present in astrocytes and other cells, including choroid plexus and ependymal cells (49). GS is expressed in the hippocampus, cerebellum, and olfactory bulbs (24). When the blood glucose is too low, the brain glycogen reserve is metabolised into glucose to fulfil its physiological requirement (50). The glycogenolysis involves three specific enzymes: glucosyltransferase, glucosidase, and glycogen-debranching enzyme (GDE). These enzymes, namely PK, GP, and GDE, play a crucial role in hydrolyzing α-1,6-glycosidic branch point bonds to release glucose

(51). However, the metabolic fate of brain glucose depends upon the cell type and glycolytic enzymes present in the astrocyte. In addition to generate ATP, glucose is crucial for fatty acid, amino acid, and neurotransmitter generation. In neurons, glucose is metabolized through several pathways, including glycolysis, PPP, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (52). The glycolytic pathway converts glucose to pyruvate, which is then transported into mitochondria to generate acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is used to form NADH and $FADH_2$, The energy carried by these reduced agents finally used for ATP production in the mitochondria (Figure 1).

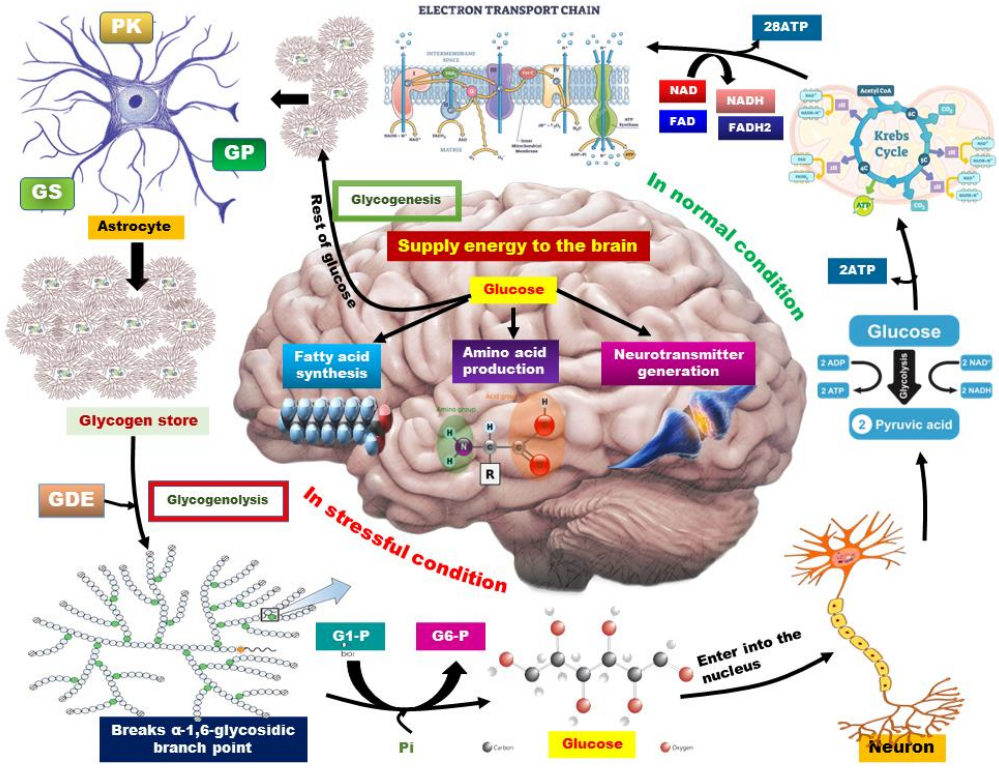

Fig. 1. The process of glucose metabolism in the brain.

This graphical abstract represents that in stressed condition the brain glycogen storage has been broken down in the astrocytes and undergoes into the process of glycogenolysis to produce glucose. Whereas in normal condition, the brain glucose is used for the production of fatty acid, amino acid and neurotransmitters as well as enters into the neurons where it is used as energy source by entering into the glycolysis, Krebs cycle and ETC chain and then stored as glycogen in astrocytes through the process of glycogenesis. The left side signifies the stressed condition whereas right side as normal condition.

GS: glycogen synthase, GP: glycogen phosphorylase, PK: phosphorylase kinase, GDE: glycogen-debranching enzyme, G1P: glucose-1-phosphate, G6P: glucose-6-phosphate, ATP-adenosine-tri-phosphate, NAD: nicotinamide-adenine-dinucleotide (oxidized), NADH: nicotinamide-adenine-dinucleotide (reduced), FAD: flavin-adenine-dinucleotide (oxidized), $FADH_2$- Flavin-Adenine-Dinucleotide (reduced).

2.2. Glucose transporters in the brain.

To perform normal cellular activities brain needs a continuous supply of glucose across the cell membrane of microvascular endothelial cells to reach neurons and glial cells. However, the cell membrane limits the passive diffusion of glucose and other nutrients in and out of

cells. Instead, the movements of glucose depend on a particular saturable transport process of two distinct classes of glucose transporters including glucose transporters (facilitated transport; GLUT) and sodium-dependent glucose transporters (secondary active transport; SGLT), each with a unique set of kinetic properties to transfer glucose across the cell membranes and tissue barriers. The majority of cells express a wide range of glucose transporters, and the pattern of expression in various organs is correlated with particular metabolic demands (Table1) (53). GLUT family proteins transfer glucose bidirectionally along a concentration gradient. The isoforms of GLUTs have different glucose affinity, indicating adaption to the different metabolic needs of each cell (54). A high molecular weight isoform of GLUT-1 (55 kDa) is mainly responsible to transport glucose from the blood to cells. GLUT3 and GLUT-8 are mainly found in neurons with apparently balanced distribution (55). On the other hand, GLUT-5 is highly expressed in microglial cells, and its inefficiency leads to a significantly poor supply of glucose to the brain. GLUT-4 is insulin dependent glucose transporter (56). In hypothalamic nuclei, neuronal expression of GLUT2 and GLUT4 has been documented to implicate the central regulation of glucose homeostasis, food intake, and/or energy balance. Apart from the GLUT1-5 transporters, several other cloned isoforms are present, including GLUT-x1 (also called GLUT-8), GLUT-9 (recently called GLUT-6), GLUT-10, GLUT-11, and GLUT-12 (57). GLUT-8 is a hormonally regulated transporter susceptible to diabetes and stress (58). On the other hand, SGLTs transport glucose and galactose along a concentration gradient while also transporting Na^+ ions (59). Under hypoglycemia and hypoxemic circumstances, SGLT1, which is ubiquitously expressed in neurons, may play a crucial role in glucose metabolism (60). However, alterations in the expression of the BBB glucose transporter cause the onset of diabetes (61, 62). The GLUT isoforms and their activities in neuronal system have been summarized in the table 1.

Table 1. Summary of GLUT and SLT isoforms in brain.

Type	Gene	Site expressed in the brain	Substrate/transporters
Facilitative/sodium independent	GLUT1	Brain endothelial and epithelial-like brain barriers, glial cells, blood-tissue barriers, and peripheral nerves.	Glucose, galactose, mannose, glucosamine, ascorbic acid
	GLUT2	Astrocytes	Mannose, galactose, fructose, glucose, glucosamine
	GLUT3	Neurons, brain endothelial cells	Glucose, galactose, mannose, xylose, dehydroascorbic acid
	GLUT4	Hippocampal neurons, cerebellar neurons	Glucose, dehydroascorbic acid, glucosamine
	GLUT5	Brain microglia	Fructose
	GLUT6	Brain, peripheral	Glucose
	GLUT8 (Insulin-responsive)	Neurons	Glucose
	GLUT10	Brain	Glucose and galactose
Sodium-Glucose Co-transporter/Sodium-dependent	SGLT1	Brain (cortical, pyramidal, and Purkinje neuronal cells)	Glucose, galactose, water
	SGLT2 SGLT3 SGLT4	brain	Glucose, galactose mannose, fructose
	SGLT6	Brain (neurons)	Myo-inositol, glucose

2.3. Brain glucose intolerance in hyperglycemia.

The glucose neurotoxicity in diabetes is associated with cellular dysfunction through the following mechanisms i) increased polyol pathway flux, ii) elevation of advanced glycation end products formation, iii) activation of protein kinase C (PKC) and iv) increased hexosamine pathway flux (63). Since the glucose content in the plasma is five folds higher than that in the brain (64, 65), the endothelial cells are more prone to develop hyperglycemia than the brain parenchymal cells (66). Impairment in cerebral vasculature leads to disruption in the blood-brain barrier in diabetes, aging, and neurodegenerative diseases as well (66). The level of cognitive impairment and the progression of AD is strongly correlated with the decline in cerebral glucose metabolism, which reflects the severity of synaptic malfunction and neurodegeneration (67). It has been suggested that disturbed cerebral glucose metabolism causes oxidative stress, inflammation, mitochondrial malfunction, autophagy impairment, excitotoxicity, and apoptosis, which in turn causes Aβ deposition and tau hyperphosphorylation (68).

Insulin resistance, seen in T2DM is associated with an increased risk of dementia and may be attributed to poor insulin signalling in neurons (12). Although brain glucose transport is not insulin-dependent, however in certain subcellular compartments it is controlled by insulin (19). Insulin signalling has been found mostly in neurons and astrocytes that may regulate glycogen metabolism (69). During low fuel supply, brain glycogen is rapidly mobilized for supporting glutamatergic neurotransmission (70, 71). Brain glucose utilization is diminished with the age or with the progression of AD (72). Willette *et al*. (73) reported that peripheral insulin resistance is correlated with decreased glucose metabolism in AD subjects. Insulin is important in the specific areas of the brain including the hypothalamus which is the main regulatory part of the body's energy homeostasis (74). While mitochondria are the energy generating centre, their dysfunction directly associates with neurodegenerative disorders (75). Mitochondrial dynamics, biogenesis or mitophagy in neurons and astrocytes are also regulated by insulin (76). Thus, the loss of insulin-mediated regulation of mitochondrial metabolism may lead to a reduction in the energy supply to neurons and astrocytes (19).

Additionally, mitochondria also contribute to the breakdown of synapses through various factors including impaired ATP synthesis, Ca^{2+} signalling, elevated ROS, imbalanced metabolites (precursors of neurotransmitters) etc. that causes irregular mitochondrial dynamics, and mitochondria-dependent cell signalling transduction (77). Oxidative metabolism in astrocytic mitochondria and excitatory glutamatergic neurotransmission are tightly coupled (78), which is essential for memory and brain function (79). Notably, astrocytes also serve as the brain's primary glycogen source, which is almost absent in neurons (80). Likewise, lactate produced by astrocyte glycogenosis and glycolysis has been implied for maintaining memory and brain function (79). In the hippocampus, insulin resistance is linked to abnormalities in astrocytic glycogen metabolism which may cause synaptic dysfunction associated with diabetes (81). This indicates that central insulin signalling impairment is an important factor for diabetes-induced brain injury (19). Interestingly, insulin also regulates the gene expression of memory function via the mitogen-activated protein kinase (MAPK) pathway (12, 82). Insulin also participates in regulating the key mediator of cellular activity i.e. AMP-activated protein kinase (AMPK) which might afford neuroprotection through metabolic controls (83). The brain metabolism and its relation to diabetes have illustrated in the Figure 2.

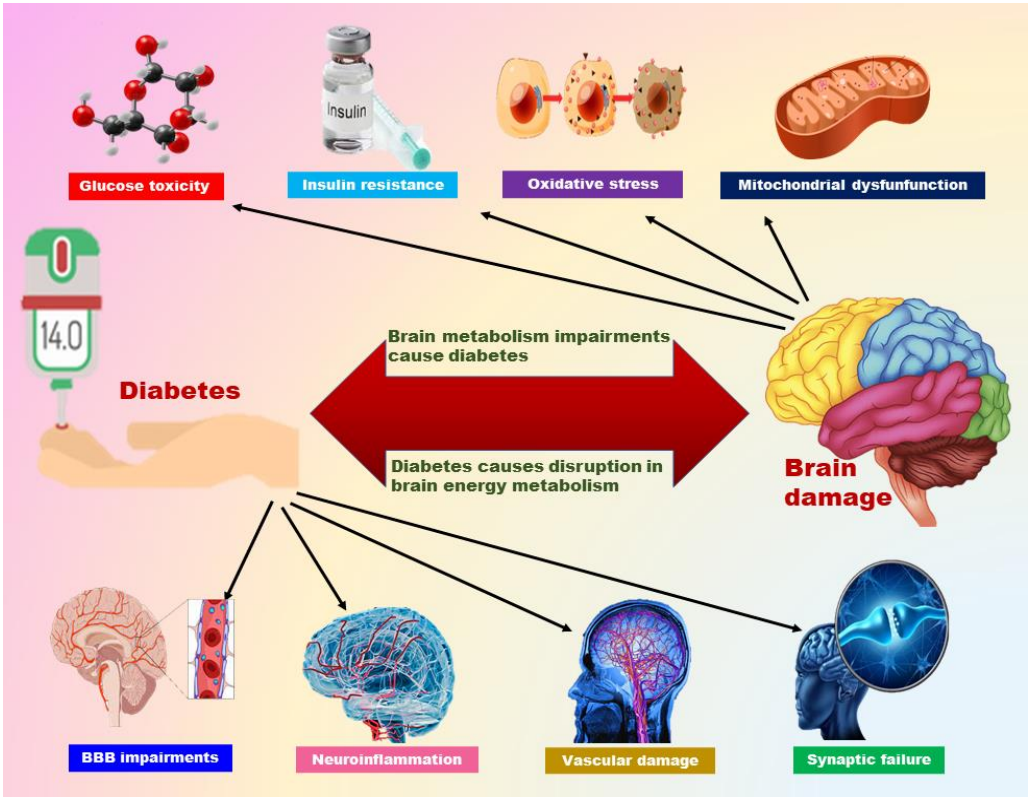

Fig. 2. Potential relationship between brain energy metabolism and diabetes.

This graphical abstract represents that both the brain damage and diabetes are associated with each other. As brain damage causes the glucose toxicity, insulin resistance, oxidative stress, mitochondrial dysfunction, it finally results in the progression of diabetes. On the other hand, diabetes also induces brain damage by causing the BBB impairment, neuroinflammation, vascular damage and synaptic failure. BBB: blood brain barrier.

3. IMPORTANCE OF B VITAMINS IN BRAIN ENERGY METABOLISM AND DIABETES

The B vitamins serve as cofactors are necessary for the synthesis of neurotransmitters and myelination of the spinal cord therefore, enable the CNS to function properly (84–86). B vitamins can cross the BBB and/or choroid plexus by the active transport mechanism. After cellular uptake, all B vitamins with a turnover rate ranging from 8% to 100% per day, remain in high concentration in the brain. For example methyltetrahydrofolate (the active form of folate) is four times higher in the brain than that in plasma whilst biotin and pantothenic acid levels in the brain are 50% higher than that in plasma (87–89).

3.1. Thiamine (Vitamin B_1).

Thiamine is converted to thiamine pyrophosphate (TPP) with the action of thiamine pyrophosphokinase. TPP acts as a cofactor of several enzymes required in brain glucose metabolism including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. TPP undergoes further phosphorylation to form thiamine triphosphate (TTP) or dephosphorylated to thiamine monophosphate (TMP) and thiamine diphosphate (TDP). Thiamine phosphorylation and dephosphorylation processes in the brain indicate the cellular

localization of thiamine metabolizing enzymes as well as the phosphate esters themselves (90). Thiamine phosphorylated derivatives present in higher concentrations in neurons than in other brain cells (90). Previous reports have shown that clinical findings of AD are mostly related to significant loss of neurons with the concomitant decrease of thiamine metabolites (91, 92). Wernicke's Encephalopathy (WE), a thiamine deficiency disorder is characterized by lowering the concentration of TPP and its dependent enzymes. It has been proclaimed that severe neuropathological damage is associated with WE including neuronal disintegration, mild endothelial swelling, sparing and destruction of neutrophils (93), and brain cell death (94). Potential reasons encompass impaired cerebral energy metabolism and localized lactate build-up, both of which may be triggered by diminished α-KGDH activity, and excessive release of excitotoxic amino acids (94). Thiamine levels were found to be 15% lower in red blood cells of diabetic patients than normal subjects (95). Alterations in erythrocyte transketolase activity have been linked to thiamine depletion in both type 1 and type 2 diabetes, however, the percentage of affected people varies among studies, ranging from 17% to 79% (96). It has also been demonstrated that insulin-deficient rats exhibit a substantial reduction in the transfer of free thiamine and TMP but a concomitant rise in TDP levels. Insulin deficit is associated with a reduction in the rate of thiamine transport across the colon (97). Thiamine deficiency results in a substantial decrease in insulin production and secretion (98). As a result, insulin deficit may increase thiamine deficiency and vice versa (99). Studies have been proposed on the relationship between vitamin B1 and DM. Watson *et al*. (100) reported that 36-47% of the population suffered from thiamine-deficient hyperglycemia. Low plasma thiamine level was observed in type 1 DM. Additionally, it has been also reported that plasma thiamine levels decreased by 76% in type 1 and 75% in type 2 diabetic patients related to increased renal clearance of thiamine (101).

3.2. Riboflavin (Vitamin B_2).

The two flavoprotein-dependent co-factors flavin adenine mononucleotide (FMN) and flavin adenine dinucleotide (FAD) catalyse several important enzymatic pathways. They primarily involve in the synthesis and conversion of other vitamins such as niacin, folate, and vitamin B6 as well as the synthesis of all heme proteins including hemoglobin, nitric oxide synthase, P450 enzymes, and proteins in the redox cycle. FAD and FMN also act as co-factors in the brain's lipid metabolism (102). The role of riboflavin in the glutathione redox cycle is considered as its indirect antioxidative action. Alam *et al*. (103) have reported that riboflavin reduces fasting blood glucose level in a dose-dependent manner while increases calcium and GLUT-4 expression as calcium is required for insulin secretion. Function as the antioxidant, riboflavin preserves mitochondrial function, improves many neurological conditions including AD, PD, and multiple sclerosis (MS) (104). Recent studies have elucidated that riboflavin prevents oxidative stress-mediated damage in the AD brain via modularization of the Nrf2 pathway (105). Since autoimmune responses are directly linked to T1DM and T2DM, riboflavin as a potential antioxidant and immunomodulatory agent might be beneficial against diabetes-induced neurological disorders (106).

3.3. Niacin (Vitamin B_3).

A plethora of enzymes involved in brain metabolism is dependent on niacin derivatives such as nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). NAD+ is a crucial coenzyme for the processes of glycolysis, the TCA cycle, and the conversion of carbohydrates to lipids (107). Beyond energy production niacin also acts as an antioxidant vitamin required for the conversion of folate to tetrahydrofolate derivative. Niacin deficiency causes several

neurodegenerative disease-related symptoms such as dementia, and depression (108). Niacin has been widely recognized as a critical regulator of neuronal survival and development in the CNS (108). Nicotinamide can be converted to NAD by specific enzymes or methylated by nicotinamide-N-methyl transferase (NNMT) to N_1-methyl nicotinamide (108). Impairment in the function of NNMT hinders methylation of NA that compromised the availability of free NAD+, which ultimately has an impact on the activities of NAD+-consuming enzymes. NNMT plays important role in brain energy metabolism and the development of many disorders, such as obesity, diabetes, aging, Parkinson's disease, and cancer (109) because methylated nicotinamide could not be further converted into NAD+. The interaction between nicotinamide methylation and NAD+ regeneration indicates that NNMT may increase fat accumulation and limit fuel oxidation. In the event of elevated NNMT expression, the availability of nicotinamide may be compromised, hence impeding the functionality of NAD^+-dependent activities (110). Moreover, NNMT gene is significantly associated with regulating glucose metabolism. The downregulation of NNMT reduces the insulin level and improves glucose tolerance. Hong *et al*. (111) have reported that reduced NNMT expression in primary hepatocytes lowers glucose synthesis, expression of glucose-6-phosphatase catalytic (G6pc), and phosphoenolpyruvate carboxykinase 1 cytosolic (Pck1) while over expression of NNMT leads to increased glucose production and elevated G6pc and Pck1 expression levels. On the other hand, NNMT knockdown mice exhibited decreased fasting glucose and reduced conversion of pyruvate to glucose. All indicate NNMT involves in gluconeogenesis. In stressful conditions, nicotinamide promotes neuronal survival via multiple mechanisms including i. inhibition of cytochrome c release, ii. prevention of caspase 3 and caspase 9, iii. suppressing the degradation of FOXO3a, iv. maintenance of protein kinase B-dependent phosphorylation of FOXO3a (112). However, few studies have been done on the effect of niacin in diabetes, but niacin administration has been found to elevate high-density lipoprotein (HDL) cholesterol, lowering triglyceride and low-density lipoprotein (LDL) cholesterol (113). These modifications in lipid metabolism possess a role in diabetes-induced atherosclerosis and cell adhesion molecules (CAM) that have been observed in atherogenesis (114). Studies have depicted that niacin supplementation prevents monocyte adhesion to endothelial cells in diabetic individuals (114).

3.4. Pyridoxine (Vitamin B_6).

Apart from its role in the folate cycle vitamin B_6 is essential for neurotransmitter synthesis and amino acid metabolism. The biosynthesis of dopamine, serotonin, γ aminobutyric acid (GABA), adrenaline, and melatonin requires vitamin B_6 as a co-factor. The melatonin biosynthesis route involves the enzymatic activity of aromatic amino acid decarboxylase, which involves the presence of pyridoxal-5-phosphate (PLP) as a co-factor (115). A mild deficiency of vitamin B_6 can negatively affect GABA and serotonin synthesis which in turn inhibits the neural activity of GABA and promote disordered sleep and behaviour, loss of cardiovascular function, and impaired hypothalamus pituitary control of hormone secretion (24). Vitamin B_6 also regulates glucose metabolism in the brain (116). The association between low plasma PLP and diabetes was first reported by Lekem and Hollenbeck (117). Substantial evidences correlates low plasma PLP and the occurrence of diabetes (118, 119) and reduced PLP level was observed in gestational diabetes *mellitus* (GDM) (117). Similar results were also found by Spellacy *et al.* who described pyridoxine therapy attenuates glucose intolerance and maintains insulin levels in gestational diabetic women (120). The underlying mechanism lies in the involvement of vitamin B_6 in the kynuramine pathway. Impaired tryptophan metabolism is observed in different forms of diabetes associated with pregnancy, oral contraceptives, and emotional and metabolic stress decreasing the bioavailability of PLP (121, 122). Xanthurenic acid excretion is increased in the case of GDM which was reduced by PLP administration

(121). In addition, vitamin B6 acts as a co-factor in cystathionine synthase and cystathionine lyase enzymes which are required for homocysteine metabolism. Thereby PLP deficiency leads to elevated homocysteine levels which are linked to obesity-induced insulin resistance and diabetes (123).

3.5. Biotin (Vitamin B_7).

The primary function of biotin is to act as a prosthetic group of carboxylases (124). Enzymes that require biotin as a coenzyme include acetyl-CoA carboxylase (ACC), geranyl-CoA carboxylase (GCC), 3-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), propionyl CoA carboxylase (PCC), and urea carboxylase (UC) (125). Biotin plays a crucial role in maintaining glucose harmony in cells through gluconeogenesis, insulin receptor transcription, and preserving β cell function (126). The physiological function of biotin is to increase the expression of hepatic glucokinase activity which was first observed in 1968 (127). Biotin controls the expression of glucokinase at both the transcription and translational levels (128). Later, *in vitro* studies also reported that biotin augments the expression and activities of pancreatic glucokinase (128) hence enhancing the glycolysis pathway, and improving insulin function in muscles by promoting guanylate cyclase activity (129), to increase insulin receptor synthesis, and secretion (130–132). According to Hemmati *et al*., the administration of biotin as an adjuvant, in conjunction with an insulin regimen, has the potential to enhance glycaemic management and reduces plasma lipid concentrations in individuals with poorly managed type 1 diabetes (129) consequently, the levels of blood glucose, ketone bodies, triglycerides, and free fatty acids are maintained (133). Lazo *et al.* have reported that biotin supplementation increases β cell functioning and diminishes CAM in rodent models (134). Additionally *in vivo* studies also suggest a potential corelation between biotin administration and improved glucose tolerance (135, 136). The potential mechanism behind the reduction in blood glucose in diabetic patients by biotin involves the synthesis of glycogen and reducing gluconeogenesis (137).

3.6. Folic acid (vitamin B_9) and cobalamin (vitamin B_{12}).

These two vitamins are interrelated due to their intrinsic role in the folate and methionine cycle. The scarcity of vitamin B_{12} restricts the formation of folate as it remains trapped in methyltetrahydrofolate (138). Folate deficiency usually accompanied with reduction in purine or pyrimidine synthesis as well as genomic and non-genomic methylation which impedes the process of neuron differentiation. These cause hippocampal atrophy, progression of demyelination, and disintegration of cellular structure. Consequently, these effects have major implications on the generation of normal action potential (139). Folate and vitamin B_{12} deficiency downregulate of folate-dependent proteins and DNA and RNA synthesis causes foetal developmental disorder and megaloblastic anaemia (138, 139). Diabetic patients with folic acid and vitamin B_{12} deficient have increased level of oxidative stress due to hyper-homocysteinemia. One of the major complications related to diabetes is peripheral neuropathy which has been associated with hyper-homocysteinemia. Therefore, vitamin B_{12} deficiency might be considered as a predisposing factor to diabetic complications (140–142). The combined treatment of pyridoxine, folate, and vitamin B_{12} has shown the ability to recover retinal edema and hyperlight sensitivity in individuals with diabetic retinopathy (143) and also provide protection in conjunction with hyper-homocysteinemia (118). The actions of B vitamins on brain glucose metabolism and diabetes has been summarized in table 2 and illustrated in the figure 3.

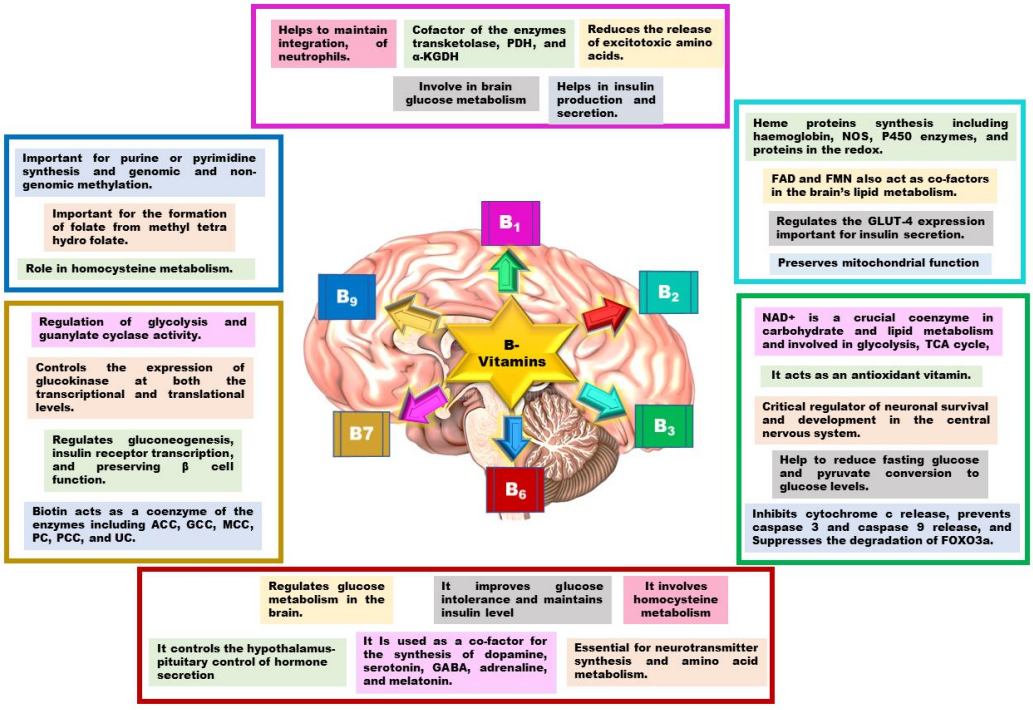

Fig.3. Effects of B vitamins in brain glucose metabolism and diabetes.

This figure illustrated how B vitamins functions in the brain glucose metabolism and reduce the predisposition of diabetes through its different antioxidant and metabolic activities and also through the production of different neurohormones.

PDH: pyruvate dehydrogenase, α-KGDH: α-ketogluterate dehydrogenase, FAD: flavin adenine dinucleotide, FMN: flavin mono nucleotide, GLUT-4: glucose transporter-4, NAD: nicotinamide adenine dinucleotide, TCA: tricarboxylic acid, FOXO: forkhead transcription factor, GABA: γ aminobutyric acid, ACC: acetyl- CoA carboxylase, GCC: geranyl-CoA carboxylase, MCC: 3-methylcrotonyl-CoA carboxylase, PC: pyruvate carboxylase, PCC: propionyl CoA carboxylase, UC: urea carboxylase.

Table 2 Summary of the protective action of B-vitamins against diabetes and neuro-disorders.

Names	Study	N	Route and duration	Parameters measured	Key findings	Ref.
B_1,B_6	Human study	30	Orally daily for 5 months	Glucose, HbA1c, Insulin, TPP, PLP, AGE DNA	Combined administration of vitamin B1 and B6 to diabetic nephropathy patients declines DNA glycation in leucocytes. Surprisingly B6 alone did not show any effect.	(144)
B_1	Randomized control trial	12	Orally daily for 1 month	Blood glucose HbA1, creatinine, total cholesterol	Significant decrease in the level of glucose and leptin in drug naïve patients with T2DM	(145)
B_2	Experimental study	6	Orally daily for 28 days.	Glucose, MDA level, GSH, antioxidant enzymes, GLUT4 expression-comet assay	From this study, it has been concluded that riboflavin acts as an antioxidant against lipid, protein, and DNA damage as well as can reduce diabetic complications.	(103)

B_3	Randomized controlled trials	2110	NA	Total cholesterol, LDL, HDL, plasma glucose, HbA1c, hemoglobin	This study reported that niacin supplementation can improve lipid profile without interfering with the glycaemic level in T2DM patients.	(146)
B_6	Experimental study	4	In drinking water for 70 days	Glucose, insulin, AGE	Administration of pyridoxamine dose-dependently can reduce AGE formation and insulin resistance in obese diabetic KK-A^y mice. However, fasting blood glucose level has not been altered.	(147)
B_6+ B_9+ B_{12}	Human study	20 (eyes)	Orally L-methyl folate calcium, PLP, and methyl cobalamin twice daily for 6 months.	Microperimetry measurement, mean retinal central thickness	In this pilot study, B vitamins significantly improve mean retinal threshold sensitivity for eyes with mild to moderate non-proliferative diabetic retinopathy.	(143)
B_7	Experimental study	15	Oral supplementation of Cr-Pic and biotin is given for a period of 70 days.	Circulating glucose, cortisol, total cholesterol, MDA	This study reported that chromium picolinate (Cr-Pic) and biotin combinedly ameliorate insulin resistance, dyslipidemia, hepatic and renal damage as well as pathophysiological alterations in the liver, kidney, and pancreatic tissues in high-fat diet and streptozotocin-induced T2DM.	(148)

TPP: thiamine pyrophosphate, PLP: pyridoxal-5-phosphate, AGE: advanced glycation end product, MDA: malonaldehyde, GSH: reduced glutathione, LDL: low density lipoprotein, HDL: high density lipoprotein.

4. IMPORTANCE OF MELATONIN IN BRAIN ENERGY METABOLISM AND DIABETES

Melatonin is present in almost every living organism to regulate the circadian rhythm of these organisms (149). In vertebrates, the direct release of melatonin into the blood and CSF by the pineal gland is the major source of circulating melatonin, however, it is also generated in a variety of cells, tissues, and organs primarily for local consumption (autocrine and paracrine activities) (150, 151). The suprachiasmatic nucleus (SCN) of the hypothalamus also known as the primary circadian clock, precisely regulates the activation and deactivation of this intricate neuronal network controlling pineal melatonin synthesis. Melatonin production exhibits a circadian rhythm through this pathway, which is closely synchronized with the cycle of light and dark (152). Melatonin is essential for the preservation of the internal circadian temporal rhythm, synchronizing a variety of physiological activities, such as energy metabolism, and ensuring that they occur in harmony (153). It is used to improve clinical outcomes of several neurological diseases including dementia, AD, PD, MS, stroke, and brain ischemia/reperfusion but also in traumatic CNS injuries (traumatic brain and spinal cord injury). Additionally, experimental data support its direct and indirect antioxidant properties, including scavenging free radicals, promoting antioxidant enzymes, boosting the activities of other antioxidants, or shielding other antioxidant enzymes from oxidative damage. Melatonin is a neuroprotective substance in neurodegenerative pathologies when brain oxidative damage has been established as a common link (154).

4.1. Regulation of melatonin in the brain.

Originally, melatonin was believed only to produce in the pineal gland but subsequent studies by Stefulj *et al*. showed that gene expressions of melatonin-synthesizing enzymes AANAT and hydroxyl-indole-O-methyltransferase (HIOMT) are also in other regions of the rat brain (155). Currently, it is well known that melatonin is exclusively synthesized in the mitochondrial matrix of the mouse brain (156), indicating every cell can synthesize melatonin in brain or in other part of the body. Liu *et al*. have reported that melatonin is synthesized in cultured cortical astrocytes in rats through a cascade of enzymatic events (157). For example, serotonin (which is derived from tryptophan) is converted into N-acetyl serotonin (NAS) by the enzyme AANAT. N-acetyl serotonin is converted to melatonin utilizing the enzyme HIOMT (158).

Melatonin acts through two G protein-coupled receptors namely MT1 and MT2 which are widely distributed in the CNS including the hippocampus, caudate putamen, suprachiasmatic nucleus, reticular thalamic nucleus, supraoptic nucleus, and inferior colliculus (159). Additionally, both receptors are also widely distributed in neurons, glial cells of the cerebral cortex, cerebellar cortex, and thalamus (160). Although several authors proposed the existence of a putative MT3 melatonin receptor subtype, recent studies have provided evidence that the MT3 melatonin receptor is a cytosolic quinine reductase 2 enzyme rather than a membrane receptor (161). Intracellular melatonin can act on the mitochondrial MT1 signal-transduction pathway, which prevents the release of the stress-induced cytochrome c and the activation of the caspase enzyme, therefore, reduces inflammation and cell death. The locally produced melatonin seems to guard against neurodegeneration, known as autocrine signaling (162). However, there are numerous ways that melatonin works through its membrane receptors to prevent oligodendroglial damage, including improved membrane fluidity, decreased edema, polymorphonuclear cell infiltration, prevention of nuclear factor-kappa-B (NF-κB) translocation to the nucleus, and the subsequent reduction of pro-inflammatory cytokines expression, all of which have important roles in inflammation (163, 164). Melatonin may also affect astrocyte reactivity or death by increasing astrocyte anti-oxidative defense (165). Melatonin receptors and its effect on inflammatory regulation appear to involve in the neuroprotective pathway, which promotes oligodendrocyte maturation (154).

4.2. Regulation of brain energy metabolism by melatonin.

The brain is particularly vulnerable to injury caused by free radicals because of its inherent biochemical and physiological traits, which include a high need for energy and polyunsaturated fatty acids (PUFA) (166). The accumulation of abnormal or misfolded proteins, protofibril formation, dysfunction of the ubiquitin-proteasome system, excitotoxic insult, oxidative and nitrosative stress, mitochondrial injury, and failure of axonal and dendritic transport are thought to be common unifying events in many slowly progressing neurodegenerative disorders (167). However, mitochondria play a central role in causing neural damage. They are the main source of ROS. Their dysfunction results in an abrupt reduction in ATP production and a decrease in tricarboxylic acid (TCA) cycle activity. This dysfunction in energy production processes contributes to various brain pathologies (168). Melatonin is primarily responsible for establishing an optimal energy balance by controlling the flow of energy to and from the reserves, as well as directly regulating energy expenditure by activating brown adipose tissue and browning of white adipose tissue. Melatonin levels fall as a result of aging, shift work, or light settings at night, which also causes insulin resistance, glucose intolerance, sleep disturbances, and metabolic circadian disorganization, a condition known as chrono disruption (149). Melatonin regulates energy balance and metabolism, which have a distinct 24-hour

rhythm (169). In general, the active/wakefulness phase of the day is linked to energy acquisition, eating, and subsequent energy intake, use, and storage. This is a period characterized by increased adipose tissue lipogenesis and adiponectin production, as well as elevated insulin secretion, high glucose uptake by insulin-sensitive tissues, hepatic and muscular glycogen synthesis and glycolysis, and high central and peripheral sensitivity to insulin and glucose tolerance. The normal fasting phase necessitates the utilization of stored energy for the maintenance of cellular functions, which distinguishes the rest/sleep phase of the day, in contrast with insulin resistance, enhanced hepatic gluconeogenesis and glycogenolysis, adipose tissue lipolysis, and leptin release are all present throughout this portion of the daily cycle (149) thus it also regulates brain metabolism in that way. Melatonin interacts with molecules and signalling networks such as insulin-like growth factor 1 (IGF-1), Forkhead box O (FoxOs), sirtuins, and the mammalian target of rapamycin (mTOR) signalling pathways and all of them affect energy consumption (170).

4.3. Crosstalk between brain, melatonin, and diabetes.

The T2DM and its associated disorders, such as obesity, abnormal protein processing, oxidative stress, and proinflammatory cytokines will activate inflammatory pathways, resulting in low-grade chronic inflammation, insulin resistance, and impaired neuronal insulin signaling in the periphery (171). However, T2DM is a potential risk factor associated with the development of AD (172). The BBB disruption associated with T2DM, along with elevated levels of ROS, MMP-2, and IFN_{γ}, may facilitate the entry of circulating neurotoxins into the brain due to selectivity loss on neurons and ultimately accelerate the course of AD (173). The M1 proinflammatory state that results from macrophage infiltration causes an increased release of proinflammatory cytokines and chemokines, which can cross the BBB and disrupt brain functioning (174). These alterations can be protected by melatonin through inducing the expression of NADPH oxidase-2 and inhibition of MMP-9 in brain microvascular endothelial cells (175). Another proposed underlying mechanism is the impairment of insulin signaling (176). AD patients even without T2DM also showed signs of insulin resistance. Through the MAPK and Akt signalling pathways as well as Nrf2 activation, and insulin receptor activation promotes glucose uptake, mitochondrial activity, anti-apoptosis, and autophagy (177). Insulin thus plays a crucial role in the development, maintenance, and function of neurons in addition to being a hormone for glucose homeostasis (178).

Evidence has supported the circadian rhythm of melatonin in pancreatic insulin secretion (179, 180). Melatonin deems to has a negative influence on the activity of the β cells to control their insulin decreasing as well as a reduction in glucose tolerance in rats (181, 182). High insulin and low glucose level has been found during the day when melatonin concentration is reduced. Paradoxically low insulin level was also measured in presence of high melatonin and glucose level during the night (183). In an, *in vivo* and *in vitro* study it was found that melatonin affects insulin secretion that is mediated by the MT1 and MT2 receptors. Melatonin also shows protective effects on pancreatic β-cells, which are extremely vulnerable to oxidative stress, and ROS formation. Comparing diabetic and nondiabetic rats, diabetic rats have decreased plasma melatonin levels and AANAT activity. The insulin receptor mRNA increased while AANAT mRNA dropped in the pineal gland, indicating a close relationship between insulin and melatonin (184). By these findings, melatonin concentration declines with age whereas insulin synthesis are increased which proposes the fact that melatonin inhibits age-related hyperinsulinemia (185). Corresponding to these findings the reduction of melatonin levels in diabetic hamsters has been reported (186–188). Melatonin supplementation along with exercise elevated the expression of genes involved in mitochondrial biogenesis and function in T2DM rats, including mtTFA, PGC1α, Nrf-1, and Nrf-2. Additionally, taking melatonin and working

out together effectively scavenges harmful free radicals, indicating that melatonin administration exerts its anti-diabetic effects by counteracting oxidative pathways (189).

On the other hand, melatonin has a preventive role in hyperglycemia whereas pinealectomy increases the risk (190). The gene expression of GLUT4 is reduced in pinealectomized rats resulting in glucose intolerance and insulin resistance which is ameliorated by melatonin (191). Furthermore, melatonin level is decreased in human dental pulp cells in T2DM subjects. Melatonin at pharmacological doses was found to improve SOD activity in hyperglycemic dental pulp cells (191). Another study by Oliveira *et al*. described that streptozotocin-induced diabetic rats with the treatment of insulin (1.5 U/100gm/day) and melatonin (0.2mg/kg/day in drinking water) improves insulin sensitivity as well as glucose metabolism of white adipose tissues (192). Decreased melatonin production has been reported in diabetic animal models which were protected by exogenous melatonin administration (100mg/kg/day in drinking water for 8 weeks) in the high-fat diet-fed mouse with insulin resistance (193). In patients with poorly controlled T2DM addition of melatonin and zinc acetate to metformin reveals better results than metformin alone (194). Thus, melatonin plays an important role in preventing the development of diabetes by modulating Aβ build-up, insulin resistance, glucose metabolism, and BBB permeability.

4.4. Role of melatonin against diabetes-induced alterations in CNS.

Diabetes perturbs various structural and functional integrity related to the PNS and CNS (195). Cerebrovascular alterations such as neurotropic changes like decreased IGF, loss of vascular reactivity, and reduced blood flow in the brain indicate apoptosis in neuronal cells and subsequent cognitive impairment in the hippocampus (196, 197). DM is associated with poor cognitive development, AD, and dementia. Since oxidative stress is a major contributory factor in the development of diabetic complications, antioxidant administration may restore physiological functions to some extent (198–200). A plethora of studies have reported that diabetes-induced hippocampal neuronal cell damage has been prevented by antioxidant therapy (201–203). Melatonin by its antioxidant efficacy provides neuroprotective effects in different circumstances (204, 205). Melatonin administration prevents glial fibrillary acidic protein (GFAP) and S100B, prime astrogliosis indicator, and reduces lipid peroxidation in a streptozotocin-induced diabetic rat model (206,207). Melatonin exerts its function by enhancing the brain's antioxidant machinery, decreasing brain NOSs activity, and plasma cytokine levels inhibiting apoptosis, and maintaining CNS homeostasis (208–210). Another protective mechanism of melatonin lies in the inhibition of oxidative stress-mediated poly (ADP ribose) polymerases (PARPs) hyperactivation which can cause excess cellular energy depletion and cell death (211). A combined therapy of nicotinamide (300, 1000 mg/kg/day) and melatonin (3, 10 mg/kg/day) ameliorated high glucose-induced alterations in GABA neurotransmitter and glutamate levels in diabetic rats. The study revealed that suppression of the PARPs overactivation pathway can be beneficial in the treatment of DM-related CNS disorders (212).

4.5. Role of melatonin against diabetes-induced neuropathy.

One of the most common and disabling consequences of DM is diabetic neuropathy (DN), which harms the patient’s quality of life and imposes a considerable economic burden on the healthcare system. DN is a common adverse consequence associated with both type 1 and type 2 diabetes. Additionally, several studies have revealed that various kinds of neuropathy are also present in pre-diabetic patients (213). Worldwide, the prevalence of DN in diabetes patients ranges from 9.6 to 88.7%. Age, types of diabetes, glucose management, severity of the

disease , and the accessibility of medical facilities could all contribute to this difference. Distal axon branching in particular, neurofilament polymers, which are crucial structural scaffolds of the axon, gradually cease under chronic DM. This loss of neurofilament polymers is thought to be triggered by decreased mRNA expression of the neurofilament gene (214). Animal studies in diabetic rats also link endoplasmic reticulum stress to the peripheral nerve damage caused by diabetes, which would impact nerve function (215). Similarly, it has been shown that hyperglycemia changes the expression patterns of heat shock proteins (HSPs) and PARP as well as the function of important plasticity molecules including growth-associated protein 43 (GAP43; also known as neuromodulin) and tubulin (216, 217). Data indicate that disruption in these networks promotes aberrant protein processing, oxidative damage, and mitochondrial dysfunction, which results in the loss of peripheral nerve function even if the exact causes of injury are yet unknown (218). Moreover, increased glucose loads cause glucose metabolism to occur through the polyol and hexosamine pathways, increasing ROS and causing inflammation, both of which are mostly caused by mitochondrial damage (218). However, melatonin has a beneficial impact on diabetic neuropathy by reducing oxidative stress and inflammatory reactions. Numerous metabolic processes, including the polyol pathway and the mitochondrial energy-production complexes, are activated by hyperglycemia, which results in the release of reactive intermediates. Additionally, a high glucose level activates the PKC pathway, which results in NF-kB activation. Melatonin reduces oxidative stress and inflammation, suppresses reactive intermediates and NF-kB, activates Nrf2, and up-regulates the production of antioxidant enzymes, all of which prevent the development of diabetic neuropathy (219). In DN patients, hyperglycemia has been linked to higher concentrations of leptin, malonaldehyde (MDA), and pro-inflammatory cytokines (TNF- and IL-6). Leptin, pro-inflammatory cytokines, and hyperglycemia were all attenuated in the melatonin-treated group, while levels of adiponectin, an anti-inflammatory adipokine, were elevated. Additionally, melatonin lowered brain MDA levels and reduced oxidative stress while raising total antioxidant capacity and GSH levels (213). The effects melatonin in brain glucose metabolism and diabetes are summarized in table 1 and illustrated in Figure 4.

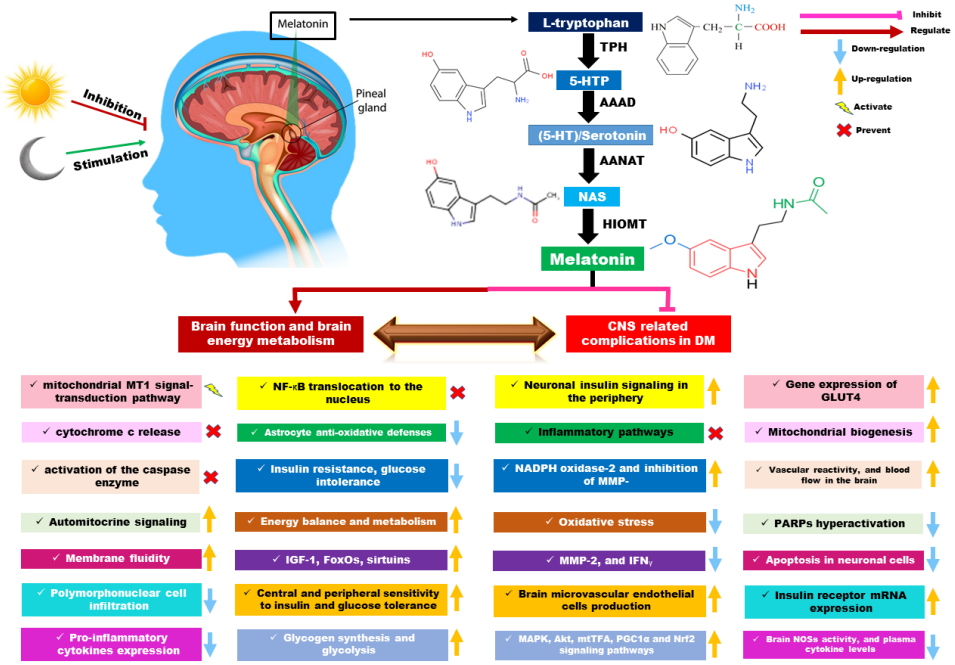

Fig. 4. Effects of melatonin in brain glucose metabolism and diabetes.

This figure illustrated melatonin synthesis pathways as well as its regulatory action on brain function and energy metabolism. Melatonin can reduce the CNS complications related to diabetes mellitus by upregulating, downregulating, inhibiting or activating the different signals and protein expressions and reducing oxidative stress under the condition of diabetes mellitus.

TPH: tryptophan hydroxylase, 5-HTTP: 5-hydroxytryptophan, AAAD: aromatic amino acid decarboxylase, 5-HT: hydroxy tryptamine, AANAT: arylalkalylamine-N-acetyl transferase, NAS: N-acetyl serotonin, HIOMT: hydroxyindole-O-methyl transferase, MT1: melatonin recpetor-1, FOXO3a: forkhead transcription factor, NF-kB: nuclear factor-kappa-B, IGF 1: insulin-like growth factor 1, MMP: matrix metalloprotenase 2, IFN γ: interferon gamma, NADPH: nicotinamide adenine dinucleotide phosphate (reduced), AMPK: activated protein kinase, MAPK: mitogen-activated protein kinas, PARP: poly ADP ribose polymerase.

4.6. Summarization of the protective effects of melatonin on diabetes.

Type of Study	Dose and duration	Route	Parameters measured	Key findings	Ref.
In vivo	10mg/kg b.w in male Wistar rats for 2 weeks.	I.p.	Total antioxidant capacity, GSH, GPx lipid peroxidation, IL-1β, and IL-4	Melatonin ameliorates diabetes-induced brain and erythrocyte damage through its antioxidant efficacy	(209)
In vivo	10 mg/kg b.w in male Wistar rats for 7 days.	I.p.	Specific neuronal protein, neural and glial markers like neural cell adhesion molecule (NCAM) and glial fibrillary acidic protein (GFAP), and lipid peroxidation.	Melatonin improves NCAM, GFAP, and cognitive behaviour.	(207)
In vivo	1 mg/kg b.w in male Wistar rats for 4 weeks	I.p.	Blood glucose, hematological parameters RBC, WBC, hemoglobin, hematocrit	Melatonin inhibits membrane protein peroxidative damage, and non-enzymatic glycosylation of protein, and prevents diabetes-induced hematological alterations in rats.	(208)
In vivo	10mg/kg b.w in male Wistar rats for 2 weeks.	I.p.	NOS	Melatonin administration is beneficial in reducing oxidative stress-induced diabetes by suppressing NOS	(210)
In vivo	3 and 10mg/kg b.w in Sprague-Dawley rats for 2 weeks	I.p.	Glutamate, GABA, MDA level. Oxidative stress-PARP pathway	Melatonin intervention inhibits oxidative stress-PARP pathway and improves neuro behavioural pathway	(211)
In vivo	50 mg/kg b.w in male Wistar rats for 45 days.	I.p.	MDA GPx CAT Immuno-histochemistry TEM	Melatonin significantly enhances antioxidant enzyme activity and provides neuroprotective effects by preserving glial cells and declining vascular damage.	(220)
In vivo	3,10 mg/kg b.w in Sprague-Dawley rats	Oral	TNF-α, IL-6, Nrf-2, COX-2	Melatonin modulates neuroinflammation in diabetic rats by reducing inflammatory markers like TNF-α and enhancing Nrf-2 expression.	(221)

i.p.: intraperitoneal, GPx: glutathione peroxidase, NCAM: neural cell adhesion molecule, GFAP: glial fibrillary acidic protein, RBC: red blood cells, WBC: white blood cells, NOS: nitric oxide synthase, GABA- γ: aminobutyric acid, MDA: malonaldehyde, PARP: poly ADP ribose polymerase, CAT: catalase, TEM: transmission electron microscope.

5. CONCLUSION

In the brain, glucose metabolism seems to be the principal mechanism for producing energy supporting synaptic activity and ionic equilibrium. Memory and other cognitive and emotional functions are boosted or controlled by insulin in the brain, which also centrally modulates body metabolism. T2DM is characterized by insulin resistance, which also contributes to inflammation and oxidative stress in addition to hyperglycemia. Furthermore, uncontrolled diabetes *mellitus* can impact the brain's general oxidative metabolism in a frightful condition. The biochemistry and functioning of the brain are substantially impacted by severe hyperglycemia. Thus, the development of diabetes through impaired brain metabolism and diabetes-induced disruption in brain metabolism are interrelated and vice versa process involves various underlying mechanisms. B vitamins and melatonin play important roles in brain metabolism under diabetic condition. The B vitamins operate as cofactors in many catalytic reactions required for synthesizing and activating neurotransmitters, allowing the CNS to function properly. Whereas, melatonin, as a broad-spectrum antioxidant, scavenges free radicals in several physiological circumstances. We can therefore conclude from this analysis that melatonin and B vitamins may be crucial for the preservation of brain glucose metabolism and the prevention of the onset of diabetes *mellitus*. Melatonin can therefore be an alternative when combined with B vitamins, and this pairing can result in more assertive outcomes for protecting brain metabolism-related diabetes *mellitus*.

ACKNOWLEDGEMENTS

Manisha Mukhopadhyay thankfully acknowledges the receipt of UGC Senior Research Fellowship (ref no.1558/(NET-JULY 2018), Govt. of India. Priyanka Ghosh thankfully acknowledges the receipt of the UGC Junior Research Fellowship (ref no.1571/PWD (NET-NOV2017), Govt. of India. AC is supported from a research project awarded to her by the Department of Science and Technology, Govt. of West Bengal, India. DB is also supported from departmental BI grant of University of Calcutta.

AUTHORS CONTRIBUTION

Dr. DB and Dr. AC contributed to the conception and critical revision of the manuscript and approved it. MM drafted the manuscript and prepared the table. PG prepared figures, table and edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AANAT- Arylalkalylamine- N-Acetyl Transferase
ACC-Acetyl- Coa Carboxylase
Acetyl CoA- Acetyl Coenzyme A
AD- Alzheimer's disease
ADP-Adenosine Diphosphate
AFMK- N^1-Acetyl-N^2-Formyl-5-Methoxykynuramine
AMK- N^1-Acetyl-5-Methoxykynuramine
AMPK-Activated Protein Kinase

ATP-Adenosine Triphosphate
BBB-Blood-Brain Barrier
CAM- Cell Adhesion Molecules
CAMP- Adenosine Monophosphate
CNS-Central Nervous System
CSF-Cerebro Spinal Fluid
DNA-Deoxyribonucleic Acid
DN-Diabetic Neuropathy
ETC-Electron Transport Chain
FAD-Flavin Adenine Dinucleotide
$FADH_2$- Flavin Adenine Dinucleotide (Reduced)
FMN-Flavin Adenine Mononucleotide
FOXO3a-Forkhead Transcription Factor
FoxOs -Forkhead Box O
G6P- Glucose-6-Phosphate
G6pc- Glucose-6-Phosphatase
GABA-γ Aminobutyric Acid
GAP 430- Growth-Associated Protein 43
GCC-Geranyl-Coa Carboxylase
GDE-Glycogen Debranching Enzyme
GDM- Gestational Diabetes Mellitus
GFAP- Glial Fibrillary Acidic Protein
GLUT-Glucose Transporter
GP-Glycogen Phosphorylase
GS- Glycogen Synthase
HDL-High Density Lipoprotein
HIOMT-Hydroxyindole-O-Methyl Transferase
HSPs- Heart Shock Proteins
IFN γ- Interferon Gamma
IGF 1- Insulin-Like Growth Factor 1
LDL-Low Density Lipoprotein
MAPK- Mitogen-Activated Protein Kinase
MCC-3- Methylcrotonyl-Coa Carboxylase
MDA- Malonaldehyde
MMP 2- Matrix Metalloprotenase 2
MS-Multiple Sclerosis
MT1-Melatonin Receptor1
MT2-Melatonin Receptor 2
MT3-Melatonin Receptor 3
mTOR -Mammalian Target Of Rapamycin
NA- Nicotinic Acid
NADH- Nicotinamide Adenine Dinucleotide (reduced)
NAD-Nicotinamide Adenine Dinucleotide
NADPH-Nicotinamide Adenine Dinucleotide Phosphate (reduced)
NADP-Nicotinamide Adenine Dinucleotide Phosphate
NAS- N-Acetyl serotonin
NF-kB Nuclear Factor-Kappa-B
NNMT-Nicotinamide-N-Methyl Transferase
Nrf2-Nuclear Factor 2
PARP- Poly ADP Ribose Polymerase

PC- Pyruvate Carboxylase
PCC- Propionyl CoA Carboxylase
Pck1- Phosphoenolpyruvate Carboxykinase 1
PD-Parkinson's Disease
PKC-Protein Kinase C
PK-Phosphorylase Kinase
PLP- Pyridoxal-5-Phosphate
PPP-Pentose Phosphate Pathway
PUFA-Polyunsaturated Fatty Acids
RNA-Ribonucleic Acid
ROS-Reactive Oxygen Species
SCN- Suprachiasmatic Nucleus
SGLT- Sodium-Dependent Glucose Transporters
T2DM-Type 2 Diabetes
TCA cycle-Tri Carboxylic Acid Cycle
TDP-Thiamine Diphosphate
TMP-Thiamine Monophosphate
TPP- Thiamine Pyrophosphate
UC- Urea Carboxylase
WE-Wernicke's Encephalopathy
α-KGDH- Alpha Ketogluterate Dehydrogenase

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Please cite this paper as:
Mukhopadhyay, M., Ghosh, P., Chattopadhyay, A. and Bandyopadhyay, D. 2023. An insight into the importance of B vitamins and melatonin in the prevention of diabetes through modulation of the brain energy metabolism- a comprehensive review. Melatonin Research. 6, 3 (Sep. 2023), 397-430. DOI:https://doi.org/https://doi.org/10.32794/mr112500160.