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The Glymphatic System in Diabetes-Induced Dementia

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The glymphatic system has emerged as an important player in central nervous system (CNS) diseases, by regulating the vasculature impairment, effectively controlling the clearance of toxic peptides, modulating activity of astrocytes, and being involved in the circulation of neurotransmitters in the brain. Recently, several studies have indicated decreased activity of the glymphatic pathway under diabetes conditions such as in insulin resistance and hyperglycemia. Furthermore, diabetes leads to the disruption of the blood-brain barrier and decrease of apolipoprotein E (APOE) expression and the secretion of norepinephrine in the brain, involving the impairment of the glymphatic pathway and ultimately resulting in cognitive decline. Considering the increased prevalence of diabetes-induced dementia worldwide, the relationship between the glymphatic pathway and diabetes-induced dementia should be investigated and the mechanisms underlying their relationship should be discussed to promote the development of an effective therapeutic approach in the near future. Here, we have reviewed recent evidence for the relationship between glymphatic pathway dysfunction and diabetes. We highlight that the enhancement of the glymphatic system function during sleep may be beneficial to the attenuation of neuropathology in diabetes-induced dementia. Moreover, we suggest that improving glymphatic system activity may be a potential therapeutic strategy for the prevention of diabetes-induced dementia.

Keywords: glymphatic system, diabetes-induced dementia, sleep, cognitive decline, norepinephrine

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INTRODUCTION

The relationship between type 2 diabetes mellitus (T2DM) and dementia, also called "type 3 diabetes", has emerged as a critical health issue across the world as it is fast increasing in incidence (1). There are several studies supporting the relationship between diabetes and dementia. A recent meta-analysis indicated that individuals with T2DM have a 65% increased risk for Alzheimer's disease (AD) (2). A population-based longitudinal study has reported a 16% increased risk for dementia in T2DM patients compared with nondiabetic patients (3). Furthermore, many T2DM patients have cognitive impairments (4) and even patients in the prediabetic stage of insulin resistance exhibit a decrease in memory function and dysfunction of cognitive flexibility and cognitive control (5). Moreover, patients with chronic hyperinsulinemia exhibit insulin resistance and cognitive dysfunction (6). Taking into consideration the previous evidence for the relationship between diabetes conditions, including insulin resistance and hyperglycemia, and cognitive decline (5), the neurological changes in diabetes-induced dementia should be investigated to elucidate the underlying mechanisms and thus support the design of appropriate therapy and prevention in clinical practice.

Current studies highlight the role of the glymphatic system in neurodegenerative diseases such as AD, suggesting that it influences the clearance of amyloid-beta (Aβ) peptide (7). In addition, the roles of the glymphatic system in the central nervous system (CNS) include the regulation of astrocyte activity (8), neurohormones (9), and glucose metabolism (10); modulation of apolipoprotein E (APOE) circulation (11); and regulation of insulin resistance in the brain (12, 13). Diabetes has been shown to contribute to the impairment of glymphatic activity, leading to declined cognitive function (14). Sleep has been known to promote the activity of the glymphatic pathway, subsequently enhancing the efficiency of the brain-clearance system (15), and ultimately improving memory function and synaptic plasticity (16). Here, we have reviewed recent evidence for the relationship between glymphatic pathway dysfunction and diabetes-induced dementia. Furthermore, we have suggested a therapeutic approach for alleviating the neuropathological symptoms of diabetes-induced dementia through the improvement of glymphatic system function.

WHAT IS THE GLYMPHATIC SYSTEM?

In the CNS, approximately 68% of the total water volume is within the intracellular compartment, whereas the remaining 32% of the water exists in the extracellular compartment (8). The extracellular fluid is distributed into the interstitial fluid (ISF), cerebrospinal fluid (CSF), and blood compartments (8). In the CNS, a variety of nutrients circulate through the brain, but it is also essential to remove efficiently the metabolites (17). The CSF produced by the choroid plexus contributes to the delivery of nutrients to the brain parenchyma and the clearance of interstitial toxic waste (18, 19). The CSF is absorbed inside the CNS via filtration and reabsorption of water through the capillaries into the ISF of the surrounding brain regions (20, 21). The CSF enters the para-arterial spaces, mixes with the ISF, and is finally removed from the brain through the paravenous spaces (18, 22). The ISF with the toxic peptide wastes enters the lymphatic circulation through the paravenous space (7, 23). The ISF drained into the paravenous space can eliminate the solutes from the interstitial space similar to the function of the lymphatic system outside the brain (18).

The perivascular space of cerebral blood vessels is the place where the CSF/ISF exchange occurs (18, 24). In addition, the glial cells that provide the outer boundary of the perivascular space have an important function in the clearance and waste turnover (25, 26). Iliff et al. demonstrated that fluorescent dextran injected into the cisterna magna in mice was found in the basement membrane of parenchymal capillaries and in the perivascular spaces of caliber draining veins. This paravascular clearance system was named as the glymphatic system by merging the words "glial" and "lymphatic", because of its dependence on glial cells and also due to its functional resemblance to the peripheral lymphatic system (18). In other words, the glymphatic system is a paravascular pathway that lies in the space between the vascular adventitia and the vascular end-feet of astrocytes (27). The glymphatic system has greater vascular permeability and contributes to the clearance of macromolecules from the brain parenchyma (27). Moreover, the glymphatic pathway contributes to CSF influx into the brain parenchyma through para-arterial spaces to exchange solutes with the ISF (28). Previous studies about the glymphatic pathway have fundamentally altered the traditional model of CSF hydrodynamics (18, 29) and shown that CSF can be recycled back into the brain and exchanged with ISF (29–31). Current studies have reported that the glymphatic pathway involves the dural lymphatic vessels that finally drain toward the cervical lymph nodes (23, 32, 33).

The glymphatic pathway has important diverse roles. Some studies have highlighted the role of the glymphatic pathway in waste drainage. Indeed, it was demonstrated that the glymphatic pathway could be the first step of the brain drainage system (34). Another study reported that the CSF containing toxic waste circulates in the arachnoid space and flows to the dural venous sinuses (7, 35). Moreover, the role of the glymphatic system in nutrient delivery was reported by demonstrating that lipoproteins and small molecules could be delivered from the CSF to the brain parenchyma via the glymphatic pathway (36). Other researchers have shown that the glymphatic system is crucial for the distribution of nutrients throughout the whole brain (37, 38). Additionally, several studies identified the role played by the glymphatic pathway in hormone circulation and signal transduction. It was reported that the glymphatic pathway is not only involved in the volume transmission and the paracrine system, but also in the activation of astrocytic Ca^{2+} signaling within the cortex (30) and in the opening of *N*-methyl-D-aspartate (NMDA) receptors in cultured astrocytes (39). Furthermore, the glymphatic pathway could be involved in regulating the circulation of norepinephrine, the major neuromodulator of arousal (40) that is related with cognitive decline (9), and which plays a role in AD neuropathology (41). Moreover, the glymphatic pathway influences not only the CNS, but also other organs via the circulatory system (42). In this view, current anatomical studies support the fact that the glymphatic pathway is connected with the peripheral system through glymphatic efflux sites, including arachnoid granulations, perineural spaces of cranial and spinal nerves (43), and meningeal lymphatics (23). Based on these observations, the function of the glymphatic pathway is deemed indispensable, and further studies are necessary for the identification of its relationship with various neurological changes.

GLYMPHATIC SYSTEM DYSFUNCTION AND ALZHEIMER'S DISEASE

As mentioned earlier, the glymphatic system acts as an effective waste-clearance pathway for the brain (28). Previous studies demonstrated that dysfunctions of the glymphatic system aggravate neuropathological symptoms of various neurological diseases such as stroke and AD (8, 44). One magnetic resonance imaging (MRI) study indicated that alterations of the glymphatic system could be used as disease risk indicators for neurodegenerative disorders, including AD (45). Impairment of the glymphatic pathway can be the result of abnormal

changes in CSF influx dependent on arterial pulsatility (8, 29). The AD is characterized by several neuropathologies, including Aβ accumulation and the tau tangle formation in various brain regions (46). Blood-brain barrier (BBB) breakdown increases the accumulation of Aβ in the blood plasma, ISF, and CSF (47), causing synaptic dysfunction in the brain. Furthermore, BBB disruption causes inflammation that also contributes to glymphatic dysfunction, suppresses CSF-to-ISF turnover, and impairs glymphatic clearance (48, 49). Amyloid-beta peptide exists in the normal brain, circulating blood, and CSF (50). While the normal brain is able to control Aβ influx and efflux through glymphatic drainage, the AD brain cannot control this process. Therefore, toxic Aβ accumulates in the brain parenchyma and vascular structures (51), and ultimately triggers BBB disruption and vasculature impairment (16).

Amyloid-beta clearance via BBB transport depends on the glymphatic pathway (52), as toxic Aβ can be transported across the BBB through specific transporters such as the low-density lipoprotein receptor-related protein-1 (53). However, when the amount of Aβ exceeds the capacity of the efflux transporter, Aβ is cleared via ISF flow in the glymphatic system (54, 55). The glymphatic system drains over 60% of the brain Aβ to the lymph nodes using the convective flow caused by arterial pulsations (56). The increased permeability of the BBB triggers glymphatic pathway impairment and ultimately leads to the defective clearance of Aβ by BBB transport in dementia (42, 57). Thus, the glymphatic system is considerably relevant to AD progression by transporting Aβ and other metabolites out of the brain (15).

The dysfunction of the glymphatic pathway increases the accumulation of toxic waste products in the brain (58), and is associated with impaired cognitive function recorded in behavioral tests (59, 60). Moreover, it is associated with the dysregulation of water transport into astrocytes (8). Aquaporin-4 (AQP4), a water transport channel expressed in the astrocytic end-feet near the capillaries, is considered to be critical for water movement between the cellular and ventricular compartments (61). Loss of AQP4 results in impairment of CSF influx and CSF-to-ISF turnover (62), aggravating glymphatic pathway dysfunction (28). The loss of AQP4 polarization has been related to glymphatic dysfunction in the brains of mice and considered to be a predictor of AD in humans (63). Additionally, the decrease in AQP4 expression contributes to reduced Aβ clearance (63–65) and tau clearance (66) through the glymphatic system (67), and has been shown to impair water permeability *in vitro* (68). Moreover, AQP4 is associated with the modulation of neurotrophic factor-dependent synaptic plasticity (69), and its absence results in defects in memory consolidation (70, 71). Collectively, the glymphatic system is affected by AQP4 expression in astrocytes and associated with AD progression.

Furthermore, a recent study suggested that an increase in CNS norepinephrine levels and ISF secretion are the results of reduced glymphatic influx in AD mouse models (9). Noradrenergic neurons located in the locus coeruleus supply norepinephrine to various brain regions (72). Elevated norepinephrine levels result in the contraction of the extracellular volume fraction, reduction of CSF influx, and brain ISF (15). Locus coeruleus-derived norepinephrine increases BBB permeability by elevating Na^+/K^+-ATPase activity, leading to augmentation of ISF secretion, and subsequently contributing to the glymphatic function (73). The noradrenergic system in the brain has critical roles in cognitive activities, including attention, perception, and memory function (41, 74). Loss of locus coeruleus neurons and abnormal levels of CSF norepinephrine were observed in the AD brain (75, 76). In addition, several subtypes of adrenergic receptors have been shown to control the production of Aβ (77) or mediate Aβ toxicity (78), involved in AD pathogenesis. Altogether, norepinephrine contributes to the function of the glymphatic system and is implicated in the neuropathology of AD including memory loss.

The *APOE* gene, the only strongly confirmed genetic risk factor for AD, has been associated with cognitive impairment (79), lipid metabolism, and various brain pathologies (80). The CSF is a major source of *APOE* for ISF because it circulates through the brain parenchyma via the glymphatic pathway (15, 81). The CSF contributes to the delivery of APOE to the brain via the glymphatic system, for molecules including Aβ (9), lipophilic molecules (30), and tau (82). Apolipoprotein E has been known to regulate transport and metabolism of cholesterol in the periphery and CNS (83), and is further associated with neurite growth, synaptic plasticity, and cognitive function (84). The *APOE* polymorphisms influence the structure and function of the glymphatic pathway (85) and there is a strong correlation between the *ε4* allele and neurodegeneration (86).

In conclusion, dysfunctions of the glymphatic pathway and subsequent impairment of metabolite circulation aggravate the onset and development of AD. Further studies on the implication of the glymphatic system in AD are necessary for the development of effective therapeutic strategies for AD.

THE GLYMPHATIC SYSTEM AND DIABETES-INDUCED DEMENTIA

Diabetes has been known to be a risk factor for various complications including hypertension, cardiovascular diseases, and neurological diseases, such as stroke and AD (87, 88). Recently, diabetes-induced dementia has been highlighted in CNS studies, showing that diabetes features, including insulin resistance and hyperglycemia, can trigger impairment of memory function, neuronal cell damage, and neuroinflammation (18, 89–91). A recent study demonstrated synaptic dysfunction through the loss of synaptic proteins in hyperglycemia-induced dementia (92). Moreover, in line with the diagnosis of diabetes in patients with cortical embolism due to atherothrombosis and stroke, diabetes conditions may alter the arteriolar structure and influence the perivascular space in the brain (93). A previous study demonstrated that Aβ plaques were accumulated in the brains of diabetes patients affecting cognitive function (94). Other experimental studies showed that diabetes induced by high-fat and/or high-sugar diets triggered Aβ accumulation in the brain (95–98). Therefore, more study on

the mechanisms linking diabetes and dementia is necessary for understanding of the onset and progression of diabetes-induced dementia.

Type 2 diabetes mellitus is characterized by enhanced glymphatic CSF influx and a slowing of the interstitial solute clearance, leading to cognitive decline (13). Several studies have reported diabetes-associated cerebrovascular dysfunctions, neurodegenerative processes, and cognitive impairments following abnormal glycemia and insulinemia (5, 10, 12, 99). Another study has reported that hyperglycemia could result in cerebral neurovascular dysfunction, neurotoxicity, and impairment of neural insulin metabolism, leading to cognitive impairment (100). Chronic microvascular dysfunction caused by hyperglycemia can also cause severe cognitive dysfunction in diabetes patients (5, 10, 99).

Moreover, diabetes is associated with vascular pathology. It contributes to the development of small blood vessel disease and triggers the impairment of glymphatic activity, leading to cognitive dysfunction (14, 101, 102). Several studies have shown that BBB integrity was compromised and permeability was dramatically increased in the brain of diabetes patients (103). The BBB protects the brain against toxic components that may cause synaptic dysfunction or generate neurotoxins and maintains homeostasis (104, 105).

Hyperglycemia caused by diabetes is also related to neuronal pathogenesis by inducing the generation of excessive reactive oxygen species (ROS) and microvascular complications (106) and by suppressing the supply of vitamin C as an antioxidant and scavenger of free radicals into the brain, subsequently promoting oxidative stress in the brains of diabetes patients (107, 108). In addition, diabetes results in abnormal cerebral neovascularization and neurovascular remodeling (109). Brain endothelial cells are vulnerable to hyperglycemic stress in diabetes (110) and diabetes-induced hyperglycemia is associated with neurodegenerative diseases such as AD (111). Hyperglycemia promotes the generation of excessive superoxide species and boosts the activation of the protein kinase C (PKC) and advanced glycation end products (AGE) pathway, leading to increased BBB permeability mediated by the disruption of tight junction proteins and increased vascular endothelial growth factor (VEGF) expression (112, 113).

Moreover, one study demonstrated that the correlation between diabetes and AD depends on the *APOEε4* allele, which was involved in lipid homeostasis in diabetes (114). In diabetes patients, the increase of *APOEε4* increases the risk for AD compared with nondiabetic patients (115).

In conclusion, diabetes triggers the disruption of the BBB and increase of APOE and ultimately aggravates cognitive decline through metabolite imbalance due to glymphatic pathway dysfunction. Thus, the investigation and the understanding of the role of the glymphatic system in diabetes-induced dementia are necessary for the development of an efficient treatment for diabetes-induced dementia.

THE IMPORTANCE OF SLEEP IN DIABETES-INDUCED DEMENTIA

Sleep is necessary for the bulk flow of brain ISF and clearance of solutes, and is also involved in memory function and synaptic plasticity through several mechanisms, including Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signaling (16, 116–118). It was reported that astrocytes undergo contraction during sleep, and subsequently, the extracellular space is enlarged and the flow of ISF is enhanced. These processes promoted the clearance of macromolecular metabolites from the brain, during sleep (15). The disturbance of glymphatic transport due to inadequate sleep may mediate neuropathologies in AD, given that sleep disruption aggravates the assembly of Aβ plaques and tangles (119, 120). Recent studies have focused on the effect of sleep deprivation on synaptic plasticity and on structural changes of brain regions related to learning and memory (121, 122), and the progression of AD (123–125). Moreover, impaired glymphatic transport results in a 40% decrease in the clearance of Aβ in the brain of mice (54). Sleep disturbance is also associated with the deterioration of diabetes conditions such as insulin resistance (126), the dysregulation of energy and glucose homeostasis in healthy adults (127, 128), and the dysregulation of body weight (129). Thus, the influence of sleep on glymphatic transport is an important aspect of manipulation to control glymphatic system dysfunction in diabetes-induced dementia.

During sleep deprivation, norepinephrine secretion is increased (130), while glymphatic fluid transport is reduced (131). Diabetes conditions, such as hyperglycemia, also cause changes in the CSF concentrations of norepinephrine (132–134). Norepinephrine results in vasoconstriction of the pial arteries (135) and leads to the reduction of CSF inflow during sleep deprivation (9). In addition, several studies have demonstrated that the impairment of glymphatic pathway activity caused by sleep deprivation triggered APOE-related neuronal dysfunction in AD, leading to cognitive decline (11, 16). Hence, the modulation of norepinephrine secretion and other related pathways may enhance the function of the glymphatic system and ameliorate memory in diabetes-induced dementia.

Sleep is influenced by the hormone melatonin, which is mainly produced in the pineal gland, which receives input from the suprachiasmatic nucleus in the hypothalamus (136, 137). Melatonin is the major hormone regulating the circadian rhythm (138) and is also known to regulate memory function by acting on hippocampal neurons involved in memory formation (139, 140). Several studies have reported that melatonin could control hippocampal synaptic plasticity by binding to the melatonin specific receptor (141) and alter synaptic transmission and long-term potentiation in the hippocampus (142). In addition, melatonin could regulate calcium influx by controlling the conductance of voltage-gated Ca^{2+} ion channels and NMDA receptors (143, 144) in gamma-aminobutyric acid (GABAergic) neurons (145). Based on these studies, supplementation with melatonin has been considered as an effective method to alleviate sleep onset latency and to improve sleep quality in children

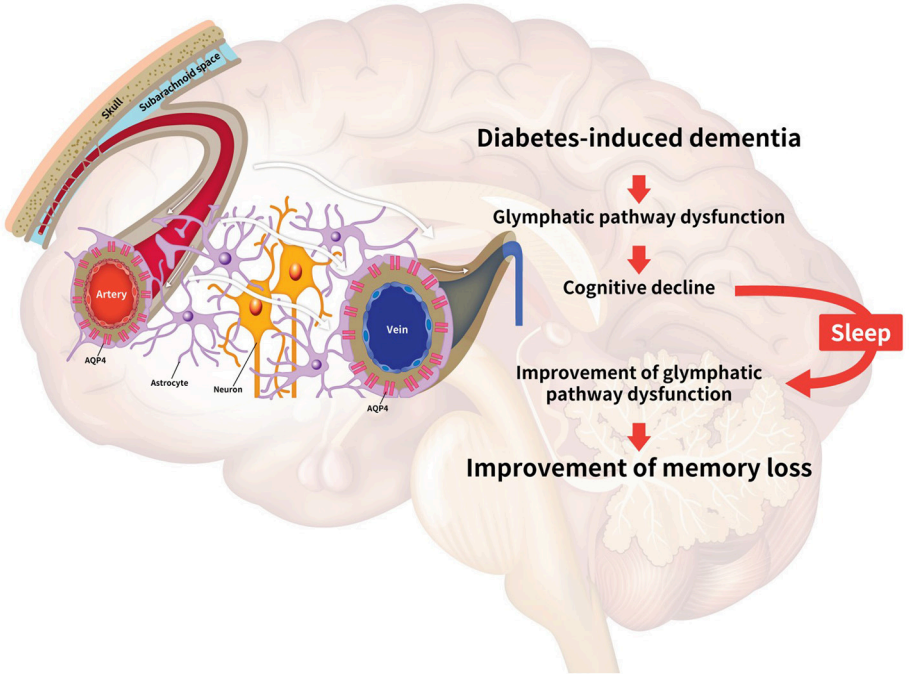

FIGURE 1 | Schematic image illustrating the relationship between the glymphatic system and sleep. Diabetes conditions trigger the impairment of the glymphatic pathway. The decrease of glymphatic activity results in reduced efficiency for clearing toxic peptides, dysregulation of glucose metabolism, insulin resistance, and dysregulation of apolipoprotein E (APOE) circulation in the brain, leading to cognitive decline. Sleep improves the clearance of toxic amyloid-beta (Aβ), the secretion of norepinephrine, and the circulation of APOE and melatonin in the brain. Collectively, sleep is associated with the alleviation of the impaired glymphatic function, leading to the enhancement of memory in diabetes-induced dementia. The white arrows indicate the glymphatic flow.

(146) and adults (147, 148). Furthermore, the increase of melatonin secretion during sleep improves the sleep quality by enhancing the amplitude of circadian oscillations through melatonin receptors MT1 and MT2 (149).

Dysregulation of melatonin results in cognitive impairment by synaptic dysfunction. Recently, two studies have suggested that impairments of the sleep/wake cycle owing to sleep disturbances increase T2DM risk (128, 150). A genome-wide study revealed the relationship between single nucleotide polymorphisms in the *MTNR1B* gene (encoding MT2) and T2DM (151). In addition, decreased serum melatonin levels have been found in both diabetes mouse models and diabetes patients with hyperinsulinemia (152). Oral administration of melatonin alleviated hyperglycemia, hyperinsulinemia, and hyperlipidemia in T2DM rats (153, 154). Melatonin suppressed the levels of cytosolic cyclic adenosine monophosphate and/or cytosolic guanosine monophosphate and regulated insulin secretion via these receptors (155). Moreover, a study demonstrated that sleep disturbance in AD is related to the physiological changes in melatonin function (156). Furthermore, given that melatonin administration could attenuate the rate of AD progression, inhibit the accumulation of Aβ (157, 158), decrease neuronal cell death (159, 160), and reduce insulin resistance (152), the decrease in melatonin levels due to sleep disturbance might be associated with the impairment of the glymphatic system in diabetes-induced dementia. Diabetes triggers memory dysfunction in rats, which can be alleviated by melatonin treatment (161). Considering previous evidence, we suggest that melatonin administration should be considered as an approach to reduce neuropathology in diabetes-induced dementia.

A recent study demonstrated that impaired sleep duration was recorded in hyperglycemia patients (162). Epidemiological studies also showed that short duration and poor quality of sleep increase the risk of diabetes in adults (163, 164). Consequently, sleep impairment is strongly related to diabetes pathologies such as hyperglycemia (165).

The study reported that the lateral decubitus body position during sleep leads to an enhanced influx of a fluorescent CSF tracer into the cerebrum with a reduction of interstitial solute retention and an increase of clearance efficiency (43). Smooth glymphatic flow during sleep contributes to the improvement of paracrine signaling, whereas the decline in glymphatic flow suppresses the perivascular lipid transport, the astrocytic Ca^{2+} signaling within the cortex (30), and the opening of NMDA receptors (166). Moreover, a recent study suggested that AQP4-mediated glymphatic pathway improvement could be used as a therapeutic treatment for AD patients (167). The *AQP4* gene could regulate the progression of cognitive dysfunction in AD, and this was related to poor sleep and Aβ burden (168). The genetic variation in *AQP4* was also identified to be a factor correlating sleep and Aβ accumulation in the brain (169).

Based on the previous evidence stated, the sleep-induced metabolite clearance through the glymphatic system has a critical role in neuropathological features, including excessive accumulation of Aβ in brains with diabetes-induced dementia. Thus, we highlight that the improvement of glymphatic system function by the regulation of sleep may be a promising and effective strategy to reduce the neuropathological symptoms observed in diabetes-induced dementia.

CONCLUSIONS

In diabetes-induced dementia, the glymphatic system dysfunction characterized by the failure of interstitial solute clearance leads to extracellular solute accumulation and cognitive decline. Even though there is no experimental approach providing a direct relationship between sleep and the glymphatic system, many studies have implicated their relationship. Thus, we highlight the necessity for further exploration of the improvement of glymphatic system through sleep modulation toward attenuation of the neuropathology in diabetes-induced dementia. Here, we have reviewed the dysregulation of the glymphatic pathway in diabetes-induced dementia, the effects of sleep on glymphatic system function, including the improvement of toxic peptide clearance, the enhancement of melatonin secretion, the regulation of APOE expression, the improvement of synaptic plasticity, the regulation of norepinephrine levels, and the alleviation of insulin resistance (11, 120, 128, 130, 170, 171) (**Figure 1**).

Hence, we suggest that the improvement of glymphatic function by sleep regulation may be a novel target for attenuating neuropathological symptoms such as memory loss in diabetes-induced dementia, through the enhancement of the circulation of melatonin, APOE and norepinephrine, and reduction of Aβ aggregation in the brain.

AUTHOR CONTRIBUTIONS

Y-KK and JS wrote the manuscript. JS and KN prepared the figure.

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