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Blood-brain barrier dysfunction in ischemic stroke and diabetes: the underlying link, mechanisms and future possible therapeutic targets

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Abstract: Ischemic stroke caused by occlusion of cerebral artery is responsible for the majority of stroke that increases the morbidity and mortality worldwide. Diabetes mellitus (DM) is a crucial risk factor for ischemic stroke. Prolonged DM causes various microvascular and macrovascular changes, and blood-brain barrier (BBB) permeability that facilitates inflammatory response following stroke. In the acute phase following stroke, BBB disruption has been considered the initial step that induces neurological deficit and functional disabilities. Stroke outcomes are significantly worse among DM. In this article, we review stroke with diabetes-induce BBB damage, as well as underlying mechanism and possible therapeutic targets for stroke with diabetes.

Key words: Blood-brain barrier, Diabetes mellitus, Hyperglycemia, Inflammation, Ischemic stroke

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Introduction

Diabetes mellitus (DM) is a major risk factor for ischemic stroke with its incidence ranging between from 1.8- to nearly 6-fold [1]. Previous study reported that stoke patients with DM show essentially different response to treatment and poor outcome, resulting in increased mortality [2-4]. DM involves microvascular and macrovascular changes, and blood-brain barrier (BBB) permeability that facilitates inflammatory response following any stroke [5]. Hyperglycemia was reported to aggravate BBB damage by affecting both active transport mechanisms and tight junction (TJ) protein [6-9]. Disruption of BBB may be powerfully associated to other functional abnormalities of the cellular response to ischemia [10]. We reviewed the existing literature on stroke current knowledge of stroke with diabetes-induce BBB damage, as well as its underlying mechanism and possible therapeutic targets for stroke with diabetes.

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Structure and Physiological Function of Blood-Brain Barrier

BBB is an essential structure for the central nervous system (CNS) that comprises endothelial cells (ECs), basement membrane (BM), end feet of astrocytes, and pericytes (Fig. 1A) [11, 12]. The contact between all these cells and the functional interactions and signaling from a dynamic functional

unit, which is known as the neurovascular unit (NVU).

Cells of blood-brain barrier

The ECs are a single layer of squamous shape cells that line the interior of brain capillaries. The ECs of brain have unique properties that exceedingly limit the paracellular influx of solution. The ECs were separated from pericytes and end feet of astrocytes by BM that are composed of fibronectin, collagen type IV, nidogen, laminin, heparin sulfate proteoglycans, and other glycoproteins [13]. BM equips an anchor for many signaling processes at the vessel and also equips barrier for molecules and cell to cross before accessing the brain parenchyma. BM damage by matrix metalloproteinase (MMP) is the considerable element of BBB disruption and neutrophil infiltration. ECs of brain are held together by TJ proteins. TJ proteins are composed of the transmembrane proteins claudins, occludins, and junction adhesion molecules, and the cytoplasmic proteins zona occludens that provide a high-resistance physical barrier to ions and molecules [14]. Another characteristic of central nervous system ECs is the low expression of leukocyte adhesion molecule [15]. Therefore, immune cell never cross an unstimulated BBB to protect the healthy CNS [16].

Astrocytes are abundant cell type in the brain parenchyma are associated with BBB by endfeet protrusions ensheathing the capillaries. They play important role in recycling of neurotransmitter and ions, synapse formation, regulation of extracellular potassium levels, nutrition of neuron, and control of inflammatory responses in CNS [17]. Pericytes are cells that wrap around the vascular ECs in an approximate 3:1 pericyte-to-EC ratio. Previous study reported that, pericytes are important for cerebral blood flow and BBB integrity [18, 19].

Tight junction

TJ proteins have several functions in the ECs. ECs in CNS are held together by TJ proteins, which provide a high-resistance epithelial barrier [20]. Claudins occludins and members of junctional adhesion molecules (JAMs) are transmembrane molecule that are essential for the paracellular barrier formation (Fig. 1B). Claudins are a class of more than 25 different family members and these proteins are of primary importance for optimal establishment of TJ proteins. A previous study reported that a size-selective leak of BBB was found in claudin-5-deficient mice [21]. Claudin-5 has been shown to be largely identified by ECs in CNS. Moreover, cldn12 and cldn3 are other claudins that have been expressed at the BBB [19, 21, 22]. Occludin was found localizing to epithelial cells and It is highly enriched CNS ECs. A previous study found that occludin may not be important for the resistance of barrier, as described by occludin knockout mice which showed a normal function of BBB and high-resistance barrier [23]. JAMs are members of an immunoglobulin superfamily. It is localized in many tissue including leukocytes, epithelial and ECs. JAM4 has been found in the BBB [19]. However, a previous study reported that JAMs are not necessary for TJ proteins component. The transmembrane adhesion complexes are linked to the cytoskeleton through a

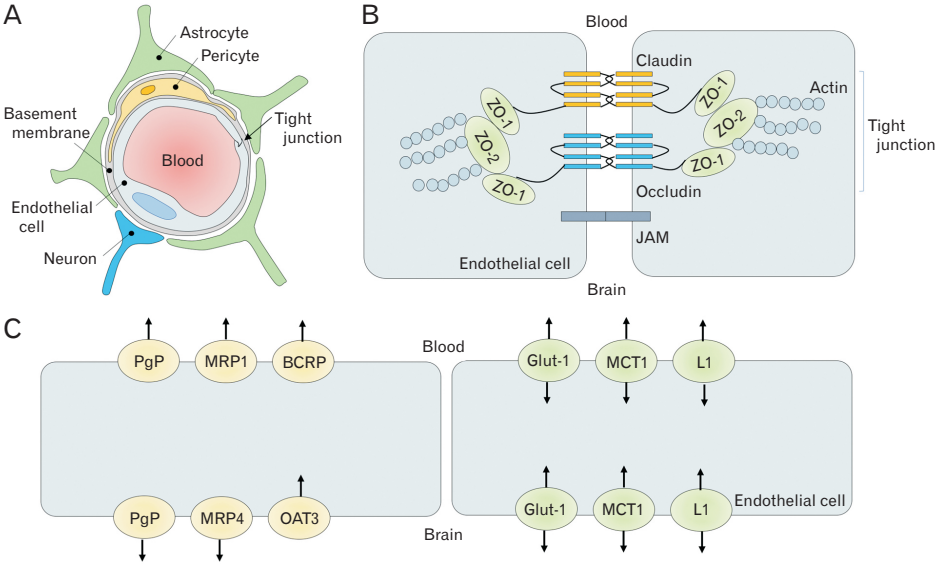

Fig. 1. Structure and functionality of the BBB. (A) Structure of BBB is composed of ECs, BM, astrocyte end feet and pericytes. (B) Tight junctions on ECs (C) Transporter of BBB for molecular traffic across the BBB. BBB, blood-brain barrier; BM, basement membrane; ECs, endothelial cells; Glut-1, glucose transporter; ZO-1, zona occuldens-1.

series of cytoplasmic adaptors such as zona occuldens-1 (ZO-1), ZO-2, Cingulin, Jacop, membrane-associated quanylate kinases, and membrane palmitoylated proteins [24].

Transporter

There are two main types of membrane transporter proteins at the level of the brain microvascular endothelium including efflux transporters and nutrient transporters (Fig. 1C) [20]. Efflux transporters are implicated in drug transporter at BBB, including P-glycoprotein (P-gp), breast cancer resistant protein and the multidrug resistance-associated proteins. These transporters are located to the lumenal surface of ECs and transport compounds across the BBB into the blood circulation. P-gp is the main efflux transporter that involved in transport substrates into blood [25]. P-gp deficient could be developed various neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease and stroke [26].

ECs in CNS express a many nutrient transporters that stimulate the movement of specific nutrients across the BBB into the brain parenchyma. There are many solute carrier classes of facilitated transporters, including slc2a1 (glucose), slc7a1 (cationic amino acids), slc7a5 (neutral amino acids, L-DOPA), and slc16a1 (lactate, pyruvate). Dysfunction of glucose transporter (glut-1) causes an epileptic syndrome. Glut-1 carries glucose across the BBB, while glut-3 is the main neuronal glucose transporter [27]. Insulin-sensitive glut-4 also plays important role in carrying glucose to brain [27].

Diabetes Mellitus and Blood-Brain Barrier Dysfunction

DM is a condition where there is increase blood sugar or glucose levels that is a major cause of heart attack, kidney failure and stroke. There are two main types of diabetes: insulin-dependent (type 1 DM, T1DM) and insulin-independent (type 2 DM, T2DM). T1DM is a disease in which the pancreas loss of beta cells that fails to provide enough insulin, while T2DM is characterized by insulin resistance, a condition in which cells are not respond to utilize insulin. A chronic state of low-grade inflammation, endothelial dysfunction, dyslipidaemia, insulin resistance, and hyperglycemia or high blood sugar, is a characteristic symptom of diabetes that can lead to serious complications at the microvascular level, described by experiment both *in vitro* and *in vivo* study [28]. Changes in plasma glucose levels (hyperglycemia or hypoglycemia) have been related with BBB transporter functions, and oxidative stress in the CNS capillaries [29].

Gluts at the BBB sustains energy demands of CNS. Glut-1 and glut-3 are major transporters at BBB. Previous studies reported that concentration of brain glucose increases in streptozotocin (STZ) induced-diabetics rat as measured by NMR spectroscopy [30]. Moreover, hyperglycemic animals were found to have down-regulation of BBB glucose transporter. Prolonged hyperglycemia in STZ-induced diabetic rats showed down-regulated glut-1 and glut-3 expression

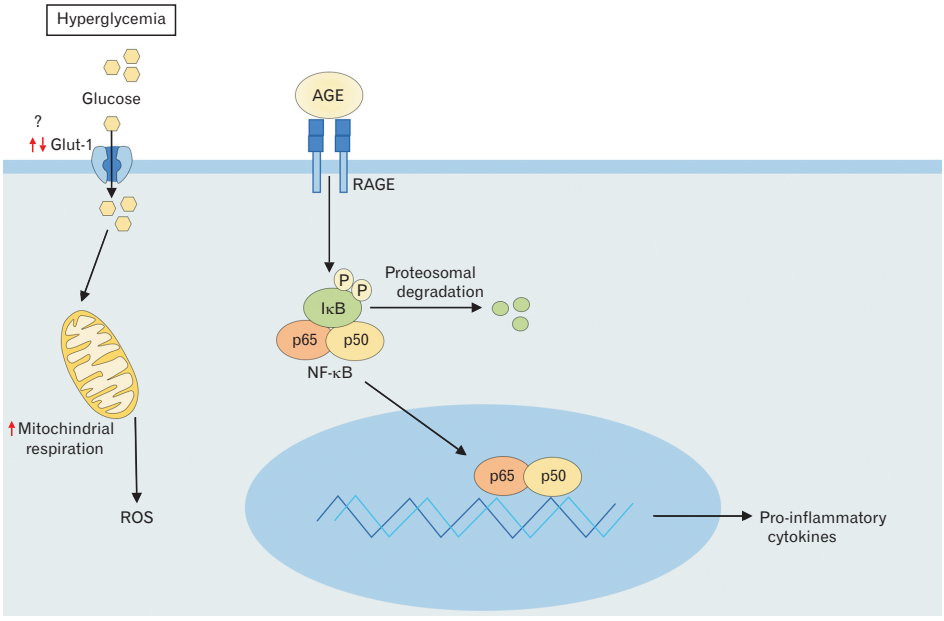

Fig. 2. Pathological mechanism of inflammation induced by hyperglycemia. Glut-1, glucose transporter; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species.

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[29]. On the other hand, other studies showed that there was no significantly change in the BBB glucose transporters in DM. Previous study reported that there were no significant changes in the expression of glut-1and glucose uptake in STZ-induced diabetic rats [31]. In human experiment, acute hyperglycemia did not significantly change in regional glucose metabolism as measured by high-field magnetic resonance spectroscopy. Moreover, a previous study reported that plasma glucose levels did not change in dependence of hippocampus in diabetic animals.

The microvascular injury in DM caused by the overexpression of mitochondrial superoxide overproduction in the ECs. The overproduction of superoxide can activate the formation of advanced glycation end product (AGE) and protein kinase C (PKC) signaling. PKC induces BBB damage through TJ proteins disruption, ZO-1 phosphorylation, and overproduction of vascular endothelial growth factor expression. Upregulation and activation of the receptor for advanced glycation end products (RAGE) induce oxidative stress and leads to activation of nuclear factor-kappa B (NF-κB) pathway [32]. NFκB pathway activated in vascular cell that subsequently increase leukocyte infiltration and transcription of proinflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) (Fig. 2). A previous study reported that hyperglycemia can induce reactive oxygen species (ROS) production and increase proinflammatory cytokines and chemokines in many cells [33, 34]. Moreover, in hyperglycemic animals, diabetic animals and diabetic patients showed the expression of adhesion molecule on ECs [34]. Furthermore, it has been reported that ROS can activate MMPs including MMP-1, MMP-2, and MMP-9 while attenuating TIMP metallopeptidase inhibitor-1 (TIMP-1), known as a tissue inhibitor of MMPs. Particularly, MMP-9 degrade the extracellular matrix (ECM) constituents of the BM and TJ proteins including occludin, claudin-5, and ZO-1. These inflammatory events induce BBB disruption that lead to the extravasation of leukocyte into brain. Leukocyte infiltration are related to the severity of BBB damage.

The Connection Between Ischemic Stroke and Diabetics

Globally, Stroke is the second-most common cause of mortality worldwide and is a major cause of long-term disability globally [35]. World Health Organization describes stroke as a focal (or at times global) neurological impairment of sudden onset and lasting more than 24 hours (or leading to death) and of presumed vascular origin. The risk factors for stroke are age, race, sex, hypertension, cardiac disease, smoking, alcohol use, obesity and DM. It may be mentioned that DM is the major cause of mortality in patients with stroke [36]. The patients with DM are associated with an increased risk of ischemic stroke. Moreover, hemorrhagic strokes are relatively less common in diabetes DM than in nondiabetic individuals.

Ischemic stroke causes a decrease in the blood flow sufficient to alter normal cellular function. Oxygen and glucose deprivation during cerebral ischemia triggers a cascade of events that includes the disruption of membrane potential due to the reduction in ATP production and mitochondrial membrane damage, which leads to a release of excitatory neurotransmitters such as glutamate. Binding of glutamate to its receptors resulting in increases calcium influx leading to mitochondrial function impairment via activation of protein kinase, phospholipase, protease, nitric oxide synthase and release of free radicals. ROS may result in tissue injury through several mechanisms. As they are potent oxidizing and reducing agents, ROS directly damage cellular membranes through lipid peroxidation. The excessive production of ROS can induce apoptosis. In addition, ROS also increase leukocyte adhesion molecule and cytokine gene expression by activating the NF-κB signaling the pathway that important role in the inflammatory process and frequently associated with BBB damage and followed by brain edema [37, 38].

Inflammatory responses were observed in the brain following stroke. ROS can activate downstream signaling pathways, NF-κB signaling pathway. NF-κB composes of a family of transcription factor that play a role in inflammation.NF-κB activation causes a phosphorylation-induced the degradation of inhibitory κBα and the nuclear translocation of p65 subunit, causing the infiltration of peripheral inflammatory cells, activation of microglia, and overproduction of inflammatory mediators, such as cytokines, chemokines, and MMPs. Overexpression of iNOS and COX-2 have appeared as important determinants of ischemic stroke that lead to the progression of brain injury. Increasing amount of ROS after I/R activates astrocytes and microglia to produce proinflammatory cytokines such as TNF-α, IL-6, and IL-1β. Most of these cytokines can induce the production of adhesion molecules such as inter selectins, immunoglobulin superfamily (ICAM-1, VCAM-1) and integrins. Adhesion mol-

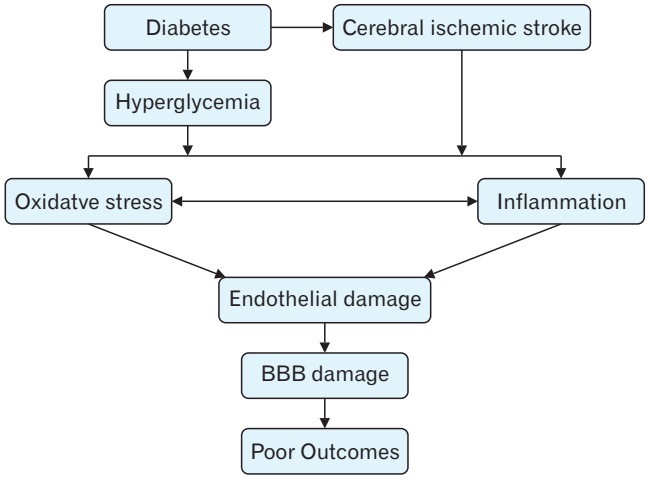

Fig. 3. Neuroinflammatory mechanism involved in aggravating BBB damage in stoke with diabetic. BBB, blood-brain barrier.

ecules on activated endothelial in turn lead to the adhesion of circulating leukocytes causing infiltration of immune cells into the brain parenchyma. The inflammatory cells release a variety of cytotoxic molecules, such as pro-inflammatory cytokines, especially production of ROS and activation of MMPs. Particularly, MMP-9 degrade the ECM constituents of the BM and TJ proteins including occludin, claudin-5, and ZO-1 [39, 40]. These inflammatory events induce BBB disruption that lead to the extravasation of serum constituents as serum proteins and serum immunoglobulin G (IgG) into brain. IgG entry and extravasation are related to the severity of BBB damage (Fig. 3).

Hyperglycemia is serious problem in DM. It has been reported that prolonged hyperglycemia causes a progressive functional impairment of neuronal in brain. Ischemic stroke is typical and are typical CNS complications associated with DM due to the vascular supply impairment. A previous study showed that patients with DM are have a higher risk of experiencing stroke than healthy people. Moreover, 50% of stroke patients were diagnosed with high blood sugar or hyperglycemia [2, 41]. Hyperglycemia is strongly related to high mortality and morbidity level in ischemic stroke patients with by increased ROS production damaging BBB. A previous study reported that AGE-RAGE system activated by hyperglycemia causes important role in increasing oxidative stress and inflammatory response in brain [42]. In animal study, ROS production and products of anaerobic metabolism increase permeability of the BBB, worsen brain edema and aggravate brain damage [43]. Altered glycemic conditions in patients with diabetic are prodromal to BBB damage. The increased incidence of hemorrhagic transformation in patients with post-stroke hyperglycemia also points to possible disruption of BBB integrity [44]. Therefore, prolonged high blood glucose following stroke is a factor for BBB disruption that leads to worse functional outcome, hence treatment strategies to normalize blood sugar levels after stroke are essential.

The Possible Therapeutic Targets

We reviewed the most recent finding that associated to the pathophysiology of high blood glucose in ischemic stroke. The therapeutic targets were also discussed in this present review as shown in Table 1 [46, 52, 60, 63, 64, 66-73, 76, 80, 81, 83, 88-90, 92-96].

Angiotensin receptor blocker

Angiotensin receptor blocker (ARB) is widely used by patients with hypertension that bind to and inhibit the angiotensin II receptor type 1 [45]. Previous study reported that ARB can improve ECs functions and remodel left ventricular hypertrophy [46]. Moreover, ARB also decrease cardiovascular mortality, myocardial infarction, sudden cardiac arrest, and stroke [46]. Animal studies have also showed protective effects of ARB against organ damage in animals with DM, or hypertension with or without metabolic syndrome. The effects of ARB appear to be linked to improved insulin sensitivity and decreased arterial stiffness, sympathetic activity, and inflammatory response [47-49]. Moreover, ARB can elicit anti-atherosclerotic effects through activating of peroxisome proliferator-activated receptor gamma (PPARγ) [50]. Therefore, ARB is accordingly suggested as the first line antihypertensive drugs in patients with cardiovascular diseases [51]. Previous study suggested that the use of ARB before onset may be useful for long-term functional outcome following ischemic stroke in diabetic patients [52]. However, the mechanism of ARB on hyperglycemia with ischemic stroke have not been clarified.

Antihyperglycemic

Hyperglycemia on admission is associated with increased mortality and poor functional outcomes in patients with stroke [53, 54]. Hyperglycemia might occur in response to stress as a consequence of severe stroke [2]. Although improved glycemic control has been shown to reduce the risk of microvascular complications of T2DM, its benefit for macrovascular risk reduction has been unclear [55-59]. There

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Table 1. Therapeutic targets for diabetic stroke

Therapeutic targets	Agent	Mechanism of action	Outcome		Authors
			Basic studies	Clinical studies	
ARB	ARB	AT1 inhibition	Against organ damage in animals with DM		O'Keefe et al. [46], 2001
				Useful for long-term functional outcome following ischemic stroke in diabetic patients	Kuwashiro et al. [52], 2012
Antihyperglycemic	Pioglitazone	GLP1-receptor agonist	Reduced stroke risk		Bonnet and Scheen [60], 2017
	Glucose-lowering agent	Blood glucose reduction	Increased stroke risk		Bonnet and Scheen [60], 2017
Anti-oxidants	Molecular hydrogen	Anti-oxidants effect	Showed an antioxidant effect in acute ischemic stroke		Li et al. [63], 2019
	Edaravone	Free radical scavenger		Neuroprotective in the patients with noncardioembolic acute ischemic stroke	Shinohara et al. [64], 2009
Anti-inflammatory	D-4F	mimics apoliprotein-A1, reduce MMP-9 level, prevented the loss of TJ proteins, decreased NVU damage	Improved functional outcome in diabetic stroke animals and attenuated neuronal damage in brain		Ning et al. [66], 2017
	DMT	MMP-9 regulation		Can be a possible therapeutic target for acute ischemic stroke	Iwasawa et al. [67], 2016
	IOs	Anti-inflammatory agents, decreased oxidative stress and inflammatory response	Decreased oxidative stress and inflammatory response in STZ-induced diabetic mice		Wang et al. [68], 2017
	MCC950	The blocked of NLRP3 inflammasome	Ameliorated stroke with diabetic mice and improved survival rate during recovery phases of ischemic stroke		Hong et al. [69], 2019
	BMSC	HMGB1 regulation	Contribute to the beneficial effect following stroke in T2DM rats		Hu et al. [70], 2016
		Ang1/Tie 2 signaling pathway	Attenuated BBB disruption and improved outcome after stroke in T2DM rats		Xiang et al. [71], 2017
	Vasculotide	An Ang1 mimetic peptide, decreased RAGE expression, MCP-1 levels and TNF-α levels	Decreased inflammatory response in stroke with diabetic rats as well as reduced BBB disruption		Venkat et al. [72], 2018
	S1P	Downregulating STAT3 signaling pathway	Inhibition of S1P is a potential treatment for protection of BBB		Nakagawa and Aruga [73], 2020
		Activating insulin signaling pathway	Improved insulin resistance and mitochondrial function in apolipoprotein M knockout mice		Kurano et al. [76], 2020
	Recombinant FGF21	Regulation of microglia and peripheral macrophages via NF-κB and PPARγ signaling pathway	Showed anti-inflammatory after transient focal cerebral ischemia and reperfusion		Wang et al. [80], 2020

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Table 1. Continued

Therapeutic targets	Agent	Mechanism of action	Outcome		Authors
			Basic studies	Clinical studies	
		Increasing PPARγ activity and upregulation of BBB junctional complex proteins	Showed protective effects on acute BBB damage and improving long-term neurological outcomes following diabetic stroke		Jiang et al. [81], 2020
MMPs inhibitors	Exendin-4	Analog of GLP-1	Reduced activation of MMP-9 as well as decreases infarct volume in brain		Darsalia et al. [83], 2014
Tau		Activation of GSK3β	Diabetes-exacerbated poststroke dementia might be related with abnormal tau phosphorylation		Zhang et al. [88], 2010
				an increase of the tau level was found in human cerebrospinal fluid in stroke patients	Hesse et al. [89], 2001; Vos et al. [90], 2017
Natural products	Sesamol (3,4-methylenedioxyphenol)	Reduced oxidative stress, inflammation, acetylcholinesterase	Reduced oxidative stress, inflammation, acetylcholinesterase, and cognitive deficit in diabetic rats		Kuhad and Chopra [92], 2008
	8-O-acetyl shanzhiside methyl ester	Downregulating HMGB1 and NF-κB signaling pathway	Reduced BBB damage in diabetic cerebral ischemia and reperfusion injury		Zhang et al. [93], 2014
	Rosmarinic acid	Downregulating HMGB1 and NF-κB signaling pathway	Attenuated the brain damage in diabatic stroke rat		Luan et al. [94], 2013
	ECP	Antioxidant properties	Reduced infarct volume and neuronal apoptosis in MCAO rat model		Kim et al. [95], 2012
		Activation of AMPKα	Decreased glucogenesis		Yoon et al. [96], 2017

ARB, angiotensin receptor blocker; MMPs, matrix metalloproteinases; DMT, downstream microvascular thrombosis; IOs, inonotus obliquus polysaccharides; BMSC, bone marrow stromal cell; FGF21, fibroblast growth factor 21; ECP, ecklonia cava polyphenols; AT1, angiotensin II receptor type 1; GLP1, glucagon-like peptide-1; TJ, tight junction; NVU, neurovascular unit; HMGB1, high mobility group box 1; Ang1, angiopoietin-1; RAGE, receptor for advanced glycation end products; MCP-1, monocyte chemoattractant protein 1; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-kappa B; PPARγ, peroxisome proliferator-activated receptor gamma; GLP-1, glucagon-like peptide-1; GSK3β, glycogen synthase kinase 3β; AMPK, activated protein kinase; DM, diabetes mellitus; STZ, streptozotocin; BBB, blood-brain barrier; S1P, Sphingosine 1-phosphate.

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is still uncertainty regarding the cardiovascular outcome benefits or neuroprotective effect of glucose-lowering treatment after stroke. Previous study reported that pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, conferring possible reduction stroke risk, while other classes showing a neutral impact (DPP-4 inhibitors, insulin) and some glucose-lowering agents being associated with an increased risk of stroke [60]. Currently, the accumulated evidence suggests that metformin, pioglitazone and semaglutide possible protect against cerebral ischemic stroke. These agents do not represent only a way of regulating glucose and but also offer the opportunity to reduce stroke risk. Surely, new data from ongoing and future studies will provide additional information to choose effective treatment for decreasing stroke risk in T2DM patients [61].

Anti-oxidants

Hyperglycemia and AGE can induce ROS production that lead to neuronal cell death. Anti-oxidant strategies are believed to be a promising treatment for ischemic stroke [62]. A previous study reported that oxidative stroke is more pronounced in diabetic acute cerebral ischemic stroke patient than in nondiabetic acute cerebral ischemic stroke patient. Additionally, counterbalancing antioxidant capacity are more pronounced in diabetic acute stroke patients. A blocked of ROS is suggested to terminate apoptotic process and may reduce neurological deficit. Previous study showed the neuroprotection of molecular hydrogen, as an antioxidant, in acute ischemic stroke [63]. Moreover, Edaravone, a free radical scavenger and agent used for treatment of amyotrophic lateral sclerosis, was found to be neuroprotective in the patients with noncardioembolic acute ischemic stroke [64]. However, using of antioxidants did not fully translate successfully in to the clinical application despite the role of ROS in mediating brain damage. The lack of clinical evidence on the benefit effects of anti-oxidant in stroke with diabetes need to be ascertained in detail in further research.

Anti-inflammatory

Hyperglycemia causes oxidative stress, which further results in inflammation following BBB damage. Agents Bradykinin 1 receptor (B1R) is an important role in persistent pain and inflammation. Activation of B1R was found to be a cause of hemorrhage in stoke with diabetes animals [65]. B1R activation increased MMP-9 overexpression causing cerebral hemorrhage. B1R blocking lead to the reduction of NVU barrier damage causing less cerebral hemorrhage.

Moreover, D-4F, a peptide that mimics apoliprotein-A1, was found to improve functional outcome in diabetic stroke animals through reduction of inflammatory process. Furthermore, D-4F also reduced MMP-9 level, prevented the loss of TJ proteins, decreased NVU damage, and attenuated neuronal damage in brain. Additionally, treatment of stroke with diabetic rats decrease BBB disruption and white matter damage thereby improving functional outcome [66]. These provide concrete evidence that D-4F is a promising neuroprotectant for stroke with diabetes.

Downstream microvascular thrombosis (DMT) is known to be a contributing factor for incomplete reperfusion in acute ischemic stroke that induced by ischemia and further aggravated by high blood sugar. A common link of the DMT mediators is MMP-9 activation. Previous study reported that DMT mediators can be a possible therapeutic target for acute ischemic stroke where high blood glucose increases cerebral ischemia and reperfusion injury [67].

Study showed that inonotus obliquus polysaccharides (IOs) and metformin, used as anti-inflammatory agents, decreased oxidative stress and inflammatory response in STZ-induced diabetic mice [68]. Moreover, IOs can be a promising novel agent for treatment related to neuronal protection.

NLRP3 inflammasome is significantly associated to diabetics and stroke. A previous study reported that the blocked of NLRP3 by MCC950 ameliorated stroke with diabetic mice and improved survival rate during recovery phases of ischemic stroke [69].

Other studies have demonstrated bone marrow stromal cell (BMSC) treatment of stroke reduces BBB disruption and improves functional outcome after stroke in T2DM rats. Regulation of high mobility group box 1 (HMGB1) and RAGE expression by BMSC treatment may contribute to the beneficial effect following stroke in T2DM rats [70]. Furthermore, BMSC conditioned medium can attenuates BBB disruption and improve outcome after stroke in T2DM rats through angiopoietin-1 (Ang1)/Tie 2 signaling pathway [71].

Moreover, previous study revealed that diabetes related with reduction of Ang1 that has powerful vascular protective effects. Vasculotide, an Ang1 mimetic peptide, that has anti-inflammatory effects. Vasculotide decreased RAGE expression, MCP-1 levels and TNF-α levels in stroke with diabetic rats as well as reduced BBB disruption. It is suggested that vasculotide-induce neuroprotective effects in stroke with diabetes [72].

Sphingosine 1-phosphate (S1P) is a main bioactive lipid mediator in the immune system, infiltration of the peripheral blood cells into the CNS, endothelial barrier integrity, and inflammatory responses [73-75]. During disease states such as cardiovascular disease and diabetic, S1P elicits both harmful and beneficial effects depending on the receptor type that is activated. Previous study indicated that inhibition of S1P is a potential treatment for protection of BBB in both *in vitro* and *in vivo* model after ischemia through downregulating STAT3 pathway [73]. Moreover, Apolipoprotein M/S1P also has protective effect against insulin resistance through activating insulin signaling and improving the mitochondrial functions in apolipoprotein M knockout mice [76].

Human fibroblast growth factor 21 (FGF21) is an endocrine member of fibroblast growth factor family that plays important role in glucose metabolism, lipid metabolism and energy balance [77-79]. Previous study demonstrated that the anti-inflammatory effect of recombinant FGF21 on transient focal cerebral ischemia and reperfusion occurs through regulation of microglia and peripheral macrophages via NF-κB and PPARγ signaling pathway [80]. Moreover, recombinant FGF21 has been showed protective effects on acute BBB damage following diabetic stroke through increasing PPARγ activity and upregulation of BBB junctional complex proteins [81]. In addition, it has beneficial effect for improving long-term neurological outcomes in T2DM [81]. Therefore, recombinant FGF21 might be a potent candidate of the disease-modifying strategy for treating diabetic stroke.

Anti-inflammation is considered a prime target for development of new stroke with diabetes therapies. However, these facts need to be studied in detail in future.

Matrix metalloproteinases inhibitors

MMP-9 are proteolytic enzymes that play an important role in neuroinflammatory disorder through BBB damage. Previous study reported that upregulation of MMP-9 expression in diabetic patient has an important relation with the level of blood glucose. Zhong and coworkers [82] investigated between MMP-9 levels and the prognosis of 300 acute ischemic stroke patients. They found that increased risk of disability and mortality were related with high serum MMP-9 levels. Therefore, blockage of MMP-9 may act potential treatment agents for stroke with diabetes. Exendin-4, a long-acting analog of the hormone GLP-1, was investigated the effect on attenuating glucose levels in hyperglycemic mice and cerebral ischemic stroke [83]. The data showed that GLP-1 reduces activation of MMP-9 as well as decreases infarct volume in brain. Moreover, a previous study revealed that GLP-1 exhibits antioxidant effect that attenuates inflammatory response in T1DM and prevents the ECs dysfunction. It was concluded that anti-MMP-9 is a potential therapy for stroke with diabetic, but clinical trials in patients are limited.

Tau protein

Tau protein mainly expressed in adult human brain that plays a crucial role both in neurogenesis and stoke [84]. Tau hyperphosphorylation was found following cerebral ischemic damage in rat brain and hypoxia-dependent in vascular dysfunction model [85-87]. Previous study reported that diabetes-exacerbated poststroke dementia might be related with abnormal tau phosphorylation through activation of glycogen synthase kinase 3β (GSK3β) in hippocampus [88]. Moreover, the change in pattern of phosphorylation of tau associated with BBB dysfunction in brain ischemia. In clinical studies, an increase of the tau level was found in human cerebrospinal fluid in stroke patients [89, 90]. Nowadays, researcher have found several methods to regulate the tau levels such as methylene blue, AMK-activated protein kinase (AMPK)-related kinase Nuak1, ERK inhibitor, GSK3β [84].

Naturals products

Several studies investigated the natural compounds in diabetic rats with stroke. A previous study reported that curcumin reduced neuronal apoptosis in brain and cerebral infarct volume, by upregulating glut1 and glut3. These results suggested that curcumin may protect DM-related cerebral infarction [91]. Sesamol (3,4-methylenedioxyphenol) is a natural organic compound that is found in sesame seed. A previous study revealed that sesamol reduced oxidative stress, inflammation, acetylcholinesterase, and cognitive deficit in diabetic rats [92]. 8-O-acetyl shanzhiside methyl ester, an iridoid glucoside isolated from leaves of Lamiophlomis rotate kudo, reduced BBB damage in diabetic cerebral ischemia and reperfusion injury through downregulating HMGB1 and NF-κB signaling pathway [93]. Furthermore, rosmarinic acid, commonly found in species of the Boraginaceae, was investigated in a cultured neuronal cell line and experimental ischemic stroke with diabetes. Rosmarinic acid attenuated the brain damage in diabatic stroke rat through HMGB1 and NF-κB signaling pathway [94]. Moreover, Ecklonia cava polyphenols (ECP), having a strongly antioxidant properties, significantly reduced infarct volume and neuronal apoptosis

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in MCAO rat model [95]. In *in vitro* study, it blocked the rise in cytosolic calcium in differentiated SH-SY5Y cells exposed to H_2O_2 [95]. Previous study reported that this compound decreased glucogenesis through modulating of AMPKα pathway [96]. These findings suggest that ECP may have a therapeutic potential for the treatment of stroke, as well as diabetic stroke. There are several naturals products can reduce BBB damage in stroke with diabetic animals. However, there is limited evidence for clinical efficacy.

Conclusion

Ischemic stroke is a crucial cause of ischemic stroke. DM induces microvascular and macrovascular changes, and BBB breakdown that facilitates inflammatory events after stroke. BBB disruption has been considered the initial step that induce neurological deficit and functional disabilities. Functional outcomes in stroke are significantly worse among DM. Hyperglycemia is a serious problem in DM and is strongly related to high mortality and morbidity level in ischemic stroke patients that is caused by increased ROS production and future inflammation damaging BBB. Anti-oxidant, anti-inflammatory properties may possibly the therapeutic targets for stroke with diabetes. Moreover, natural compounds may be alternative treatment for diabetic after stoke.

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Conceptualization: PM. Data acquisition: PW. Data analysis or interpretation: SD. Drafting of the manuscript: PW. Critical revision of the manuscript: SD, PM. Approval of the final version of the manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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