Review Article

Targets, Treatments, and Outcomes Updates in Diabetic Stroke

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Goal: Due to multiple failures to translate basic research, the need for novel therapeutic targets and strategies is still urgent to save a larger number of the stroke patients' population and to reduce the toxicity of the current stroke therapy. *Method*: We summarize the most recent, within past 5 years, basic and clinical diabetic stroke research findings. *Findings*: We aim to examine the most current understanding of stroke and neurovascular unit integrity, especially in presence of hyperglycemia and/or diabetes mellitus. From there, we are comparing the meaningful findings that aim at treating diabetic stroke to see where they differ, where they succeed, and where they open questions for new therapeutic strategies. *Conclusion*: The need for more clinically effective neuroprotective strategies is still mismatched with the bench side findings.

Key Words: Diabetes mellitus (DM)—neurovascular unit (NVU)—metalloproteinase(s) (MMPs)—MMP-2—MMP-9—hyperglycemia (HG)—blood-brain barrier (BBB)—stroke—neuroprotection

Introduction

The pharmacological option to treat acute ischemic stroke (AIS) has not changed in recent years and remains as tissue plasminogen activator (t-PA). The aim of this review is to contrast the most recent findings related to the pathophysiology of hyperglycemia and/or diabetes in AIS. Additionally, we will compare the different treatment strategies used to protect the neurovascular unit (NVU) from damage. We wanted to contrast the therapeutic targets that may have recently emerged then match them with the most current pharmacological and nonpharmacological treatment strategies. Finally, we specifically linked that target-therapy pair to an outcome in the experimental side versus the clinical side to gain potential insights about the translational applicability and/or new directions of the research in the diabetic stroke arena.

There are about 90,000 AIS cases in USA per year, making it the fourth common cause of death due to a cardiovascular disease.[1] There is also 1 FDA-approved drug for treatment to restore flow, t-PA. For many practical reasons, only 5-15% of eligible patients at best get to receive this treatment which is one reason that fuels AIS research. Additionally, t-PA itself can cause an adverse event that could be lethal, which is bleeding. Unfortunately, it is the very same most undesirable outcome when treating AIS. That is AIS conversion to the worse type of stroke, hemorrhagic stroke.

Accordingly, most of the research in stroke continues to aspire to find new and effective therapeutic targets. Another area of research is to optimize the use of t-PA by minimizing its bleeding toxic potential. Both approaches mandate a most up-to-date understanding of the molecular factors and pathways responsible for maintaining the integrity of the NVU. The NVU can be compromised by (1) Stroke itself or by (2) Hyperglycemia or by (3) Diabetes, a common comorbidity in AIS patients, or by (4) t-PA itself. The article will not extensively look at reasons why many of the current failures have occurred, but it will rather take a fresh look on the potential new trends in treating diabetic stroke and/or potential unique outcome benefits for these different strategies. By taking this perspective, we aim at shedding light for newer directions and further novel investigations in the field.

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Design/Method

The database used for our research was Pubmed.gov. Here, we used a varying combination or keyword searched. This list included: Diabetes mellitus (DM), NVU, blood-brain barrier, neurovascular injury, metalloproteinase(s) (MMPs), MMP-2, MMP-9, MMP-3, hyperglycemia (HG), middle cerebral artery occlusion (MCAO), neuroprotection, tissue plasminogen activator (t-PA), and stroke. All articles referenced were limited with a search time parameter, that is within the past 5 years to look for the most updates within this time frame.

Upon collecting only, the most recent and most relevant articles (Tables 1 and 2), we structured the flow of the article to begin with the most current updates in our standing for the pathophysiological changes behind NVU damage in setting of hyperglycemia and/or diabetes and AIS. We then discussed the role of endothelial dysfunction, hyperglycemia, and MMPs in stroke pathophysiology. The next section contains different pharmacological strategies for either providing neuroprotection and/or prevention of neurovascular damage. They include different antioxidants novel MMPs inhibitors and the recent use of intranasal insulin. The last section is followed with nonpharmacological strategies that link to the same pharmacological targets including modulating oxygen tension and natural products delivered via nanoparticles systems.

Results

Pathophysiology of NVU Damage in Diabetes and Ischemic Stroke

Role of Hyperglycemia in Causing Inflammation

Higher levels of glucose may be a type of a stress injury to the endothelial cells of brain causing damage which manifests as inflammation. Markers of NVU disruption, specifically pro−inflammatory molecules and nitrite production as surrogate markers for inflammation in diabetic patients, were investigated by one group.[2] All these pro−inflammatory markers were elevated and overexpression of miR-Let7a to disrupt hyperglycemia-induced brain endothelial cells inflammation resulted in neurovascular protection seen as reduced apoptosis and lower level of inflammation detected as lower nitrite production.

The complexity of the immune-inflammatory responses and targets in AIS are vast. To try and minimize reperfusion injury, Mizuma et al studied this response and showed that damage-associated molecular pattern inflammatory mediators release play a large role in terms of ischemia/reperfusion injury, especially regarding lesion size and edema caused by weakening of the NVU barrier.[3]

Role of Endothelial Dysfunction in Causing NVU Damage

ROCK-pathway (rho-associated, coiled-coil-containing protein kinase): thromboxane A2 (TxA2) receptor (TPr) activation causes NVU disruption via vascular contraction eventually causing edema. Interestingly, the activation of this receptor was reported in cardiac ischemia as well as being a downstream effector of Endothelin-1 (ET-1).[4] Zhao Z et al found that *in vitro* TPr agonist U46619A and hyperglycemia have a similar effect in causing NVU disruption using human brain microvascular endothelial cells.[5] Using streptozotocin (STZ) type 1 diabetes mellitus (T1DM) model, they concluded these effects were mediated via ROCK signaling. Hyperglycemia can be looked at once again as an inflammatory stimulus causing endothelial dysfunction within the NVU vascular component. Similarly, Posada-Duque et al studied the role of RhoA/ROCK inhibitors as a strategy of NVU long-term recovery past the ischemic event occurrence.[6] They concluded that Rac, a Rho GTPase, and synaptic adhesion proteins such as p120 catenin and N-catenin are neuroprotective specially against cerebral infarction. They also proposed that statins pleiotropic neuroprotective effect works through the same pathway.

MMP-9 overexpression: The link between NVU endothelial dysfunction, MMPs, and apoptosis was studied by Mishiro et al.[7] Using STZ mice model, there was an interesting differential damaging effect of chronic hyperglycemia (HG) on NVU injury. While HG worsened hemorrhagic conversion/hemorrhagic transformation (HT) after MCAO, it did not worsen the size of infarct. The mitochondrial caspase activation causing apoptosis to NVU and consequently NVU injury was proposed to be partially mediated by matrix metalloproteinase-9 (MMP-9). In the coming section, we will discuss in more details the role of other MMPs as it has been an extensive research area in the cerebrovascular diseases domain.

Role of MMPs

del Zoppo et al researched the correlation between the expression of MMP-3 in an ischemic stroke model and HT. Higher level of MMP-3 in experimental AIS showed a direct correlation with HT as well as worse neurological outcomes.[8] Hafez et al were able to show that inhibitions of MMP-3, either using UK 356618 or via knockout, resulted in significant reduction of HT.[9]

In a review by Jickling et al, that focused on the temporal expression of MMPs, it was proposed that early HT is probably related to increases in other type of MMPs, mainly MMP-2 and MMP-9.[10] On the other hand, late motor complications are probably related to elevations in levels of MMP-2, MMP-3, MMP-9, and endogenous t-PA.

Zhao et al studied the diabetic-induced neuropathy. Ghrelin, a 28-amino acid found to be neuroprotective. Ghrelin

Table 1. *Pharmacological strategies for NVU protection in diabetic stroke*

Author	Pathophysiology	Pharmacological target(s)	The outcome(s) that improved experimentally	The outcome(s) that improved clinically
Lioutas et al	Lower blood glucose	IV insulin in mild hyperglycemia		Greater infarct area, more hypoglycemia
Kumari et al	Inflammatory process	Thiazolidinediones	Less infarct without lowering HG	
Blacker et al	Inflammatory process	Minocycline IV with t-PA	Less infarct, edema and HT	
Fan et al	Lower BG	Insulin therapy with t-PA	Less infarct, edema and HT vs t-PA alone	
Song et al	Pro-inflammatory molecules and nitrite production	miR-Let7a	Less apoptosis and inflammation	
Mizuma et al	Immune-inflammatory responses	(DAMP) inflammatory mediators	Less infarct and edema	
Mozaffarian et al	(ROCK) signaling	Thromboxane A2 (TxA2) receptor (TPr)	Activated by hyperglycemia and results in impairment to the BBB	
Zhao et al	(ROCK) signaling	RhoA/ROCK	Inhibitors of RhoA/Rock stop neurodegeneration and decrease cerebral infarction	
Mishiro et al	Mitochondrial caspase activation	MMP-9	Apoptosis and endothelial dysfunction in NVU	
del Zoppo et al	Increased MMP-3 levels	MMP-3	Less HT	
Jickling et al	Increased MMP-2 and MMP-9 levels	MMPs	Increased NVU damage and increased HT risk	
Zhao et al	Ghrelin affect neuroinflammation	NGF metabolism and synaptic degeneration	Decreased neuroinflammation and regulation of MMP levels	
Yang et al	ROS	Heme oxygenase-1 (HO-1) blockade	Terminated neuronal apoptosis	
Hu et al	Bradykinin 1 receptor activation	Bradykinin 1 receptor blockade	Less edema	
Ahmadi-Eslamloo et al	Inflammation	Anti-inflammatory and MMP-9 inhibition	Improved functional outcome and Less Edema and decreased white matter damage	
Desilles et al	DMT induction by ischemia, potential drug target	MMP-9	Decreased ischemia/reperfusion cerebral injury with DMT modulators	
Wang et al	Inflammatory and ROS	ROS	Restored superoxide dismutase, catalase, glutathione and malondialdehyde. Down-regulated IL-2 receptors and MMP-9	NA
Neuhaus et al	PPAR-alpha activation	PPAR-alpha blockade	Less edema and t-PA activity	NA
Hu et al	ERK induction	MMP-2 and MPP-9	Less degradation of the extracellular matrix (ECM) of NVU	NA
Simao et al	PKal inhibition	PKal	Reduction of t-PA ADRs (HT, infarct volume, MMP-9 activity, and edema)	Improvement of t-PA's safety

(*Continued*)

Table 1 (*Continued*)

Author	Pathophysiology	Pharmacological target(s)	The outcome(s) that improved experimentally	The outcome(s) that improved clinically
Zhong et al	MMP modulation	MMP-9	NA	Higher serum MMP-9 levels were associated with increased risk of mortality and major disability
Aggarwal et al	Activity and expression of MMP	MMP-9	Improved memory and cognitive function	NA
Bhatt et al	Doxycycline and aspirin use for inhibition of MMP-9	MMP-9	Increased NVU protection and decreased diabetic neuropathy	NA
Ceriello et al	MMP-9 activation and infarct growth	GLP-1 agonist	Less infarct growth and MMP-9 activation	NA
Wang et al	ROS and MMP-9 activation	MMP-9 inhibition	Less endothelial dysfunction and inflammation	NA
Kanazawa et al	Vascular remodeling	Anti-VEGF	Less endothelial leakage	NA
Coucha et al	Vascular remodeling	Anti-VEGF	Less vascular remodeling	NA
Lioutas et al	HG	CNS	NA	Prevented cognitive decline using Intranasal insulin

Table 2. *Nonpharmacological strategies for NVU protection in diabetic stroke*

Author	Pathophysiology	Pharmacological target(s)	The outcome(s) that improved experimentally	The outcome(s) that improved clinically
Opris et al	Inflammation and Oxidative Stress	ROS	Anti-inflammatory and antioxidant effect, reduced MMP activity and inflammation in liver	
Pandey et al	Antioxidant effect on MMPs activity	MMP-2 and MMP-9	Less edema and HT with improved neurological function	
Ahmadi-Eslamloo et al	Vanadium use for HG and decreased oxidant production	BG and Brain tissue	Lowered BG equivalently to insulin while protecting the brain tissue	

was tested to reveal its effects on the brain's astrocytes, MMP-9, IL-6, nerve growth factor (NGF), tumor necrosis factor, and other factors involved in neuronal inflammation.[11] The group was able to show that ghrelin inhibited neuroinflammation as well as prevented the breakdown of NGF and synaptic degeneration via modulation of MMPs levels.

Pharmacological Strategies for NVU Protection in Diabetes and Stroke

Antioxidants

HG can cause neuronal apoptosis. High glucose levels induce reactive oxygen species (ROS) which in turn increase the expression of heme oxygenase-1. This finding has been shown in rats' astrocytes by Yang et al.[12] A blockade of ROS is proposed to terminate this apoptotic process. However, for multiple reasons discussed in other literature outside the scope of this review, the approach of using antioxidants has not translated successfully into the clinical domain despite scientific evidence on ROS role in mediating NVU injury.

There is an ongoing phase 2 clinical trial, neuroprotection in AIS that investigated molecular hydrogen as an antioxidant and is estimated to be completed in August 2019. However, it is used in combination with minocycline as an MMP inhibitor. Interestingly, a drug approved to treat amyotrophic lateral sclerosis, has been studied in the Japanese clinical trial, *Edaravone (radical scavenger) versus sodium ozagrel (antiplatelet agent) in acute noncardioembolic ischemic stroke (EDO trial)*.[13] Edaravone was found to be neuroprotective in about half of the patients with noncardioembolic AIS as evident by lower modified Rankin score 0-1, indicating the least severe type of motor injury following stroke. As there is clinical guidelines differences between USA and Japan as well as potential population differences, these results may need to be further studied in a more representative US population.

Anti-inflammatory Agents

Bradykinin 1 receptor (B1R) activation was found to be the cause of hemorrhage in diabetic stroke animals with or without HT.[14] As B1R gets activated, both mRNA and protein expression of MMP-9 increased causing hemorrhage. B1R signal was blocked, right immediately prior to reperfusion, using both extracellular regulated kinase (ERK) inhibitor, U0125; and the nuclear factor-Kappa B (NF-kB) inhibitor; PDTC. This led to the preservation of the NVU barrier integrity causing less hemorrhage during the 8 hours post reperfusion period.

Another group, Cui et al, studied diabetes mellitus of type-1 (T1DM) in stroked animals by using D-4F, which is a peptide that mimics apolipoprotein-A1.[15] D-4F possesses anti-inflammatory properties which improved functional outcome in these diabetic stroke animals, decreased NVU injury, specifically leakage, and lowered MMP-9 levels, increased the expression of the tight junction proteins, and reduced the damage to the ischemic neurons in brain.

Downstream microvascular thrombo-inflammation (DMT) is induced by ischemia and further exacerbated by HG. A common link for many of the DMT mediators is activation of MMP-9 as a downstream molecular player. Many DMT mediators can be a potential therapeutic target for AIS used to study how hyperglycemia increases ischemia/reperfusion cerebral injury.[16]

The effects of inonotus obliquus polysaccharides (IOs) on the mechanisms of oxidative stress and inflammation in diabetes were studied by Wang et al using STZ mice.[17] Metformin and IO1-4 or IO5 were used in the study as anti-inflammatory drugs. The data was significant in showing recovery of major defense systems against ROS such as catalase, glutathione, malondialdehyde, and superoxide dismutase to almost normal values. Additionally, both interleukin-2 (IL-2) receptors and MMP-9 were downregulated. The study was successful at showing that possibly by altering oxidative stress and inflammatory factors caused by T1DM, IOs can be a promising novel treatment for neuroprotection.

Peroxisome Proliferator-Receptor Alpha (PPAR-Alpha) Agonists

The role of PPAR-alpha in both stabilizing the NVU barrier and preventing further compromise in traumatic brain injuries in general was recently reviewed by Thal et al.[18] It was proposed that PPAR-alpha activation can have two effects. First, stabilizing the NVU and second, preventing further degradation of tight junction proteins by inhibiting transcription of MMPs. Neuhaus et al showed that using the PPAR-alpha agonist, WY-14643, protected against stroke.[19] In this study, both NVU damage and t-PA activity were reduced. Of note, thiazolidinediones such as pioglitazone used in clinical practice to treat type-2 diabetes mellitus (T2DM) are classified as a PPAR-gamma agonist.

MMPs Inhibitors

t-PA, the sole FDA-approved pharmacological intervention for AIS, causes bleeding as an adverse drug reaction. This happens via ERK induction causing elevations in MMP-2 and MMP-9 levels. Ischemic injury triggers caveolin-1 (Cav-1) s-nitrosylation of MMP-9 which augments hemorrhage induced by t-PA. SB-3CT was used to block MMP-2 and MMP-9 leading to less degradation of the extracellular matrix of the NVU.[20]

In another clinical study, the effects of t-PA on plasma kallikrein (PKal) were studied in murine and human plasma of AIS patients. PKal inhibition, using a Klkb1$^{-/-}$ mice model, reduced the t-PA-mediated adverse effects like edema, infarct volume, MMP-9 activity, and HT. This

shows PKal as a therapeutic target when administered prior to t-PA in treatment of ischemic stroke to improve the safety of t-PA.[21]

Zhong et al examined the association between serum MMP-9 levels and the prognosis of AIS in humans. The investigators measured MMP-9 levels in about 3000 patients.[22] The outcome was analyzed 3 months after stroke. The data showed that higher serum MMP-9 levels in acute phase of ischemic stroke were associated with increased risk of major disability and mortality. The study further highlights the clinically important role of MMP-2 and MMP-9 in AIS injury and the need for successful MMPs modulators as potential novel therapeutic agents for AIS.

S-nitro glutathione (GSNO) supplementation as an anti-MMP-9 was used in a diabetic STZ mice model. As diabetes is known to increase the activity of MMP-9 and its expression, GSNO successfully reduced MMP-9 levels and tissue inhibitor MMP-1. The resulting restoration of NVU integrity was shown by improved memory and cognitive functions.[23,24] Bhatt et al in a study using STZ diabetes model showed that a combination of doxycycline and aspirin was protective against diabetic neuropathy by inhibiting MMP-9.[25]

Some existing MMPs inhibitors, for example GM6001, can decrease tight junctions' protein damage and provide NVU protection by preserving occludins and ZOL-1. Yet, their adverse events profile is serious given the involvement of MMP-9 in many physiological processes. The approach of studying already existing drugs for other effects goes beyond the use of minocycline. Some groups experimented with the use of antidiabetic drugs and demonstrated potential anti-MMPs activities for these agents. Exendin-4, a glucagon-like peptide-1 (GLP-1) receptor agonist was studied to understand its effect on reducing glucose levels in hyperglycemic mice and ischemia. It was shown to reduce MMP-9 activation as well as to inhibit infarct growth.[26] The previous study revealed that exendin-4 provides neuroprotection against ischemic injury. Ceriello et al investigated the effect of GLP-1 and its activity on MMP-14.[27] GLP-1 exhibits antioxidant properties that protect the endothelial function and reduces inflammation in T1DM. MMP-14 is activated by acute hyperglycemia and hypoglycemia because of its generation of oxidative stress. GLP-1 was shown to counteract these MMP-14-mediated effects because of its antioxidant activity.

Antiangiogenic Agents

Abdelsaid et al's past experimental evidence has shown that high glucose levels compromised the NVU integrity by causing permeability to increase.[28] Yan et al investigated the mechanism of this increased permeability secondary to HG using *in vitro* animal microvascular endothelial cells.[29] HG increased the permeability, significantly reduced the expression of the following tight junctions proteins, zona occludens protein-1 (ZO-1) and occludin, causing disruption in endothelial cells integrity. Vascular endothelial growth factor (VEGF) inhibition reversed these effects by increasing the expression of occludin and ZO-1 thus leading to a significant improvement in cells tight junctions' integrity seen as less leakage. These results were also duplicated in the cells of human brain microvascular endothelium.

Another study focused on the different pathways that may be beneficial in reducing hemorrhagic transformation after t-PA use.[30] Some of the possibilities are the VEGF pathway along with recombinant angiopoietin-1 protein treatment. Additionally, it was noted that a new potentially therapeutic target, progranulin, may be successful in suppressing vascular remodeling. Coucha et al have shown the importance of vascular remodeling in worsening stroke outcomes in T2DM.[31]

Intranasal Insulin

Here, the researchers investigated the use of intranasal insulin in stroke patients to reduce cognitive decline. Insulin central functions include neuronal homeostasis via preserving neurons growth and plasticity among many other functions. They found that this route is efficacious because it bypasses first pass metabolism and allows for the maximum distribution to the central nervous system (CNS). In their study, Lioutas et al found this route to be especially preferable in older patients as it has shown to prevent cognitive decline.[32]

Nonpharmacological Strategies for NVU Protection in Diabetes and Stroke

Oxygen Tension Modulation

Hyperbaric oxygen was investigated in hemorrhagic transformation in hyperglycemic animal models. It reduced mitochondrial dysfunction, a major contributor to oxidative injury. It also maintained the viability of the penumbra and the noninjured tissues. Through different mechanisms, like reactive oxygen species/thioredoxin-interacting protein/Nod-like receptor protein 3 pathway, hyperbaric conditioning was able to reduce hemorrhagic transformation.[14]

Natural Products Conjugated to Nanoparticles

Opris et al used natural products conjugated to gold nanoparticles (NPs) and showed NPs to have an anti-inflammatory effect.[33] They also evaluated the antidiabetic effect of NPs of the natural product *Sambucus nigra* L. This extract was given to diabetic rats to assess the antioxidant status, liver function, and MMP-2 and MMP-9 activities. Decreased cyclooxygenase-2 (COX-2) expression and pro-MMP-2 activity after treatment were significant. NPs were showed to have an anti-inflammatory and antioxidant effects as well as reducing of MMPs activity and inflammation in liver.

Resveratrol was studied to understand its antioxidant effect on MMPs activity in animals' brain. Resveratrol was found to relieve brain edema, improve neurological function, and lower cerebral infarct volume by occupying the active site of MMP-2 and MMP-9.[34]

The effectiveness of vanadium compounds in lowering blood glucose in diabetic rats was found to be as effective as insulin in a MCAO model. By lowering blood glucose, the vanadium compounds also play a role in reducing the production of oxidants which in return minimizes NVU damage thus protecting the brain tissue.[35]

Conclusions

Many roads start with HG and lead to MMPs. By reviewing the most recent work in preclinical and clinical diabetic stroke, three major pathophysiological pathways were found to be actively investigated. (1) The major inflammatory stimulus, HG, which is a major contributor to NVU injury, (2) endothelial dysfunction within the NVU that ensues from HG/diabetes with the resultant vascular remodeling and the compromise in NVU integrity, and finally (3) MMPs as key players in causing digestion of tight junctions proteins and increasing HT incidence.

The strategies experimented to target the above 3 pathways included multiple approaches. We will state them backward, from the clinical side to the bench side. Interestingly, when Simao et al targeted PKal pathway, they were able to see a reduction in the adverse drug events (ADRs) profile of t-PA which included reducing HT, reducing infarct volume, and reducing edema.[21] All these improvements in t-PA safety profile were accompanied by a significant reduction in MMP-9 activity (Table 1). The work of this group highlights the successful approach of lowering t-PA toxicity by coadministration with another agent.

Zhong et al, once again highlighted the importance of increased MMP-9 levels as markers associated with poorer neuro-functional outcomes in AIS.[22] The need for finding that specific and clinically useful MMP inhibitor remains to be elusive. Aggressive lowering of HG using high doses of insulin IV was found to be determinantal by increasing infarct size and causing hypoglycemic events.[36] There have been numerous reports, experimental and clinical, that highlighted the importance of a more balanced targeting of HG levels.[37,38] In what seems to be a clinical validation to this, is Lioutas et al's work that used intranasal insulin therapy to deliver insulin into CNS showing a prevention in cognitive decline as evidence of some level of neuroprotection effects of insulin using this route and novel delivery system.[32]

Fan et al used insulin with t-PA to lower the incidence of HT and improve its safety, a therapeutic intervention with a promising clinical applicability, to guard against HG and/or diabetes worsening effects on AIS neurological outcomes.[39] Neuhaus et al used PPAR-alpha modulators to lower t-PA activity which resulted in less edema.[19] Another group, Kumari et al, was able to show a reduction in infarct volume using thiazolidinediones which is a current T2DM treatment with PPAR-gamma modulation activity.[40] Minocycline was coadministered t-PA with results showing less HT and edema.[41]

While most of the other studies showed experimental evidence of NVU protection (Tables 1 and 2), we are yet to see the translational applicability of these strategies. Many studies targeted MMP-2, MMP-9, and MMP-3 with successful experimental reduction in NVU damage outcomes. Other studies, for example, Coucha et al, targeted vascular remodeling and VEGF pathways to protect the NVU.[31]

Examining the above results shows that there is a need to develop newer and more specific MMPs inhibitors to treat diabetic AIS. Development of newer anti-VEGF agents could potentially be a new therapeutic strategy to treat diabetic stroke.

There are no sources in the current document. Targeting both HG and/or diabetes by using already existing drugs on the market to study their potential in improving AIS stroke seems to be an effective and a practical approach. Aiming to reduce t-PA ADRs has been shown to be successful clinically.

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