Review Article

Diabetes Associated Memory Impairment: Perspective on Management Strategies

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ABSTRACT

The comorbidity of diabetes and memory impairment is rapidly increasing and imposes a great burden on the healthcare worldwide. It is one of the most alarming illnesses especially to elderly people. Diabetes mellitus is the peril element for memory dysfunction and memory impairment in the old age. Hyperglycemia is a pathological condition associated with diabetes and memory impairment. The pathogenesis of memory impairment has been correlated with hyperglycaemia induced metabolic derangements, reactive oxygen species, advanced glycation end products and neurophysiological alterations, neuronal abnormalities. Long term hyperglycaemia elicits enhanced glycation pathway, increased non-enzymatic glycation of various structural proteins, moreover increased oxidative stress as well as altered the advanced glycation end products activity and proinflammatory pathways activation that are all inter-related for the cause and development of memory impairment. These in turn activate or suppress the AGE/RAGE activity or activate amyloidogenesis and proinflammatory pathways which furthermore resulting in functional and structural derangement of nerve cell. Furthermore, the aspect of these studies highlight and encourages which escalating the perspective of memory impairment and opening a new window for the development of new therapeutics. Memory impairment is materializing new complication of type 2 diabetes that feels necessity for further study. This review study highlights the functioning of pathogenic mechanisms and pathways involved in the development of diabetes associated memory impairment and also the current therapies with their drawbacks as well as the advanced therapy.

Keywords: AGE/RACE, Cognitive dysfunction, Hyperglycemia, Reactive oxygen species

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INTRODUCTION

Diabetes disease consider as a main threat to worldwide public health since the numeral of diabetic patients is hastily increasing globally. Diabetes mellitus (DM) is a group of metabolic disease illustrate by chronic hyperglycemia resultant from deficiency in insulin secretion, insulin action or both [1]. Multiple risk factors associated with impaired metabolism of carbohydrate, lipid and protein, frequent urination, increased thirst and hunger [2, 3]. In DM, the homeostasis of protein, carbohydrate and lipid metabolism is inappropriately regulated by insulin hormone resulting in rise of fasting as well as postprandial blood glucose levels. As the condition of hyperglycemia progresses, increases in tissue or vascular damage may lead to obesity, hypertension, advancing age, accumulation of harmful agents in the vascular endothelium causing development of microvascular complications. DM and correlated complications are associated with many pathological conditions which are responsible for abridged quality of life and augmented peril factors for mortality and morbidity. The chronic hyperglycemia and uncontrolled type 2 diabetes mellitus (T2DM) is a significant factor in the advancement and succession of micro (diabetic nephropathy, neuropathy and retinopathy) and macro (peripheral arterial

disease, stroke and coronary artery disease) vascular complications [4-6]. Urbanization, increase in obesity and physical inactivity are the main reasons for the occurrence of diabetes [7].

According to the International Diabetes Federation (IDF), Diabetic patients in India will rise to 101.2 million by 2030 and it is expected that it will raise upto 438 million within 20 years. Every year, 7 million people are suffering from DM [1]. The increased prevalence of diabetes mellitus represents a significant burden to human health because of its long lasting and serious diabetic complications, all of which contributes to increase the diabetes associated morbidity and mortality [8].

The exact mechanism of DM is still a mystery but it has been found that both genetic and environmental factors are responsible for the onset of DM. The Type 1 diabetes mellitus (T1DM) was formerly termed as Insulin-dependent DM (IDDM) or juvenile diabetes; it is due to autoimmune demolition of the insulin-producing β-cells resulting in low or no production of insulin hormone. Similarly T2DM, previously termed as non-insulin dependent DM (NIDDM), was usually associated with aging [9]. Gestational diabetes mellitus (GDM); is states by blood glucose intolerance of unpredictable severity with onset of first identification during pregnancy. Hyperglycaemia throughout pregnancy is found to be connected with various maternal and perinatal adverse results. Their child will have enduring increase risk of obesity, glucose intolerance and metabolic syndrome whereas the mothers will have a higher risk of metabolic syndrome and diabetes in the point of future [10].

Symptoms of diabetes include polyuria, polydipsia, glycosurea, weight loss, tiredness, blurred vision etc [11]. Individual can experience different sign and symptoms of diabetes like augmented appetite, a tickly sensation and/or lack of sensation in the hands or feet, slow-healing wounds, common infections, vomiting and stomach pain.

DIABETES INDUCED MEMORY IMPAIRMENT

Diabetes mellitus is coupled with slowly progressive end-organ damage in the brain. Memory impairment is common and valuable complication of DM. It is one of the most alarming illnesses especially to elderly people. Mild to moderate impairments of memory functioning has been account in patients with DM [12]. Memory impairment is illustrated clinically by progressive memory and orientation loss and other memory shortfall which together with impaired judgment and making of decision, apraxia and language disturbances [13]. These are classically accompanied by a variety of neuropsychiatric symptoms (i.e. depression, apathy, anxiety, agitation, delusions, and hallucinations). Emerging epidemiological data indicate that DM is a significant comorbid risk factor for developing late onset memory dysfunction, suggesting a causal link between glucose dysfunction and memory impairment pathogenesis [14, 15]. A growing body of evidence suggests that hyperglycemia is fundamental to the development of irregular memory impairment, designating irregular memory impairment as “type 3 diabetes” [16].

Memory impairment is projected to become an epidemic among the elderly in the coming decades. The Asia Pacific Regional Conference 2014 updated the estimates of memory impairment prevalence data for the region, such as the estimate that the number of people with memory impairment above the age of 60 years in India will increase from 23 million in 2015 to almost 71 million by 2050 [17]. In developed countries, 10% of the population, 65 years or older, have memory impairment. The prevalence doubles every five years after the age of 60 and reaches nearly 50 percent after the age of 85 years. The prevalence of DM memory impairment has been rising in many regions of the world.

Hyperglycemia come into sight to be interconnected to the memory aberration in patients with DM. Diabetic memory impairment develops on a milieu of hyperglycemia and related metabolic imbalances primarily oxidative stress. Hyperglycemia results more production of free radicals which has been recognized as the source of additional complications. Studies up to date have well-known core pathways that are coupled to DM induced

memory impairment, such as stimulated polyol pathway, advanced formation of glycation end products (AGE's), and other cascades of stress responses. On other hand, the glucose metabolism and insulin signaling are vital for normal brain function. Insulin signaling impairment, is associated with DM is known to influence the expression and metabolism of amyloid-beta (Aβ), DM might, furthermore aggravate the synthesis of Aβ, synaptic impairment in addition to nerve cell death in patients with memory impairment [18]. With the increase in the number of elderly individuals with T2DM, the number of diabetic patients with memory impairment has been growing.

Current significant advances in pharmacological therapy have made a variety of interventions available. Memory impairment, however, has not been targeted by the current management strategies of DM. Memory impairment in patients with DM creates a large burden for patients and society. The current review study is intended to highlight the role of various mechanisms and pathways are involved in the progression of diabetes associated memory impairment and detail on advanced treatment as well as the drawbacks of current therapy. In contrast to the future perspective, the regulation and advanced treatment of these mechanisms and pathways alteration which are concerned in the pathophysiology of diabetes associated memory impairment helps to treat diabetic complications and other related disorders also.

PATHOPHYSIOLOGY OF DIABETES INDUCED MEMORY IMPAIRMENT

It has been established that DM is associated with memory dysfunction. There are various factors which leads to the growth of diabetes induced memory impairment are not clearly understood. Furthermore, numerous hypotheses have been projected which plays an important role in the pathophysiology of diabetes induced memory impairment.

Oxidative stress: is the dynamic force for memory impairment in diabetes: Oxidative stress in diabetes occurs due to several pathways including enzymatic, non enzymatic as well as mitochondrial pathways [19]. Oxidative stress is states that usually as excessive production and/or insufficient removal of reactive oxygen species (ROS) [20]. Oxidative damage plays a vital role in the pathogenesis of DM induced memory impairment and other neurological diseases [21]. Oxidative stress appear to be capable; to encourage Aβ accumulation and that the beginning of Aβ deposition is linked with an amplify in the level of ROS and RNS; to affect Amyloid precursor protein (APP) either directly, by rising APP levels or indirectly, by amend APP processing and both molecular pathways could increase levels of Aβ [22] which furthermore mainly participate in the pathways of DM induced memory impairment. In diabetic state, AGE's are found to be one of major source for increased oxidative stress. In oxidative stress lipid peroxidation is favored in brain because of lipid rich constitution. This further causes decline in membrane fluidity and causes damage to receptors, enzymes which then cause alteration in neurotransmission [23]. Other mechanisms found to be involved for the oxidative stress in diabetic condition involves protein glycation, glucose autoxidation and the polyol pathway. Increased glucose level itself can cause deregulation of ROS and reactive nitrogen (RNS) generating pathways [20]. ROS has been also concerned in neurodegenerative diseases like memory impairment.

In the memory impaired brain, the job of ROS has been well recognized with the bio-markers for protein, lipid peroxidation, RNA oxidation and DNA. During DM, persistent hyperglycaemia leads to increased production of ROS [24]. There are several conditions which cause the disturbance in stability between ROS formation and cellular defence pathways which cause cell dysfunction and devastation resulting in tissue injury. A number of enzymes are concerned in the antioxidant mechanism of body and these enzymes comprise catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD). The amplification in the level of ROS in diabetes could be due to their increased formation and/ or decreased destruction by antioxidants of body. The molecular level of these antioxidant enzymes significantly influences the vulnerability of a variety of tissues to oxidative stress and is related with

the development of memory impairment in diabetes [11].

Role of AGEs in diabetes induced memory impairment: Increased blood glucose level alters function through a range of mechanisms including polyol pathway activation, enhances production of AGEs moreover diacylglycerol activation of protein kinase C (PKC), and raised glucose shunting in the hexosamine pathway [25, 26]. AGEs are considered significant bio-markers of oxidative stress and accumulating during aging and diseases, markers of carbonyl stress, which accrue due to an amplified level of sugars and reactive dicarbonyl compounds for example glucose, fructose, deoxyglucose, glyoxal, methylglyoxal, and triosephosphates [27]. AGEs are modified heterogeneous, intracellular and extracellular bio molecules [28]. AGEs product are formed because of non-enzymatic reaction of glucose which is in excess with proteins, nucleotides, and lipids that may have role in altered neuronal homoeostasis and repair mechanisms [29]. These products interfere with nerve cell metabolism and axonal transport and thus play a role in disrupting neuronal integrity and repair mechanisms [30]. AGEs bind with one of their receptor, named receptors of advanced glycation end products (RAGE) and exert their actions partly by influencing intracellular functions. RAGE has been identified as a receptor involved in Aβ-induced neuronal dysfunction. Increased levels of AGEs and RAGE are found in diabetic human tissue. RAGE exist in the blood vessel wall cells and transport Aβ across the blood brain barrier (BBB) and the membrane of nerve cell from the systemic circulation to ease their accumulation in brain [31, 32].

Role of RAGE's pathway in Diabetes induced memory impairment: Molecular mechanisms underlying diabetes induced memory impairment remain poorly understood. Varieties of theories with supporting particulars exist, including probable causative roles for hyperglycemia, hypoglycemia [33], amyloid deposition [34] vascular diseases and insulin resistance. Diabetes mellitus is coupled with slowly progressive end-organ damage in the brain. Mild to moderate memory impairment functioning has been reported in patients with DM [12]. The pathophysiology underlying the advancement of memory impairment in patients with diabetes has not been completely revealed. Memory impairment is familiar and costly complication of DM. In T2DM, the high blood glucose level promotes formation of AGEs, the pathways that mediate the toxic effects of hyperglycemia are varied, but comprise the gathering of AGEs; increase in the formation of free radicals such as ROS and reactive nitrogen species (RNS) [35], enhanced vascular inflammation leading to microvascular changes that can result in micro infarcts and widespread brain atrophy. The enhanced formation of AGEs, mechanism alters hyperglycemia and may be effective in the brain and induce the alteration in memory function that have been detected in patients with DM. Glucose metabolism and insulin signaling plays an important role for normal functioning of the brain. Insulin signaling impairment, is associated with T2DM is recognized to affect the expression and metabolism of Aβ, T2DM might, furthermore aggravate the synthesis of Aβ, synaptic impairment in addition to nerve cell death in patients with memory impairment. In hyperglycemia, ROS could increase Aβ production by enhancing the expression of β-secretase and RAGE, consequently, an increase in local inflammation within the brain [36].

A frequent pathological element between DM and memory impairment has been the presence of AGEs-modified proteins in both diseases [37, 38]. These modified proteins are ligands for RAGE, as is Aβ peptide [39]. In contrast to RAGE, low-density lipoprotein receptor-related protein-1 (LRP-1) reconciles transport of Aβ peptide expels of brain. In memory impaired patients, the RAGE is elevated while the LRP-1 is lowered [32]. The underlying mechanism of AGEs and RAGEs in the pathogenesis of DM induced memory impairment is not yet surely known, but activation of RAGE by ligands that are closely linked to memory impairment, including Aβ peptide, AGEs, and S100 proteins [40], appears to trigger several signal transduction cascades leading to neuronal loss. AGEs positive neurons and astroglia increase in memory impairment

with the progression of disease, which might contribute to several forms of neuronal dysfunction in memory impairment by course, such as inflammatory activation of microglia, in turn direct cytotoxicity via formation of free radicals, presumably mediated through activation of their receptor "RAGE" [41]. Microglia is believed to play an active role in regulating Aβ levels and the amyloid burden in the brain.

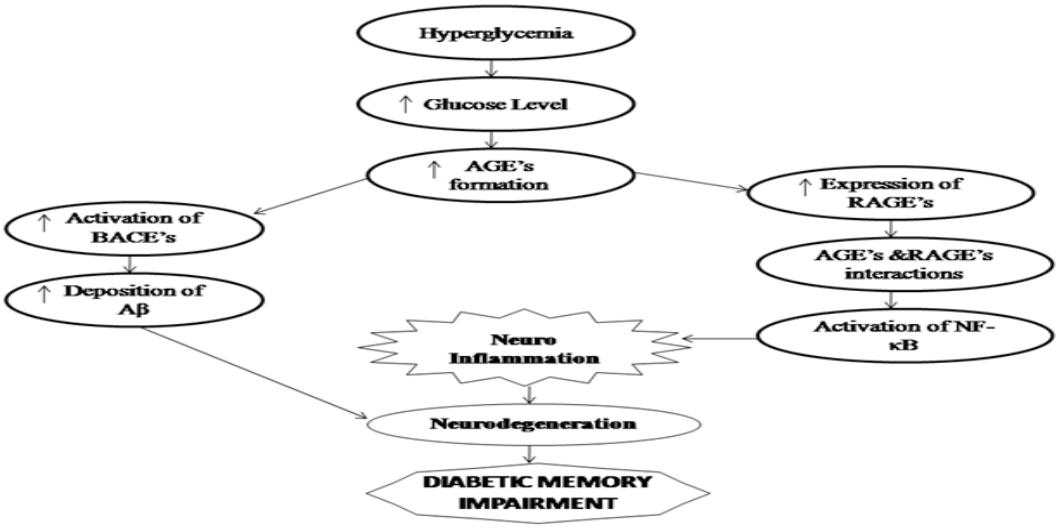

Figure1: Pathophysiology of Diabetes induced memory impairment via hyperglycemia and AGE's.

On binding of ligands (AGEs and A*β*), RAGE turn on intracellular signaling pathways via phosphatidylinositol-3 kinase (PI3K) moreover mitogen-activated protein kinases (MAPK), Erk1 and Erk2. Those pathways culminate in the activation of the transcription factor nuclear factor kappa B (NF-*κ*B) and subsequent transcription of a variety of factors, including endothelin-1, tissue factor, interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)-*α* [42]. NF-κB regulates a number of activities including inflammation and apoptosis in nerve cell [43]. The activation of NF-*κ*B and induction of cytokines can also make a payment to neuronal plasticity and the cellular response to cellular dysfunction when chronically activated resulting neurodegeneration [44]. Remarkably, NF-*κ*B induces the expression of RAGE, leading to a positive loop, which amplifies the cellular response to external stress. Furthermore, the engagement of RAGE by AGE's triggers the generation of ROS via the activation of NADPH oxidase (NOX) [41]. Cells around senile plaques express higher levels of RAGE in microglia from diabetic memory impaired brains during disease progression [31, 45]. The overactivation of RAGE in microglia provokes considerable increases in Aβ levels in the hippocampus and cortex [46], signifying a possible role of RAGEs in the development of cerebral dysfunction [47]. Thus, RAGE can be regard as a key mediator of age-induced oxidative stress by its capability to amplify a hassle signal, which contributes for the progression of neurodegenerative processes in irregular memory impairment. Herein, we summarize all studies indicating that RAGE participates in memory impairment progression.

CURRENT THERAPY FOR DIABETIC MEMORY IMPAIRMENT

At the moment there are no efficient pharmacotherapeutic options for prevention and treatment of diabetic memory impairment. Every diabetes drugs may affect memory impairment indirectly through effects on circulating concentration of insulin, inflammatory marker, glucose, and by production of reactive oxygen species and AGEs. The current therapy for diabetes induced memory impairment as follows;

Metformin: Metformin is belongs to an oral biguanide, generically available diabetes drug that is the first-line treatment for T2DM in the American Diabetes Association treatment algorithm [48]. Somewhat little is known about metformin outcome in the CNS. Although human study about metformin's

CNS penetration are missing, there is confirmation from clinical studies that metformin does cross the BBB and activates AMPK in CNS tissue [49, 50]. In nerve cell lines, contact to metformin sensitizes neurons to insulin and also prevents memory impairment pathology in neurons chronically exposed to a hyperinsulinemic environment [51]. However, metformin has also been reported to increase β-secretase-1 (BACE-1) transcription and associated generation of Aβ in neuronal cell lines [52].

Metabolic hormones: There are three metabolic hormones have shown promise in preclinical models of memory impairment: Glucagon-like-peptide-1 (GLP-1), amylin and leptin. All hormones readily cross the BBB. One benefit of these agents (and metformin) over insulin is that they do not cause significant hypoglycemia and can therefore be safely administered at relatively high doses peripherally.

***Glucagon-like-peptide-1*:** The hormone GLP-1 have glucose-lowering effects include improved insulin secretion, decreased delayed gastric emptying, glucagon secretion, improved insulin sensitivity and augmented satiety in multiple tissues [48]. Preclinical studies of GLP-1 agonists in memory impairment models have been encouraging. These agents have been shown to act as a growth factor in the brain which causing neurogenesis and synaptogenesis furthermore protecting against oxidative injury. In memory impairment models, GLP-1 agonists reduce levels of memory impairment pathologic markers, together with oligomeric Aβ and Aβ plaque load, decrease microglial activation, and improve memory behaviors [53].

***Amylin*:** Amylin, also called islet amyloid polypeptide (IAPP), is a peptide hormone that is co-secreted with insulin from β-cells in the pancreas. Amylin enthusiastically crosses the BBB and its receptors which are distributed extensively throughout the brain in the parabrachial nucleus, amygdala, hypothalamus, and dorsal raphe. Jackson et al. described oligomeric and plaque-like accumulations of abnormal amylin in brain parenchyma and cerebral vasculature that was present in patients with diabetes as well as in people with memory impairment [54]. The Pramlintide is a soluble, nonaggregating synthetic analog of amylin. It is approved as an adjunctive therapy to insulin for the treatment of DM. Chronic infusion of pramlintide recover memory performance in the recognition task and also modulates synapses, decreases oxidative stress and inflammatory markers in the hippocampus [55], and increases hippocampal neurogenesis.

Numerous diabetic drugs are in clinical use and which therapies, if any will be effective at improving cognitive function are indistinguishable. Currently, established treatments are only symptomatic in nature, which are trying to counter-balance the neurotransmitter interruptions of the cognitive disease. Current symptomatic treatments and new potential disease-modifying therapies for memory impairment that are currently being studied in phase I–III trials [56]. These compounds can be grossly divided into anti-amyloid agents and drugs that target other pathological mechanisms. Anti-amyloid entities can be subdivided into drugs intended to block or inhibit the overproduction and aggregation (accumulation) of Aβ or to favors its clearance from the brain [57]. Pharmacological compounds that support the clearance of Aβ from the nerve cell, or prevent its aggregation, may represent a strategy to delay the progression of the pathological process in memory impairment.

Cholinesterase inhibitors: The cholinesterase inhibitors have been known to enhance the neurotransmitters level in brain by stimulating the reduced activity of cholinergic neurons in memory impaired patient, this chemical entity inhibits the cholinesterase enzyme from breakdown of neurotransmitter acetylcholine (Ach), resulting in enhancement of neurotransmitter acetylcholine [58]. Three cholinesterase inhibitors (donepezil, rivastigmine and galantamine) are approved for the treatment of mild to moderate memory impairment.

N-methyl-D-aspartate receptor (NMDA) antagonist: Glutamate is found in the neuronal pathways associated with learning and memory. In 2003, the FDA approved memantine (Namenda), a non-competitive NMDA receptor antagonist, moreover which has been used to treat moderate to severe

stages of memory impairment, by blocking NMDA receptors and inhibiting their overstimulation by glutamate, protects the brain cells from damage caused by glutamate [18, 58].

DRAWBACKS OF THE CURRENT THERAPY OF MEMORY IMPAIRMENT

For memory impairment disease, there is not a single therapeutic element that exerts anything beyond a marginal, unsustained symptomatic effect along with little and/or no effect on disease progression [59]. In the case of memory impairment and its predecessors, mild cognitive impairment (MCI) and subjective cognitive impairment (SCI), comprehensive combination therapies have not been explored. To date, licensed treatments for memory impairment treat only symptoms; they can help with the memory, behavioral and functional aspects of the condition but do not alter the disease process. Reviewing the evidence for the use of cognitive enhancers, the National Institute for Health and Care Excellence (NICE) did not recommend the use of memantine other than in research. However, an updated guideline recommended donepezil, galantamine and rivastigmine for mild as well as moderate memory impairment [60].

Early evidence shows no convincing benefit of combining memantine with a cholinesterase inhibitor [61]. Various other drugs and supplements have been assessed as possible treatments for memory impairment, including gingko biloba, indomethacin, vitamins E and B-12, folic acid, selegiline and metrifonate; there is no convincing evidence of benefit for any of them. The promise of improvements in memory functioning has helped reduce the negativity around the diagnosis and management of memory impairment, contributed to more people being diagnosed early and changed the direction of service development [62]. However, the availability of these drugs may have resulted in memory impairment treatment being prioritized over that for other forms of memory and over the later stages of memory, where the drugs are less useful.

ADVANCED THERAPIES FOR MEMORY IMPAIRMENT

Current pipeline therapies target cholinergic and glutamatergic neurotransmission and decrease symptoms in patients with moderate-to-severe memory impairment; however, there is no evidence of disease-modifying effects [63]. Although the large volume of new drug entities promotes optimism for the future treatment of memory impairment, many recent phase 2 and phase 3 trials have not been successful [64].

Anti-amyloid therapy: Anti-amyloid strategies comprise pharmaceutical compounds with distinct mechanisms of action, namely drugs that *(i)* facilitate the clearance; *(ii)* inhibit the production; or *(iii)* prevent the aggregation of Aβ [65]. Both active and passive immunization target the reduction of intracerebral Aβ load by eliciting humoral response against the Aβ peptide, moreover facilitating its clearance from the brain by immune-mediated mechanisms [66].

Secretase inhibitors: The secretase inhibitors have also been suggested to show beneficial effects in the patients presented with memory impairment by a mechanism involving in the inhibition of breakdown of Amyloid precursor protein (APP) in cell membrane into Aβ fragments [67].

α-secretase activators/modulators: Since α-secretase and β-secretase compete for the same substrate of APP, furthermore the upregulation of α-secretase activity may decrease the amount of APP available for the β-secretase enzyme and therefore decrease Aβ secretion as well as have therapeutic potential. Many studies indicated that the currently effective drug for memory impairment all can increase α- secretase activities. Deprenyl, is a neuroprotective agent used to slowdown memory impairment progress [68].

***β-secretase inhibitors*:** The therapeutic potential of β-secretase (also named β- site APP cleaving enzyme, BACE-1) inhibitor which has been recommended by numerous studies. Lateral ventricles injection of BACE-1 inhibitor led to a significant dose- and time-dependent lowering of brain Aβ40 and Aβ42, a robust decreased sAPP-β and an increased sAPP-α secretion. An inhibitor of β-secretase (GRL-8234) was recently investigated in young transgenic mice with decreased soluble Aβ in the brain tissue and with rescued behavior performance [69].

***γ-secretase inhibitors/modulators*:**
Treatment of memory impairment with γ-secretase inhibitors DAPT resulted in decreased Aβ levels in plasma and cerebrospinal fluid (CSF). The γ-secretase inhibitors like BMS-299897 and MRK-560. The LY450139 dihydrate, another γ-secretase inhibitor. Semagacestat, a non-selective gamma-secretase inhibitor which has been examined as a potential management for the memory impairment patients [70].

Aβ-aggregation inhibitors: The neurotoxic effect of Aβ has been documented on numerous occasions and thus decreasing its neurotoxicity or inhibiting its aggregation may have therapeutic potentials. The first drug was a β-sheet breaker iAβ5p, which showed that intrahippocampal injection of it resulted in improved spatial memory and decreased amyloid plaque deposits [32]. Tramiprosate (3APS, Alzhemed) is a compound that binds to soluble Aβ and inhibits the formation of neurotoxic aggregates that memory impairment to amyloid plaque deposition in the brain.

Aβ-degrading enzymes: Aβ peptide could be degraded by a kind of protease called Aβ degrading enzyme, rather than being cleared from the vascular system by the so-called "vascular pathway". The following proteinases have the abilities of degrading Aβ peptide: neprilysin (NEP) [71], insulin degrading enzyme (IDE), plasmin, endothelin converting enzyme (ECE) 1 and 2 and angiotensin-converting enzyme (ACE).

M1 muscarinic agonists: M1 muscarinic receptors play a role in an apparent linkage of three major hallmarks of memory impairment: Aβ peptide; tau hyperphosphorylation and loss of cholinergic function conductive to cognitive impairments [32]. Talsaclidine, is a functionally selective muscarinic M1 agonist that stimulates non-amyloidogenic α-secretase processing in vitro. M1 agonists may act through decreasing γ-secretase and increasing α-secretase activities that finally decreased Aβ secretion and it also decreased tau phosphorylation.

Immunotherapy: Both active (vaccination) and passive (monoclonal antibodies) immunization are studied in memory impairment patients. Active immunization against Aβ-42 resulted in decreased plaques and improved cognitive function. Passive immunotherapy in memory impairment patients with repeated intravenous administration of human immunoglobulin against Aβ peptide resulted in stopped cognitive decline and slight improvement in functional scores. Several passive immunotherapeutic agents have been evaluated by random clinical trials (RCTs) over the past years, i.e. bapineuzumab, solanezumab, gantenerumab, ponezumab, and crenezumab. These monoclonal antibodies possess elevated affinity to antigenic determinant epitopes of Aβ, binding either to soluble forms or in plaques furthermore recognized by B- and T-cells to promote its clearance from the brain [72].

Monoamine oxidase inhibitors: MAO inhibitor deprenyl is an anti-Parkinson drug used to inhibit dopamine degradation in the brain. A neuroprotective agent, deprenyl has been used to slow the development of neurodegenerative diseases such as memory impairment [73]. Concerning its neuroprotective pathways, including regulation of activation of PKC, APP processing and MAPK signaling pathways furthermore inhibition of cell death markers and upregulation of neurotrophic factors rationalize its application to memory impairment treatment.

CONCLUSION

Diabetic memory impairment is an important complication of diabetes, with implications for patient morbidity and mortality. It is one of the most alarming illnesses especially to elderly people. After long time of searching, at rest a need of effective treatments for diabetic memory impairment. Evidently, additional fundamental research is looked-for the molecular, cellular, systemic, and behavioral levels. There is a considerable bunch of evidence implicating production and accumulation of advanced glycation end products as a key factor in the maturity of type 2 diabetic memory impairment and the normal aging process furthermore through this evidence, is an important therapeutic direction for research and treatment of the disease. The currently marketed medications for memory impairment disease are the cholinesterase inhibitors and memantine.

Vitamins and food supplements have not been shown to be effective. No pharmacologic approaches have been established to prevent or delay onset of diabetic memory impairment. The objective of this review is to highlights the functioning of key mechanisms and pathways concerned in the progression of diabetes associated memory impairment.

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