



## A REVIEW ON DIABETES INDUCED MEMORY IMPAIRMENT

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### ABSTRACT

AD is a progressive neurotic degenerative brain disorder that occurs gradually and results in memory loss, unusual behaviour, personality changes. Diabetes is a group of complex metabolic disease characterized by hyperglycemia. The development of cognitive dysfunction in patient with diabetes includes many hypothesis include potential causative role of hyperglycemia, vascular disease, insulin resistance, hypoglycaemia and amyloid deposition. AGE'S are considered significant biomarkers of oxidative stress and markers of carbonyl stress which occur due to an amplified level of sugars and reactive dicarbonyl compounds. Metformin is an oral biguanide, generically available diabetes drug that is the first line treatment for type 2 diabetes. there is confirmation from clinical studies that metformin does cross the BBB and activates AMPK in CNS tissue. 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.

**KEYWORDS:** Oxidative stress, amyloid beta, advanced glycation end products.

### INTRODUCTION

Learning and Memory: The brain is basically responsible for learning and memory, thinking, perceiving, behaviour and curiosity.

- Learning is defined as the act of acquiring new or modifying the existing knowledge, behaviours and skills. It is a process by which new information acquired by the brain about the events occurring in the given surroundings
- Memory is a process in which the acquired information are encoded, stored and retrieved. Encoding is a process in which information is received, processed and combined.<sup>[1]</sup>

**Alzheimer's disease:** It is a progressive neurotic degenerative brain disorder that occurs gradually and results in memory loss, unusual behaviour, personality changes. it is the most common form of onset of adult dementia and attention deficit disorder.<sup>[2]</sup>

AD is a progressive neurological disorder it starts with loss of short term memory. Brain area associated with cognitive functions, particularly the neo cortex and hippocampus are the regions that mostly affected.

It is a form of cortical dementia which is characterized by massive loss of neurons and disrupted signalling between cells in the brain. Appearance of amyloid fibrils and plaques are the characteristics of AD.<sup>[3,4]</sup>

**Pathophysiology of Alzheimers disease-** it include various theories.<sup>[5]</sup>

- Senile plaques
- Neurofibrillary tangles
- Acetylcholine effect
- Oxidative stress

**Senile plaques:** polymorphus beta amyloid protein deposits are found in the brain of AD and normal aging which are called senile plaques

In the formation of senile plaques in Alzheimer dementia amyloid precursor protein (APP) immunoreactive neuritis are involved.<sup>[6]</sup>

Amyloid beta deposits from beta pleated sheets in AD brain serves as a major constituent of senile plaques.<sup>[7,8]</sup>

**Neurofibrillary tangles:** the NFTs induce neuronal as well as synaptic death by interfere with the cytoskeletal integrity. The limbic areas are selectively vulnerable to the formation of NFTs in the course of aging

In low limbic stage the first and initial level of NFT distribution occur & the next level of NFT distribution occur and the next level of NFT density is the high limbic stage

The high limbic state of NFT distribution is associated with mild cognitive impairment & pre-clinical AD<sup>[9,10]</sup>

**Acetylcholine effect:** Brain regions that are involved in memory a neurotransmitters called acetylcholine are found in those areas

In the hippocampus and frontal cortex due to cholinergic abnormalities like down regulation of choline acetyltransferase [a enzyme involved in synthesis of acetylcholine] a decrease in the level of the acetylcholine in brain occurs

The cholinergic neurons count is generally lowered in the nucleus count is generally lowered in the basalis of AD brain.

Presynaptic receptors are involved in mood and memory functioning by influencing the release of neurotransmitters involved. Reduction in the level of acetylcholine also reduces the release of neurotransmitters which are important for memory via affecting the presynaptic nicotinic receptors.<sup>[9,10]</sup>

**Oxidative stress:** In AD associated cognitive impairment oxidative stress plays an important role there is markedly increase levels of protein oxidation in brains of AD patients.

The key molecular and cellular components which underlying cognitive functions are damaged by the oxidative stress. In both astrocyte and neuronal cell culture amyloid beta has been shown to induce ROS production<sup>[11]</sup>

In AD there are various sources that generate free radicals and ultimately produced oxidative stress such as iron, activated microglia and advanced glycation end products.<sup>[12]</sup>

**Diabetes mellitus:** it is a group of complex metabolic disease characterized by hyperglycemia.<sup>[13]</sup> Patients with type 1 & 2 diabetes mellitus have been implicated as causes of cognitive dysfunction.<sup>[14]</sup>

**Type 1 Diabetes mellitus:** It may be caused by destruction of beta cells of the islets of langerhans after certain viral infections or due to an autoimmune process

It is characterized by inability of the beta cells to produce insulin and it may be severe if not treated.

**Type 2 Diabetes mellitus:** In type 2 diabetes mellitus body's tissue become less responsible to insulin, leading to increasing blood glucose levels and this is associated with increasing insulin resistance<sup>[15]</sup>

DM cause a variety of functional and structural disorder in the central and peripheral nervous system.<sup>[16]</sup>

### **Mechanism linking cognitive impairment and diabetes mellitus**

The development of cognitive dysfunction in patient with diabetes includes many hypothesis include potential causative role of hyperglycemia, vascular disease, insulin resistance, hypoglycaemia and amyloid deposition.<sup>[17]</sup>

**Relation between insulin & cognitive function:** In AD a deficit in insulin signalling is associated with the accumulation of pathological beta amyloid peptide and hyperphosphorylated tau protein.

Insulin resistance impaired the insulin release, in the amyloid beta IDE a protein is involved and insulin & amyloid beta may co pete for degradation. In the post-mortem hippocampus of AD patients IDE expression is found. Through the pathway of docosaheaxaemic acid oxidative stress and micro inflammation mediate insulin resistance in the brain.<sup>[18]</sup>

### **Linkage between acute hyperglycemia and cognitive impairment**

Hyperglycemia is characteristic feature of all types of diabetes and could cause cognitive impairment by several different mechanism.

Organ damage done by hyperglycemia through increase in reactive oxygen species in particular superoxide which could then lead to increase polyol pathway activation, increase formation of AGE'S, activation of protein kinase c and increase glucose shunting in the hexosamine pathway. There is alteration in regional cerebral blood flow and also cause osmotic changes in cerebral neurons due to acute changes in blood glucose.<sup>[19]</sup>

### **Role of amyloid & insulin resistance in cognitive dysfunction**

AD patient have a decrease in cerebral spinal fluid insulin levels, suggesting that there may be impaired insulin transport across the blood brain barrier or increase insulin catabolism that occurs for the impaired central insulin action.

In AD by promoting the formation of senile plaques insulin resistance may indirectly contribute to cognitive dysfunction.

The pathological hallmarks of AD are intracellular neurofibrillary tangles and extracellular senile plaques composed of beta amyloid. Insulin degrading enzyme degraded the beta amyloid.

The burden of cerebral senile plaques are potentially increase when the metabolism of Amyloid precursor protein & beta amyloid are affected by the insulin and insulin resistance.<sup>[20]</sup>

### Pathophysiology of diabetes induced memory impairment

There are various factors which leads to the growth of diabetes induced memory impairment are not clearly understand. Furthermore, numerous hypothesis have been projected which plays an important role in pathophysiology of diabetes induced memory impairment.

**Oxidative stress:** The excessive production and/or insufficient removal of reactive oxygen species (ROS) state the oxidative stress.

Oxidative stress appear to encourage amyloid beta accumulation and that the beginning of amyloid beta 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 amyloid beta 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 increase oxidative stress.

In oxidative stress lipid peroxidation is favoured 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.<sup>[21]</sup>

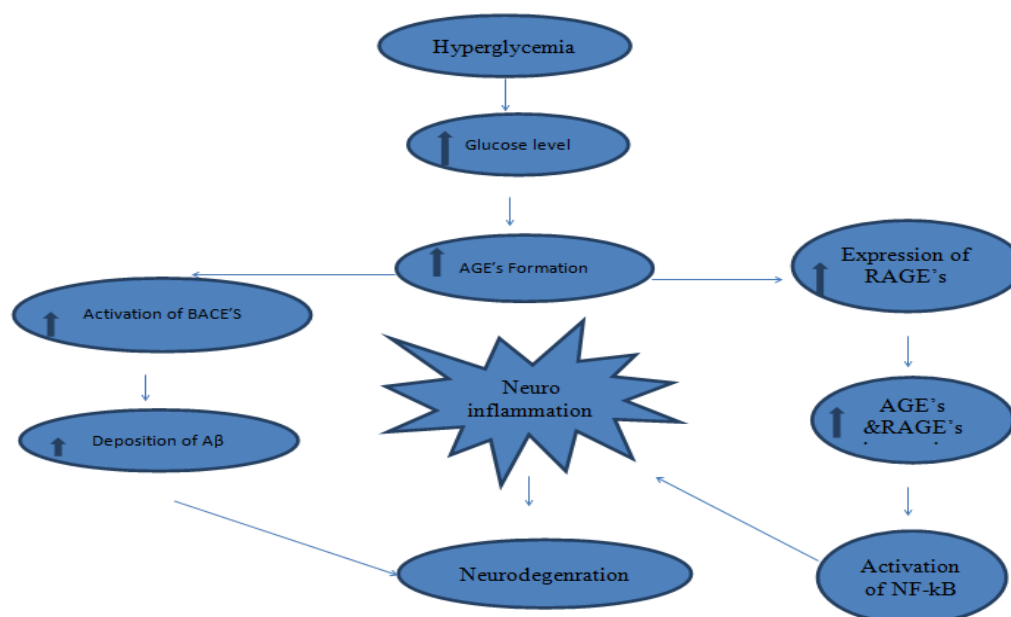
**Role of AGE'S in diabetes induced memory impairment:** AGE'S are considered significant biomarkers of oxidative stress and markers of carbonyl stress which occur due to an amplified level of sugars and reactive dicarbonyl compounds for eg-glucose, fructose, deoxyglucose etc

AGE'S 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 mechanism

The products interfere with nerve cell metabolism and axonal transport and thus play a role in disrupting neuronal integrity and repair mechanism.<sup>[22]</sup>

AGE'S bind with one of their receptor, named receptors of advanced glycation end products (RAGE) and exert their action partly by influencing intracellular functions.

RAGE has been identified as a receptor involved in amyloid beta induced neuronal dysfunction. Increased levels of AGE'S and RAGE are found in diabetic human tissue. RAGE exist in the blood vessel wall cells and transport amyloid beta across the blood brain barrier and the membrane of nerve cell from the systemic circulation to ease their accumulation in brain.<sup>[23]</sup>



**Fig. 1: Role of AGE'S in diabetes induced memory impairment.**

**Role of RAGE'S pathway in diabetes induced memory impairment:** In type 2 diabetes mellitus, the high blood glucose levels promotes formation of AGE'S, the pathways comprise the gathering of AGE'S, increase in the formation of free radicals such as reactive oxygen species and reactive nitrogen species, enhanced vascular inflammation leading to microvascular changes that can result in micro infarcts and widespread brain atrophy.

The enhanced formation of AGE'S, 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. Insulin signalling impairment is associated with type 2 diabetes mellitus and is recognized to affect the expression and metabolism of amyloid beta.

In hyperglycemia reactive oxygen species could increase amyloid beta production by enhancing the expression of beta-secretase and RAGE, consequently an increase in local inflammation within the brain.

A frequent pathological element between diabetes mellitus and memory impairment has been the presence of AGE'S modified proteins in both diseases. These modified proteins are ligands for RAGE as is amyloid beta peptide. In contrast to RAGE, low density LRP-1 reconciles transport of amyloid beta expels of brain.

In memory impaired patients, the RAGE is elevated while the LRP-1 is lowered.<sup>[24]</sup> Activation of RAGE by ligands that are closely linked to memory impairment, including amyloid beta, AGE'S and S100 proteins, appears to trigger several signal transduction cascades leading to neuronal loss.

Cells around senile plaques express higher levels of RAGE in microglia from diabetic memory impaired brain during disease progression. The over activation of RAGE in microglia provokes considerable increases in amyloid beta signifying a possible role of RAGE'S in the development of cerebral dysfunction. Thus, RAGE can be regarded as a key mediator of age induced oxidative stress by its capability to amplify a hassle signal, which contributes for the progression of neurodegenerative process in irregular memory impairment.<sup>[25]</sup>

**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 drug may affect memory impairment indirectly through effects on circulating concentration of insulin, inflammatory marker, glucose, and by production of ROS and the AGE'S. the current therapy for diabetes induced memory impairment as follows:

**1) Metformin-** Metformin is an oral biguanide, generically available diabetes drug that is the first line treatment for type 2 diabetes. there is confirmation from clinical studies that metformin does cross the BBB and activates AMPK in CNS tissue. 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. However metformin has been reported to increase beta secretase-1 (BACE-1) transcription and associated generation of amyloid beta in neuronal cell lines.<sup>[26]</sup>

**2) Metabolic hormones-** There are three metabolic hormones 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 hypoglycaemia and can therefore be safely administered at relatively high doses peripherally.<sup>[27]</sup>

**3) 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 impairment patient, this chemical entity inhibit the cholinesterase enzyme from breakdown of neurotransmitter acetylcholine resulting in enhancement of neurotransmitter acetylcholine. Three cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are approved for the treatment of mild to moderate memory impairment.

**4) 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.<sup>[28]</sup>

#### Advanced therapies for memory impairment

**1) Anti- amyloid therapy:** Anti amyloid strategies comprise pharmaceutical compounds with distinct mechanism of action, namely drugs that-

- a) Facilitate the clearance
- b) Inhibit the production, or
- c) Prevent the aggregation of amyloid beta

Both active and passive immunization target the reduction of intracerebral amyloid beta load by eliciting humoral response against the amyloid beta peptide moreover facilitating its clearance from the brain by immune- mediated mechanism.<sup>[29]</sup>

**2) Secretase inhibitors:** The secretase inhibit to show beneficial effects in patients prevented with memory impairment by a mechanism involving inhibition of breakdown of amyloid precursor protein (APP) in cell membrane into amyloid beta fragments.<sup>[30]</sup>

**3) Amyloid beta aggregation inhibitors:** The neurotoxic effect of amyloid beta has been documented on numerous occasions and thus decreasing its neurotoxicity or inhibiting its aggregation may have therapeutic potentials. the first drug was a beta –sheet breaker iA $\beta$ 5p, which showed that intrahippocampal injection of it resulted in impaired spatial memory and decrease amyloid plaque deposits.<sup>[23]</sup> Tramiporate is a compound that bind to soluble amyloid beta and inhibit the formation of neurotoxic aggregates that memory impairment to amyloid plaque deposition in the brain.

**4) M<sub>1</sub> muscarinic agonists:** M<sub>1</sub> muscarinic receptors play a role in an apparent linkage of three major hallmarks of memory impairment: A $\beta$  peptide; tau hyperphosphorylation and loss of cholinergic function conducive to cognitive impairments. talsaclidine is a functionally selective muscarinic M<sub>1</sub> agonist may act

through decreasing  $\gamma$ -secretase and increasing  $\alpha$ -secretase activities that finally decreased  $A\beta$  secretion and it also decreased tau phosphorylation.<sup>[23]</sup>

**5) Immunotherapy:** Both active (vaccination) and passive (monococcal antibodies) immunization are studied in memory impaired patients. Active immunization against  $A\beta$ -42 resulted in decreased plaques and impaired cognitive function. Passive immunotherapy in memory impairment patients with repeated intravenous administration of human immunoglobulin against  $A\beta$  peptide resulted in stopped cognitive decline and slight improvement in functional scores. several passive immunotherapeutic agents have been evaluated by random clinical trials over the past years i.e bapineuzumab, solanezumab, gantenerumab, ponezumab and crenezumab. these monoclonal antibodies possess elevated affinity to antigenic determinant epitopes of  $A\beta$ .<sup>[31]</sup>

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