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THE DEVELOPMENT OF DEMENTIA IN DIABETIC AND ALZHEIMER PATIENTS

Misbah Sultana, Saima Jadoon and Arif Malik

Institute of Molecular Biology and Biotechnology, University of Lahore, Pakistan.
saima.jadoon95@gmail.com; misbahbiochemist@gmail.com; drarifmalik.uol@gmail.com

ABSTRACT

Dementia and diabetes are the are two major disorders that are found to be linked on Biochemical and Molecular level and it is because that pancreatic cells have molecular similarity with neuronal cells on the transcription and protein levels as well. Both diseases have similar genes in common as their causative agents and dementia is one of the advanced complications of the disease as 50-52% of the population with type 2 diabetes mellitus (T2DM) has greater risk for the development neuronal degeneration and AD (Alzheimers disease) is one of the most common form or cause of the dementia in the individual. In AD it is a common observation that about 80% of the receptors specifically insulin is diminished so the disease is prevailed in the individual. People with diabetes or unable to control blood glucose may have greater uptake of glucose through dietary source which is also one of the reason in the development of the mental disorder. Out of the studies it is concluded that insulin play important role in prevalence of dementia and AD. Impairment in insulin can be one of the leading causes in AD. In these diseases Tau protein and Amyloid beta proteins are significant role players in the formation of plaques in the patients with the dementia or more easily the AD.

Keywords: Alzheimer disease, T2DM, Dementia, Prophetic factors.

Abbreviation: AD (Alzheimer Disease), T2DM (Type 2 Diabetes Mellitus), RAGE (Receptor for Advanced Glycation End-products) and TLRs (Toll-like receptors), COX (cyclooxygenase) and AA (Arachidonic acid).

INTRODUCTION

Congenital diseases like Diabetes and number of central nervous system (CNS) diseases are seen to be affecting the human species from decades so the association and correlation among the diseases are seen and observed in the individuals number of factors involved in the neural diseases are initiated with the stress conditions that may be occurred due to hyperglycemia condition caused or reasoned by the diabetes. Vast diabetic effect in brain are considered and studied and also the structural nervous system involved in the physiological and multiple pathogenical factors are considered to be involved in the pathogenic infections of cerebral tissue in number of infections which can be termed as diabetes and hypoglycemic conditions which are achieved by the alteration or changes in the cerebrovascular fluid and not only this but the role of insulin in the brain and the mechanism of hypoglycemic which can cause the damage. Diabetes is now a days one of the most common disease which is encountered in the number of diseases while not only restricted to the diabetes but also other associated diseases are seem to be the causative factors for the individuals like neuropathy, angioplasty, retinopathy and peripheral neuropathy (Chow *et al*., 2010).

Mostly all of the mentioned diseases which are the reason for the number of deaths per year have a deep association in between one another likewise there is the requirement to link the diabetes with the brain associated disorders like dementia and AD etc. It is a greatly believed fact that evidences revealed that the symptoms for both diseases and so the prognosis could be same as well so the emergence of one disease because of the other disease is also the factor in the disease. Person with the diabetes is always on the big risk of dementia as he/she would have a disturbed metabolism so the stress could be seen in the individuals as well. Heart, CVD and several other risks are also exposed to the one who is already diseased with any of the congenital disorder like diabetes or diabetes mellitus (Silbert and Kaye, 2010). With the text it can be considered the link between both diseases is quite obvious and believed from real old times so the correlation between both diseases are contributing factors in the society.

It can also be the reason of cognitive dysfunction also an observation is made which tells that neurotransmission, electrophysiological and severe abnormalities are also observed at structural levels and also risk of depression and tension are seem to be increased in the patients. Theories for the aging process and dysfunction of cerebral fluid in diabetes is one of the common encountered phenomenon which is often related with the cell death by the exposure of oxidative stress and also involves the production of free radicals. It also have seem to effect tissue and damaging it greatly which may also take it to the extent in the change in the potential of cell to get activated by the action redox sensitive genes (Arancio *et al*., 2004). Brain is one of the most sensitive organ as it is

known with the fact that once neural cells are damaged they are not often repaired with the normal action of body hence in the same way it is considered much sensitive to the oxidative damage as well so resultantly if high oxygen is consumed more lipid content is seen and in the same relatively decreased antioxidant enzymatic and as well as non-enzymatic activities are seen (Cardoso *et al*., 2013).

MECHANISM OF ALZHEIMER DISEASE

Although both diabetes and Alzheimer have a lot of biochemical and neuropathological things in common including formation of β-amyloid aggregates in pancreatic islets and brain cells, formation of AGES (advanced glycation end products), AOPPs (Advanced oxidation protein products), oxidative stress, nitrosative stress, inflammation, defected insulin signaling, obesity, aging and mitochondrial dysfunction. The neurodegenerative Alzheimer's disease has a complex/enigmatic mechanism which is still of intense research. It is well-established/known that oxidative stress and inflammation are linked processes where the onset of one mechanism subsequently leads to the development of the other and hence vice versa. Alzheimer disease (AD) is neurodegenerative related to age which affected approximately five billion populations of US (Reed-Geaghan *et al*., 2009). Alzheimer disease characterization is via two neuropathic promises; amyloid protein plaques and neurofibroma tangles. In AD patients extracellular aggressions of beta amide which are amyloid plaques, formed throughout their brain. Amyloid plaques are sultry stockpile that accumulates outside neurons. Amyloid is a protein which is habitually present in body but in case of AD it divides inappropriately creating a form beta amyloid which is toxic to nerve cells. Another hallmark which is neurofibrillary tangles are aggregates of hyperphosphorylated or abnormally phosphorylated Tau protein, they are combined to form paired helical filaments which is a vital element of NFTs (Maes *et al*., 2009).

The development of AD includes biochemical processes which ultimately result in neural loss and cell death as in apoptosis. The MTL (median temporal lobe) is the first region of the brain to show neuronal loss. Some other parts also show loss such as hippocampus, amygdala, entorhinal cortex and parahippocampal cortex (Coracil *et al*., 2002). AD neurodegeneration is diagnosed across the regions of subcortical and neocortex. Parietal, temporal and frontal cortices became vestigial during their evolution i.e. atrophy. Majority of Alzheimer's disease instances are due to genetically inherited mutations among 3 genes; APP (amyloid precursor protein), PS1 (presenilin1) or PS2 (presenilin 2). The symptoms that appear due to these genes occur at earlier age (Brandenburg *et al*., 2008). Neuropathology of Alzheimer's disease is linked with PCA (posterior cortical atrophy) and logopenia aphasia. PCA is also called Benson's syndrome, distinctive Alzheimer's disease variant, which is responsible for atrophy of the posterior cerebral cortex, leading to advanced disorder of complex visual process. Logopenia aphasia is cognitive impairment of which involves a progressive loss of language function it is described clinically by impairments in naming and sentence repetition .Majority of vascular dementia diagnosis or vascular associated MCI involves the incidence of clinically important cognitive damages. Front temporal dementia (FTD) includes various disorders with varying symptoms. FTD is characterized with personality and behavioral changes, disinhibition, ennui, lost compassion determined neurotic behaviors. PPA (primary progressive aphasia) is other type of Front temporal dementia, classified into two types; SD (semantic dementia) and PNFA (progressive non fluent aphasia). SD is progressive neurodegenerative disorder characterized by loss of semantic memory in both verbal and nonverbal realms. PNFA altered because of tau pathology while mutational changes in the GRN (Granulin) gene results in TDP-43 health problem leading to symptoms of PNFA. FTD also features motor dysfunction and motor neuron diseases (Tesseur *et al*., 2006).

ROLE OF INFLAMMATION IN ALZHEIMER DISEASE

A great number of studies on AD brains related to biochemistry and neuropathology show evidence that inflammation is the key pathway that is activated in this debilitating disease. Inflammation in AD is owing to various cellular and molecular mediators. Microglia, astrocytes, oligodendrocytes and neurons make up the cellular mediators whereas the molecular mediators: complement system, cytokines and other soluble signaling proteins, PRRs (Porcine Reproductive and Respiratory Syndrome) including RAGE (Receptor for Advanced Glycation End-products) and TLRs (Toll-like receptors), COX (cyclooxygenase) and AA (Arachidonic acid) metabolites are involved in AD. Alzheimer Disease is one of the metabolic associated disorder that may emerge with the aging and is exceeded one affected with such disease have plaques formed in the lining of brain sections of brain are considered and observed with lots of plaque with in it and due to these tangles and plaque function of brain is seemed to be disrupted and disturbed on a vast range so actions and motility of a person is affected and so complete or partial memory loss is observed with the age in the individuals in the disease if one get into it on clinical level the common observation is seem that there are roles of two proteins seen in the metabolism of disease which may be termed as Tau proteins (proteins that stabilize microtubules) and Amyloid β proteins these proteins are elevated and

its activity is seen inside the disease like Alzheimer Disease and it may also reason in the memory loss or dementia like diseases. And so these proteins can be seen as one of the biomarker in the disease and so amyloid plaques are found throughout the brain which is the deposition of amyloid β proteins throughout the brain and brain is believed to be reduced in its function and efficacy these plaques are formed by the deposition of these amyloid β proteins throughout the brain or in the synaptic cleft in the brain so the signaling in the brain is disturbed on the huge level (Maes *et al*., 2007).

ROLE OF PROTEINS IN EMERGENCE OF ALZHEIMER DISEASE

Alzheimer's disease is characterized by accumulation amyloid beta protein which are aggregates of Amyloid beta peptide are found in brain of AD patients. Their accumulation leads to the formation of plaques. These plaques act as a hurdle in transmission of insulin signaling which add to the pathogenesis of Alzheimer's disease. This aggregation has two important consequences; decreased neurogenesis and increased tangle synthesis (Tesseur *et al*., 2006). A few components of amyloid beta protein can convert into tumor necrosis factor (TNF) which can activate JNK pathway (c-Jun N-terminal kinase pathway) block insulin receptor and play role in prevalence of diabetes (Sheta *et al*., 2006). Amyloid beta derived diffusible ligands also contribute to impaired insulin signaling. Patients with high levels of insulin or insulin resistance are at a higher possibility of getting AD. Synthesis of acetylcholine is inhibited by hypoglycemia that also acts as a leading factor in prognosis of AD. To put it in a nut shell it can be said that high or low levels of insulin act as a leading cause of Alzheimer's disease. AD patients have 80% less number of insulin receptors when compared to healthy individuals. Abnormally phosphorylated tau protein gathers to form neurofibrillary tangles. In brain insulin receptors are important for cognition because they activate signaling pathways which regulate long term wisdom and memory (Brands *et al*., 2004).

Homocysteine is found to play a major role in several diseases and disorders like dementia, diabetes, CVD, Schizophrenia and several types of cancers some of the enzymes important in themetabolism so the disruption in the metabolism can cause the emergence of disease and with the aging homocysteine like amino acids are deposited in the body and with the deposition of these amino acids cause formation of amyloid proteins which are responsible for the amyloid plaques. And the tangles are formed in the brain and oxidative stress is formed and due to this stress cells are hyper metabolized and causes mitochondrial lining to be stressed and JNK pathway is initiated which causes the insulin binding to be restricted and inhibited and diabetes is caused within the individual and this disease is the responsible factor for many other diseases like mental disorders and like dementia and AD and HD (Tesseur *et al*., 2006). Extracellular and intracellular stress is the contributing factor in devastating the disease.

DEMENTIA AND ITS RELATED DISORDERS

PD (Parkinson's disease) is a neurodegenerative disorder that mainly affects motor neuronal system and is caused due to accumulation of enclosures of the alpha synuclein also called Lewy bodies and it is characterized by visual deliriums, alterations in intellect and extemporaneous motor Parkinsonism. Seventy to eighty percent of patients develop understanding damage plus dementia through the disease timespan. There are 2 types of Parkinson's dementia; one type is in which affected individuals develop intellectual defect signs after one year of motor symptoms, while the other type is Lewy body where individuals had cognitive symptoms appearing in a year from motor symptoms (White *et al*., 2005). Intellect defect symptoms in Parkinson's disease dementia and Lewy body's dementia are varying, but often feature impairments in visual recognition and distinguishing ability, execution of various functions, language or memory. Huntington's disease is an autosomal recessive neurodegenerative progressive brain disorder caused by (Cytosine adenosine guanine) which are dinucleotide recaps in the gene which is coding for protein Huntington. Pathophysiology includes progressive degeneration of corticolimbic circuitry which is GABAergic interneurons (Sofroniew and Vinters, 2010). Clinical symptoms of Huntington's disease include motor symptoms such as jerky involuntary movements, slowness of movement, muscular spasm and abnormal posture, incoordination and perceptive symptoms, visual functional changes. Multiple sclerosis (MS) is neurodegenerative which degenerate myelinated surroundings of the neurons leading to noteworthy debility of neuronal conduction (Fassbender *et al*., 2004). The accurate reason of multiple sclerosis is still not known but it's intended to be due to the consequence of autoimmune syndrome (where myelin cells are attacked by inflammatory cells) or dysfunction of myelin precursors. MS represents an advanced or relapsing-remitting form. Symptoms of multiple sclerosis are varying, in severe cases it causes blindness or paralysis while in moderate cases it causes limbic numbness (Rohrer, 2012).

HAND disorders which are HIV associated cognitive disorders are classified on base of severity levels in three types ANI, HMD, HAD. Asymptomatic neurocognitive impairment characterizes perceptive weakening below age and education standards. HIV associated mild neurocognitive disorder features intellectual disability and mild

impairment in daily functions. HIV associated dementia features mental damage same as ANI (Cartier *et al*., 2005). Prion associated diseases are sporadic neurodegenerative type of syndrome triggered by impaired processing of prion protein. Different prion linked dementia variants show varying symptoms, including different progression rates and onset.

MECHANISM OF PATHOPHYSIOLOGY INVOLVED IN BRAIN DEGENERATION

Brain cells has high influence towards oxidative stress, so that the reactive oxygen species produced under stress in brain which are involved in many neurodegenerative disorders such as diabetes mellitus. Under normal condition there is balance between ROS and the free radicals, any imbalancement leads towards the stress and may be fatal to the individual hence, it can also be stated as the lipid peroxidation due to which radicals are produced (Mitew *et al*., 2010). Prior to all studies it is first observed that oxidative damage to the macro-species like lipids and proteins may be seen with once is aging years in its life and product of the reaction may persist in the brain and this deposition may be increased as one is gone through the span of his or her life so with the progressive age one or more than one related people are seem to be affected adversely. Similarly the activity of superoxide dismutase (SOD) and catalase (CAT) are discussed mainly and they are found in the antioxidant defense of the brain of any diabetic person Moreover if we tend to know the possible cause of the neural damage which may also include auto-oxidation of GLU and synthesis of free radicals, higher lipid per-oxidation and it is also encountered within the reduction of tissue concentration which tend to have lower molecular weight of anti-oxidants which can be listed as reduced Glutathione. Substitution in Glutathione levels in the diseased individuals can also be the contributory factor of increased pathway which is known as Polyol Pathway this pathway states the depletion and reduction of NADPH (Zhang *et al*., 2013). Likewise higher level of another stress marker named MDA with an increased Glutathione di sulfide reductase activity and lower down Manganese superoxide dismutase also known as (MnSOD) and GSH activity is also decreased it also represented oxidative phosphorylation system characterized by the lowered mitochondrial energization potential and Adenosine Tri Phosphate level in repolarization lacking phase (Cunningham *et al*., 2005).

INFLAMMATION IN THE DIABETIC INDIVIDUALS

A biological process which is termed as inflammation in this process various acute and chronic conditions may alter the rigidity of tissue membrane and it also deviated the normal level of homeostasis in the tissue by the help of several different mechanisms (Reines *et al*., 2004). Appropriate mechanism is one of the essential part in the prevention of amplification in excessive amount of the initial inflammatory responses and it also take the number of developing factors of disease and collateral damage of the tissue and organ in some cases. Now the factors which are pathogen associated molecular patterns termed as PAMS and DAMS which are Damage associated molecular patterns which are basically receptors that are involved in the glycation and product which is named RAGE. And it is also found in the cell signaling pathway which are intercellular like Map kinase, P13 kinase hence such discussed signaling events of reactions mimic the expression of cytokines and chemokines not only this but enzymes and growth factors which are required for tissue repair however there are some situations that are again play role in the persistent cellular stress or we can it as the stress conditions that occur in the cell again and again. As the result of all discussed particular conditions conclusion can lead towards the significant change in tissue function and persistent de-arrangement of homeostasis. These are the most typical examples of the pathological process or infections which may be associated to the chronic inflammatory alterations in the individuals (Soares *et al*., 2009).

So in the result ROS species are also eradicated are one of the most accepted results the stimulation and release of immune cells in acute and chronic inflammatory stages and it is associated with the redox equilibrium by the enhancement of oxidative generation. NFκB transcription factors are those which are enlighten in the mammalian cells only these proteins are one of the most persistent in species as well. In mammals the same described family is basically consisted of five members which can be p50, then p52, moreover p65, c-Rel and RelB these above mentioned are the five explained members of the above mentioned family while all of the members are either homo-dimerize or they can be hetero-dimerize. Identical roles of these family members in the DNA binding and dimerization not only this but nuclear localization and also its interaction or association with the IκB induces stimuli or plural stimulation/ activation of inhibitory proteins (Coracil *et al*., 2002).

Now getting into the mechanism of same family dimer is stated as NFκB dimer is present the cytoplasm of the cell which is surrounded by the inhibitory proteins mentioned above which are stated as the IκB proteins and as the NFκB induces a stimulation it activates the inhibitory protein phosphorylated complex which is the reason for the degradation in the canonical NFκB activation pathway. So now coming to the inhibitory proteins which is responsible for the degradation of DNA-binding Domain and localization sequence of NFκB at nuclear level and

though it also allows the movement or you can say the translocation towards the major part of cell named as nucleus so the target specie is regulated in response. Once NFκB enters the nucleus of the cell through transcription, which deviates cellular process such as immunity, inflammation, proliferation and apoptosis (Vaughan and Jat, 2011).

AFFECT OF DIABETES ON THE NEURONAL DISEASES

As we all know that the nervous diseases are the number of reason for the deaths annually around the globe so if we consider the causes beyond these Neural diseases we will get to know the effects of several other diseases which may regulate or cause a specific mentioned disease in the patients already acquired with any congenital or hazardous diseases. So if we take the person with diabetes we can assume that he is on the point to be exposed with several other life threatening diseases hence events to occur for the CNS disorders in the diabetic patients are way more than any other individual and if so he is exposed to any other concluding factor the risk of the disease may be elevated to the number of the times. So coming on to the fact about the diabetes we will get to know that diabetes is the over nutritional disorder which is usually proceeded by the metabolic symptoms like it may be up or down regulated in the mentioned case. However, over nutrition is also taken as the independent environmental factor that initiates the immune system to ignite the typical form of inflammation which may lead to the dysfunction in the hypothalamus particularly which is also related to CNS number of times. This is further involved in several of metabolic functions of the body that includes controlling the hunger conditions and energy expenditures and last but not least biomolecule metabolism is regulated in the diseased conditions (Reines *et al*., 2004).

Syndrome which is related to CNS or more specifically in hypothalamus contributes in the development of over nutrition of those particular metabolic syndromes and related disorders which may be insulin resistance, obesity, obesity related or caused hypertension while the intercellular oxidative stress includes T2D which is now a days a progressive neurodegenerative disorder and in case of ER (Endoplasmic Reticulum) high glucose level is present due to the production of free radical that ultimately cause protein glycosylation and protein turn over. And final consideration is ER stress may involve in apoptosis (which is cell death) which leads in higher amount in hyperglycemic patients induced hippocampal synopsis and neural implementation and enhances the diabetic impairment effect (Cunningham *et al*., 2005).

ROLE AUTOPHAGY CELLS IN DIABETIC BRAIN

Autophagy which is a normal physiological mechanism that deals with the destruction of cells inside the body and hence it is responsible for the maintenance of normal functioning by degrading proteins and new cells are formed. It is known primarily as pro survival mechanism of cell in stress condition that is a contributory factor again in the cell death under pathological conditions its defect is linked with the metabolic disorder like diabetes, alcoholism and lipid abnormalities. And in number of cases the described pathogenesis is related to failure of autophagy machinery this mechanism is responsible for the removal of defective/degenerated proteins which are present in the cytosol which is the liquid media of the cell. In order to maintain equilibrium environment there is the requirement of damaged/ defective proteins from Endoplasmic reticulum ER (Yasojima *et al*., 1999). Chronic stress inside the cell which may be ER or mitochondrial stress visualize as most sensitive upstream occasions it may also considered as helpful to restoration of the activity of intracellular homeostasis by acquiring a number of hazardous molecules which may be as misfolded or unfolded proteins present inside the lumen of Endoplasmic Reticulum when these type of stresses remain unattended or untreated after a prolonged autophagy and the up-regulation also contribute in the process called autophagy. In the pathogenic infections within the different age groups the pathway may belong to autophagy can related to many pro-inflammatory signaling via oxidative stress pathway (Xiang *et al*., 2002). Due to hyperglycemic conditions, several changes and down regulation can be seen wit in the body. As the topic indicates diabetes a concluding factor in the neural diseases we consider a diabetic brain would have decrease antioxidant activity and so the oxidative stress would be increased. Number of factors is found to be affecting like Polyol pathway, lipid peroxidation, and advance glycation end product and off course glycated proteins and over nutrition would be there. With the over nutrition one term comes into the consideration that the glucose and glucose end products would be increased as well so the acidification can be seen and all above explained family of NFκB and it inhibitor proteins found working. Due to ROS, ER stress and mitochondrial dysfunction is seen.

GLIAL CELLS-FRIEND OR FOE

Microglias are macrophages localized in the brain which keep inflammation/ inflammation associated receptors and mediators in check. Moreover under normal circumstances these brain remodelers screen various brain/cranial parts in order to eliminate apoptotic neurons, potential intruders, and detritus and release factors facilitating tissue rebuilding accordingly (Watson *et al*., 2009). Besides they also actively participate in immune responses in a myriad of CNS disorders. In vitro and in vivo studies have shown that when the brain enters diseased state, these

macrophages start releasing inflammation associated factors which are elevated in AD brains, hence contributing to neurodegeneration. These resident macrophages also affect other neurons in the vicinity and most importantly change the phenotype of microglia from M1 to M2. Activated microglias secrete ROS which in turn has been further implicated to activate neighboring microglial cells (Fiala *et al*., 2007).

Apart from this they also activate cytokine receptors and the pro-inflammatory cytokines IL-6, TNF-a, interferon g (INF-g) and IL-1b along with complement proteins and associated receptors (Li *et al*.,2004). Besides growth factors including macrophage colony stimulating factor (MCSF), chemokines including CXCL8, monocyte chemotactic protein 1 (MCP1), RANTES, macrophage inflammatory protein 1a and 1b (MIP1a, MIP1b) and its receptor are also activated (Duan *et al*., 2008). Aside a wide range of activated-microglial induced release of receptors includes formyl peptide (FP) receptors, CD40, scavenger receptors and Fc receptors (Cartier *et al*., 2005). Other worth mentioning receptors are the pathogen recognition receptors (PRRs) toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE) which have a major role in inflammatory processes (Melnikova *et al*., 2006). Both microglia and AD brain studies have reported altered NF-kB and PPAR gamma transcription factors (Pacher *et al*., 2007). Besides secreting inflammatory mediators they also release substances counter-acting inflammation including IL-4, IL-10, IL-13, and TGF-β (Fassbender *et al*., 2004).

ROS and Aβ have the potential to activate microglial cells in the brain. Under normal circumstances microglia detect Amyloid β in the brain and engulf it in order to remove it from the brain, but these macrophages lack the potential to chop the amyloid deposits it has eaten, leading to frustrated phagocytosis. This process leads to change in macrophage phenotype, activating it (Pacher *et al*., 2007). Microglia only gets rid of amyloid deposits and pathogens therefore playing good in maintaining normal physiological environment of the nervous system but once activated the good macrophage turns bad and starts destructing and killing neurons. A therapeutic approach in AD is to target those agents which cause change in resident macrophages of the brain. Astrocytes have the ability to reach out approximately 100,000 synapses where they connect with neurons in order to help in the maintenance of ionic concentrations, control of energy metabolism, tempering oxidative stress (OS) and remodeling processes. Moreover they are involved in the release and reprocessing of neurotransmitters. It is a worrisome fact that any deviation in normal function, eventually leads to injurious results. Astrocytes are similar to microglia in that they are highly sensitive to environmental changes. Astrocytes and microglia have a common feature that any change detected by them leads to morphological and functional changes in them (Cameron and Ladreth.,2010) .Some studies say that astrocytes upon activation take up Aβ and degrade it while others say that activated astrocytes surround the amyloid deposits in AD. It is observed that amyloid plaques have large quantities of MCP1 which attracts the astrocytes towards amyloid aggregates. Astrocytes via their wide range of expressed receptors on them including RAGE bind with the amyloid β (Meister., 2007). Astrocytes release MMPs which degrade the amyloid deposits. Moreover it secretes inflammatory factors including IL-1b, TNF-a, INF-g and IL-12, and increases release of transcription factors (Abbas *et al*., 2002). Nitrative stress also spikes with the increase in NO and iNOS generation. Besides calcium levels get disturbed when exposed to amyloid plaques (Khoury and Luster, 2008).Usually oligodendrocytes and their secreted myelin have important roles in neurotransmission. During AD, abnormalities in the gray matter are associated with amyloid beta deposits whereas white matter is associated with myelin defects (Rohrer, 2012). They are more prone to OS owing to their minimum levels of glutathione and greater iron content. Healthy neurons express certain molecules that provide protection to neurons against inflammation. But in AD deficiency of these molecules especially fractalkine, CD200 and CD59 have been observed (Godoy *et al*., 2008).

COMPLEMENT SYSTEM

The complement system plays an important role in neurodegenerative disorders and complement proteins are made by neurons and glial cells. These proteins have been linked with amyloid plaques and NFT's in AD. Apart from its role in clearing/removing protein aggregates and degenerative cells, these proteins are largely expressed in multifarious disorders including AD (Katsel *et al*., 2009).Amyloid β and tau have been reported to trigger the complement system but unchecked activation may lead to inflammation (Gasque *et al*., 2000).

CYTOKINES AND SOLUBLE PROTEINS

Cytokines play important role in CNS development and their levels are decreased in AD. When levels of cytokines and chemokines change in the CNS the CSF levels are also affected mouse models have shown these changes in cytokines and chemokines affect cognition and amyloid genesis. Moreover TGF beta levels have been reported to be increased in AD patients whereas its receptor is down regulated. Cytokines can potentially trigger glial cells and hence contribute to inflammation (Liang *et al*., 2007).

PATHOGEN-RECOGNITION RECEPTOR (PRRs)

The immune system recognizes intruders via specialized receptors which include toll-like receptors, NOD-like receptors, RAGE etc. These receptors have their role in injured CNS, possibly AD, activate transcription factor NF-kB and certain inflammation-associated genes (Rogers *et al*., 1993). TLRs are expressed on various cells including microglia cells and amyloid β has been known to bind to these pathogen recognition receptors. TLR2 and TLR4 is involved in AD. CD14 being the co receptor of TLR4 has the potential to trigger secretion of various substances from microglia, most notably NO, proinflammatory cytokine IL-6 and neurotoxic factors. Surprisingly, microglia fails to activate NF-kB or p38 MAP kinase signaling or phagocytosis in the absence of CD14, TLR2, or TLR4 (Brandenburg *et al*., 2008). Basically TLR activate microglia in order to clear amyloid deposits and mouse studies show that any abnormality in TLR signaling leads to cognitive impairments, hence a great increase in amyloid deposits has also been observed (Ulusu *et al*., 2003). The TLR response varies depending on the type of amyloid whether it's a monomer, oligomer or fibrillar form of amyloid. The other PRR of great importance in AD is the receptor for advanced glycation end products (RAGE). It plays vital role in inflammation by activating major inflammatory pathways Jak/Stat and NF-kB signaling. These receptors have been known to be a receptor for amyloid β, where it activates transcription factors NF-kB and MAPK pathways. This leads to both cognitive impairements and enhanced synaptic transmission abnormalities. RAGE is reported to be upregulated in AD brains (White *et al*., 2005).

ARACHIDONIC ACID METABOLITES

There are two COX enzymes in our body where COX 1 is ubiquitous, expressed by microglia and has implications in generation of prostanoids, while COX 2 finds its role in inflammation and is involved in proinflammatory prostanoids synthesis. Moreover COX 2 is produced by neurons, found in post synaptic sites where it regulates synaptic transmissions. COX 2 may be neuroprotective in nature (Rasool *et al*., 2014).

It has also been observed in various studies that increased COX-2 expression in diseased states is the cause of apoptosis of neurons, cognitive deficits and highly excessive increase in amyloid deposits. This supports the harmful role of COX 2 in causing neurodegeneration and AD (Antinori *et al*., 2007). Keeping in view the role of prostanoids receptors specific in AD-associated inflammation, these receptors are now considered as potential therapeutic targets to control inflammation instead of orthodox NSAIDS. Genome wide association studies (GWAS) have helped in finding AD genes, clusterin and CRI are some examples which are related to the complement system .Moreover inflammatory cytokines, chemokines, acute phase proteins have also been reported to have role in AD risk. In AD brains changes in inflammatory pathways have been seen, and increase in inflammatory genes has been seen with the advancement in aging process. Hence these genes have potential association with AD too (Melnikova *et al*., 2006). The use of different techniques has provided us the information that factors responsible for immunity have been found to be changed in brain, blood, CSF and plasma of AD individuals. But it is yet to be established whether these changes mean anything in causing AD and should they utilized for diagnostic purposes or not (Tan *et al*., 1999).The search for efficacious AD drugs has been in demand for quite a while. Many drug targets specific for AD have been identified but with little success (Vaughan and Jat.,2011). The need of the hour is to find efficient, robust AD drugs which can prevent, treat or cure AD. But we have not been successful in achieving our target. Cyclooxygenase-2 (COX-2) inhibitors have gone through clinical trials but success rate is very low .Inflammation associated pathways are modified in AD and it is inflammation that causes disease advancement and neurodegeneration in AD (Gasque *et al*., 2000).

DISCUSSION

Diabetes and many other diseases are affecting the human beings from decades. Scientists have worked alot on diabetes and related diseases that affects the brain. Hyperglycemia and hypoglycemia are the common conditions which badly affect the memory of human species. Diabetes, now-a-days is found to be one of the most common disease among the human beings irrespective of age and gender. Parkinson's and Alzheimer are the common disease which occurs due to diabetes by affecting the brain. Alzheimer and dementia are a neurodegenerative disease that involves biochemical processes due to which loss of neurons takes place and cell death occurs. Many factors are involved which significantly leads to disease. Inflammation and proteins also play their role in the development of AD. As there is balance between ROS and free radicals so once this balance is affected, oxidative stress generated and thus insulin level fluctuates and causes diabetes mellitus.

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