Review Article

Culprits of Neurodegeneration in Alzheimer's Diseases: Bench to Bedside Impression

Aasheesh Kumar[1], Avishek Roy[2]*

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of the brain and around 60% of dementia cases are associated with sporadic AD. Dementia particularly beyond 65 years of age, is the chief problem; therefore, it is called the senile dementia of Alzheimer's type (SDAT). Besides SDAT, patients manifest anxiety, delusion, aggression, memory loss and cognitive impairment. To understand the pathophysiology of the disease various animal models of Alzheimer's disease like streptozotocin, polyC, amyloid beta, hp-tau and APOE 4 Tg mice are widely used in the discovery of potential targets for AD treatment. The actual pathophysiology of the disease is not known yet. Hypotheses proposed for the onset of AD are proteinopathies like tauopathy and amyloid-beta deposits, neuroinflammation, oxidative stress, cholinergic deficit and impaired insulin signaling. To date, there are no therapeutic interventions available; only a few drugs are recommended to AD patients; only to harness temporary symptomatic relief. Understanding the actual culprits of the disease is necessary to retain lost neurons in the brain by stimulating NPCs present in the brain with some non-invasive techniques. Neurogenesis could be a potential compensatory pathway for neurodegeneration and related global brain atrophy in Alzheimer's disease, which can retain functional deficits.

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Introduction

In 1906, AD was discovered by Alois Alzheimer, a German psychiatrist and neuroanatomist. He did extensive studies on a 51-year-old lady – 'Auguste Deter', for whom he was treated for paranoia, progressive sleep and memory disturbances, aggression and confusion. In his paper – "Plaque Only" he explained the morphological changes in the cerebral cortex damaging the area due to plaque formation and associated psychological changes. Alzheimer's disease is the most prevalent neurodegenerative disorder of the brain which is progressive as well as irreversible. It is thought to be a disease of old age. Based on the onset of the disease, AD is divided into two categories – Early Onset Alzheimer's Disease and Late Onset Alzheimer's Disease. Former is seen between 30-55 years of age and it is due to the familial run or genetic makeup of the patient while late onset AD is mainly seen after 65 years of age. Among these two forms of AD, the sporadic form is predominant and it accounts for more than 99% of AD cases.

[1]Department of Biotechnology, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

[2]Department of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

Correspondence to: Aasheesh Kumar, Department of Biotechnology, All India Institute of Medical Sciences (AIIMS), New Delhi, India. E-mail: aasheeshaiims@gmail.com

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Epidemiological Surveys

Alzheimer's disease is the most prevalent neurodegenerative disease of the brain. Around 60% of dementia cases are associated with sporadic AD. There are 47 million people suffering from disease worldwide and we are investing around $100 billion in caring for Alzheimer's patients. Prevalence of the disease is estimated at about 3.4%.[1] Due to its chronic and irreversible nature, it remains incurable and thus is considered a major healthcare challenge and global burden [2]. The prevalence of AD is presumed to nearly quadruple in the next 50 years and by that time approximately 1 in 45 individuals will be affected with the disease [3]. Approximately 200,000 people younger than 65 years suffer from early-onset AD. It is expected that by 2050, one new case of AD will develop every 33 or nearly a million cases per year. The total estimated prevalence is expected to be 13.8 million worldwide [4]. Alzheimer's disease is predicted to affect 1 in 85 people globally by 2050. According to the Alzheimer's and Related Disorder Society of India Association survey 2010, Maharashtra,

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Delhi & Jharkhand are the states with the highest cases of AD in India. Females & Americans are affected more by the disease. Alzheimer's Association of America (USA, 1980), Alzheimer's Disease International (UK, 1984), Alzheimer's and Related Disorder Society of India Association (India, 1993) and many other organizations are working in various countries to manage the disease.

Symptoms

Dementia is the main psychological issue with AD patients particularly at age beyond 65 years; therefore, it is called the Senile Dementia of Alzheimer's Type (SDAT). Dementia is the general term used for a group of problems related to planning, language, speech, interpretation, reasoning, perception, and posture. Besides SDAT, patients also show anxiety, delusion, aggression, memory loss and cognitive impairment. Dementia is the main psychological issue with AD patients particularly at age beyond 65 years; therefore, it is called the Senile Dementia of Alzheimer's Type (SDAT). Dementia is the general term used for a group of problems related to planning, language, speech, interpretation, reasoning, perception and posture. Besides SDAT, patients also show anxiety, delusion, aggression, memory loss and cognitive impairment. Patients also show abnormal behavior such as anxiety, depression, sleeplessness, delusion, and agitation. Cognitive impairment is also an important symptom of the disease; a person shows poor memory, accountability and learning ability. There are three stages of disease in due course of its progression, manifesting different disease symptoms [4].

Early Stage - Short-term memory loss, handling money, new learning, decreased attention and finding words.

Middle Stage – Sleep disturbances, wandering, disinhibition, agitation, social isolation, language skill decline, paranoia, hallucinations, sundowning and resistance

Late Stage – Non-recognition of self or others, 24-hour caring required, incontinent and communication profoundly impaired.

Animal models of Alzheimer's disease

To understand the pathophysiology of the disease; various animal models of Alzheimer's disease from lower invertebrates – *Drosophila* and *Caenorhabditis elegans* to higher vertebrates - dogs, cats, wolverines, monkeys and chimpanzees were studied [5-7]. Rodent models of AD are easier and cheaper to create and responses to introduced toxins are easy to study. Aluminum like heavy metals is hazardous for various metabolic processes; excess accumulation of Al causes brain lesions in rats. [8-10] AD was provoked in the Sprague Dawley rats by administering $AlCl_3$ orally with 0.5 mL/100 g body weight for 25 days and then supplemented with 30 mg/kg of ononin orally for 25th day to 36th day.[11] Non-transgenic mice models of AD include the injection of various drugs like scopolamine (muscarinic antagonist), and ibotenic acid (chemical lesion induction) in mice. [12,13] Aβ is the main culprit of the disease; so, i.c.v., injection with its synthetic analog was directly used to induce sAD in the mice.[14] Administered of $A\beta_{25-35}$ (5 μL/unilateral, bilateral, single dose) in the hippocampus establish a complex rat model of Alzheimer's disease.[15] Various molecules like polyC and LPS, which promote neuroinflammation were also used to induce the disease in mice and rat models.[16,17] Colchicine injection may be used to create a tubulin disintegration model.[18] Transgenic models for the disease are mainly created in mice. Genetic mutations like mutation in the amyloid precursor protein (APP) gene at β or γ sites prevent their degradation by respective secretases.[19] Most familial AD models can be created by a mutation in presenilin 1 and presenilin 2, which are transmembrane proteins required for the efficient formation of γ secretase complex; which leads to Aβ plaques. APP-BACE 2 (Type 1 transmembrane β-site cleaving enzyme) mutated mice prevent the function of key APP cutter i.e. secretase β.[20] Apolipoprotein 4 increases the risk of Alzheimer's disease; nowadays APOE 4 Tg mice are used to study AD. Tau mutations also lead to Alzheimer's disease, one of the tau mutated mice is JNPL3. Other transgenic mice are APP23,[21] Tg2576,[22] 3xTg [23]. There is no single animal model which is an absolute mimic of the disease. So, the biggest challenge is to develop an animal model that has NFTs, Aβ plaques, neuroinflammation, and neurodegeneration, which are the characteristic features of AD. Streptozotocin is a nitrosourea glucosamine compound that creates an Insulin Resistant Brain State (IRBS) and excitotoxic effect of glutamate. It also reduces acetyl coenzyme A & cholinesterase acetyltransferase and increases acetylcholinesterase in the hippocampus of the brain.[24] Over 2 to 3 mg/kg body weight i.c.v., injection of streptozotocin, (a beta cytotoxic and neurotoxic drug) can also be used to induce neurodegeneration in brain areas which can result in cognitive impairment and dementia due to synaptic loss, which are the symptoms of AD,[25-28] wherein they observed short term spatial memory loss after 2 weeks of STZ injection at a dose ranging from 1.5-3.0 mg/kg of body weight into lateral ventricles.

Neuronal death was characterized by chromatolysis i.e., the dissolution of Nissl granule in the soma of the neuron. Impairment of insulin signaling and degeneration of hippocampus neurons in CA1, CA2, and CA3 regions has been reported in the STZ rat model of AD [28]. The mechanism of action of streptozotocin along a timeline from introduction to a manifestation of the mimics of some clinical symptoms is described in Figure 1.

Pathophysiology

Global atrophy of the brain is characterized by enlarged ventricles, widened cerebral sulci, and ventricular dilation; this is due to extensive neurodegeneration in the patients. AD is a proteinopathy, where the accumulation of misfolded proteins, like deposition of extracellular Aβ plaques and intracellular neurofibrillary tangles, are predominant which induces oxidative stress and neuroinflammation resulting in irreversible neuronal loss. The neocortex (entorhinal) cortex and hippocampus are the two most vulnerable regions of the brain; therefore, cognitive deficits including dementia, delusions, anxiety, and depression have a cause-effect relationship with the neuronal loss in AD. There is not a single culprit that accounts for the cause of the disease; complexity in treatment arises due to its wide range of pathophysiology. Various hypotheses are proposed to explain the causative factors for the onset of Alzheimer's disease. Several genes and gene products basically signaling molecules, cholinergic molecules, apoptotic proteins, energy-yielding molecules and the transport or cytoskeletal proteins are found to be involved. Some of the hypotheses proposed for the onset of AD are neuroinflammation, oxidative stress, cholinergic deficit and impaired insulin signaling.[29]

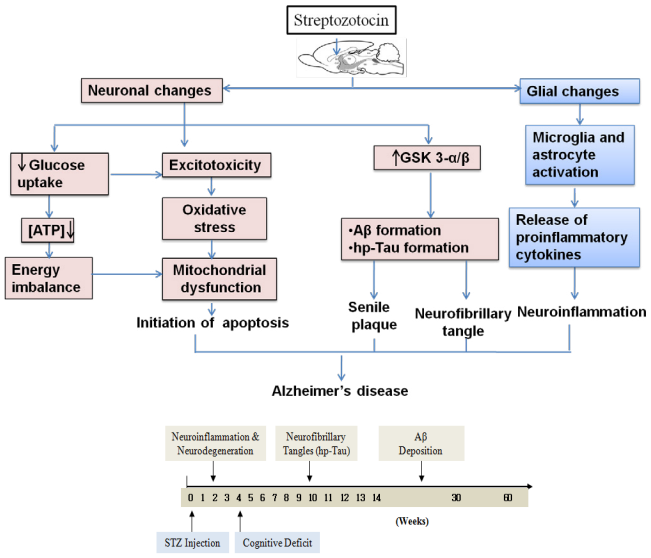

Figure 1: Progression of sporadic AD after STZ injection in rats (Nazem et al., 2015)

Amyloid Cascade Hypothesis

Two hallmarks of AD are senile amyloid beta plaques which are extracellular deposits 1 to 42 amino acids long fragments of APP; and neurofibrillary tangles of hyperphosphorylated tau protein, which are a microtubule association protein**.** Aβ plaque is the deposit $A\beta^{1\text{-}42}$ of the APP cleaved by the specific enzymes called secretases. APPs are transmembrane glycoproteins that help in neurite outgrowth, cell survival and cell signaling (Figure 2). They after cleavage by the secretases get oligomerized outside the neuron forming a plaque. The β-secretase is a membrane-bound aspartyl protease, β-site amyloid precursor protein cleaving enzyme (BACE1) also called Asp2, memapsin 2 is the main enzyme responsible for initiating Aβ generation.[20] Although the amount of γ-secretase is not elevated in AD, alterations in it lead to the production of longer forms of Aβ, which are the major genetic cause of early onset or familial AD.[21] These plaques are detrimental to the neuronal functioning. Apolipoproteins also help in the aggregation of Aβ and are therefore considered a risk factor in AD. APP gene is present on chromosome 21, Down's child is more prone to disease, having an extra copy of that chromosome.[30] Presenilin 1 and Presenilin 2 are helpful in APP processing; their presence also intensifies the disease. Moreover, in a meta-analysis, the APOE 4 gene was recognized as a potential risk factor for the disease [31]. The amyloid deposits outside the neuron activate microglial cells with PRRs, CD33, and TLRs, which in turn secrete cytokines like IL-1, IL-6, IL-12 and TNF-α. Continuous dialogue between the Aβ plaques and the innate immune response results in inflammation of the brain.

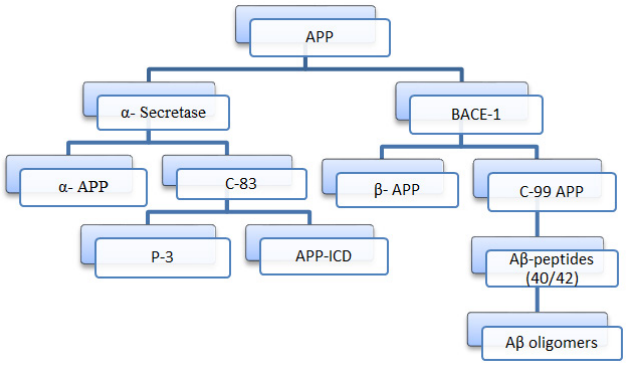

Figure 2: Cleavage of Amyloid Precursor Protein (APP)

Taupathy

Tauopathy is the second key feature of the AD brain. Tau proteins are found inside the neuron and they are concerned with maintaining microtubule assembly and are also known as microtubule association proteins. Tau has six different isoforms and a balance between 3R and 4R isoform is very necessary for survival; tauopathies are characterized by specifically an imbalance in the ratio of 4R/3R tau isoforms. Tau is also needed for maintaining the structure of cytosolic microtubules and so provides stability to it [32]. Like MAP1 and MAP2, tau is also a phosphoprotein and its biological activity is regulated by the degree of its phosphorylation in the cell.[33] Normal brain tau contains 2–3 moles of phosphate per mole of the protein which appears to be optimum for its interaction with tubulin and microtubule assembly promotion.[34] But with aging various phosphokinases become dysregulated – MPK-1, CDK, etc. These kinases lead to hyperphosphorylation of the tau protein which in turn causes disassembly of microtubules and as a result interferes with the transportation of various crucial metabolic byproducts, essential for neuronal survival. The aggregation of paired helical filaments (PHF) made up of hyperphosphorylated tau, results in the formation of flame-shaped neurofibrillary tangles (NFTs) which are intracellular and responsible for the death of the cell depicted in Figure 1.[35] The normal form of cytosolic tau proteins in AD brain are same as in normal aged brain but the level of total tau proteins is about four to eight folds higher in the former and this increase is due to neurofibrillary tangles solely of the abnormally hyperphosphorylated tau proteins.[36] Therefore, untangling the NFTs could be a potential target for drug discovery for the management of AD-related symptoms (Figure 3).

Oxidative Burden Model

Oxidative insult is the major detrimental pathophysiological change marked in the AD brain. The imbalance between the antioxidants and oxidants in favor of oxidants inside the cell is the main reason behind the oxidative burden. Besides this, there is also a change in the balance of redox transition metals like iron and copper. Molecular oxygen present in the water gets reduced into superoxide radicals which in turn produces hydrogen peroxide. Further reduction of hydrogen peroxide yields ROS which react with biomolecules like lipids, proteins and nucleic acid and alter their structure and function. There may be dysfunction of an antioxidant system like glutathione which leads to oxidative stress.[37] The brain has in abundance peroxidation-susceptible lipid cells, which are prone to oxidative insults. Another important source of oxidative stress comprises RNS including nitric oxide (NO). Under normal conditions, there is a balance between ROS formation and antioxidants but in the case of neurodegenerative diseases like Alzheimer's, this balance is lost.[38] Moreover, abnormal deposition of Aβ and intracellular neurofibrillary tangles is associated with the oxidative burden,[39] as high concentration of copper is found in amyloid plaques.[40] Hyperphosphorylation of τ protein into paired helical filaments leads to tangles. Phosphorylation is linked to oxidation through the microtubule-associated protein kinase pathway and through activation of the TF nuclear factor ƙB, thus potentially linking oxidation to the hpTau proteins.[41] Streptozotocin causes an increase in ROS/RNS production, increased lipid peroxidation, increased expression of oxidative stress marker protein NOS-2, inhibition in GSH synthesis, and alteration in GSH metabolism by GST and GSH–Px.[42]

Neuroinflammation Model

There is a chronic neuroinflammation in the hippocampal and neocortex areas in the brain of AD [43]. The accumulation of Aβ fragments increases the toxicity in the brain, which results in the induction of the innate immune responses inside the brain. The two key players of fighting against the amyloidogenic surge are astroglia and microglia. Misfolded protein and aggregated proteins bind to microglial and astroglial cells with their receptors on their surfaces and trigger the secretion of inflammatory mediators. Many genes for immune receptors are found associated with Alzheimer's disease – TREM 2 and CD33-.[44,45] In the AD brain, microglia can bind to soluble amyloid protein (Aβ) oligomers and their fibrils via cell surface receptors like SCARA 1, CD36, CD14, α6β1, integrin, CD47 and TLRs (2,4,6,9). In vitro CD36, TLR4 & TLR9 prevent accumulation of

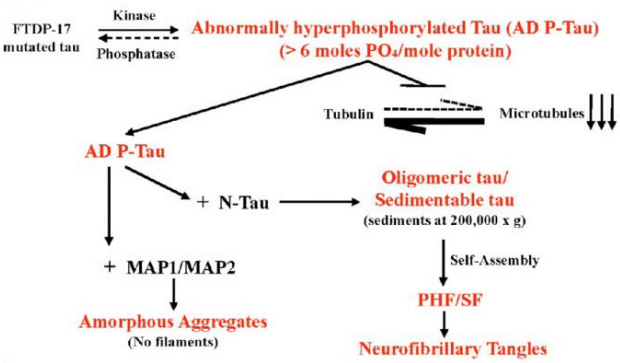

Figure 3: Mechanism of taupathy in Alzheimer's Disease

amyloid β. The interaction with glial cells triggers the secretion of cytokines like – TNF α, IL-1, IL-6 and IL-12 which enhances inflammation. In the aging CNS of mice, rats and primates, microglia show enhanced stimulation to inflammatory stimuli; this is called priming [46]. PPAR agonists lead to an increase in microglial Aβ uptake through the induction of CD36 [47]. Perivascular macrophages have some effect on the Aβ clearance. AD brain is marked by astrogliosis, which leads to atrophy in the entorhinal cortex. So, astrocytic mediated atrophy of the neural tissue has a far-reaching effect on synaptic connectivity and so, on cognitive decline [48]. Neural death is by atypical kind of apoptosis. It is seen that there is an increased level of Caspase 1 during degeneration of neurons; Caspase 1 in turn activates other caspases like Caspase 3. These dialogues between innate immunity and proteopathies result in the increased volume of brain fluid and it finally leads to neuroinflammation [49]. Decreased activity of energy-related proteins like pyruvate dehydrogenase, iso-citrate dehydrogenase and α-keto glutarate was found in AD brains leading to oxidative stress and cell death [50-52].

Cholinergic Hypothesis

Cholinergic functions in the brain play an important role in learning and memory. Cholinergic neurotransmitter system dysfunction contributes to cognitive impairment in neurodegenerative disorders like sporadic Alzheimer's disease and other related syndromes. Human basal and rostral forebrain cholinergic pathways including converging projections to the thalamus contribute vital functional roles in conscious awareness, attention, working memory, and many other mnemonic processes [53]. Acetylcholinesterase (AChE) and acetylcholine transferases (ChAT) are responsible for the hydrolysis and synthesis of acetylcholine; the activities of both enzymes are affected in AD [54]. Cognitive decline with age could also be a consequence of reduced cholinergic receptor density or binding affinity that can promote vulnerability to other Alzheimer's processes. Contemporary modification of the "cholinergic deficit" of aging and AD may reveal opportunities to reduce related clinical manifestations.[55,56] Acetylcholinesterase inhibitors (AChEIs) and NMDA receptor antagonists were most commonly used in AD studies. Cholinergic receptors that modulate cellular, synaptic, and complex activities like learning and memory processes are susceptible to afferent cholinergic loss in the hippocampus and entorhinal cortex area of the brain.[57] Establishing a potential relationship between the cholinergic pathway and AD pathophysiology is still a challenge for the scientific community working in this direction. Cholinergic receptor activity modulates other neurotransmitter systems and can assist synaptic networking via the glutamatergic pathway in most of the hippocampal area [58]. Intracellular calcium accumulation and aberration in NMDA phasic excitation are the cause of toxicity in neurons and improper cell functioning, LTP and synaptic neuroplasticity respectively. Also, In the AD brain, tonic over-excitation of NMDA receptors by glutamate is triggered by Aβ plaques. As a result, various antagonists and agonists of the central neurotransmitters are in the clinical trials for the development of therapeutic agents for the treatment of AD.

Insulin Resistance Brain State (IRBS)

Insulin is synthesized in the β-cell of the pancreas and it can cross the blood-brain barrier. Impaired insulin signaling is important in the pathogenesis of sAD [59]. AD patients have lower CSF and higher plasma insulin levels as well as decreased insulin receptor density and decreased tyrosine kinase activity.[60,61] It was also studied that insulin administration in AD subjects improves their cognitive performance.[60-62] So, two important contributors to AD etiopathogenesis are insulin signal transduction aberration and glucose metabolism. The brain was earlier considered to be an insulin-insensitive organ but insulin and insulin receptors are present throughout the brain [63]. Insulin not only regulates glucose levels but also has a significant role in neuronal growth and survival [64-65]; insulin being a neuroendocrine molecule has a neuromodulatory impact. In AD, insulin has been shown to decrease intraneural Aβ and increase extracellular Aβ levels by preventing its degradation by Insulin Degrading Enzyme (IDE) [65-66]. Cerebral glucose utilization is reduced by 45% and cerebral blood flow by approximately 20% [59]. Neuronal glucose uptake is mediated by GLUT-1 and GLUT-3. About 50% ATP decrease was found in the early stages of sAD [67]; a reduction in insulin mRNA and protein levels was also observed [68-70]. Patients with diabetes mellitus type 2 are more prone to Alzheimer's disease [71-72]. Streptozotocin is found to cease the insulin signaling pathway and disturb the energy metabolism in the brain [73].

Besides these pathophysiological aspects of AD, cell cycle re-entry and apoptotic hypotheses are also laid down. It is very necessary to integrate all the domains of AD pathophysiology to work out potential therapeutic targets for the management of AD and related syndromes.

Management of Alzheimer's disease:

To date, there are no diagnostic and therapeutic interventions available that can eradicate the disease completely. Drugs that are commonly recommended to AD patients only harness some symptomatic relief to the patients on a temporary basis. During the late 20th century, vigorous investigations were done to find suitable treatment strategies for AD; two drugs were tested - Acetylcholinesterase inhibitors (AChEIs) and NMDA receptor antagonists were most commonly used in the studies. AChEIs reduce the activity of the acetylcholine esterase enzyme responsible for ACh degradation. AChEI drugs that have been approved for AD treatment are – donepezil (1996), rivastigmine (2000) and galantamine (2001). Memantine is the most common NMDA receptor antagonist approved by the FDA that acts by reducing glutamate activity, an important neurotransmitter for learning and memory. [74] It also has the capability to block Ca^{2+} influx and thereby also reduce glutamate excitotoxicity. Memantine and Donapazil provide transient symptomatic relief only; thus, there is an immediate need for a therapeutic intervention that can attenuate the etiology as well as promote neurogenesis. Some of the potential therapeutic targets along with respective drugs are listed in Table 1 according to their cellular and molecular significance. Non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) and tDCS have been used extensively as an alternative therapy for various neurodegenerative diseases; but for AD, there are contradictory results.[75,76]

Table 1: Potential therapeutic targets and drugs for AD management

Therapeutic Targets	*Drugs*
AChEIs	Donepezil, Rivastigmine, Galantamine, Tacrine
NMDA receptor antagonist	Memantine
Aβ degrading drugs	Bapineuzumab, Salanuzumab
Aβ aggregation Inhibitors	Resveratrol
Anti-amyloid plaque drugs	Lecanemab and Donanemab
Multitarget Drugs – AChEIs and Antioxidant	Lipocrine
NSAIDs	Nilvapidine
PPARγ antagonist (Insulin sensitization)	Thiazolidinediones
Serotonin-Dopamine receptor agonists	Brexpiprazole

AChEIs – Acetyl Cholinesterase Inhibitors; NMDA - N-Methyl-D-Aspartate; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs; PPAR-γ - Peroxisome Proliferator-Activated Receptor-Gamma.

Current Scientific Research in AD

Neurogenesis is a compensatory pathway for neurodegeneration in Alzheimer's disease brain. Current scientific evidence supports a *de novo* production of neurons in the adult dentate gyrus region of the hippocampus, introducing the possibility of plasticity that could retain memory and cognitive processes. Evidence hints towards the promotion of adult hippocampal neurogenesis leading to improved pattern separation and spatial memory. In contrast, a decline in neurogenesis may underlie cognitive impairments associated with aging and disorders such as AD [77]. The olfactory bulb, hippocampus and neocortex of adult animals have new neuronal cells [78]. The two most active neurogenic areas in the brain are the granular Zone (SGZ) of the hippocampus and the sub-entricular Zone (SVZ) of the lateral ventricle [79-81]. Here, new neurons are formed throughout their lifetime; they then migrate to the olfactory bulb through the Rostral Migratory Stream (RMS). Newborn granule neurons are functionally integrated into preexisting neuronal circuits concluded from their in vitro study that the neurogenesis is due to the upregulation of the Ca_v1 channel.[82,83]

Magnetic Field Stimulation as a non-invasive stimulation of the brain for the treatment of neuropsychiatric diseases has been used for more than 50 years. The electromagnetic field drives the influx of Ca^{2+} into the NPCs which as a consequence activates the differentiation proteins like NeuroD1, NeuroD2, etc and some basic Helix loop Helix transcription factors like Mash1, Hes1, etc.[84-86] TMS induces neurogenesis in the hippocampal dentate gyrus region of lesioned animals via upregulation of expression of voltage-gated Ca^{++} ion channel [87,83]. Expression of the proneural genes, NeuroD and Ngn1, which are crucial for neuronal differentiation and neurite outgrowth was also found to be increased following magnetic field exposure [88] which in turn results in the promotion of) neuronal survival and decrease in pro-apoptotic protein Bax and increase in pre-apoptotic protein Bcl-2 perhaps by CREB phosphorylation [84, 89-90]. Neurogenesis restoration ultimately improved dementia, memory loss and cognitive impairment in AD rodent models; several clinical trials are going on in AD patients to achieve remarkable beneficial outcomes. FDA approval for the use of repetitive Transcranial Magnetic Stimulation in depression-like psychiatric disorders has

been worked out but whether for neurodegenerative disorder it is beneficial, is a question.

Conclusion

Alzheimer's disease is characterized by global atrophy of the brain which imparts functional loss like dementia, attention, memory and cognitive deficits. Understanding the actual culprits of the disease is necessary to retain lost neurons in the brain by stimulating NPCs present in the brain with some non-invasive techniques.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not Applicable

Availability of Data and Materials

None of the individual's data has been disclosed in the review.

Competing Interests

There is no competing interest till date.

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Not applicable.

Authors' Contributions

AK has reviewed literatures, prepared and submitted the manuscript; AR helped in preparation of manuscript and reviewed the manuscript.

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