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Pharmacological review on alzheimer's diseases

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Abstract
In 2013, 44 million of the world-wide population was estimated to be affected by dementia and a steep rise to ~136 million has been predicted by 2050. To date, there are no treatments with proven disease-modifying effects and AD remains the largest unmet medical need in neurology.AD pathology presents a complex interplay between several biochemical alterations, including changes in amyloid precursor protein metabolism, phosphorylation of the tau protein, oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation and neurotransmitter pathway disruption. It undergoes the anatomy of the alzheimer's diseases. Whereas these observes the changes in the brain and also the epidiomiology of alzheimer's diseases.It explains in detail about the etiology of alzheimer's may includes genetic causes,advancing age, family history and hypertension. These also includes three different phases. These undergoes with the pathophysiology, signs and symptoms as well as the diagnosis of the disease. Pharmacotherapy and the symptomatic treatments of the disease may also involved.Finally it overcomes the future directions of the alzheimer's disease.

Keywords: alzheimer's diseases, neurodegeneration, β-amyloid peptide, tau protein

Introduction

The credit for first time describing a dementing condition, which later known as Alzheimer's disease, goes to German physiatrist and neuropathologist Dr. Alois Alzheimer. Alzheimer disease an aggressive form of dementia, manifesting in memory, language and behavioural deficits. Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex.Emil Kraepelin named this medical condition Alzheimer's disease for the first time in his 8th edition psychiatry handbook. According to the World Health Organization (WHO) estimates, the overall projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050. In 2013, ~44 million of the world-wide population was estimated to be affected by dementia and a steep rise to ~136 million has been predicted by 2050 [4]. To date, there are no treatments with proven disease-modifying effects and AD remains the largest unmet medical need in neurology.AD pathology presents a complex interplay between several biochemical alterations, including changes in amyloid precursor protein metabolism, phosphorylation of the tau protein, oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation and neurotransmitter pathway disruption. Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others. AD typically manifests through a progressive loss of episodic memory and cognitive function, with later deficiency of language and visuospatial abilities. Such changes are often accompanied by behavioural disorders such as apathy, aggressiveness and depression [1-4].

Anatomy of Alzheimer's Diseases

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neurotic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures.
Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others [5-6].

Changes in the brain

Scientists continue to unravel the complex brain changes involved in the onset and progression of Alzheimer's disease. It seems likely that damage to the brain starts a decade or more before memory and other cognitive problems appear. During this preclinical stage of Alzheimer's disease, people seem to be symptom-free, but toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain. Once healthy neurons stop functioning

and lose connections with other neurons, they die.The damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories. As more neurons die, additional parts of the brain are affected, and they begin to shrink. By the final stage of Alzheimer's, damage is widespread, and brain volume has shrunk significantly.

Epidemiology of Alzheimer's Diseases

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.8 In the United States, AD is the fifth leading cause of death among older adults, and about $200 billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050). AD is a multi-factorial disease, with no single cause known, and several modifiable and nonmodifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after age 65. The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (95% of all cases). Rare genetic mutations are associated with the development of AD before age 65, which is known as 'early onset' or 'familial' AD (B5% of all cases). People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes locate don chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD [8-9].

Etiology of Alzheimer's Diseases

The cause of AD is unknown. Several investigators now believe that converging environmental and genetic risk factors trigger a pathophysiologic cascade that, over decades, leads to Alzheimer pathology and dementia.

The following risk factors for Alzheimer-type dementia have been identified.

- Genetic causes
- Advancing age
- Family history
- Hypertension

Midlife hypertension is an established risk factor for late-life dementia, of which AD is the most common type. A brain autopsy study evaluating the link between hypertension and AD found that patients using beta-blockers to control blood pressure had fewer Alzheimer's-type brain lesions on autopsy compared to patients taking no drug therapy or those taking other medications. In addition, epidemiologic studies have suggested some possible risk factors such as aluminium and previous depression. Other studies have suggested protective factors (e.g. Education, long-term use of nonsteroidal anti-inflammatory drugs) [10-11].

Genetic Causes

Although most cases of AD are sporadic (i.e., not inherited), familial forms of AD do exist. Autosomal dominant AD, which accounts for less than 5% of cases, is almost exclusively early onset AD; cases occur in at least 3 individuals in 2 or more generations, with 2 of the individuals being first-degree relatives.

Familial clustering represents approximately 15–25% of late-onset AD cases and most often involves late-onset AD. In familial clustering, at least 2 of the affected individuals are third-degree relatives or closer.

Mutations in the following genes unequivocally cause early-onset autosomal dominant AD [12]:

- The amyloid precursor protein *(*APP*)* gene on chromosome 21
- The presenilin-1 *(*PS1*)* gene on chromosome 14
- The presenilin-2 *(*PS2) gene on chromosome 1

Infection

An emerging field of research suggests a significant association between AD and chronic infection with various species of spirochetes, including the periodontal pathogen Treponemas, Borrelia burgdorferi, as well as pathogens such as herpes simplex virus type 1.In vitro and animal studies support the concept of infection resulting in chronic inflammation and neuronal destruction. Ab has been shown to be an antimicrobial peptide, so its accumulation might represent a response to infection [12].

Depression

Depression has been identified as a risk factor for AD and other dementias. RecentFramingham data have helped bolster the epidemiological association. The study showed a 50% increase in AD and dementia in toes who were depressed at baseline. During a 17-year follow-up period, a total of 21.6% of participants who were depressed at baseline developed dementia, as compared with 16.6% of those who were not depressed.In another related study, recurrent depression was noted to be particularly pernicious. One episode of depression conferred an 87–92% increase in dementia risk, while having 2 or more episodes nearly doubled the risk. According to the results of a meta-analysis of 23 population-based, prospective cohort studies, late-life depression is associated with an increased risk for all-cause dementia, vascular dementia, and AD. The risk for vascular dementia appeared to be significantly higher than the risk for AD [13].

Phases of Alzheimer Diseases

Each person with Alzheimer's disease will vary slightly in presentation according to personality. Emotional, behavioural and cognitive changes will also vary, but generally accepted by clinicians and researchers are stage model which describes broad characteristics.

First Phase

In the first phase, the 'forgetfulness phase', there is usually difficulty in recalling recent events, and a tendency to forget where objects have been placed.Names of people and places, previously familiar, may be poorly recalled and a

general disorientation persists and poor short-term memory [14].

Second Phase
The second recognized phase is known as the 'confusional phase'. Increasingly poor attention span and a decline in generalized intellectual performance are seen with a deteriorating memory. Disorientation in place, word-finding difficulty and other changes to speech may be seen.

Third Phase
The third phase, the 'dementia phase', is characterized by a lack of purpose in the person's behaviour which appears disjointed and sometimes bizarre. Remaining intellectual and selfcare abilities require constant supervision as people in this phase undergo further deterioration in memory capacity, calculating ability (dyscalculia) and aspects of language are severely affected and eventually lost. Constant assistance is required for self-care skills such as grooming, dressing, and toileting and for feeding [15-16].

Pathophysiology of Alzheimer's Disease
At first, increasing forgetfulness or mild confusion may be the only symptoms of Alzheimer's disease that are noticeable. But over time, the disease robs you of more of your memory, especially recent memories. The rate at which symptoms worsen varies from person to person also depending on the age of the person. If you have Alzheimer's, you may be the first to notice that you're having unusual difficulty remembering things and organizing your thoughts. Or you may not recognize that anything is wrong, even when changes are noticeable to your family members, close friends or co-workers and colleagues.The causes of Alzheimer's disease can be explained with the help of three hypotheses [17].

Cholinergic Hypothesis
The cholinergic hypothesis of Alzheimer's disease came about due to the combined observations of deficits in choline acetyltransferase and acetylcholine (ACh) and the fact that ACh is important in memory and learning.It was thought that reduction in cholinergic neurons as well as cholinergic neuro transmission led to the decline in cognitive and noncognitive functions. Cholinergic function loss correlated to cognitive decline, but no causal relationship was established [18].

Amyloid Hypothesis
Amyloidosis is the abnormal deposition of amyloid proteins in tissues, with the altered amyloid proteins forming an insoluble ß-pleated sheet. Reduced tissue and cellular clearance is observed in amyloid protein deposits.The membrane protein amyloid-ß precursor protein (APP) is proteolysed to form Aß, and it is the amyloid form of A that makes up the amyloid plaques (neuritic plaques) found in the brains of Alzheimer's disease sufferers. According to the amyloid hypothesis, the basis of Alzheimer's disease is the presence of Aß production in the brain. Evidence for the amyloid hypothesis was compelling, as gene mutations encoding the amyloid-ß precursor protein (APP) was found to cause familial Alzheimer's disease with sites of major mutations found in secretase and APP [19-21].

Tau Hypothesis
The Tau hypothesis revolves around the presence of neurofibrillary tangles (NFTs) in Alzheimer's disease. As a result of increased phosphorylation of Tau (originally bound to microtubules), there is an increase in free tau accompanied by loss of functioning microtubules. Phosphorylated Tau are subunits of paired helical filaments (PHFs), which form NFTs. The impaired microtubules affect axonal transport of proteins and eventually cause neuronal death [22].

Signs and Symptoms
Alzheimer's disease is a progressive condition, meaning that the symptoms get worse over time. Memory loss is a key feature, and this tends to be one of the first symptoms to develop.
The symptoms appear gradually, over months or years. If they develop over hours or days, a person may require medical attention, as this could indicate a stroke.

Symptoms of Alzheimer's Disease Include
Memory loss: A person may have difficulty taking in new information and remembering information. This can lead to:
- Repeating questions or conversations
- Losing objects
- Forgetting about events or appointments
- Wandering or getting lost

Problems with speaking, reading, or writing: A person may develop difficulties with thinking of common words, or they may make more speech, spelling, or writing errors.

Personality or behaviour changes: A person may experience changes in personality and behaviour that include
- becoming upset, angry, or worried more often than before
- a loss of interest in or motivation for activities they usually enjoy [23].

Neuropsychiatric Symptoms
This section will review the neurobiology, epidemiology, and current treatments for psychosis, agitation, apathy and depression.

Psychotic Symptoms In AD
Both delusions and hallucinations are reported in AD. In a study of 124 demented patients, 67% had psychotic symptoms. They occurred two to six times per week, persisted for 12 weeks among 32% and recurred in 50% within 12 months. Hallucinations occur less frequently than delusions in AD and rarely occur in isolation; the opposite is true for dementia with Lewy bodies and Parkinson's disease dementia. The hallucinations and delusions in AD are phenomenologically different to those in schizophrenia, psychotic depression, or mania. both kinds increase with dementia severity [24].

Agitation in AD
Agitation occurs frequently in AD. The prevalence varies greatly between studies due to the use of different definitions. The International Psychogeriatric Association consensus statement defines agitation as excessive motor activity, or verbal or physical aggression that associated with emotional distress: severe enough to produce disability; beyond what would be expected from cognitive impairment by itself; and not solely attributable to another disorder,

environmental conditions, or the physiological effects of a substance.

Apathy in AD

Apathy, characterized by lack of motivation, decreased initiative, akinesia, and emotional indifference, is the most common NPS associated with AD and a primary cause of caregiver distress. It is common in predementia states, increases in frequency as the disease progresses, and predicts conversion from normal cognition to MCI and MCI to dementia.

Depression in AD

Depression is found in 16% in population-based AD studies, and 44.3% in hospital-based studies. Depression is also common in MCI. A meta-analysis of studies found an omnibus prevalence of 32%, but depressive symptoms more prevalent in clinical (40%) versus community based (25%) samples reflecting their clinical relevance in the cognitively impaired. Depression is also a predictor of progression from normal cognition to MCI and from MCI to dementia [25].

Clinical Features

A mental state assessment should include a validated cognitive function test; and the physical examination should focus on vascular and neurological signs supplemented by investigations.

Assessment of dementia involves a two-step process,

1. It is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment.
2. Once dementia syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible.

The progression of Alzheimer disease can be divided into a series of stages [26].

1. Pre-Dementia
2. Mild
3. Moderate
4. Severe

Diagnosis of Alzheimer's Disease

In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70-90%relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics [27].

Detection Method

There are multiple brain imaging procedures that can be used to identify abnormalities in the brain, including PET, MRI, and CT scans which are considered to be preliminary tests for the detection of disease.

Each scan involves a unique technique and detects specific structures and abnormalities in the brain and associated parts. Brain imaging is not currently a standard part of Alzheimer's disease testing, however current clinical studies have shown promising results that may change the procedure used by physicians to diagnose the disease [28].

Positron Emission Tomography (Pet)

Positron emission tomography (PET) uses radiation signals to create a three-dimensional colour image of the human body. The patient is injected with a radiotracer, composed of a radioactive medicine bound to a naturally occurring chemical. For the study of the Alzheimer's disease chemical is usually glucose and is used widely. The radiotracer travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted.

Computed Tomography (Ct)

A computed tomography (CT) scan takes a series of cross sectional images of the body. With the help of a computer, the individual scans are integrated and incorporated into one detailed image. The CT scan provides the physician with information about the density of tissues in the body and in various parts of the brain. For improved clarity, a contrast dye may be injected to provide a distinction between similar tissues.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) techniques, first used in 1977, create two or three- dimensional images of the body that can be used to diagnose injury and illness.The essential component of the MRI system is the super conducting magnet, which produces a large and stable magnetic field. There are smaller gradient magnets that create weaker magnetic fields. These magnets allow for different parts of the body to be scanned [29].

Risk Factors

Age

The single greatest risk factor for developing Alzheimer's disease is age, one of the non-modifiable risk factors. Most cases of Alzheimer's disease are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5 percent of people have Alzheimer's disease. For those over 85, the risk increases to 50 percent.

Genetics

In Alzheimer's disease, there is no appearance of a genetic pattern of inheritance. A connection has been found between a gene called Apolipoprotein E and the development of Alzheimer's disease. This gene is supposed to be responsible for the protein that carries cholesterol in the blood vessels. One form of the gene, ApoE4, has been shown to increase the chances of developing the disease to a greater extent [30].

Education

It is observed that there is a connection between educational level and the risk of developing Alzheimer's disease. People with fewer years of education seem to be at a higher risk as they are unaware of the prevalent causes.The exact cause for this relationship is unknown, but it is theorized that a higher education level leads to the formation of more synaptic connections in the brain.This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses.

Pharmacotherapy of Alzheimer Diseases

AD is a public health issue, as of now, there is only two classes of drugs approved to treat AD, including inhibitors

to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to *N*-methyl d-aspartate (NMDA). Several physiological processes in AD destroy Ach-producing cells which reduce cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, which results in increasing ACh levels in the synaptic cleft [31]. On the other hand, overactivation of NMDAR leads to increasing levels of influxed Ca^{2+}, which promotes cell death and synaptic dysfunction. NMDAR antagonist prevents overactivation of NMDAR glutamate receptor and hence, Ca^{2+} influx, and restores its normal activity. Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease [32].

Symptomatic Treatments

Cholinesterase Inhibitors

According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors.This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD [33].

a. Donepe
b. ZIL:

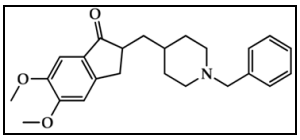

Fig 1: Donepezil

Donepezil is an indanonebenzylpiperidine derivative and a second generation of AChEIs and is considered the leading drug for AD treatment. Donepezil binds to acetylcholinesterase reversibly and inhibits acetylcholine hydrolysis, which leads to a higher concentration of ACh at the synapses. The drug is well-tolerated with mild and transient cholinergic side effects which are related to the gastrointestinal and nervous systems. It should be noted that donepezil is used to treat symptoms of AD such as improving cognition and behaviour without altering the AD progression [35].

c. Rivastigmine

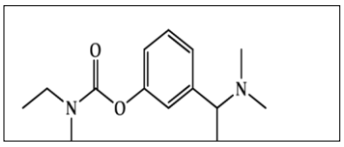

Fig 2: Rivastigmine

Rivastigmine is a pseudo irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by binding to the two active sites of AChE (anionic and estearic sites), which results in preventing ACh metabolism. BuChE is found mostly in glial cells with only 10% of AChE activity in the normal brain, whereas in the AD brain, its activity is increased to 40–90%, while ACh activity is reduced simultaneously, which suggests that BuChE action may indicate a moderate to severe dementia. Rivastigmine dissociates more slowly than AChE, which is why it is called a pseudo-irreversible, and it undergoes metabolism at the synapse by AChE and BuChE.

The drug is used in mild to moderate AD cases. It improves cognitive functions and daily life activities. Oral administration of the drug is associated with adverse effects such as nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss. In many cases, these side effects are the main reason behind stopping taking the medicine, however, they can be settled down in time and consequently, the drug becomes more tolerated [36].

d. Galantamine

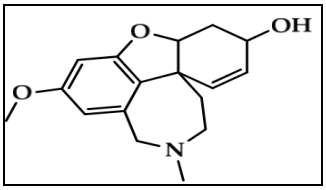

Fig 3: Galantamine

Galantamine is considered a standard first-line drug for mild to moderate AD cases. GAL is a selective tertiary isoquinoline alkaloid with a dual mechanism of action in which it acts as a competitive inhibitor of AChE and can bind allosterically to the α-subunit of nicotinic acetylcholine receptors and activate them. GAL can improve behavioral symptoms, daily life activities, and cognitive performance with good efficacy and tolerability, similar to other AChE inhibitors.

Several delivery systems were developed to improve the drug delivery to the brain: Wahba et al. attached GAL to ceria-containing hydroxyapatite particles for selective delivery of the drug to the affected regions in the brain. Misra et al. and Fornaguera et al. used solid-lipid nanoparticles and nano-emulsification approaches respectively, to carry GAL hydrobromide [37].

- Memantine

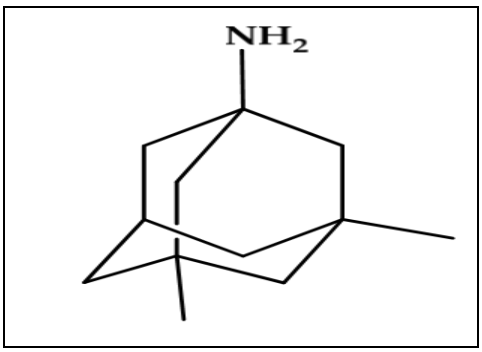

Fig 4: Memantine

Memantine is a low-affinity uncompetitive antagonist of the NMDAR, a subtype of glutamate receptor that prevents

over-activation of the glutaminergic system involved in the neurotoxicity in AD cases. Memantine is used for the treatment of moderate to severe AD alone or in combination with AChE. The drug is safe and well-tolerated, it blocks the excitatory receptor without interfering with the normal synaptic transmission due to memantine's low affinity, where it is displaced rapidly from NMDAR by high concentrations of glutamate, thus avoiding a prolonged blockage. The latter is associated with high side effects, especially on learning and memory [37].

Screening Methods

In Vivo Approach

In vivo approach relies on studying different vertebrate or invertebrate animal models to demonstrate those features responsible for pathology in AD. Transgenic animal models provide various insights such as over expression of a target gene, knock outs, knock-ins, etc to study pathologic hallmarks in a particular disease. In order to investigate the entire mechanism causing pathogenesis, it is thus required that the genes in the animal model should be as expressed at the same level as it is seen in vivo. Therefore the phenotypes for an amyloid β aggregation should involve disease pathology with amyloid deposits and increasing age to be expressed in tissues or cells [38].

Mouse as a model to study the amyloidosis the major neuropathy in ad

Mouse models with crucial significance in fad

PDAPP

The first transgenic mice to be studied and which have shown AD related phenotype was PDAPP model. This model was engineered to show over expression of human APP model known as Indian mutation one controlled by platelet derived growth factor (PDGF-β). This model has been observed to show Aβ deposition, cerebral amyloid angiopathy, hippocampal atrophy, etc. Various observations were made at different ages and therefore results and expressions of AD characteristics were recorded.

Even though this model was found to be perfect for expression of amyloid deposits but it failed to show all the neuropathology of human AD or tau pathologies. Thus, others models were referred for the latter pathologies.

Mouse Models Expressing Amyloid Beta Formation

As the majority of the patients suffer from sporadic forms of AD transgenic models expressing human (Aβ) precursor protein wild type are of the crucial importance than those model expressing mutated forms of APP.

PY.8.9

When this model over expressed with wild type human APP, it displayed no neurodegeneration. But, later, this mouse strain was treated with some another promoter resulting in an increased level of APP production. Vascular amyloid deposits were also detected in this mouse strain.

Behavioral tests or assays for in mouse models

The morris water maze (MWM)

MWM is a necessary test in order to measure the hippocampal brain deficits. This test mainly functions on the ability of the animal model under test to be able to posses learning information. The common features of the tests are the ones where the mouse is provided with a particular task and capacity of the mouse to retain those features. And variations compared to this test could be observed in other tests.

Radial arm maze

This task provided with the different arms radiating from a platform and the rodents were trained to enter each arm not more than once and grab maximum amount of food or water. This task involves testing the working memory and reference memory. This test allows evaluation of both reference memory and working memory unlike the other tests.

Radial arm water maze (RAM)

This has been structured the way to escape the limitations as encountered previously in MWM and RAM. The exception to this method is that to search for the arm placed in water among several arms. The rodent is allowed to make use of spatial cues and working arm to know or recognize the platform located in water bath.

In Vitro Approaches

In vitro approaches used to understand and find the treatment strategies of AD. The various methods integrated by the neurologists or researcher since last decade although any effective solution is yet to be attained.In order to study or inhibit the pathophysiolgical characteristics in AD causing neurotoxicity, hampering neuronal cells and other tissues in cortex and hippocampal region various in vitro assays have been established and identified. In vitro assays involved in screening of new lead molecules which can target different enzymes, Aβ and other drug target known in AD [39].

Using primary neurons and cell lines to study aβ cytotoxicity

Cultured primary neurons or cell lines provide simple and economic means of studying the role of Aβ aggregation state and the mechanism of Aβ toxicity. These could also be used as a primary P - 13 Pharmaceutical Science Biotechnology for the screening of the inhibitors of Aβ toxicity in vitro. Simple, inexpensive, and reproducible methods which would allow easy access to the toxicity of Aβ preparations and correlating an Aβ aggregation or fibrillization with its cytotoxicity.

Thus cultured cells are exposed to purified Aβ preparations (monomers, protofibrils, and fibrils) or crude preparations containing mixtures of heterogeneous Aβ species. Cell viability can determined by the MTT (3-(4,5-dimethylthiazol-2- yl)-2,5-diphenyltetrazolium bromide) reduction assay. In the case of primary neurons, subtle changes in neuronal viability can also be quantified using immunostaining (Hartley D.M et al 2010, Jan A et al 2010). A cell line with ability of differentiating into neurons are expressed or transfected with mutated genes in order to generate an AD model [40].

Different cell lines used In-vitro neuroblastoma/sh-sy5y

Neuroblastoma (SH-SY5Y) cell line has been used to develop a model for Aβ cytotoxicity in AD. By expressing these cells to neuronal lineage, it has been an important key to understand the mechanism underlying the progression of AD (Zhang L et al 2006). Once these cells become mature they are provided with conditions like exposure to toxic Aβ causing neurodegeneration.

Cholinesterase (CHE) enzyme inhibition In-Vitro

For symptomatic treatment of AD by maintaining the levels of acetylcholine (ACh) in central nervous system (CNS) is one of the important parameter. Inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) is necessary steps to up regulate the levels of acetylcholine in CNS. Past decade has shown a wide range of compounds have been screened for having potential cholinesterase inhibition activity. In the past few years the major concern related to the treatment of AD has been the drug development, which could improve the central cholinergic functions.

Ellman's Assay

The inhibition of the cholinesterase enzymes demonstrated by screening the hydrolysis of acetylthiocholine on the basis of the colorimetric method of Ellman's assay .The ability of the compounds to inhibit ChE enzymes can be measured or expressed as IC50, which can be used to quantify the concern necessary to decrease the maximum enzymatic inhibition by 50%.A color change in the reaction by development of an anionic molecules 2-nitro-4-thiobenzoate at wavelength of 412nm formed from the reaction of thiocholine with 5,5 dithiobiz-nitrobenzoic acid. The variation of absorbance at wavelength 412 nm depends on the substrate concentration and enzymatic activity of AChE or BChE.

Biophysical approach to study Aβ formation In-vitro

Aβ aggregation mechanisms are important in order to devise any strategy for treatment of AD. Therefore, biophysical methods in-vitro allows us to study the mechanism underlying the aggregation of peptides or fibrils.

Mass spectrometry

Mass spectrometry (MS) is mainly utilized for measuring the mass of a molecule that can further be used for characterizing proteins and peptides. The principle involves the sample of interest is first introduced, ionized and transferred into the gas-phase in an ion source, the produced ions are separated in vacuum according to their mass-to charge ratio (m/z) in a mass analyzer and are thereafter detected in a detector. The problems associated with transferring large biomolecules, such as proteins and peptides, into the gas-phase were resolved when two soft ionizations techniques were introduced in matrix-assisted laser desorption/ionization (MALDI and electro spray ionization (ESI) Using these techniques, fragmentation can be avoided and multiple charges can be imposed on molecules which will lower the m/z ratio making them easier to detect.

Fluorescence spectroscopy

It is usually based on the fact that some flurophores or molecules are excited from their ground state to high energy state, then they are said to be in an excited state and a photon is emitted. When the molecules they turn to its original lower energy state then also a photon is emitted with a different Wavelength.

Antioxidant assays In-vitro approach

Oxidative stress occurs, due to disturbance in the balancing of certain factors that generate reactive oxygen species (ROS), and these factors exist as a part of regular physiology and also arise from other sources in the body. Oxidative stress is mainly responsible for development of many neurodegenerative diseases like AD, PD, etc. Another implication of the oxidative stress is observed in diseases like cardiovascular or cancer like diseases and therefore initiating the treatment with antioxidants is henceforth a preventive method for attenuating the oxidative stress. Reaction of antioxidants with free radicals employs various mechanisms such as hydrogen atom transfer (HAT), single electron transfer (SET) and in combination of both HAT and SET.

DPPH Assay

his assay is usually more common for screening with natural products and is also performed easily in few steps compared to other methods. The methodology is that a molecule DPPH in order to prevent its dimerization undergo delocalization of the spare electron as a whole and this delocalization gives rise to a change in violet color, with a maximum absorption of 517 nm in the ethanol or methanol solution. When the following solution of DPPH is mixed with substrate, which then donates a hydrogen atom, it then produces a reduced form and loss of violet color is observed. To determine the antioxidant potential of a sample through this free radical scavenging, change in optical density of the DPPH radicals are observed.

Future Directions

Studies of potentially disease-modifying therapy up to now have generally been undertaken in patients with clinically detectable, established disease, while mounting evidence suggests that the pathological changes associated with dementia begin to occur several years before the emergence of the clinical syndrome. Techniques to provide earlier diagnosis are key to testing this theory in clinical trials, facilitating trials in presymptomatic phases.

Early diagnosis

Currently, earlier diagnosis of AD is primarily based on CSF and neuroimaging biomarkers, reflected in new research diagnostic criteria for AD.

Neuroimaging

Traditionally, structural neuroimaging in AD was used to rule out alternative diagnoses when presentations were atypical, eg brain tumours. However, functional imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), are now able to detect loss of neuronal function in asymptomatic individuals by measuring cerebral metabolic rates of glucose metabolism (CMRglc), a surrogate marker for neuronal activity. Patients with early AD demonstrate reduced CMRglc in parietotemporal, frontal and posterior cingulate cortices. These changes have also been shown to precede the onset of symptoms in individuals genetically at risk for AD, as well as in patients with MCI. However, there is some overlap of the hypometabolic regions found in AD with those found in other dementia subtypes, and the additional use of amyloid PET, which can estimate amyloid plaque surface area, improves diagnostic accuracy.

Better trial design

Better selection of patients for clinical trials may yield more favourable clinical outcomes. For example, the 'mild to

moderate' AD group may be too heterogeneous, and treatment effects within subgroups could be lost, as seen in the solanezumab trials. As well as earlier diagnosis, advanced biomarker analysis may also facilitate better selection of study subjects by allowing selection of patients with more uniform underlying pathology for targeted trials. This individualised approach would mirror several cancer therapies where bespoke treatment is targeted at specific patients, using markers such as HER2 [40-41].

Conclusion

Alzheimer's disease is now considered a world health concern; as a consequence, the National Institute on Aging—Alzheimer's Association reclassified and updated the 1984 criteria for higher specificity, sensitivity, and early identification of patients at risk of developing AD.The treatment of AD remains symptomatic, without alteration in the disease's prognosis.

Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression.

In conclusion, the success of AD treatment depends on its early administration and patient monitoring for disease progression using biomarkers diagnosis. Future therapies that target tau pathology and the use of combination therapy may have a potential to slow the progression of AD pathology.

Designing a potent, selective, and effective drug is urgently needed to treat patients with AD and those at risk for developing the disease.

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