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Review Article

Cognition Deficiency- Old Problems but New Challenges

***Ajay Kshirsagar[1], Sandeep Talele[1], Mahesh Ghaisas[2], Pravin Malusare[1] and Avinash Deshpande[1]**
[1]Dept of Pharmacology, Padm. Dr. D. Y. Patil Institute of Pharmaceutical Science and Research, Pimpri, Pune-18
[2]Indira College of Pharmacy, Tathawade, Wakad, Pune- 33.
**Author for Correspondence*

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects daily living through memory loss and cognitive impairment. Early symptoms include disturbances in short-term memory, attention, spatial orientation, personality and language, often in conjunction with confusion and unexplained mood swings. The symptoms can vary in severity and chronology, but they reflected a gradual expansion of degenerative change in the brain, which has been described to occur in six stages. The neurodegeneration commences in the entorhinal cortex with pyramidal cell loss, neurofibrillary tangles and neurophil threads, and then spreads in an anatomically defined pattern to other brain regions, particularly the hippocampus and parietal and temporal regions of the neocortex. In 2006, approximately 26.6 million people worldwide suffered from Alzheimer's disease and because of the growing life expectancy we can expect that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, which means that 1 in 85 persons worldwide will be affected by this disease. The two core pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles. The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain. In present review an attempt has been made to focus a light on various aspects like pathogenesis, molecular targets and pharmacotherapy's involved in neurological deficit.

Keywords: Alzheimer's disease, Cognition deficit, ApoE, Tau Hypothesis.

INTRODUCTION

Cognition and its impairment produced by a neurological disorder or pathological process have received considerable attention in the research and drug discovery communities. Strides have been made to delineate the etiology of cognitive deficit across therapeutic areas and to amend, enhance, or retain "Cognition". In doing so, perhaps paradoxically, the underlying neurophysiological mechanisms (the "cogs") and brain circuitry (the "cogwheels") that contribute to cognition and cognitive processes are being resolved. Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects daily living through memory loss and cognitive impairment (Biessels *et al.,* 1998). Early symptoms include disturbances in short-term memory, attention, spatial orientation, personality and language, often in conjunction with confusion and unexplained mood swings. Initially these symptoms are very mild and then progress, typically over a period of 8 to 10 years. The symptoms can vary in severity and chronology, but they mirror a gradual expansion of degenerative change in the brain, which has been described to occur in six stage. Neurodegeneration commences in the entorhinal cortex with pyramidal cell loss, neurofibrillary tangles and neuropil threads, and then spreads in an anatomically defined pattern to other brain regions, particularly the hippocampus and parietal and temporal regions of the neocortex. Hundred years later, in 2006, approximately 26.6 million people worldwide suffered from AD and because of the growing life expectancy we can expect that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, which means that 1 in 85 persons worldwide will be affected by this disease (King *et al.,* 1998).

The two core pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles. The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain. In the original hypothesis, this neuronal dysfunction and death was thought to be a toxic effect of the total amyloid load. As knowledge of pathological changes in Alzheimer's disease increased, research focused on more specific alterations in Aβ processing, such as the cleavage of amyloid precursor protein (APP) into Aβ peptides (Aβ 1–40 and Aβ 1–42) and the importance of Aβ oligomers (small aggregates of two to 12 peptides) (Takashima *et al.,*2008). Pharmacotherapy of AD has progressed in the past ten years from the use of psychotropic medications for

sedation to the use of rational treatments aimed at neurotransmitter replacement. The acetylcholinesterase inhibitors (AChIs) donepezil, rivastigmine and galantamine have shown consistent efficacy across the spectrum of very mild/mild/moderate and severe AD. More recent work on the effects of acetylcholinesterase inhibitors (AChEIs) on behavioral symptoms, activities of daily living and caregivers' burdens have also been encouraging. Present review focuses light on various aspects of neurological deficit (viz., pathogenesis, molecular targets and pharmacotherapy's).

Epidemiology of cognitive deficit

Hundred years later, in 2006, approximately 26.6 million people worldwide suffered from AD and because of the growing life expectancy we can expect that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, which means that 1 in 85 persons worldwide will be affected by this disease. About 40% of those AD patients will need nursing home care in the later stage of the disease, which will cause an enormous burden on the healthcare resources. (Brookmeyer *et al.,* 2007). With people living longer and the baby-boomer generation now reaching age 65, the world population of those aged 65 or more is set to increase substantially in the decades ahead with one billion more people between 2000 and 2050 , and the burden of AD is thus set to increase substantially. In 2006 the worldwide prevalence of AD was 26.6 million, and this is projected to increase to about 100 million by 2050. (Alavijeh et al., 2005; Palmer et al., 2002).

Pathology of Alzheimer's

The neurobiological basis of AD

Senile plaques are found throughout the cortex and hippocampi but there is a relative sparing of the subcortical grey matter. Senile plaques are extracellular deposits, consisting predominantly of aggregates of insoluble amyloid peptides. They are also found in a number of other neurodegenerative diseases, including Down's syndrome and dementia with Lewy bodies (DLB), as well as in normal ageing. Senile plaques can be broadly classified into two categories: diffuse and classic (neuritic) plaques as shown in figure1 (Prinja D et al., 1989).

Diffuse plaques are large (10–100 μm) areas of poorly defined β-amyloid (Aβ) deposition, which are often lacking in amyloid fibrils and are not thought to affect the structure of the surrounding tissue. *Classic neuritic plaques* are larger (50–200 μm) and consist of an amyloid core with radiating amyloid fibrils, surrounded by a corona of neuritic processes, glial cell processes, astrocytes and microglia cells. Amyloid fibrils are composed of 5–10 nm filaments, principally composed of Aβ protein, between 40 and 43 amino acids in length. Neuritic processes are often dystrophic and contain paired helical filaments. Classic plaques composed of aggregated Aβ peptides are believed to damage the surrounding neuropil (Hardy, J. 2009).

Neurofibrillary tangles are the other major histological landmark like senile plaques; they are not specific to AD and occur in normal ageing as well as in other neurodegenerative diseases, including Down's syndrome, myotonic dystrophy, post-encephalitic parkinsonism and front temporal lobe dementia with parkinsonism. Neurofibrillary tangles are neuronal inclusions composed mainly of paired helical filaments, which are formed by two filaments wound round each other with a periodic twist every 18 nm, resulting in a typical double helix Iqbal et al.,2010). Paired helical filaments are chiefly composed of the microtubule-associated protein tau, (Gozes et al., 2010) which is in a hyperphosphorylated state in neurofibrillary tangles. Neurofibrillary tangles also contain other proteins, including actin and ubiquitin. The distribution of neurofibrillary tangles does not appear to correlate closely with that of senile plaques. Neurofibrillary tangles are found throughout the neocortex, but they are also found in the deep grey matter, including the nucleus basalis of Meynert, substantia nigra, locus coeruleus and the raphe nuclei of the brainstem as shown in figure 1 (McLaurin et al.,2003). *Neuronal loss* in AD is predominantly of the large pyramidal neurons from layers III and V of the neocortex. Neocortical loss is most evident in the temporal and frontal lobes, while the parietal and occipital lobes are less involved. There is also a substantial loss of large pyramidal neurons in the hippocampus, the nucleus basalis of Meynert, the locus coeruleus and the raphe nuclei. Notably, this pattern of neuronal loss correlates well with the distribution of tangle-bearing cells (Cohen et al., 2004). Several hypotheses for pathological cascade of AD have been reported time to time, some of them can be discuss in detail as below.

Amyloid cascade hypothesis

The two core pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles. The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain. In the original hypothesis, this neuronal dysfunction and death was thought to be a toxic effect of the total amyloid load. As knowledge of pathological changes in Alzheimer's disease increased,

research focused on more specific alterations in Aβ processing, such as the cleavage of amyloid precursor protein (APP) into Aβ peptides (Aβ 1–40 and Aβ 1–42) and the importance of Aβ oligomers (small aggregates of two to 12 peptides). The Aβ 1–42 peptide aggregates more readily than Aβ 1–40 , and the ratio of these two isoforms is influenced by the pattern of cleavage from APP by α, β, and γ secretases. Small oligomers of Aβ can be more toxic than mature fibrils; Aβ56 seems to be a peptide of particular interest because it is negatively associated with cognitive decline in an APP mouse model and induces memory deficits when injected into rat brain.

The amyloid cascade hypothesis has also been more fundamentally challenged; for example, increases in Aβ might result from neuronal damage caused by another process. Why Aβ aggregates into fibrils is unclear, but Aβ sequence, Aβ concentration, and conditions that destabilise Aβ 6 are thought to be important factors as shown in figure 2. Tau, a microtubule-associated protein, is the major constituent of neurofibrillary tangles. The amyloid cascade hypothesis proposes that changes in tau and consequent neurofibrillary tangle formation are triggered by toxic concentrations of Aβ. The pathways linking Aβ and tau are not clearly understood, although several hypotheses have been proposed. Tau is a soluble protein, but insoluble aggregates are produced during the formation of neurofibrillary tangles, which disrupt the structure and function of the neuron. Tau monomers first bind together to form oligomers, which then aggregate into a β sheet before forming neurofibrillary tangles. The tau in neurofibrillary tangles is hyper phosphorylated, but whether phosphorylation is involved in tau aggregation is unclear, although it seems to be important in reducing the affinity of tau for microtubules. Once filamentous tau has formed, it can be transmitted to other brain regions. Injection of mutant pathological tau induces the formation of tau filaments in wild-type mice (Clavaguera et al.,2009)

Many phosphokinases, including glycogen synthase kinase 3β (GSK3β), cyclin dependent kinase 5 (CDK5), and extracellular signal related kinase 2 (ERK2), have been investigated as potential treatment targets to reduce tau phosphorylation. DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase 1A) primes tau molecules for further phosphorylation by GSK3β and might also be important in linking Aβ and tau (Takashima et al.,2008) However, post-mortem measurement of each of these classic pathological hallmarks only explains to a limited extent the expression of dementia in the population, and numerous other potentially modifiable factors also contribute to the clinical presentation of dementia. The amount of risk of Alzheimer's disease that is attributable to genetics is estimated to be around 70%. It has described the issues that have hampered the identification of Alzheimer's disease risk genes.

Identification of specific risk genes is problematic because the overall increase in risk conferred by a single gene is small. Additionally, not just individual genes but combinations of risk alleles need to be identified (Heyman et al., 1998).

Synapses are the primary sites of calcium in dysregulation in AD

The following proteins involved in calcium regulation are highly concentrated in pre- and or post-synaptic terminals: voltage-dependent calcium channels (L, N, and T channels), ionotropic glutamate receptors (NMDA, AMPA, and kainite receptors), metabotropic glutamate receptors, ion-motive ATPases (Na+/K+-ATPase and Ca2 +-ATPase), ER ryanodine and IP3 receptors, mitochondrial calcium-handling systems (calcium uniporter, ATP-sensitive potassium channels, permeability transition pore) as described in figure 3. Degeneration of synapses is believed to occur early in the disease process and to correlate strongly with cognitive deficit (DeKosky et al., 1996).

More direct evidence for specific alterations in synaptic calcium regulation in AD comes from studies of synapses in AD patients and animal models relevant to AD. Studies of synaptosome preparations and of transgenic mice expressing AD-linked APP and/or PS1 mutations have provided considerable evidence that synaptic calcium homeostasis is perturbed in AD, and that synaptic calcium dysregulation is an early and pivotal event in the degeneration of neurons in AD. Exposure of synaptosomes from the adult human hippocampus to Aβ resulted in impairment of the plasma membrane calcium-ATPase, as well as the sodium pump (Mark et al., 1997).

Exposure of rat cortical synaptosomes to Aβ results in impairment of ion-motive ATPases, and glucose and glutamate transport, as a consequence of membrane lipid peroxidation. Synaptosomes from PS1 mutant transgenic mice exhibit abnormal calcium homeostasis characterized by enhanced depolarization and excitatory amino acid-induced elevations of intracellular calcium (Begley et al., 1999). Evidence that altered APP processing can impair synaptic function in vivo comes from studies of APP mutant transgenic mice with

amyloid deposits in their hippocampus and cortex. For example, Chapman et al. showed that long-term potentiation of hippocampal synaptic transmission is severely impaired in aged APP mutant transgenic mice compared to age-matched wild-type mice; this occurred despite normal basal synaptic transmission and short-term plasticity.

A may directly impair synaptic function in vivo as indicated by memory impairment in rats following injection of A into the hippocampus. It was reported that synaptic plasticity in the hippocampus is altered in PS1 mutant transgenic in a manner consistent with enhanced elevations of presynaptic calcium and glutamate release (Parent et al., 1999). In another study of hippocampal synaptic function, it was shown that late after hyperpolarizations in CA3 pyramidal neurons were larger in PS1 mutant transgenic mice compared to nontransgenic control mice (Barrow et al., 2000). The latter study further showed that calcium responses to depolarization were larger in hippocampal neurons in the PS1 mutant mice, and that potentiation of CA3–CA1 synapses was increased. Collectively, the emerging data suggest that synapses are a primary site of dysregulation of calcium homeostasis in AD.

Apolipoprotein E

Apolipoproteins shuttle cholesterol from the blood into cells. Individuals with one or two copies of the E4 isoforms of apolipoprotein E are at increased risk for atherosclerotic cardiovascular disease and AD, while those with one or both of the other two isoforms (E2 and E3) are at reduced risk (Minguez et a., 2001).It has been reported that ApoE amplifies calcium signaling in lymphocytes, and (Wang et al., 1997) showed that a peptide derived from the receptor binding domain of ApoE stimulates calcium influx and release from ER in cultured cortical neurons, a neurotoxic effect. Tolar reported that a 22 kDa N-terminal thrombin-cleavage fragment of ApoE is neurotoxic, and that the mechanism involves calcium influx through NMDA glutamate receptor channels. In other studies, ApoEs were shown to modulate the effects of sAPP on calcium homeostasis in cultured rat hippocampal neurons, they enhanced the ability of sAPP to lower intracellular calcium levels with E3 being more effective than E4.

The latter study provided evidence for direct interaction between sAPP and ApoEs that accounted for the modulation of sAPP's effects on calcium homeostasis. While the data described above suggest that ApoEs might affect neuronal calcium homeostasis by direct actions on calcium-regulating proteins, other findings suggest the possibility that ApoEs can exert calcium-stabilizing effects indirectly as the result of antioxidant activities of the ApoEs. ApoEs can protect cultured cells from cell death induced by either hydrogen peroxide or Aβ, with E2 and E3 being more effective than E4.

Based upon the facts that the three different ApoE isoforms differ at key cysteine residues (ApoE2 has two cysteine residues, ApoE3 has one cysteine residue, and ApoE4 has none), and that HNE (which is produced by lipid peroxidation in AD) covalently modifies cysteine residues, here determined whether the antioxidant activities of ApoEs were due to binding of HNE. It has been found that ApoEs 2 and 3 bind more HNE than does ApoE 4, and that this HNE-binding activity was strongly correlated with the abilities of the different isoforms to protect neurons against the toxicities of HNE and Aβ (Pederson et al., 2000). Because HNE destabilizes neuronal calcium homeostasis by impairing membrane transporters, ApoEs 2 and 3 may stabilize calcium homeostasis by binding and thereby detoxifying HNE.

More recently, it was shown that ApoEs can modify nitric oxide production by microglia and neurons in an isoforms-specific manner (Colton et al., 2002), in ways consistent with adverse effects of E4 on cellular calcium homeostasis. Further studies will be required to better understand how ApoEs modulate cellular calcium homeostasis, and how such actions may affect neurodegenerative cascades in AD.

Glutamate dysfunctioning

Dementia of the Alzheimer type (DAT) is a debilitating neurological disease that affects about one in six individuals past the age of sixty. Its etiology is unknown. Patients with DAT suffer severe memory loss, personality changes, and symptoms of cortical disconnection: apraxias, aphasias and agnosias. The pathological changes in DAT brains include the presence of senile plaques, neurofibrillary tangles and granulovacuolar degeneration in cerebral cortex, amygdala, olfactory tubercle and hippocampus. Neurochemical studies indicate alterations in the cholinergic, somatostatinergic, serotonergic, noradrenergic and glutamatergic systems.

The numerous hypotheses concerning the etiology of this disorder include abnormal blood aluminium levels , viral agents, lack of trophic factors, genetic factors and selective vulnerability of specific neurotransmitter systems (Benton et al., 1982, McGeer et al., 1984). With respect to selective vulnerability of transmitter systems, the marked degeneration of cholinergic neurons in the basal forebrain has received considerable attention (McGeer et al., 1984).

However, several features of DAT cannot be explained the cholinergic hypothesis. Notably, the regional distribution of cortical cholinergic innervation from basal forebrain does not coincide with the cortical areas manifesting the greatest plaque and tangle density 3°(Mesalam et al., 1986). Lesions to the cholinergic basal forebrain neurons in rats and primates have not been shown to produce cortical plaques or tangles. In addition, basal forebrain lesions do not produce the somatostatin and catecholamine deficits seen in DAT.

Finally, the signs and symptoms of cortical disconnection in DAT are difficult to explain solely on the basis of loss of cortical cholinergic afferents. Thus, while pathology of the ascending cholinergic system is undoubtedly present in DAT, it appears that other neurochemical systems must be involved in the pathophysiology of this disease. Recently, the excitatory amino acid neurotransmitter, glutamate, has been implicated in learning and memory (Lynch et al.,1984). A subtype of glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, appears to be particularly important in these processes. In hippocampus, NMDA-receptor antagonists inhibit synaptic transmission in dentate gyrus, block the development of long-term potentiation (LTP) in vitro (a model of memory formation) 3s, and impair spatial discrimination learning and LTP in vivo (Stringer et al., 1984). NMDA- receptor-mediated excitation has also been observed in cerebral cortex. The NMDA receptor is coupled to a voltage-sensitive cation channel that is gated by Mg^{2+} and blocked by the dissociative anaesthetics ketamine and phencyclidine (PCP) .Both Mg^{2+} and the dissociative anaesthetics inhibit the excitatory actions of NMDA and the latter block the formation of LTP (Stringer et al., 1984). Furthermore, anaesthesia induced with dissociative anaesthetics has been reported to produce retrograde and anterograde amnesia of events surrounding the surgical procedure (Greifenstei et al., 1958). Thus, impaired glutamate receptor function may be associated with learning and memory impairments. In this regard, glutamate receptors, particularly the NMDA subtype, have been shown to be decreased in the neocortex of DAT patients compared to age-matched controls or Huntington s disease patients.

The largest decreases are seen in the outer cortical layers and the CA1 and CA2 regions of the hippocampus. Decreases in quisqualate and NMDA receptor subtypes also are observed throughout the CA1, CA2 region of the hippocampal formation, although changes in NMDA receptors are the most prominent, approaching 90% loss in stratum pyramidal. Muscarinic cholinergic, benzodiazepine and high-affinity GABA receptors are not significantly changed in these areas, suggesting that the decreased glutamate binding does not simply reflect cortical atrophy. Glutamate binding is also reduced in the subiculum of DAT brains. The subiculum is the primary source of hippocampal efferent fibers and shows major pathology in DAT. It is likely that glutamatergic neurotransmission in cortex and hippocampal formation is severely disrupted. The profound loss of glutamate receptors in these regions may provide an explanation for the learning and memory deficits that are prominent in DAT (Haymen et al., 1984).

Oxidative stress

Signs of oxidative stress in the brain in AD can be found in lipids and proteins as well as in nucleic acids, i.e., in RNA and in both nuclear and mitochondrial DNA (Nunomura et al., 1999,Yan et al., 1994). For example, tissue and cerebrospinal fluid levels of trans-4-hydroxy-2-hexenal (HNE), a product fatty acid oxidation, as well as HNE tissue protein adducts are elevated in AD (Nunomura et al., 1999,). Similarly, acrolein, a related, unsaturated aldehyde derived from 3 and 6 polyunsaturated fatty acid oxidation that is approximately 100 times more reactive than HNE and acrolein protein adducts are both found in increased concentration in diseased regions of the Alzheimer brain(Lovell et al., 2000). Both HNE and acrolein inhibit plasma membrane transporters, disrupt the assembly of microtubules and inhibit mitochondrial function.

HNE has also been shown to inhibit choline acetytransferase, the enzyme responsible for the synthesis of acetylcholine (Butterfield et al., 2002). Increased levels of the lipid peroxidation product malondialdehyde have been identified early in the course of the disease in the vulnerable superior and middle temporal gyri of the Alzheimer brain and not in other regions. Malondialdehyde levels have even been found increased in these regions in patients with minimal cognitive impairment, a condition that often precedes AD. F2-isoprostanes, which are prostaglandin like compounds that are nonenzymatic products of free radical catalyzed arachidonic acid peroxidation, are yet another example of a lipid oxidation product found in elevated concentrations in Alzheimer brain (Markesberry et al., 1999) and in the cerebrospinal fluid of living patients with probable AD.

Protein oxidative damage is signaled by the generation of carbonyl groups. Protein oxidation increases with age and is prominent in AD. Many of the proteins found

oxidized in AD are enzymes notably related to ATP generation or glycolysis. As with malondialdehyde, increased levels of protein oxidation have been identified early in the course of the disease in vulnerable brain regions and, as well, have been found in these regions in patients with only mild cognitive impairment. Protein oxidation sets the stage for protein glycation. This refers to the nonenzymatic attachment of glucose to oxidized proteins. Osones, or carbohydrate-2-oxoaldehydes, are derived from glycated proteins. Osones contain reactive aldehyde and ketone groups and damage cells and tissues by cross linking proteins to form advanced glycation end products (AGEs). AGEs in the presence of redox active metals such as iron can undergo redox cycling to elicit the formation ROS. AGEs can further increase ROS formation by acting on specific receptors such as the receptor for AGE; RAGE (Mamelak et al., 2002). Studies in neuronal cell lines show that AGEs can induce lipid peroxidation. AGEs have been found in amyloid plaques; neurofibillary tangles (NFTs) and isolated paired helical tau filaments (Smith et al., 1997, Yan et al., 1994).

The Alzheimer brain also shows signs of increased nitrative damage. This is revealed by the increased staining of nitrated tyrosine residues in protein that are generated in reactions between tyrosine and peroxynitrite formed from nitric oxide. Levels of 3-nitrotyrosine are greatly increased in the Alzheimer brain . Measurements of 8 hydroxy-2 deoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHG) are frequently used biomarkers for oxidative damage to DNA and RNA, respectively. The amount of 8-OHdG has been found to increase progressively with age in both nuclear and mitochondrial DNA although the rate of increase with age is much greater in mitochondrial DNA (Mecocci et al., 1993). Nevertheless, oxidized levels of nuclear DNA are even greater in AD than in age matched controls. With the use of monoclonal antibodies that can recognize the exact location of 8-OHdG and 8-OHG, it has been shown that immunoreactivity in the cytoplasm and to a lesser extent in the nucleus and nuclear envelope is significantly greater in neurons from Alzheimer brain.(Mohr et al., 1995)

Current Pharmacotherapy of AD

Pharmacotherapy of Alzheimer's disease (AD) has progressed in the past ten years from the use of psychotropic medications for sedation to the use of rational treatments aimed at neurotransmitter replacement. The acetylcholinesterase inhibitors (AChIs) donepezil, rivastigmine and galantamine have shown consistent efficacy across the spectrum of very mild/mild/moderate and severe AD. More recent work on the effects of acetylcholinesterase inhibitors (AChEIs) on behavioral symptoms, activities of daily living and caregivers' burdens have also been encouraging (Holmes et al., 2003).

Cholinesterase inhibitors

ChEIs were the first pharmacologic treatments for AD to be approved by the US Food and Drug Administration (FDA). Their major therapeutic effect in patients with AD is reported to be maintenance of a higher level of cognitive function compared with placebo over a 6- to 36-month treatment period. Because there is emerging evidence that much of the neurotoxicity of AD may be reversed with ChEI treatment. Cholinergic stabilization would appear to imply not only a slowing of disability but also a delay in disease progression. Large-scale placebo-controlled trials of tacrine, donepezil, rivastigmine, and galantamine have shown modest symptomatic benefits in patients with mild to moderate AD. To the extent that ChEIs are found to be disease modifying and neuroprotective, they should be offered early in the course of AD in hopes of preventing additional neurotoxicity and functional complications.

ChEIs block the destruction of the neurotransmitter acetylcholine (ACh) by acetylcholinesterase (AChE). Levels of ACh are diminished in cholinergic neurons of patients with AD. Cognition is further compromised by the loss of cholinergic neurons within the cholinergic pathways. Nausea, vomiting, diarrhea, dizziness, and anorexia are the most common adverse effects of ChEIs. (Holmes et al., 2003).

Glutamatergic-system modifiers

Recent research indicates that the excitatory neurotransmitter glutamate may play a role in the pathophysiology of AD. Glutamatergic neurotransmission is important in learning and memory and is severely disrupted in patients with AD. Loss of glutamatergic function in AD may be related to the increase in oxidative stress associated with the Abeta peptide. Therapies addressing oxidative stress induced by hyperactivity of the glutamate receptors include supplementation with estrogen and with antioxidants such as vitamin E (Shumaker et al.,2003).

Recent studies have suggested that donepezil and galantamine are efficacious with regard to glutamate induced excitotoxicity. Cholinergic neuron damage can lead to nuclear fragmentation and apoptotic cellular death. Overstimulation of the N-methyl- D - aspartate (NMDA) receptor by glutamate leads to

neuronal calcium overload and is implicated in the neuronal death characteristic of AD and other neurodegenerative disorders. Conversely, physiologic activation of the NMDA receptor appears to be necessary for normal cognitive function. Therefore, only compounds that finely modulate NMDA-receptor activity hold promise as treatments for AD. Memantine, a noncompetitive (channel-blocking) antagonist with moderate affinity for the NMDA receptor, appears to block pathologic neural toxicity associated with prolonged glutamate release without blocking physiologic activation of the NMDA receptor. (Peskin et al., 2006) Therapeutic doses are well tolerated (i.e., memantine exhibits none of the adverse psychoto- mimetic effects seen with earlier NMDA-receptor antagonist) and do not appear to interfere with the acquisition or processing of cognitive information(Tariot et al., 2004).

Combination therapy for AD

With tile advent of memantine, an agent that has a different mechanism of action from the acetylcholinesterase inhibitors (N-methyl-D-aspartate-receptor blockade and enhancement of cholinergic neurotransmission, respectively), the matter of cornbination therapy versus monotherapy of AD has surfaced. In the only published trial till date, the addition of memantine (5mg/ d to 20 mg/d) to stable donepezil therapy significantly improved out-comes (cognition, performance of activities of daily living [ADL], global outcome, behaviors) compared with addition of placebo.

Limitations of conventional medication

There are several side effect of antiparkinson theraries viz. "dopa-resistant" motor symptoms (speech impairment, abnormal posture, gait and balance problems), "dopa-resistant" nonmotor signs (autonomic dysfunction, mood and cognitive impairment, sleep problems, pain) and/or drug-related side effects (especially psychosis, motor fluctuations, and dyskinesias). Therefore, the current antiparkinsonian therapy cannot be considered as ideal with regard to both efficacy and safety.

Molecular Understanding of AD

RAR/RXR signal transduction: The RAR/RXR transcription factor complex is activated by ligand binding, its natural ligand being all-trans retinoic acid (all-trans RA). Retinoids are obtained from the diet in form of vitamin A (retinol and retinal), retinyl esters or b-carotene. Following cellular uptake of all-trans retinol from the plasma, the intracellular synthesis of retinoic acid occurs in two steps: retinol is oxidized first to retinal and subsequently to retinoic acid. The second NADH-dependent, thermodynamically irreversible step is catalyzed by retinaldehyde dehydrogenase (Blomhoff et al., 2006). Three known RA-synthesizing aldehyde dehydrogenases are designated as RALDH-1, -2, and -3 (also: ALDH1A1, A2, A3). Retinoic acid acts in a paracrine or autocrine fashion. The fact that RA activates nuclear transcription factors was discovered in 1987. Retinoid receptors belong to the same superfamily as PPAR, vitamin D receptor, thyroid hormone receptor (TR) and steroid receptors. They can be grouped into two families, the RAR and the RXR, each consisting of three isoforms encoded by separate genes: RARa, RARb, RARg (also: NR1B1–3) and RXRa, RXRb, RXRg (NR2B1–3). All-trans RA and 9-cis RA bind to the RAR family, whereas only 9-cis RA is a high affinity ligand for the RXR (Bastien et al., 2004).

The active transcription factor complex consists of an RAR/RXR heterodimer, ligand and co-activators. It interacts with retinoic acid response elements (RARE) in the promoters of target genes. About 500 genes have been suggested to be regulated by RAR/RXR signaling; however, a much lower number was experimentally shown to be activated via the classical RARE driven pathway. Proven target genes include enzymes, transcription factors, cytokines and cytokine receptors (Mey et al., 2001. In addition, many cases of gene suppression and non-genomic modes of action of RA and its receptors have been described. Rapid actions of RA include the regulation of gap junctions, spinule formation in the retina, and effects on dendritic spines in the hippocampus. A direct influenced on phosphorylation of the transcription factor (Schrage et al., 2006). CREB and the mitogen- activated kinase ERK1/2 has been observed. Another path of action is the repression of AP-1 (Jun, Fos) activity, which involves RAR/RXR heterodimer, but not the RARE.

In an oxygen/glucose-deprivation/reperfusion model to simulate ischemia, RA protected hippocampal neurons from cell death. In this case, RA also increased phosphorylation of ERK1/2 but reduced phosphorylation of the kinases JNK and p38 (Shinozaki et al., 2007). Cell culture studies and experiments with RARb-deficient mice indicated that RARb is required for RA-induced axonal regeneration of sensory neurons. Since RALDH-2 and RARb are induced by NGF, RA appears to act downstream of this neurotrophin, while additional neurotrophin-independent RA/ RARb activity contributes to axon outgrowth. In a mouse model of diabetic neuropathy, RA treatment raised serum levels of NGF, improved myelination in

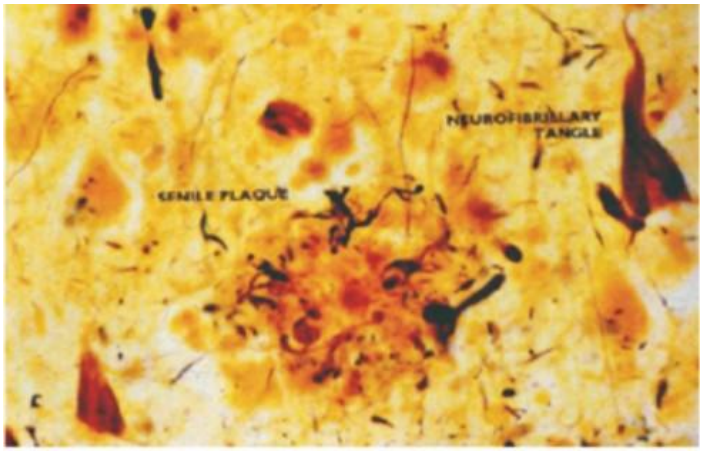

Figure 1: Neuropathological hallmarks of alzheimer disease (Prinja D et al., 1989)

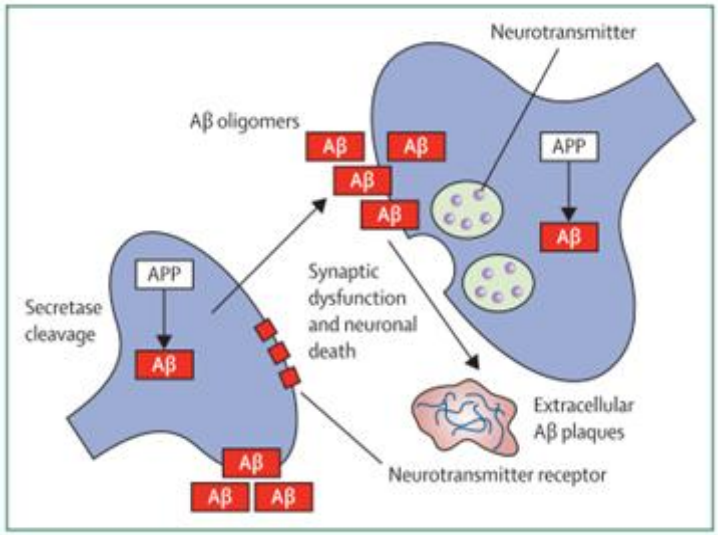

Figure 2: Amyloid cascade hypothesis (Clavaguera *et al.,* 2009)
Abbrev. *Aβ- amyloid β, APP- amyloid precursor protein*

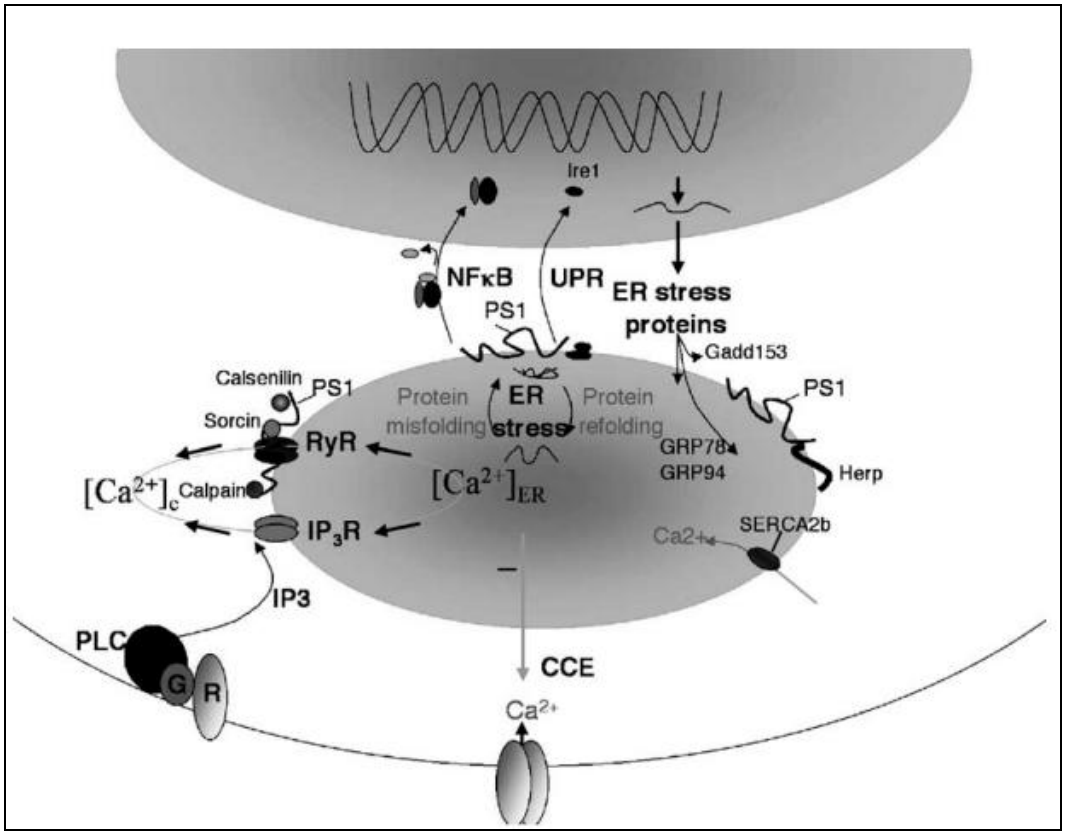

Figure 3 Calcium in deregulation in AD (Mark *et al.,* 1997**)**

peripheral nerves and caused behavioral improvements (Arrieta *et al.,* 2005).

PPAR/RXR signal transduction

Peroxisome proliferator-activated receptors (PPAR) belong to the same superfamily as the RAR. The first PPAR was discovered, cloned and sequenced in 1990, and it was named after its property to be activated by drugs that cause proliferation of peroxisomes in hepatocytes (Issemann et al., 1990). Until now, three different isoforms of PPAR, encoded by separate genes, have been identified: PPARα (NR1C1), PPARβ/d (NUC1, NR1C2) and PPAR γ (NR1C3). The different isoforms have similar structural features; however, each isoforms exhibits its own specific tissue expression pattern and distinct physiological functions depending on ligand activation. PPAR also heterodimerize with RXR, then bind as a complex to their response elements (PPRE). Different promoter-specific co-activators participate to regulate the activity of PPAR γ and other nuclear receptors. Natural ligands of PPAR are fatty acids, prostaglandins and oxidized fatty acid derivatives. They are also activated by synthetic ligands like the lipid-lowering fibrates, the anti-diabetic glitazones and by some non-steroid anti-inflammatory drugs (NSAIDs) like ibuprofen or indomethacin.

Recently, RA was shown to activate not only RAR/RXR but also PPAR/RXR heterodimer (Schug et al., 2007). Different lipid binding proteins selectively cooperate with different nuclear receptors, for instance, CRABP-II with RARa and the fatty acid binding protein FABP-5 with PPARβ/d. When a high CRABP-II concentration was available in the cell, RA activated RARa (Kd ca. 0.1–0.2 nM), but in the presence of a high FABP-5/CRABP-II ratio RA bound PPARβ/d with high affinity (Kd 10–50 nM), which induced expression of endogenous PPRE target genes in a human keratinocyte cell line. The PPARs, which have been implicated in lipid metabolism, cellular proliferation and inflammatory responses, are widely expressed, including in monocytes, dendritic cells, endothelial cells, megakaryocytes and lymphocytes, where they may be related to immune functions. PPAR γ can also

influenced gene expression independently of PPRE. The activity of a number of transcription factors, e.g., NF-kB, AP-1 and STAT-1, is inhibited by PPAR γ via direct interaction or by competition for limiting supplies of co-activators (Kielian et al., 2003). PPARα and PPARβ/d, but not PPAR γ were found in cervical, thoracic and lumbar segments of the spinal cord, in the thalamus and cerebral cortex.

Immunohistochemical staining showed that PPARβ/d is the main isoforms present in neuronal cell bodies of the spinal cord gray matter. Both receptors, PPARα and β/d, were concentrated in cell nuclei. In the white matter PPARα appeared particularly strong in PPAR β/d-negative astrocytes, whereas oligodendrocytes expressed only PPARβ/d. PPARβ/d is a factor in neuronal differentiation, and functions of this receptor in various aspects of neural physiology have been suggested. While conflicting results about the expression of PPAR γ in the CNS have been published, this receptor is expressed in microglial primary cultures and may be unregulated after injury. Endogenous PPAR ligands may mitigate the inflammatory response after spinal cord injury. To examine the effects of endogenous PPARα ligands, experimental spinal cord injury was induced in wild-type and in PPARα-deficient mice. The injury resulted in severe trauma characterized by edema, loss of myelin, neutrophil infiltration, apoptosis and increased production of TNFa. Compared to wild type animals all these parameters were augmented in PPAR α,β,γ mice. The absence of PPARα also interfered with recovery of limb function (Genovese et al., 2005).

CONCLUSION

Despite of several years of scientific efforts, still there is no satisfactory therapeutic strategy to cure cognitive impairment. A recent breakthrough in scientific and technical field has allowed researchers to understand the basic pathophysiology of the progression of diseases such as Parkinson's disease, Alzheimer's disease, schizophrenia and Attention Deficit Hyperactivity Syndrome (ADHD). Researchers have unveiled many of the new key players of the pathological cascades which lead to cognitive impairment. Many of newer compounds targeting these pathways are under preclinical and clinical investigation and can be promising therapies for cognitive impairment. Apart from the pharmacological approaches, other approaches such as dietary supplementation, herbal agents and encouragement of healthy lifestyle which is physically and mentally stimulating are going to have a big impact on cognitive research in future.

FUTURE SCOPE

Still molecular mechanism of the cognition deficit in alzheimer remained a mystery. Hence, there is an imminent need to clarify or understand molecular pathways responsible for development of AD, in order to design the target specific drugs with lesser side effects.

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