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Alzheimer's Disease and Animal Models in Retrospect

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Abstract

Alzheimer's disease (AD) is one of the neurodegenerative diseases that affect millions of people worldwide. AD could rob patients of their ability to recall, reason and carry out executive functions. Pathophysiological studies of AD have revealed the gradual loss of neurons, function and ultimate death of neurons (apoptosis). Mutations, oxidative stress, excitotoxicity, infectious diseases are among the principal causes of neuronal degeneration. Despite the prescription of a wide range of drugs to treat AD, the emergence of effective treatments to halt the progress or reverse this disease has remained elusive for years. Series of preclinical studies have been developed to ensure better understanding of the neurobiology of AD and engender the discovery of new drugs. This review provides an overview on the pathophysiology, pharmacotherapy and preclinical models of AD in an attempt to bring together current research efforts, challenges, achievements and prospect for the discovery of drugs to treat AD. Pathophysiological evidences of this neurodegenerative disease has shown the involvement of multiple neural mechanisms. So far, the research approaches and treatment of this disease still remain largely unsatisfactory. However, there are possibilities of surmounting current challenges with new technology, diagnostic criteria and translational approach that effectively reflect clinical etiology of AD in experimental animals.

Keywords: Neurodegenerative disease; Alzheimer's disease; Pathophysiology; Pharmacotherapy; Preclinical models

Abbreviations: AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; NMDA: N-methyl-D-aspartate; ATP: Adenosine Triphosphate; Ab: Amyloid Beta, H_2O_2: Hydrogen Peroxide; NO: Nitric Oxide; Ach: Acetylcholine; Aβ: β-amyloid; NGF: Nerve Growth Factor; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; GABA: Gamma-Aminobutyric Acid; CT: Computed Tomography; MI: Multiphoton Imaging; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; FDG-PET: Flouro-2-deoxy-D-glucose-positron emission tomography

Oxidative Stress and Neurodegeneration

The daily activities for human survival often constitute serious challenges and threats to human health [1]. Stressful life events that are accompanied with psychological and behavioral reactions are believed to predispose people to mental illness [2,3]. Intense oxygen release could predispose human to stress induced neurodegenerative diseases. Oxygen is a critical element for all living cells or neuron [4]. This essential element is involved in oxidative phosphorylation to generate adenosine triphosphate (ATP), a vital metabolic process to neuronal maintenance and survival [5,6].

However, excessive release of oxygen and subsequent oxidative stress have been attributed to the failure of the complex regulatory systems and disruption of cellular homeostatic processes. Oxidative stress could be associated to the imbalance in the equilibrium between oxidant and antioxidant molecules [7]. Predominant activities of prooxidant molecules could lead to a chain of effects that promote further generation of reactive oxygen species (ROS) and free radicals. These molecules are potentially neurotoxic. The high levels of oxidative stress can cause necrosis, ATP depletion and prevent the occurrence of controlled apoptotic death [8].

For normal functioning, the brain requires a high supply of oxygen and glucose to enable continuous generation of ATP pool. Hence, the brain is more susceptible to oxygen overload and free radical generation [9]. 1-2% of O_2 consumed is converted to ROS in a normal condition but in an aged brain or in an oxidative stress induced pathological condition, this percentage could increase dramatically due to a reduction in the level of antioxidants and low regenerative capacity of aged brain [9].

Meanwhile, oxidative stress and free radical generation play pivotal role in redox reactions that result into AD [7]. An age-related memory impairments correlate with a reduction in brain and plasma antioxidants [10,11]. ROS such as hydrogen peroxide (H_2O_2), nitric oxide (NO), superoxide anions and the highly reactive hydroxyl and monoxide radicals (OH·, NO·) are among the free radicals that constitute high risk to neuronal loss or damage [12-15]. Excessive oxidative activities in AD are characterized by high levels of oxidised proteins, formation of toxic species like peroxides, alcohols, aldehydes, free carbonyles, ketones, cholestenone advanced glycation end products, lipid peroxidation end products and oxidative modifications in nuclear and mitochondrial DNA [16-26]. Epidemiological evidences have shown that inflammation, stroke, hypertension, diabetes, smoking, head trauma, depression, infection, tumors, vitamin deficiencies, chemical exposure, endocrine, immune and metabolic dysfunctions constitute risk factors of neurodegenerative diseases [27,28].

In this minireview, we attempt to summarize the prevalenceof AD, current understanding of pathophysiology, treatment and preclinical research strategies of AD. We review some of the biomarker that has been targeted by drugs to mitigate degeneration of neurons. It is beyond the scope of this paper to provide full review of the broad range of hypothesis or the enormous outpouring of scientific data on AD.

Brief Facts about Alzheimer's Disease and its Prevalence

Alzheimer's disease (AD) is a chronic progressive disease

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characterized by memory loss and deficits in different cognitive domains like aphasia, agnosia, apraxia, or executive function [29,30]. These deficits could interfere with daily life or work. It is estimated that approximately 5.4 million Americans are currently diagnosed with AD [31]. The risk of being affected by AD increases dramatically with age. This disease cost the U.S. economy billions of dollars each year in direct health care costs and loss of opportunities [32] in addition to immense emotional burden on patients and society. Globally, AD is estimated to cost $604 billion in 2010 alone, a value which is expected to increase as cases of this disease (currently estimated at 36 million) triple by 2050 [33].

The prevalence rate of AD is about 7% within the age group of 65 years and above [34,35]. Nearly one-half of Americans 85 years and older have AD [31]. By 2050 it has been estimated that the headcount of people above 80 years old will approach 370 million worldwide out of which 50% of those that are older than 85 years will suffer Alzheimer's disease [36]. This dementia is a complex neurodegenerative disease caused by multiple genetic and environmental factors [37]. The understanding of the underlining pathophysiology of this neurodegenerative disease could lead to the postulation of hypothesis, development and validation of animal models. An effective animal model could promote preclinical screening of drugs prior to clinical trials and perhaps drug approval (Figure 1).

Pathophysiology of Alzheimer's Disease

For the fact that cognitive failure at the clinical onset of AD is a process that has progressed silently for many years [38], the pathophysiological processes may have evolved for years prior to diagnosis. Pathophysiological informations have continue to associate the causes of AD to the complex interactions among multiple genetic, epigenetic, and environmental factors. Both anatomical and functional alterations have been revealed in patients and individual that are at risk of developing AD. Morphometric measurements from postmortem tissues to live patients [39] by using radiological imaging techniques have advanced the understanding of pathophysiology of AD. In AD, progressive decreases in cortical thickness that correlate with cognitive decline can be detected by magnetic resonance imaging [40,41]. The electrophysiological and biochemical data on transgenic mouse models [42,43] suggest that AD could also be associated with aberrant network activity that could actively interfere with the biological processes underlying cognitive functions in addition to the silencing of neurons. Cognitive decline in AD correlates to loss of synapses and dendritic spines than loss of neurons [44].

The characteristic pathological features of AD include the loss of cholinergic function as a result of a decrease in synaptic levels of acetylcholine (ACh), increase in stress induced oxidation, β-amyloid

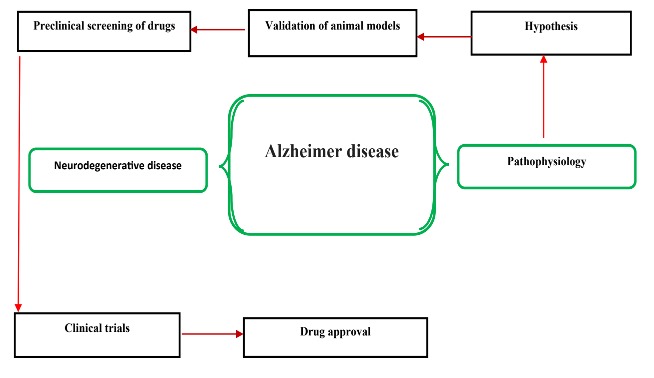

Figure 1: Graphical representation of some steps leading to the development of drugs for the treatment of Alzheimer's disease.

cascade (accumulation of amyloid cerebral plaques of abnormal proteins deposited outside neurons and neurofibrillary tangles of abnormally insoluble tau - filaments of protein that has been hyperphosphorylated inside neurons in affected brain regions) [30], steroid hormone deficiencies, depletion of other neurotransmitters, excitotoxicity caused by excessive glutamate release, loss of neural synapses, dietary factors (fatty diet, alcohol etc), mitochondrial dysfunction, inflammation, ischemia, insulin signaling, and cholesterol metabolism [45]. Despite closer correlation of NFTs with cognitive decline in AD than plaques [46], preclinical study with transgenic mice indicate that the microtubule-associated protein tau, the main constituent of NFTs, can cause neuronal dysfunction independently [47]. Pathophysiological information on AD provides critical means of improving our understanding of the underlining causes of AD and develop new approaches for treatment and prevention.

Treatment Strategies and Pharmacotherapy

The treatment strategies for AD include the use of Aβ aggregation inhibitors, antioxidants, γ-secretase modulators, NGF mimics, PPARγ agonists, HMG-CoA reductase inhibitors (statins), ampakines, calcium channel blockers, GABA receptor antagonists, γ-Secretase inhibitors, glycogen synthase kinase inhibitors, muscarinic receptor agonists, cholinesterase inhibitors, nicotinic receptor modulators, phosphodiesterase inhibitors, serotonin receptor antagonists, NGF gene therapy, non-steroidal anti-inflammatory drugs, hormone replacement therapy [48,49]. Based on these strategies, different classes of drugs have been developed and approved for the treatment of AD. One of the drugs that are currently approved by the FDA for the treatment of AD inhibit acetylcholine esterase. Cholinergic therapy remains one of the best- developed therapy that is being used totreat mild to moderate AD [50]. The loss of cholinergic function which has been associated to memory impairment can be restored with acetylcholinesterase inhibitors like tacrine donepezil, galantamine, rivastigmine, physiostigmine [48].

Tacrine is a non-competitive, irreversible inhibitor of both acetyl and butyryl cholinesterase. In the United States, tacrine was the first anticholinesterase to be approved for the symptomatic treatment of AD [51,52]. However, the high cases of hepatotoxicity and limited efficacy of tacrine have led to the restriction of its clinical application. Rivastigmine is a pseudo-irreversible inhibitor of both acetyl and butyryl cholinesterases with relatively short half-life [53]. In addition to synthetic compounds, some secondary metabolites that are isolated from plants have demonstrated good inhibition of cholinesterases. An alkaloid like galantamine is a reversible inhibitor of acetylcholinesterase. However, clinical application of these alkaloids has been reported to cause some gastrointestinal disorders [54]. Physostigmine is another alkaloid that has shown some therapeutic efficacy with high occurrence of nausea and vomiting [55]. Other anticholinesterases in development include metrifonate an organophosphorus that inhibits activities of acetylcholinesterase irreversibly [8]. The cases of muscle weakness and potential neurotoxicity have generated concerns and delayed further development [56].

The approval of drugs that could antagonize NMDA-type glutamate receptors to prevent aberrant neuronal stimulation [57] has raised the hope of an effective treatment of AD. Being the major excitatory neurotransmitter in the brain, glutamate could interact with both ionotropic and metabotropic glutamate receptor - the N-methyl-D-aspartate (NMDA) as an agonist to mediate neuroplasticity and memory formation. Meanwhile, excessive activation of the NMDA receptors by glutamate has been associated to characteristic neuronal degeneration in AD [58]. NMDA antagonists have been shown to attenuate glutamate induced neurotoxicity [59]. An NMDA receptor antagonist such as memantine, attenuates cognitive deficits in patients with mild AD [60]. However, this drug do not retard the processes of neuritic dystrophy, thereby limiting their clinical efficacy [61].

In addition, some of the neuroprotective drugs like arovastatin, ginko biloba, simvastatin, tarenflurbil, rosiglitazone, tramiprosate, xaliproden, valproate, docosahexanoic, solanezumab, semagacestat, dimebon bapineuzumab etc being used in the treatment of AD exhibit varying degree of efficacy. A mediterranean diet which is characterized by a low- to-moderate intake of saturated fatty acids, moderately high intake of fish, low-to-moderate intake of dairy products, low intake of meat and poultry, and a moderate amount of alcohol has been demonstrated to be associated with lower risk of AD [62]. The diet with component like epigallocatechin-3-gallate enriched with omega-3 polyunsaturated fatty acids have been reported to reduce Aβ generation in Tg2576 mice [63,64]. The chelation of metals like Zinc and Copper with cliquinol could reduce the concentration of heavy metals in the brain and consequently inhibit Ab aggregation and deposition of senile plaques [65].

The 5 HT_3A receptor antagonists like DAU 6215, granisetron, ondansetron, RS-56812, SEC 579 and WAY 100579 have putative pro-cognitive effects given their ability to potentiate the release of ACh and enhance cognitive function. Also in animal models, a number of biomarkers of AD have been effectively targeted. Vaccination targeting Aβ in mice has shown promising results. Vaccination of young PDAPP mice with the Aβ42 peptide inhibits the formation of neuritic Aβ plaques and reduces this biomarker in older mice [66]. Amyloid beta peptide immunization has improved cognitive impairments and reduced the formation of plaques [67]. In amyloid-forming PDAPP mice, both active and passive immunization [66,68] have shown reduction in amyloid beta, neuritic and inflammatory related pathology. Further studies have shown that immunization of amyloid forming presenilin/APP or TgCRND-8 mice [69,70] could reverse age/amyloid-related cognitive decline. Although there are hopes that these results will translate into better understanding of AD and drug design, it is still early to assess whether the results from mice are reliable predictors of efficacy in humans [71].

Some of the promising therapeutic mechanisms of drugs against AD that were proposed in the previous work include protective effect, antioxidant properties and potentiation of APP processing [72-75]. Based on the evidences of oxidative damage as well as inflammation and mitochondrial impairments in AD [76,78], series of attempts have been made to retard disease progression with antioxidants [79,80], anti-inflammatory drugs [81], or putative mitochondrial protectors [76]. In this regards, clinical data on the application of vitamin E has shown some promising results [82] except for the occurrence of blood coagulation at therapeutic dose. Unfortunately, none of these interventions has produced effective therapeutics. The results so far implies that researchers are still faced with the herculean tasks of unraveling the physiopathology of this diseases, propose correct hypothesis, and execute experimental models that can be translated. A substantial revision of the diagnostic criteria for AD remains fundermental [83].

Preclinical Models for Drug Discovery

Non-human primate models like Drosophila melanogaster, Caenorhabditis elegans, rodents among others have offered means of understanding the biology of AD and pharmacological evaluation of novel compounds on biological targets that pareticipate in the pathogenesis of AD. Unlike small animals, dogs and other primates [84-86] have shown some compelling symptoms of neuropathology with aging.

Several works in the literature have involved the postulation and test of hypothesis through the use of aged rodents, pharmacologically and surgically induced memory impairment, transgenic and non-transgenic models. Some of the animal model of AD are target-driven so as to ensure face, construct and predictive validity. This approach could facilitate translation of therapeutic studies from animals to humans.

The clearance of plaques in both mice and humans in the amyloid-beta (Aβ) immunotherapy trial of bapineuzumab [87,88] and the biological activities of gamma-secretase inhibitors (semagacestat and BMS-708163) demonstrated good example of target (Aβ levels)-focused preclinical animal data [89,90]. The failure of some promising preclinical trials to produce desirable effects during clinical trials further reinforces the idea of our limitation in physiopathological understanding of AD and inadequacy of animal modelling of this disease.

Some of the key considerations for animal studies of AD as highlighted by Shineman [91] include; (a) clear delineation of study hypothesis, (b) identification of a specific measure to assess the primary and secondary outcomes, (c) study should target translatable biomarkers, (d) issues of sex, timing of treatment and age of animals should be considered, (d) specify inclusion and exclusion criteria, (e) evaluate bioavailability of drugs, (f) carefully design appropriate statistical analysis plan prior to commencement of study, (g) conduct power analysis and estimates of sample size prior to initiation of the study, (h) treatment groups should be randomized while employing blinding procedures for assessments, (i) report both positive and negative results, (j) report details of strain, housing, diet, dropout events and in-trial exclusions, (k) report the flow of animals through the treatment plan. The principle of bench to bed requires reciprocal translation of *in vitro, ex vivo* and *in vivo* assays to clinical studies as shown in Figure 2.

Progress in radiological imaging techniques [39] has offered great opportunity for investigational and translational researches. The imaging techniques like Computed tomography (CT), multi-photon imaging (MI) magnetic resonance imaging (MRI), magnetic resonance spectroscopy, functional MRI, arterial spin labeling MRI, flouro-2-deoxy-D-glucose-positron emission tomography, (FDG-PET), PET amyloid imaging, PET tau imaging, single-photon emission computed tomography/computed tomography among others and biochemical assays on biological fluids such as plasma and cerebrospinal fluid [92-95] in rodents could permit the assessment of biomarkers (target)-drug

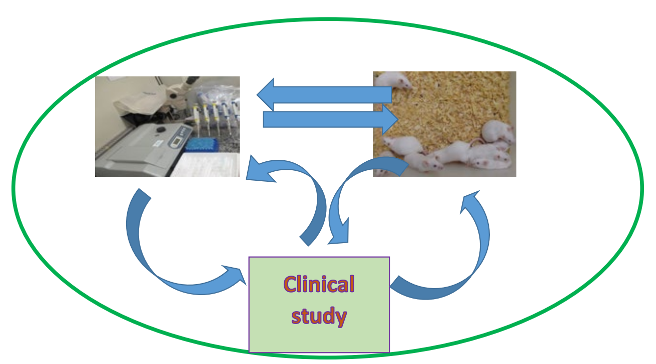

Figure 2: Showing hypothetical dynamics in the translation of *in vitro, ex vivo, in vivo* and clinical studies.

interaction, real time monitoring of biological responses to treatment and translatability of a novel therapy in a clinical trial.

Imaging could facilitate visualization of Aβ deposition in in vivo and monitoring the success of treatment [96]. Unlike MI which is compatible with human and mouse tissue, PET, CT, and MRI require a higher resolution in animals in order to capture their smaller brain structures. These imaging techniques allows for a non-invasive monitoring of pathological changes and to correlate these with behavioral changes [96]. The invention of a novel PET tracer that binds to Aβ plaques (11C-labelled Pittsburgh Compound-B) has attracted significant attention [97]. An age-dependent increase in this PET tracer in APP23 mice was found to consistently accompany an increase in the accumulation of Aβ [98]. An age-dependent memory loss has been evaluated in Tg2576 in the Morris water maze. Spatial reference memory was demonstrated to decline progressively from 6 months of age [99].

In recent times, many of the new therapeutic strategies are based on findings with transgenic animal [100]. A reasonably good approximation of AD has been achieved through transgenic mice models [101]. The first transgenic mice employed cDNA-based or yeast artificial chromosome constructs to elicit expression of human APP gene, APP751, APP695, Ab and C-terminal fragments of APP [102-108].

In an elegant study of AD's biomarker using tau models of transgenic mice, it was demonstrated that suppression of P301L tau expression in rTg4510 tau transgenic mice, which normally express the mutant protein at a high level, reverses behavioral impairments in these mice [109]. A reduction in the activity of the β-secretase BACE by crossing APP transgenic mice onto a BACE$^{-/-}$ reduced Aβ formation and deposition [110]. In contrary, the overexpression of transgenic BACE increased Aβ and plaque formation in APP/BACE Mice. BACE-deficiency also reversed the behavioral changes observed in several APP transgenic strains [110]. Gene's suppression has also been employed to anticipate the effects of new molecules designed to regulate proteins that are involved in the pathogenesis of AD [30]. The results on presenilin and β-secretase knockout mice have shown interesting results [111,112].

In addition to secretase model, apoE [113-115], axonal transport models [116], studies in fruit flies-*Drosophila melanogaster* [117,118], studies in nematodes - *Caenorhabditis elegans* [119,120] among others have been used as animal models of AD. The application of transcriptomics and proteomics are increasingly being used in animal models of AD to identify novel genes and proteins that are regulated differentially [121].

Animal models have contributed immensely to the understanding of the underlying mechanisms of AD. However, new treatments arising from the gain in pathogenic knowledge through animal models like knockout and transgenic mice are yet to engender remarkable improvement [48]. Athough there are number of interesting experimental strategies that are under investigation [42,43,122-125], for almost 10 years after the description of BACE as a potential target in Alzheimer's disease, there is no record of treatment or utility on the basis of this information [126,127]. Animal models are often limited in scope [128-131] as psychiatric diagnosis depends on the patient's verbal history of illness, reports of subjective feelings, and cognitive performance [132-139]. Animal models could not recapitulate and translate these clinical features effectively as animals rarely show disease mechanisms, symptoms or behavioral alterations that are equivalent to those in humans [128,129]. Despite the high expectation, very few of the findings in animal models have been validated in humans or successfully translated into disease-modifying therapies.

Final Considerations

The identification of different biomarkers, biological processes and possible mechanisms that are associated with all phases of AD prior to signs of functional deficits remain crucial. Since increasingly cognitive failure could correlate with series of qualitative and quantitative biological alterations, researchers could be better guided in their approach by considering all the temporal changes that take place prior to detectable clinical onset of AD. Although there seems to be a better understanding of AD among scientists, it is still too early to tell whether these understandings have greatly improved diagnosis, drug development strategies and treatment of patients. However, with the advent of innovative preclinical approaches that optimize interpretation of results, there seems to be an array of hope for effective prevention and treatment of AD. On the basis of underlining hypothesis on pathophysiology of AD, transgenic mice models have been a major breakthrough despite its limitations. Since, there are possibility of synergistic or signaling effects of biomarkers the current investigation of biomarkers in isolation may not be a holistic approach towards unravelling the entire mechanisms that are involved in the processes leading to AD. Investigative measures and drug development efforts should reflect the multifactorial attribute of this disease. Temporal measurement of neural function, identification of **vulnerable neurons** and effective use of imaging techniques could offer unique advantages for better understanding and improved treatment of AD.

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