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Alzheimer's disease: Risk factors and therapeutic targets

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ABSTRACT

Alzheimer's disease (AD), a neurodegenerative disorder, has been determined as an outcome of genetic as well as behavioral conditions. The complete understanding of its generation and progress is yet to be understood. However, there has been a significant progress in the diagnosis and identification of the associated risk factors of AD. Several of the risk factors were found connected with cholesterol. Scientists are mainly focusing on the reduction of amyloid β and stabilization of tau protein towards the development of its drugs. To modulate amyloid β, the key components of cholesterol metabolism have been attractive targets and the enzymes involved in the phosphorylation of tau have been tried to stabilize tau protein. This review article briefly highlights the symptoms, risk factors, and drug targets of AD.

1. Introduction

Alzheimer's disease (AD), a major cause of dementia, has been the 6th leading cause of death worldwide affecting more than 30 million people[1]. In comparison to other human disorders, the occurrence of AD is continuously increasing. Noticeably, women are more susceptible than men[2]. The majority of AD occurred in the elderly people (above 65 age), and the risk increased with increasing age but in rare cases it also appeared during one's 40s[3]. It takes several years (10–20) to progress and badly affect the patients. During severe stage, the patients completely rely on someone for day to day activities. This requires a large number of caretakers and huge amount of financial resources[2]. To make relief from the individual symptoms that appear in AD, different drugs are prescribed like donepezil for appetite loss, memantine for confusion but there are no drugs yet in the market to change the fundamentals of the disease[1,4]. AD bears the name of Alois Alzheimer, a German psychiatrist, who first noticed the disease in 1906. Researchers from different disciplines are working hard mainly during last few decades to completely understand its generation, progress, and treatments[2]. Several factors were found associated for the occurrence of AD; it may also be a combined outcome of several factors[5]. Key points in the metabolic systems that were found linked with amyloid beta (Aβ) and tau phosphorylation have been the targets for the potential drugs.

2. Symptoms

The existence of AD is diagnosed with a series of cognitive and anatomical examinations[4]. The disease starts from the part of brain that is responsible for new memory making. Therefore, the cognitive problem starts with the difficulty to memorize newly learned things[6]. With the progress of disease, symptoms widen with the problems of planning, performing usual works, confusion with spatial relations, mood swings, *etc.* The inability of patient to judge, read, speak, and write makes him suffer in the family and society. Finally, complete degradation of personality due to the disease requires full time caretakers[4]. The majority

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of deaths occur by other infections like pneumonia[7]. Depending upon the severity, it has been categorized into mild, moderate, and severe conditions[8]. Anatomically, the brain of AD patient is identified with aggregated extracellular Aβ proteins (plaques) and intracellular hyperphosphorylated form of tau protein (tangles)[2]. The formation of plaques and tangles obstruct the flow of nutrients and communication among the neuronal cells ultimately leading to their death[5].

The coordinated cleavage of amyloid precursor protein (APP) by α, β, and γ secretases (Figure 1) leads to usual pathway while the over activity of β secretase or reduced removal of Aβ leads to pathogenic route[5,9]. A small fraction of Aβ was found prone to misfolding and toxic to the neurons[10]. Both the pathways were reported to exist in competition and several factors determine the winning route[11].

3. Risk factors and drug targets

Two biomarkers of AD, Aβ and hyperphosphorylated tau protein have been the prime concerns towards the development of drugs. Several factors were found associated with cholesterol. Therefore, these factors have also been the targets to modulate Aβ production and clearance[5]. While the phosphorylating enzymes were focused towards the stabilization of tau protein[12]. Both the genetic and behavioral conditions have been found responsible for the disease. In a very small fraction of patients, the presence of certain genetic conditions confirms the disease while majority of the occurance was found associated with several factors lik age, apolipoprotein ε_4 (apoε_4), head injury *etc.* Figure 2 summarizes the major factors associated with AD. Inheritance of any of the mutated forms of genes in presenilin 1, presenilin 2, and APP leads to the early onset (< 65 age) of AD[13]. Note: presenilin-1 and presenilin-2 are enzymes in the γ secretase family[14].

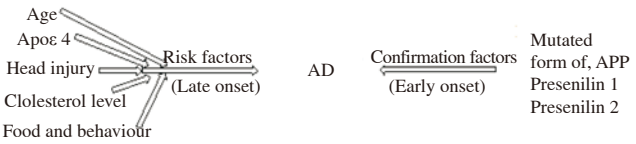

Figure 2. Factors associated with AD.

3.1. Cholesterol

The level of cholesterol in the brain is maintained by continuous synthesis, endocytosis of lipoprotein, cholesterol efflux, and synthesis of hydroxycholesterols[15]. Not only the amount of cholesterol but also its distribution within and outside of cells as well as in the cell membranes were found connected to the generation of AD[16]. Interestingly, the high level of cholesterol during the mid life was related with the AD in late life[17]. In a cell line study, the inhibition of cholesterol by lovastatin and methyl-β-cyclodextrin was able to significantly reduce the formation of Aβ[18]. Although the results are not always consistent, several agents in the cholesterol metabolism have been attractive targets for the treatment of AD[10].

3.2. Apoε_4

Apoεs play an important role in the distribution of cholesterol in the whole body[19]. They are also crucial for the maintenance of neurons by removing unwanted materials[20,21]. Three types of apoεs (apoε_2, apoε_3, and apoε_4) exist in equilibrium but apoε_4 was found to bear the pathogenic structure[22,23]. It was also found less effective to remove the toxins and repair the problematic neurons[24]. Apoε_4 was found consistently associated with the occurrence of AD though its presence could not guarantee the AD[21,25]. The occurrence of the disease in close relatives of patients indicates the chances of carrying apoε_4 by them[26]. It has been an attractive target due to its consistent association with AD[22]. Potential drug molecules have been prepared to change the site of interaction in apoε_4[21].

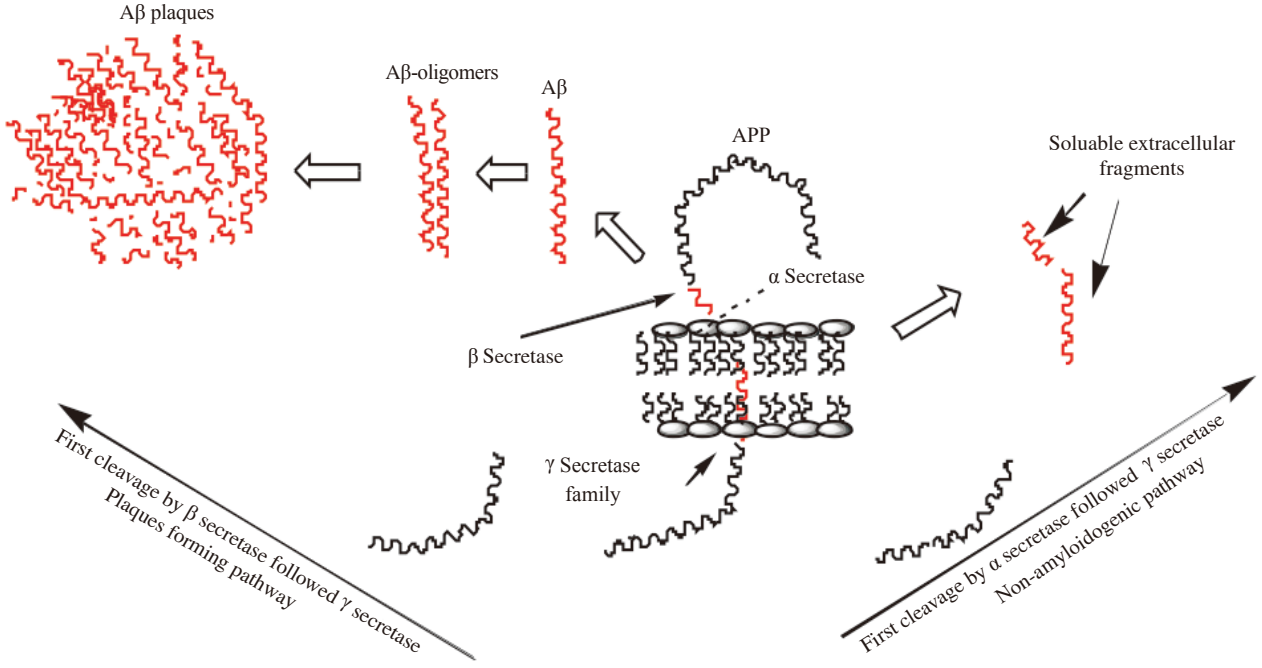

Figure 1. Processing of APP leading to normal and amyloidogenic pathways.

3.3. Acyl coenzyme A: cholesterol acyltransferase (ACAT)

ACAT, a membrane-bound enzyme, utilize long-chain fatty acids to make cholesterol esters from cholesterol and maintain the intracellular cholesterol homeostasis[27,28]. A well known ACAT inhibitor CP113818 in mice model was found to improve cognitive strength[29]. Cell based assays and animal models demonstrated that the inhibition of ACAT inhibited the formation of Aβ plaques[30]. Scientists are trying ACAT inhibitors as potential drugs for AD[31,32].

3.4. Liver X receptor (LXR)

LXR is involved in the regulation of lipids, glucose, and deals with inflammation[33]. The effectiveness of macrophages to remove harmful materials was liked with LXR[34]. It plays an important role in intracellular cholesterol balance by promoting cholesterol efflux, and uptake[33,35]. Oxysterols which are able to cross blood brain barrier, are LXR agonists in the form of its ligands[36]. Even though the results are not consistent, the alteration in the role of LXR by modulating its ligands like 27-hydroxycholesterol have been tried to reduce Aβ[37,38].

3.5. Tau phosphorylation

Tau, a cytoplasm soluble protein, plays an important role in transport and signal transmission among the neurons[33]. It is one the major microtubule stabilizing proteins. Kinases that are involved in the phosphorylation of tau were targeted for the treatment of AD. Glycogen synthase kinase-3β (microtubule associated kinase) plays a role in the phosphorylation of tau protein[39]. Many kinases, mainly the glycogen synthase kinase-3β has been a therapeutic target for the treatment of AD[12,40,41].

3.6. Diabetes mellitus

Metabolisms of lipid were found closely related with glucose equilibrium[42,43]. Like AD, diabetes is also a disorder mostly in the elderly. The occurrence of diabetes was found connected to the risk of having AD[44].

3.7. Mitochondrial functioning

Some reports have mentioned that the age dependent reduced effectiveness of mitochondria leads to the late onset of AD[45]. In a mice model, the generation of Aβ and its toxicity was connected with malfunction of mitochondria[46].

3.8. Head injury

The strikes on the head whether moderate or severe were found associated for the generation of AD[47]. The players who use frequent strike by head were found high prone for the AD[48].

4. Future prospective

Several potential drugs with the purpose of the treatment of AD are under different stages of clinical trials[49,50]. Researchers are applying different approaches with dedication. Hopefully, in near future there will be a significant progress to cure one of the challenged neurodegenerative disorder. Like other human disorder, AD has also been related with behaviors. Therefore, the application of healthy practices in food, exercises, and mental activities can significantly reduce the likeliness of this disease.

Conflict of interest statement

I declare that I have no conflict of interest.

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