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Alzheimer disease: From AI prediction of pharmacotherapy to its drug formulation

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Abstract

Alzheimer disease (AD) is an age-associated neurodegenerative disorder. AD has been studied in the past three decades, yet no success medication is approved to date. The disease causing is a complex process and may involve multi-factorials which is a leading cause of death and a serious burden to families. AD is the most prevalent type of dementia and remains the fifth leading cause of death among Americans aged 65 and older. From literature review, two most disease-causing targets, namely, IDO1 and APOE4 are reported. In this study, we have chosen these two targets for new and or re-purpose molecules prediction by AI algorithm. The selected targets are believed to have potential in ameliorating the progression of AD. Target IDO1 is mainly involve in decreasing energy transfer to neuron. Inhibition of IDO1 may improve neuron energy transfer. As for APOE4, the processes mediated by APOE4, including cholesterol transport, synapse formation, modulation of neurite outgrowth, synaptic plasticity, destabilization of microtubules, and β-amyloid clearance, suggest potential therapeutic target. In this study, molecules that inhibit these two targets via AI prediction are conducted. Finally, an alternative method of NDA drug formulation using FDA drugs database and PAMPA dissolution is proposed for first in human (FIH) clinical study. The comparison between the use of FDA drugs' ADME parameters and the new molecules' in vitro ADME parameters for the design of FIH oral drug formulation is addressed.

Keywords: *In Vitro* To *In Vivo* Correlation (IVIVC); Maximum Plasma Concentration (Cmax); Parallel Artificial Membrane Permeability Assay (PAMPA); Administration Distribution Metabolism and Excretion (ADME); Indoleamine-2,3-Dioxygenase 1 (IDO1); E4 Allele of Apolipoprotein E (APOE4)

1. Introduction

Known as the leading cause of death among the population of 65 years and older, Alzheimer's Disease (AD) is an increasingly prevalent issue in the modern world toda[1] Although there have been multiple attempts at developing treatments to slow the progression of AD symptoms, it is now more important than ever to develop ones that prevent or even reverse AD.

Currently, treatments and medication for AD have been focused on slowing the progression of symptoms. However, recent studies have shown that AD is a multifaceted disease, having multiple potential factors that can lead to the cognitive decline of AD patients [2, 3]. These studies urge people to start considering other directions when developing medication for AD, including the development of drugs that target multiple potential factors involved in the AD pathogenesis [4].

One of the most promising starting points in developing more effective AD drugs is the identification of genes and proteins that have been proven to be linked to AD's pathogenesis. Two of such include the Apolipoprotein E (APOE4)

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and indoleamine 2,3-dioxygenase (IDO1) gene. APOE4 has been proven to be linked to the accumulation of β-amyloid plaques between neurons and insulin resistance in neurotic cells, both of which are possible factors leading to loss of cognitive ability commonly seen in AD patients[5]. Studies have also revealed that the IDO1 gene suppresses lactate transfer between astrocytes and neurons, leading to the energy loss of neurons and therefore, the weakening of cognitive ability[6]. Finding compounds that target and inhibit APOE4 and IDO1 will be the first step to developing multi-therapeutic medication that may prevent or reverse AD.

To discover new or existing compounds that can possibly be developed into effective AD drugs, researchers are starting to rely on artificial intelligence (AI). The advancement in AI drug prediction has dramatically improved the new drug candidates screening. The success of a new drug application (NDA) relies not only on early stage drugs screening and preclinical studies but also PK/PD prediction prior to clinical study. Several important databases like Protein Data Bank (PDB), PubChem, and ChemBL etc. have made new drug search easier with the help of fast AI computation. The drug-target interactions has become the crucial parameters that has enabled successful application of machine learning (ML) tools to accurately predict new molecules structures[7, 8]. AI will continue to benefit from open access to structural, biological, chemical, and biochemical data as new algorithms are applied to predicting small-molecule, ligand binding and protein-protein interactions[9].

This article examines the possible development of AD medication targeting APOE4 and IDO1. It also explores the use of AI prediction models and large online databases to predict lead compounds that may be developed into effective AD drugs. Finally, an alternative NDA oral dosage prediction using PAMPA is also discussed.

2. . Materials and methods

OpenTarget, PubChem, Uniprot, PDB, ChemBL, SEA, SwissTarget, and SwissADME are tools used in computational biology and drug discovery, each contributing distinct functions to various aspects of the drug development process[10,11,12]. For the AI prediction purpose, the disease targets of AD can be referred from a number of review articles[13,14]. Due to its characteristics of multi-factorial disease in AD, e.g., potential targets include IDO1 (indoleamine-2,3-dioxygenase 1) and APOE4 (ε4 allele of Apolipoprotein E), both of which have been proven to be linked to several steps in the AD pathogenesis. In the case of IDO1, the studies highlight a disruption of glial carbohydrate metabolism with disease progression. It was reported that inhibition of IDO1, which metabolizes tryptophan to kynurenine (KYN) in the first step of the kynurenine pathway, rescues hippocampal memory function and plasticity in preclinical models of amyloid and tau pathology by restoring astrocytic metabolic support of neurons[6]. In APOE4, the processes mediated by APOE4, including cholesterol transport, synapse formation, modulation of neurite outgrowth, synaptic plasticity, destabilization of microtubules, and β-amyloid (Aβ) clearance[5]. APOE4 is responsible for elevating cholesterol in the brain to a greater extent than APOE3, and APOE2 carriers. Thus, cholesterol transport may play an important role in the progression of AD.

2.1. Inhibition of indoleamine-2,3-dioxygenase 1 (IDO1)

A recent study revealed a noticed disruption of astrocytic and microglial metabolism in AD subjects. Astrocytes exist in approximately a 1:1 ratio to neurons, and are essential to regulation of neurotransmitter levels and bioenergetic support of neurons. Particularly, astrocytes generate lactate which is exported to neurons to fuel mitochondrial respiration and support synaptic activity[6]. Fig. 1 indicates pathogenic pathways of IDO1 where IDO1 is expressed in astrocytes and microglia but not in neurons, and levels increase in response to inflammatory stimuli. It was reported that KYN generated by IDO1 suppresses astrocytic lactate transfer to neurons resulting in the loss of neuron energy.

Therefore, a pharmacologic inhibition to IDO1 may restore hippocampal glucose metabolism and spatial memory not only in preclinical models of amyloids accumulation but also in a model of tau accumulation. An AI inhibition prediction of new and or repurpose molecules from the database for IDO1 is performed in the following.

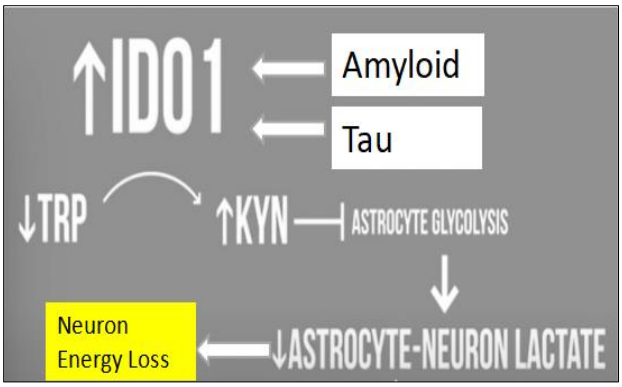

Figure 1 Pathogenic pathways of IDO1

2.2. Inhibition of ε4 allele of Apolipoprotein E (APOE4)

The APOE protein circulates through the blood stream as part of a large lipoprotein molecule where it plays an essential role in regulating cholesterol and lipid metabolism, as well as cellular signaling and repair[4,5]. In the brain, astrocytes are the major source of APOE, while the liver produces APOE in the periphery. APOE4 is responsible for elevating cholesterol in the brain to a greater extent than APOE3, and APOE2 carriers. Thus, cholesterol transport may play an important role in the progression of AD. Fig. 2 shows APOE4's impact on AD pathology. APOE not only functions to traffic lipids through the PNS and CNS, but also interacts heavily with the tripartite synapse (presynapse, postsynapse, and astrocytes) and neuronal signaling. APOE is essential in regulating neuronal signaling, but the APOE4 isoform negatively impacts these signaling systems. APOE4 competitively inhibits LRP1/Aβ binding, thus contributing to an overall increase in Aβ load (Fig. 2). Instead of targeting amyloid using antibodies or trying to destroy plaque burden itself, future therapies could possibly inhibit APOE/Aβ competition or enhance Aβ clearance by increasing expression or altering functionality of LRP1. APOE is also involved in microtubule formation and polymerization and thus promotes cytoskeletal integrity.

Recent post-mortem analysis of AD brains reveals a more significant association of APOE4 with τ filaments and tangles that exists in the presence of brain Aβ than in the absence of brain Aβ. Autophagy is a physiological process through which cells dispose of damaged organelles to make room for newly regenerated ones. APOE4-expressing astrocytes show reduced degradation of Aβ in the mouse model, which is improved in the presence of the autophagy inducer rapamycin. Neuronal APOE4 interferes with insulin receptor trafficking by trapping the receptor to endosomes, ultimately leading to altered glycolysis. APOE also impairs trafficking of other membrane-bound receptors such as LRP1[5]. This neuronal membrane receptor has also been implicated in glucose metabolism. Since APOE4-mediated insulin resistance can contribute to impaired cognition and dementia, targeting the glucose metabolic pathways to reduce the glycemic load in brain could be an alternative therapeutic approach to mitigate the APOE4-mediated effects. Finally, hyperactivity of mitochondria-associated endoplasmic reticulum proteins is present in APOE4-treated astrocytes. These proteins are specifically designated for cholesterol transport, and alteration of their function leads to an imbalance in lipid-mediated cellular processes.

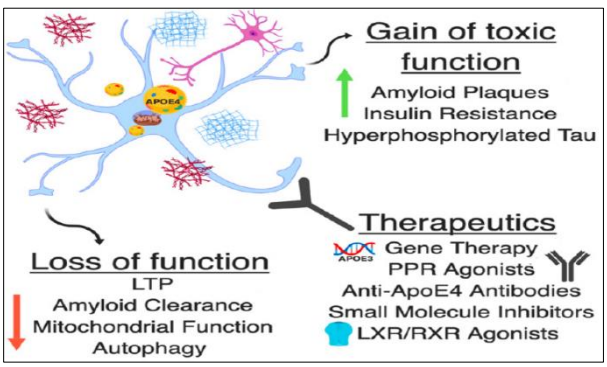

Figure 2 APOE4's impact on AD pathology

2.3. AI prediction of molecules for targets "IDO1" and "APOE4"

With the aforementioned promising pre-clinical data for the disease targets in AD. The help of AI and databases, enable us to predict and analyze the new and or repurposed molecules. Data shown in Table 1 indicates the predicted results. From Table 1, cell assay for IDO1 with molecules IC50<100 nM, indicate good inhibition for IDO1. These molecules have high predicted GI absorption and good BBB permeation. It also meets rule of five and toxicity class. As for APOE4, molecules having pharmacophore[14] may also produce the derived new molecules using Tanimoto similarity for target APOE4. As shown in Table 1, three new molecules are generated with high predicted GI absorption, good BBB permeation and Pgp requirement, also meets rule of five and toxicity class. These molecules indicate good topographical polar surface area (TPSA) and moderate solubilities. Further molecular docking, dynamic modeling, and cell activity analysis is required for lead molecules validation.

Table 1 Targets prediction of small molecules inhibits IDO1 and APOE4

Alziheimer Target : IDO1	**Molecules by Bioactivity**									
Patent	**PubChem ID**	**Vendor**	**MW**	**TPSA**	**IC50 -nM**	**GI Absorption**	**BBB Permeant**	**Pgp Substrate**	**#RO5**	**Toxicity Class**
NA	163408937	PubChem	293.32	66.06	84	High	Yes	No	0	4
NA	148651756	NA	345.14	77.74	113	High	Yes	No	0	4
NA	118706945	ZINC	406.09	66.58	85	High	Yes	No	0	4
Alziheimer Target : APOE4	Molecules by Similarity									
Patent	PubChem ID	Vendor	MW	TPSA	xlogp	GI Absorption	BBB Permeant	Pgp Substrate	#RO5	Toxicity Class
NA	12458020	NA	284.3	66.9	2.5	High	Yes	No	0	3
NA	71296520	PubChem	294.4	58.1	2.9	High	Yes	No	0	3
NA	133277399	PubChem	252.33	58.1	2	High	Yes	No	0	3

2.4. An alternative method in oral NDA formulation development

According to the USFDA guidance[15], a pharmaceutical active dose (PAD) is recommended following MRSD (maximum recommended starting dose). Usually, the ADME simulation with PBPK model (Method 1) is employed to predict PAD for clinical study[16,17,18]. However, the prediction of PK parameters, e.g., Cmax and AUC usually deviate from clinical study. An alternative PAD estimation (Method 2) in Fig. 3 is proposed by using FDA approved drugs' PK database and PAMPA dissolution[19, 20]. The in-vitro predicted ADME parameters of NDA can be used to compare with FDA approved drugs' database. Therefore, a oral drug's plasma curve can be predicted together with PAMPA dissolution.

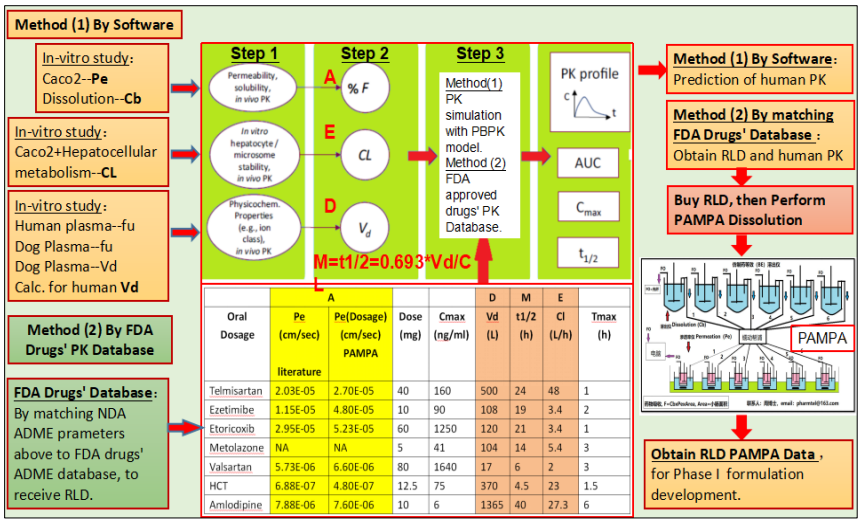

Figure 3 Prediction of clinical PK for oral NDA formulation

3. Conclusion

Alzheimer's disease (AD), a neurodegenerative disorder, is characterized by memory loss and damages in cognitive functions. An integrating system of biology and computational drug discovery was developed in this work. This built upon existing computational tools and databases to accelerate the pace of drug discovery for Alzheimer's disease. Drug target interaction offers an important AI prediction of molecules and their relationship to targets. With the help of various AI prediction tools, scientists can perform in-silico calculation in line with QSAR to find out the hit molecules. Further calculation of molecules in human GI absorption, Pgp substrate, CYP metabolism, BBB penetration, and toxicity, may result in lead compounds for oral formulation development. In this study, we have demonstrated using various AI tools and databases to find out effective molecules for AD targets both IDO1 and APOE4. In order to further develop these effective molecules into oral formulation, an alternative NDA method in oral NDA formulation development was proposed using FDA ADME database and PAMPA dissolution apparatus. Together, with the help of alternative oral NDA formulation design and AI prediction, the development of first in human formulation for clinical study can be performed.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors have declared no conflict of interests.

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