RESEARCH ARTICLE

Computational Analysis of BACE-1 Involved in Alzheimer's Disease Using Zebrafish (*Danio rerio*) as A Model

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ABSTRACT- Beta-site amyloid precursor protein cleaving enzyme (BACE-1) is a single-membrane protein belongs to the aspartyl protease class of catabolic enzymes. This enzyme involved in the processing of the amyloid precursor protein (APP). The cleavage of APP by BACE-1 is the rate-limiting step in the amyloid cascade leading to the production of two peptide fragments Ab40 and Ab42. Inhibition of BACE-1 was expected to stop the amyloid plaque formation and emerged as an interesting and attractive therapeutic target for Alzheimer's disease. The Zebrafish (*Danio rerio*) has been established as an excellent vertebrate model for the study of developmental biology and gene function. Zebrafish possess genes orthologous to those mutated in familial Alzheimer's disease and research using Zebrafish has revealed unique characteristics of these genes that have been difficult to observe in rodent models. We were identified and described the expression of BACE-1, the Zebrafish otology of human BACE-1. Computational approach was used to identify the molecular chemical features required for the inhibition of BACE-1 enzyme. Despite its potential, only few compounds targeting BACE-1 have entered the clinical trials. In this study, we were investigated that Cibacron Blue functioned as an inhibitor and was retrieved from the Pubchem database at NCBI. This paper also dealed with the binding mechanism of Cibacron Blue with BACE-1 through molecular docking coupled with molecular dynamics simulations. The computational analyses revealed that hydrophobic contact is a major contributing factor to the binding of Cibacron Blue with BACE-1.

Key-words- Amyloid precursor protein (APP), BACE-1, Molecular Docking, Zebrafish, Cibacron Blue

INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegerative disease [1]. AD is characterized by progressive memory loss and can include impairment of speech and motor ability, depression, delusions, hallucinations, aggressive behavior and, ultimately, increasing dependence upon others before death. BACE1 expression is tightly regulated at the level of transcription and translation [2]. It was reported that a G/C polymorphism in exon 5 of the BACE-1 gene might be associated with some sporadic cases of AD. Although genetic analyses from our and other laboratories have failed to uncover any mutation in the BACE-1 coding sequence or any disease associated SNP in its promoter region in AD patients,

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increased β-secretase levels and activity have been reported in AD [3]. BACE-1 levels were elevated in neurons around plaques. BACE-1 mRNA levels tended to increase as miR-107 levels decreased in the progression of AD [4]. We were reported that hypoxia, a common vascular component among AD risk factors, increased BACE-1 expression, resulting in both increased Aβ deposition and memory deficits in AD transgenic mice [5]. Recently we found that both NF-κB and BACE-1 levels were increased in sporadic AD patients, and NF-κB facilitated BACE-1 gene expression and APP processing. Thus, increased BACE-1 expression by NF-κB Pubchem database signaling in the brain could be one of the mechanisms underlying AD development [6]. Together these studies indicate that BACE-1 deregulation plays an important role in AD pathogenesis [7]. Zebrafish as a model for AD has been use and of the Zebrafish brain and a better characterization of the injury caused by alterations in the major neuro transmitter systems are needed [8,9]. Despite the progress in this field, we still need a better understanding of AD, which supports the growing importance of further innovative research using

experimental models of neuro-degeneration [10]. Alzheimer's disease is the major cause of senile dementia, flewing out 10% of 65 years old and 50% of 85 years old global population [11,12]. The major fisiopathologic characteristics of Alzheimer's disease are the deposition of extracellular neuritic plaques and the presence of intracellular neuro-fibrillary tangles in memory-related areas of the brain [13]. The plaques are composed by the β-amyloid peptide with 40 or 42 residues, result from hydrolysis of the amyloid precursor protein by the β-secretase 1 (BACE-1) on the amyloidogenic pathway, that begins with the BACE-1 and which inhibition is considered one of the most promising treatments available of Alzheimer's disease [14,15].

MATERIALS AND METHODS

Protein Sequence Retrieval- National Center for Biotechnology Information (www.ncbi.nih.nlm.gov/) database provides a protein sequence database for characterization and analysis of protein sequences. The BACE1 protein sequences of *Homo sapiens* and *Danio rerio* were retrieved from the protein database at NCBI. The sequences were further prepared, in FASTA format for the characterization.

Characterization of the BACE-1- The two sequences were subjected to PROTPARAM tool at EXPASY server for predicting the physicochemical parameters of both sequences. The physicochemical analysis was calculated by ProtParam tool (http://web.expasy.org/protparam/), including pI, total number of negatively and positively charged residues, the instability index (II), aliphatic index, and grand average of hydrophilic (GRAVY).

Secondary structure prediction- These secondary structures were predicated by SOPMA tool of BACE1 in human and Zebrafish. Secondary structure prediction was performed by using SOPMA [16] server (https://npsa-prabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_sopma.html). SOPMA is using homologue method of Levin *et al.* [17]. According to this method, short homologous sequences of amino acids tend to form a similar secondary structure.

Protein and ligand Preparation- The FASTA format protein sequence was subjected to SWISS Model server (http://swiss-model.expasy.org/) for predicting the templates for the BACE-1 sequence. The target template alignment and final 3D structure were predicted.

Molecular Docking studies- The predicted 3D structure was docked with the specific inhibitor retrieved from the Pubchem database and the binding energies and efficiency were studied using HEX software, it is a new version of HEX 8.2 server. It is offline and also online, but we have done offline.

RESULTS AND DISCUSSION

Protein Sequence Retrieval- Protein sequence of BACE1 was retrieved from the NCBI database, it was 501aa long in human and 505aa long in *Danio rerio*.

Characterization of the BACE1- The physicochemical analysis of both the protein was performed using Protparam and results were shown in Table 1. This protein had amino acids with molecular weight. Protparamtool computed that the Theoretical pi of protein nature and Instability index of the protein, which represents protein stability. The GRAVY, index protein the total number of positively charged residues and the total number of negatively charged residues.

Table 1: Physico-chemical analysis of both Human and *Danio rerio*

Number of amino acids	505	501
Molecular weight	55661.4	55823.8
Theoretical pI	6.19	5.31
Total number of negatively charged residues (Asp+Glu)	46	55
Total number of positively charged residues (Arg+Lys)	41	42
Total number of atoms	7743	7801
Instability index	48.35	43.85
Aliphatic index	86.32	88.14
GRAVY	-0.015	-0.056

Secondary structure prediction- The secondary structure of the protein was predicted using SOPMA server Table 2 and Table 3. It was observed that random coil, alpha helix, extended strand Random coils have important functions in proteins for flexibility and conformational changes such as enzymatic turnover as it is shown in the (Graph 1 and Graph 2).

Table 2: Secondary structure prediction

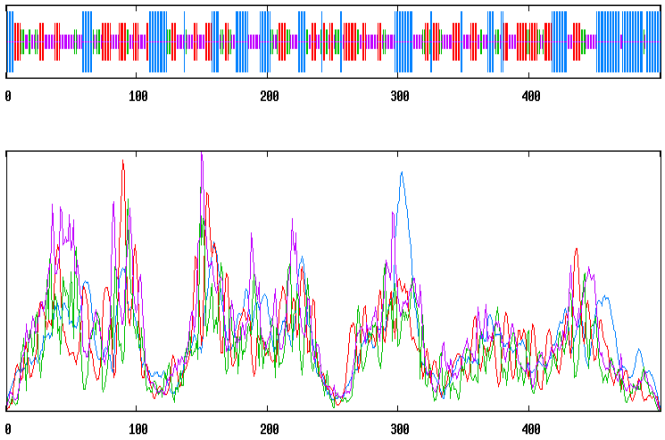
Alpha helix (Hh)	147	29.34%
3_{10} helix (Gg)	0	0.00%
Pi helix (Ii)	0	0.00%
Beta bridge (Bb)	0	0.00%
Extended strand (Ee)	125	24.95%
Beta turn (Tt)	62	12.38%
Bend region (Ss)	0	0.00%
Random coil (Cc)	167	33.33%

Table 3: Secondary structure prediction

Alpha helix (Hh)	133	26.34%
3_{10} helix (Gg)	0	0.00%
Pi helix (Ii)	0	0.00%
Beta bridge (Bb)	0	0.00%
Extended strand (Ee)	138	27.33%
Beta turn (Tt)	49	9.70%
Bend region (Ss)	0	0.00%
Random coil (Cc)	185	36.63%

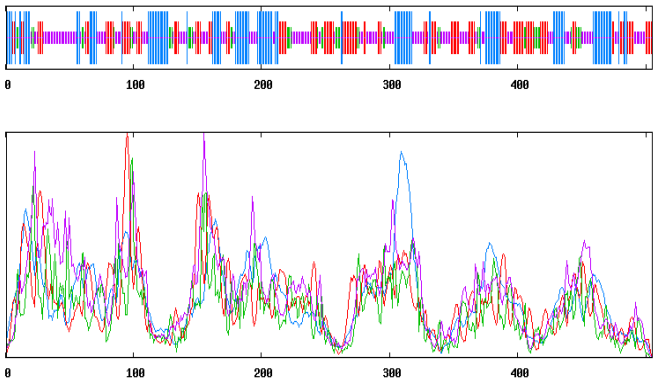
Secondary Structure Predication

1) The Secondary Structure Predication of *Homo sapiens*



Graph 1: Showing the number of Secondary structure of the protein

2) The Secondary Structure Predication of *Danio rerio*



Graph 2: Showing the number of Secondary structure of the protein

Protein and ligand Preparation- Protein and ligand were prepared by subject in the SWISS Model server for predicting the templates for the BACE1 sequence. The target template alignment and final 3D structure were predicted by Hex 8.6 version.

Molecular Docking studies- The predicate 3D structures were docked with Cibacron Blue compound and it show Binding Energy with respective to Homo sapiens in the "Fig. 1", "Fig. 2" and -352.5 with respective *Danio rerio* as shown in the "Fig. 3", "Fig. 4 ".

Docking Studies

Docking studies of *Homo sapiens*

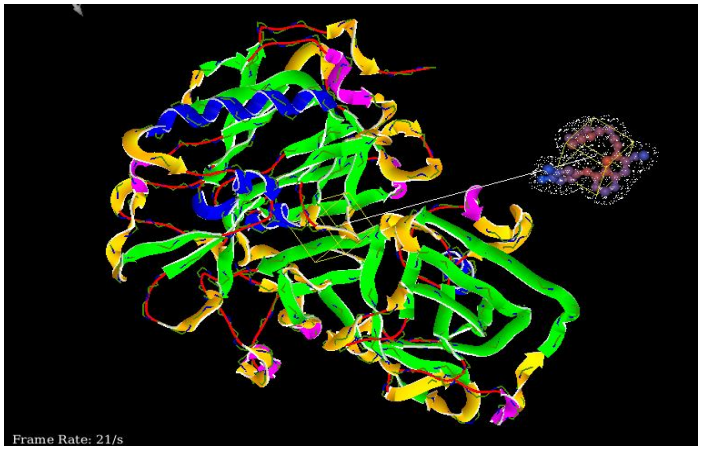


Fig. 1: Before docking

Fig. 2: After docking

Docking studies of *Danio rerio*

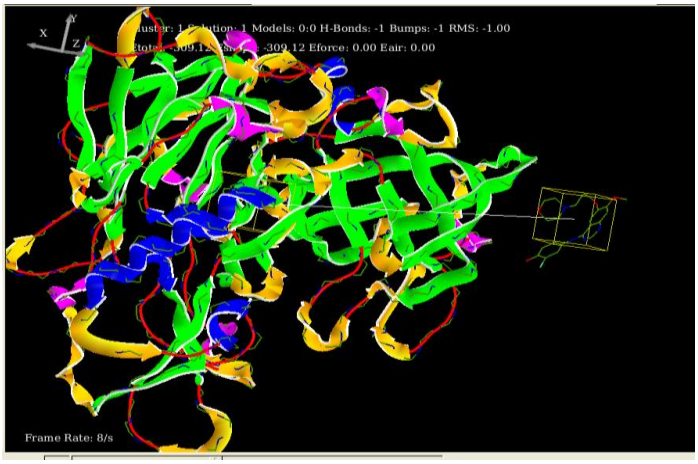


Fig. 3: Before docking

Fig. 4: After docking

CONCLUSIONS

The sequence annotation of the primary sequence of BACE-1 in *Homo sapiens* and *Danio rerio* was performed for further sequence analyses. According to this literature conserding BACE-1 as a target some drugs were screened againsed targate using Pubchem. Cibacron Blue shows a potential inhibitor againsed BACE-1 the docking analyzed revealed that hydrophobic contact is major contributing factor to the binding of Cibacron Blue with BACE-1. Hence, it was invested that Cibacron Blue functioned as an inhibitor for BACE-1.

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