Journal of Proteomics & Bioinformatics - Open Access

Research Article
OPEN ACCESS Freely available online
doi:10.4172/jpb.1000157
JPB/Vol.3 Issue 11

Structure Based Drug Designing for Diabetes Mellitus

K. Ramanathan[1]*, H. Karthick[2] and N. Arun[3]

[1]Department of Bioinformatics, Thanthai Hans Roever College,Perambalur, India
[2]Department of Bioinformatics, PRIST University, Thanjavur, India
[3]Department of Biochemistry, Thanthai Hans Roever College, Perambalur, India

Abstract

In recent years much work has been invested in to developing computer algorithms to facilitate research in the field of molecular biology. A large focus has been on structure based drug designing. In this work we address a specific suitable ligand for diabetes mellitus. We have been retrieved that the Gene and Protein which is responsible for diabetes mellitus and target binding site has been identified. The list of drugs are retrieved which are used to treat diabetes mellitus and the best drug ligand has been identified based on molecular docking. We also described that the hydrophobic activity of the ligand. Finally we have observed that the ligand acetohexamide has the highest hydrophobic activity when compared with other drugs. These findings suggest the possible involvement of systematic mechanism of drug designing process.

Keywords: Diabetes mellitus; Drug designing; Hydrophobic activity; Molecular docking

Introduction

Diabetes is a disease in which blood glucose levels are above normal. People with diabetes have problems converting food in to energy. It is also defined as chronic disorders of carbohydrate metabolism due to the lack of insulin result in the hyperglycemia and glycosuria. Drug design is the approach of finding drugs by design, based on their biological targets. Drugs may be defined that bind in to active region and inhibit this key molecule.

Diabetes mellitus

Type 1 diabetes is an autoimmune disease. An autoimmune disease results when the body's system for fighting infection turns against a part of the body. Type 2 diabetes is most often associated with older age, obesity, physical activity and certain ethnicities. In Pre-diabetes, blood glucose levels are higher than normal but not high enough to be characterized as diabetes. Pre-diabetes also increases the risk of heart disease and stroke with weight loss and physical activity. Diabetes mellitus is a complex, Multifactor and polygenic disease likely to be caused by one or more gene alterations action in combination with non-genetic factors (Hamilton et al., 2007).

Insulin is a hypoglycemic hormone and it is composed of two peptide chains referred to as chain A and chain B. These chains are linked together by two disulfide bonds. Insulin is a small protein with a molecular weight of about 6000 Daltons. It is synthesized in significant Quantities only in beta cells of the Pancreas.

Drug designing

Drug designing is the approach of finding drugs based on their targets and typically a drug target is a key molecule involved in a particular metabolism or signaling Pathway that is specific to a disease condition or Pathology or to be infectivity or survival of a microbial Pathogen. Some approaches attempt to stop the functioning of the pathway in the diseased state by causing a key molecule to stop functioning. However these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules (Ahmad et al., 2005).

Docking

Docking is a method which predicts the preferred orientation of one molecule to a record when bound to each other to form stable complex knowledge of the preferred orientations in turn may be used to predict the binding strength of association or binding affinity between two molecules. Docking is frequently used to predict the binding orientations of small molecules drug candidates to protein targets in order to in turn predict the affinity and activity of the small molecule. The receiving molecule that primarily binds to a small molecule or another protein or a nucleic acid called receptor. A molecule that forms the complementary partner in the docking process called ligand (Bharatam et al., 2007).

Ligand

Acetohexamide is the first generation sulfonylurea medication used to treat diabetes mellitus type 2, particularly in people whole diabetes cannot be controlled by diet alone. Acetohexamide lowers blood sugar by stimulating pancreas to secrete insulin and helps the body use insulin efficiently. The pancreas must produce insulin for this medication to work. It is an oral anti diabetic agent and is metabolized by the reductive conversion of the acetoxy group to a secondary alcohol metabolite. We tested whether reductase activity for acetohexamide can be found in human erythrocytes. Acetohexamide interact with other drugs such as alcohol, Beta blockers, cisapride, clofibrate, rifampin etc. If we missed to take dose, skip the missed dose and take only the next regularly scheduled dose. If acetoheaxamide will be a overdose it cause symptoms include hunger, nausea, anxiety, cold sweats, weakness, drowsiness and coma.

Methods

The Protein sequence which is responsible for diabetes mellitus retrieved from NCBI. This IRAK protein has 712 amino acids and 3 hits in the sequence. Then the lists of drugs for diabetes mellitus are retrieved from drug bank and analyzed the hydrophobic activity for

***Corresponding author:** K.Ramanathan, Department of Bioinformatics, Thanthai Hans Roever College,Perambalur, India, E-mail: ramanathanbio@gmail.com

Received September 16, 2010; **Accepted** November 24, 2010; **Published** November 26, 2010

Citation: Ramanathan K, Karthick H, Arun N (2010) Structure Based Drug Designing for Diabetes Mellitus. J Proteomics Bioinform 3: 310-313. doi:10.4172/jpb.1000157

each drugs. Hydrophobic activity is calculated by ALOGPS tool. The distribution of the Log P and Log S values for each drugs shows the highest hydrophobic activity of the drug. The structure of the protein retrieved from Protein data bank and binding sites of the receptor was calculated by PROSITE tool. The structure of the acetohexamide was taken from drug bank and both the structures were docked by Hex 5.1tool.Finally all the results are compared and discussed.

Results and Discussion

Result for each drug

Acetohexamide:

- mol_N logP logS SMILES
- mol_1 1.72 -3.83 CC(=O)c1ccc(cc1)S(=O)(=O)NC(=O)NC2CCCCC2

Metformin:

- mol_N logP logS SMILES
- mol_1 -1.41 -1.76 CN(C)C(=N)N=C(N)N

Phenformin:

- mol_N logP logS SMILES
- mol_1 0.30 -3.02 c1ccc(cc1)CCN=C(N)N=C(N)N

Miglitol:

- mol_N logP logS SMILES
- mol_1 -2.29 0.47 C1C(C(C(C(N1CCO)CO)O)O)O

Tolazamide:

- mol_N logP logS SMILES
- mol_1 1.40 -3.01 Cc1ccc(cc1)S(=O)(=O)NC(=O)NN2CCCCCC2

Gliclazide:

- mol_N logP logS SMILES
- mol_1 1.52 -3.23 Cc1ccc(cc1)S(=O)(=O)NC(=O)NN2CC3CCCC3C2

Voglibose:

- mol_N logP logS SMILES
- mol_1 -2.33 -0.15 C1C(C(C(C(C1(CO)O)O)O)O)NC(CO)CO

DRUG NAME	DRUG ID	Log P	Log S
ACETOHEXAMIDE	DB00414	1.72	-3.83
METFORMIN	DB00331	-1.41	-1.76
PHENFORMIN	DB00914	0.3	-3.02
MIGLITOL	DB00491	-2.29	0.47
TOLAZAMIDE	DB00839	1.4	-3.01
GLICLAZIDE	DB01120	1.52	-3.23
VOGLIBOSE	DB04878	-2.33	-0.15

Table 1:

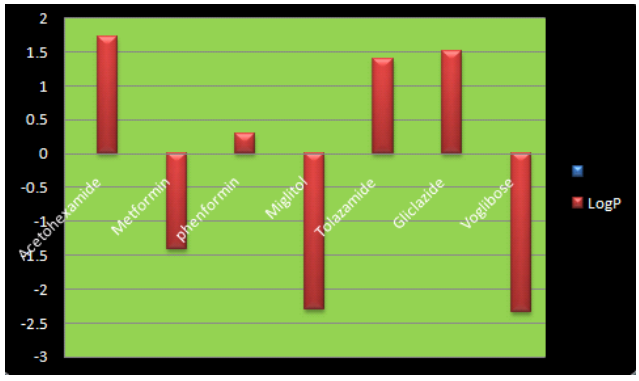

Figure 1: Log P values for all drugs.

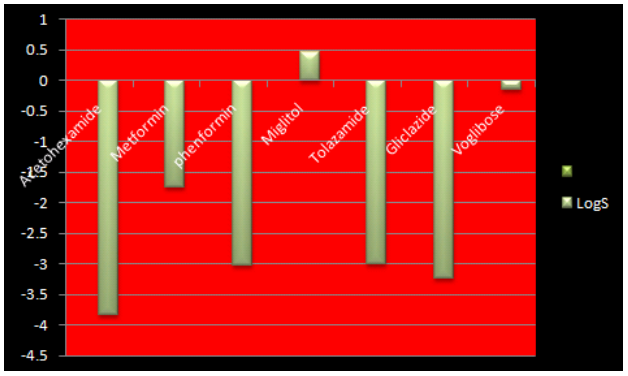

Figure 2: Log S values for all drugs.

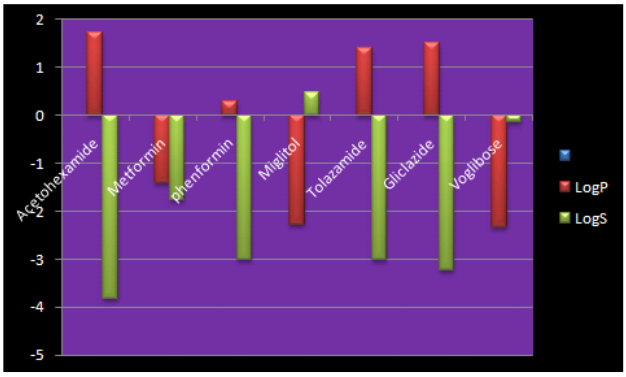

Figure 3: Log P and Log S values for all drugs.

These drugs are treated for diabetes mellitus and the smile value for each drugs are retrieved from drug bank and submitted in to ALOGPS 2.1 tool. This tool provides the result with Log P and Log S values for each drug.

In Table 1, we compared Log P and Log S values for each drug. The drug Acetohexamide has the highest Log P value (1.72) when compared with other drugs and it has log S value (-3.83).So, the hydrophobic activity of the Acetohexamide is higher. The drug Metformin has very low Log P value (-1.41) and Log S values (-1.76). The very low content of hydrophobic effect is present in Phenformin (0.3) but it has negative Log S value (-3.02).

The Log P value is negative in Miglitol (-2.29) and Log S value has (0.47).This shows that hydrophobic activity is very less. The Log P value (1.4) and Log S value (-3.01) for Tolazamide shows that the activity of the drug is very less. The hydrophobic activity of the drug Gliclazide is higher due to Log P value (1.52) and it has Log S value (-3.23).The drug Voglibose has Log P value (-2.33) and it has Log S value (-0.15).

Figure 1 shows that the comparison of Log P values for each drug. From this graph, we can easily understand, the drugs Acetohexamide,Phenformin, Tolazamide and Gliclazide has Positive Log P values and Metformin,Tolazamide and Voglibose has Negative Log P Values Acetohexamide has highest Log P value (1.72) when compared with rest of the drugs.

Figure 2 From this graph, we can analysed the Log S values for the drugs involved in our analysis.Acetohexamide has very low Log S

Research Article
OPEN ACCESS Freely available online
doi:10.4172/jpb.1000157
JPB/Vol.3 Issue 11

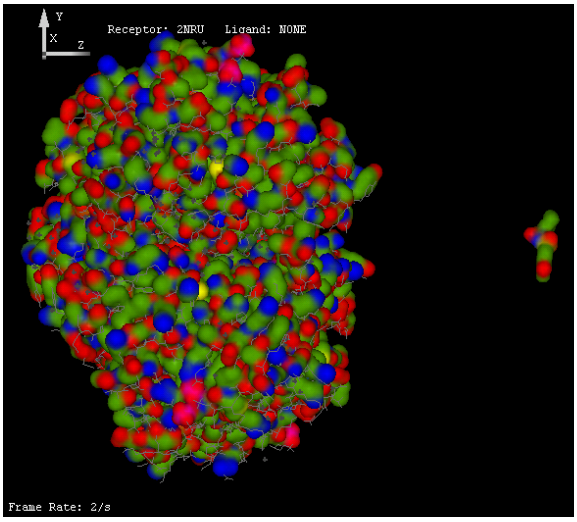

Figure 4: Screen Shot of Receptor and Ligand before Docking.

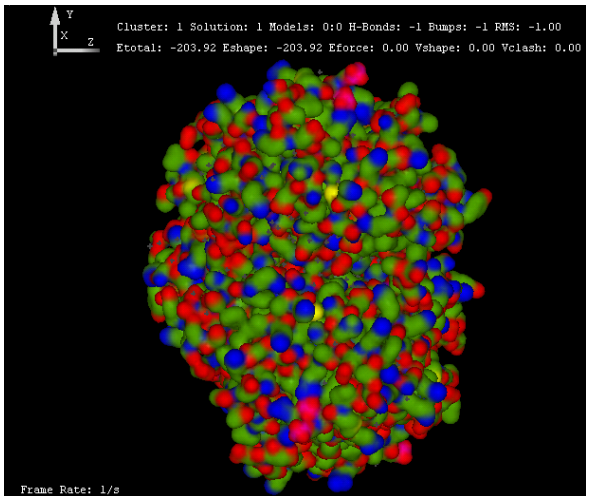

Figure 5: Screen Shot of Receptor and Ligand after Docking.

value (-3.83) but it has good hydrophobic effect.Miglitol is the only drug which has positive Log S value (0.47) and the rest of the drugs are negative Log s values.

From this Figure 3 we can understand the comparison of Log P and Log S values for each drugs. The red colour shows that the Log P values and the Green colour shows that the Log S values for the drugs Acetohexamide, Metformin Phenformin, Miglitol, Tolazamide, Gliclazide and Voglibose respectively.

Figure 4 shows that both the receptor IRAK protein and the Ligand Acetohexamide ready to bind with each other.

Figure 5 shows that the Ligand Acetohexamide binds with the receptor IRAK Protein through Hex 5.1 tool. The docked Eforce and Etotal values are displayed in this screen.

From this Figure 6, we can easily understand the docked position of the receptor and Ligand. The Green colour shows that the IRAK Protein and the Red colour shows that the Ligand Acetohexamide.

Figure 7 shows that the Atoms and Bonds that are present in the drug Acetohexamide. Here Hydrogen Bond plays a major role between receptor and Ligand. The contribution of carbon, Nitrogen and Oxygen atom is higher in Acetohexamide.

Prosite result analysis

The Protein IRAK is responsible for diabetes mellitus and the sequence can be retrieved from NCBI and identifies the binding Site using PROSITE tool. This result from Table 2 shows that 3 hits present in the Protein including 2 patterns and 1 profile. It also shows that the positions of the binding sites present in the IRAK Protein (212-521,218-239,336-348).The position 218 and 226 is for NP_BIND and the proton acceptor site is present in the position 340.The ligand Acetohexamide binds in this position.

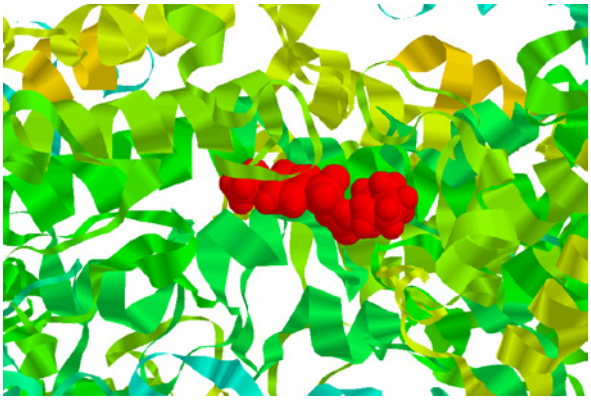

Figure 6: Screen Shot of Receptor and Ligand by Docking.

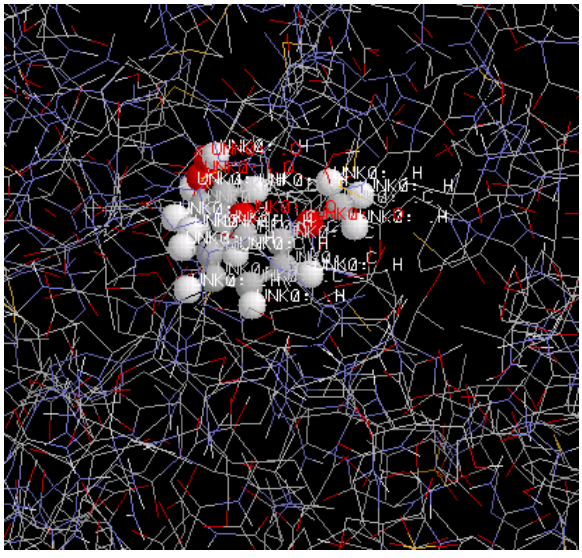

Figure 7: Screen Shot of Labeling the Ligand.

HITS in IRAK Protein	3
Position of HITS in Protein	212-521,218-239,336-348
NP_BIND	218,226(ATP by similarity)
BINDING	239 (ATP by similarity)
ACT_SITE	340 Proton acceptor(By similarity)
Patterns	2
Profiles	1
Protein kinase domain Distinct Patterns	PS50011
Protein kinase ATP Binding region	PS00107
Serine/Threonine kinase active site region	PS00108

Table 2:

Conclusion

In this article, we have observed results that the drug acetohexamide has good hydrophobic effect based on Log P value and the IRAK Protein has 3 active sites. The docked results were identified by molecular docking method. The list of drugs are collected from drug bank which are used to treat Diabetes mellitus and identified the best drug based on hydrophobic activity. Finally, we concluded that the ligand acetohexamide has the highest hydrophobic activity.

References

1. Ahmad FK, He Z, King GL (2005) Molecular targets of diabetic cardiovascular complications. Curr Drug Targets. 6: 487-494.
2. Bharatam PV, Patel DS, Adane L, Mittal A, Sundriyal S (2007) Modeling and informatics in designing anti-diabetic agents. Curr Pharm Des 13: 3518-3530.
3. Bagust A, Beale S (2005) Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Econ 14: 217-30.
4. Coyle D, Lee KM, O'Brien BJ (2002) The role of models within economic analysis: focus on type 2 diabetes mellitus. Pharmacoeconomics. 20: 11-9.
5. Del Prato S (2002) In search of normoglycaemia in diabetes: controlling postprandial glucose. Int J Obes Relat Metab Disord 3: S9-17.
6. Feinglos MN, Bethel MA (1998) Treatment of type 2 diabetes mellitus. Med Clin North Am 82: 757-790.
7. Greenbaum CJ (2002) Insulin resistance in type 1 diabetes. Diabetes Metab Res Rev 18: 192-200.
8. Hamilton SJ, Chew GT, Watts GF (2007) Therapeutic regulation of endothelial dysfunction in type diabetes mellitus. Diab Vasc Dis Res. 4: 89-1022.
9. Hui H, Zhao X, Perfetti R (2005) Structure and function studies of glucagon-like peptide-1 (GLP-1): the designing of a novel pharmacological agent for the treatment of diabetes. Diabetes Metab Res Rev 21: 313-331.
10. McCrimmon RJ, Frier BM (1994) Hypoglycaemia, the most feared complication of insulin therapy. Diabete Metab 20: 503-512.
11. Morishit M, Goto T, Nakamura K, Lowman AM, Takayama K, et al. (2006) Novel oral insulin delivery systems based on complexation polymer hydrogels: single and multiple administration studies in type 1 and 2 diabetic rats. J Control Release 110: 587-594.
12. Mende CW (2006) Improving antihypertensive therapy in patients with diabetic nephropathy. South Med J 99: 150-167.
13. Soria B, Andreu E, Berná G, Fuentes E, Gil A, et al. (2000) Engineering pancreatic islets. Pflugers Arch 440: 1-18.
14. Wong FS, Wen L (2003) The study of HLA class II and autoimmune diabetes. Curr Mol Med 3: 1-15.
15. Zhang J, Li C, Chen K, Zhu W, Shen X, et al. (2006) Conformational transition pathway in the allosteric process of human glucokinase. Proc Natl Acad Sci USA 103: 13368-13373.