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Pranlukast; An Alternative Potential Leptin Stimulator: Structure-Based Virtual Screening Study

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Abstract

Background: Leptin is secreted by adipocytes, transported into the brain and binds to its receptor in the hypothalamus, and activates JAK-STAT3, leading to increase in "anorexigenic peptides" which normally inhibit food consumption and reduce weight.

Objectives: In the current study, a hybrid approach of molecular docking and virtual screening was performed, for the identification of active alternative compounds to manage obesity disorders.

Methods: Screening was performed using structure-based drug design against approved FDA drugs; molecular modeling was done using AutoDockVina; only top 10 conformers' ligands with highest and best scores were selected. In order to increase the likelihood of successful docking, in silico Virtual Screening (VS) of selected compounds were filtered according to their molecular weight and partition coefficient; a molecular weight of less than 500 and a partitioning coefficient (log P) of less than 5 filtering is applied.

Result: Here, we report the screening of four compounds that have showed maximum binding affinity against Leptin receptor, obtained through the ZINC database. A VS approach coupled with docking energies illustrated that Pranlukast could be potential stimulator compounds for targeting Leptin receptor.

Conclusion: We proposed that Pranlukast may be more potent Leptin receptor stimulator analogue based on the binding energy values.

Further work can be extended to study the receptor ligand interactions experimentally and evaluation of their biological activity would help in designing novel therapeutic lead for the management of obesity disorders.

Keywords: Pranlukast; Molecular docking; Leptin; Virtual screening

Introduction

The conclusion of the human genome project has given rise to an increase in number of novel therapeutic targets for drug discovery. At the same time, high-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been advanced and contributed to many structural details of proteins and protein–ligand complexes. These progresses let the computational strategies to permeate all aspects of drug discovery nowadays [1-5], such as the VS techniques [6] for hit identification and approaches for lead optimization.

Compared with outdated experimental High-Throughput Screening (HTS), virtual screening is a straighter and rational drug discovery approach and has the benefit of low cost and effective screening [7-9].

The World Health Organization (WHO) and the National Institutes of Health (NIH) [10,11] have defined overweight as having a Body Mass Index (BMI) between 25.0-29.9 kg/m^2; and obesity as having a BMI greater than 30.0 kg/m^2. Whereas the BMI is defined as the weight in kilograms divided by the height in meters squared (kg/m^2), is the most commonly used measure of obesity due to its low cost and easiness.

Obesity is associated with an enlarged threat of death; the risk of death is increased by 20% to 40% in overweight patients and by 2- to 3-fold in obese compared with normal-weight patients [12].

Obesity is also associated with increased risk of many chronic diseases such as diabetes, hypertension, heart disease, and stroke [13].

Leptin is secreted by adiposities, and act on the brain to hinder food consumption and reduce weight [14,15], and when injected directly into the cerebral ventricle or hypothalamus, intensely inhibited food consumption and decreased weight and fat in animals lacking Leptin [14,16,17].

In rodents, studies have established that Leptin is transported into the brain, binds to its receptor in the hypothalamus, and activates JAK-STAT3, leading to suppression of "orexigenic peptides" and increase in "anorexigenic peptides" which normally decrease food intake [16].

Leptin levels fall rapidly in response to fasting and induce profound changes in energy balance and hormone levels [15,17]; Low Leptin levels induce overfeeding and suppress energy expenditure, thyroid and reproductive hormones, and immunity [15,18,19].

Pranlukast is the first leukotriene receptor antagonist on the marketplace and is available in Japan for the management of asthma. It has been revealed to block bronchoconstriction induced by leukotriene D4 (LTD4) and antigen [20,21].

Obesity has received considerable attention as a major health hazard. In the present study, a hybrid approach of molecular docking and virtual screening were performed, for the identification of active alternative compounds for the management of obesity.

Materials and Methods

Ligands preparation and optimization

Ligands for the study (FDA approved drugs) were collected from ZINC database [22] in SDF format, the duplicate were removed and converted to PDBQT format using Open babel [23].

Protein preparation and optimization

The crystallographic structure of Leptin Receptor-antibody complex was retrieved from protein data bank with a resolution ([Å]: 1.95, R-Value: 0.171) [24].

Interactive visualization and analysis of molecular structures were done using UCSF Chimera [25] for better understanding of active site.

Geometry optimization and pre-docking procedure

In order to prepare the selected compounds for docking, hydrogens and Gasteiger charges were added [26] and all the hetero-atoms and water molecules were removed from protein structure.

The protonated protein initially optimized in order to remove all the bad steric clashes using UCSF Chimera software for 100 steepest descent steps at root-mean-square gradient of 0.02 with an update interval of 10 and using AMBER ff12SB force field [27] force field, while Ligands where minimized for 200 steepest descent steps at root-mean-square gradient of 0.02 with an update interval of 1 and using MMFF94 force field [28] using Open babel.

Docking strategy and setup

All computational docking studies were carried out using AutoDockVina (Scripps Research Institute, La Jolla, CA, USA) installed in a single machine running on MSI (Core-i7-6700HQ processor, 12 GBs of DDR4 RAM, NvidiaGeforce GTX 960 m Graphic Card, 1 TBs HDD Memory) with Windows as an operating system.

Docking studies were performed for each ligand (other parameters were kept default) as follows:

The unnecessary chain was deleted; N-Acetyl-D-Glucosamine, Cysteine, Ethylene Glycol, Acetate Ion and Sodium Ion of co-crystallization were deleted.

The docking was done with the default settings as follow:

10 conformers of the ligand were retained with highest and best score by default.

A grid box centered covering the Leptin receptor with a dimensions (Angstrom) of (X: 74.95 Y: 74.97 Z: 66.58).

The scoring configuration of the ligand–Target complexes was selected on energetic grounds (kcal/mol); best poses with the lowest binding energy was chosen for each compound.

The docking scores and docking binding energy of selected ligands were then presented.

Results and Discussion

Obesity comes increasing risks of cardiovascular disease (mainly heart disease and stroke)-world's number one cause of death, killing 17 million people each year, diabetes (Type-2) which has rapidly become a global epidemic, musculoskeletal disorders-especially osteoarthritis, some cancers (endometrial, breast, and colon) (84).

Our goal is to find a lead compounds that may possess anti-obesity activities to target Leptin receptor using Molecular docking which enables a scientist to virtually screen a number of candidate compounds based on their binding ability and binding orientation with a target molecule of known three-dimensional structure. It also allows one to select compounds with strong affinity for the target site.

In the current investigation; to elucidate alternative stimulatory compounds against human Leptin receptor, a total of 1428 approved FDA drugs were screened and analyzed for their stimulatory action against human Leptin receptor.

In order to increase the likelihood of successful docking, in silico VS of selected compounds were filtered according to their molecular weight and partition coefficient.

A molecular weight of less than 500 and a partitioning coefficient (logP) of less than 5 filtering is applied to increase likelihood of oral absorption [29].

In the current study, top 10 selected compounds that have shown stronger binding at the receptor's binding site in experiments have shown high binding energy in range between (-10.1 to -9.2 kcal/mol) when analyzed using AutoDockVina.

Although much of the research effort has been devoted to the satiety and weight-reducing actions of Leptin in the hypothalamus, the increasing recognition of obesity as an inflammatory disease has made researchers to explore the effects of leptin on immune systems [30].

Leptin increases interleukin-2 secretion and proliferation of naive T cells. According to this view, Leptin might represent an important target for immune intervention in a variety of immune pathophysiological conditions [31].

Obesity is often associated with elevated inflammatory conditions reflected in the general increase of blood cytokines and inflammatory markers. Interestingly, the immunological response (such as the T cells function) in the ob/ob mice or congenital Leptin-deficient humans is also severely suppressed despite the excessive fat stores [18,32].

Das UN stated that, obesity may be a low-grade systemic inflammatory disease. Overweight and obese children and adults have elevated serum levels of C-reactive protein, interleukin-6, tumor necrosis factor- alpha, and Leptin, which are known markers of inflammation [33].

These studies may explain that, Pranlukast a leukotriene receptor antagonist could be possible anti-obesity drug.

Biswajit Satapathy in 2004 analyzed the protein Leptin, to establish its relation in obesity [34].

Their results showed that Fluoxetine Hydrochloride is more potent Leptin receptor stimulator analogs based on their binding energy values.

When using Autodock-Vina Fluoxetine Hydrochloride and Pranlukast showed binding energy values (-7 and -9.4 kcal/mol respectively), which indicate that Pranlukast could have more stability on binding with Leptin receptor (Table 1) (Figure 1).

Ligand name	Binding energy (kcal/mol)
Digitoxin	-10.1
Saquinavir	-9.6
Dihydroergotamine	-9.6
Lomitapide	-9.5
Gliquidone	-9.5
Pranlukast	-9.4
Suramin	-9.3
Nilotinib	-9.3
Natamycin	-9.3
Itraconazole	-9.2

Table 1: The docking binding energy of selected compound (ranked by the kcal/mol).

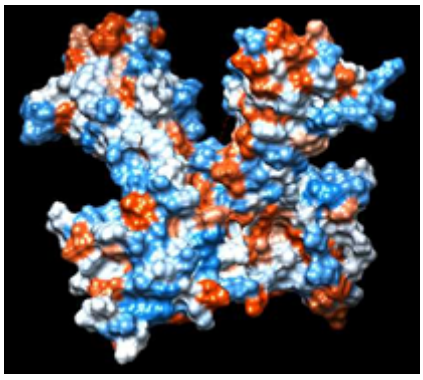

Figure 1: Molecular surface representation of Leptin receptor.

Conclusion

This study stresses the importance of small molecule libraries and their use to enhance drug discovery process prior synthesis.

The above observations show that the Pranlukast is strongly bound to the Leptin receptor active site; therefore, molecular docking experiments will guide to biologically confirm these results.

Further, work can be extended to study the receptor ligand interactions experimentally and evaluation of their biological activity would help in designing compounds based on virtual screening techniques.

In conclusion, this analysis suggests that the Pranlukast could be efficacious in the treatment of obesity disorders.

References

1. Jorgensen WL (2004) The Many Roles of Computation in Drug Discovery. Science 303: 1813-1818.
2. Bajorath J (2002) Integration of virtual and high-throughput screening. Nature Reviews Drug Discovery 1: 882-894.
3. Langer T, Hoffmann RD (2001) Virtual Screening An Effective Tool for Lead Structure Discovery. Current Pharmaceutical Design 7: 509-527.
4. Walters WP, Stahl MT, Murcko MA (1998) Virtual screening- an overview. Drug Discovery Today 3: 160-178.
5. Kitchen DB, Decornez H, Furr JR, Bajorath J (2004) Docking And Scoring In Virtual Screening For Drug Discovery: Methods And Applications. Nature Reviews Drug Discovery 3: 935-949.
6. Gohlke H, Klebe G (2002) Approaches to the Description and Prediction of the Binding Affinity of Small-Molecule Ligands to Macromolecular Receptors. Angewandte Chemie International Edition 41: 2644-2676.
7. Moitessier N, Englebienne P, Lee D, Lawandi J, Corbeil CR (2008) Towards the development of universal, fast and highly accurate docking/scoring methods: a long way to go. British Journal of Pharmacology 153: 7-26.
8. Shoichet BK, McGovern SL, Wei B, Irwin JJ (2002) Hits, leads and artifacts from virtual and high throughput screening. Molecular Informatics: Confronting Complexity.
9. Bailey D, Brown D (2001) High-throughput chemistry and structure-based design: survival of the smartest. Elsevier Current Trends.
10. Organization. WHO Obesity.
11. Stevens J (2008) Population-Based Prevention of Obesity: The Need for Comprehensive Promotion of Healthful Eating, Physical Activity, and Energy Balance: A Scientific Statement from American Heart Association Council on Epidemiology and Prevention, Interdisciplinary Committee for Prevention (Formerly the Expert Panel on Population and Prevention Science). Ed American Heart Association. EU.
12. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, et al. (2006) Overweight, Obesity, and Mortality in a Large Prospective Cohort of Persons 50 To 71 Years Old. New England Journal of Medicine 355: 763-778.
13. Field AE, Coakley EH, Must A, Spadano JL, Laird N, et al. (2001) Impact of Overweight on the Risk of Developing Common Chronic Diseases During a 10-Year Period. Archives of Internal Medicine 161: 1581-1586.
14. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, et al. (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372: 425-432.
15. Ahima RS, Prabakaran D, Mantzoros C, Qu D (1996) Role of Leptin in the Neuroendocrine Response to Fasting. Nature 382: 250.
16. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW (2006) Central nervous system control of food intake and body weight. Nature 443: 289-295.
17. Flier JS (1998) What's in a Name? In Search of Leptin's Physiologic Role1. The Journal of Clinical Endocrinology & Metabolism 83: 1407-1413.
18. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, et al. (2002) Beneficial effects of Leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital Leptin deficiency. The Journal of Clinical Investigation 110: 1093-1103.
19. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, et al. (2004) Recombinant Human Leptin in Women with Hypothalamic Amenorrhea. New England Journal of Medicine 351: 987-997.
20. Yamaguchi T, Kohrogi H, Honda I, Kawano O, Sugimoto M, et al. (1992) A Novel Leukotriene Antagonist, ONO-1078, Inhibits and Reverses

Human Bronchial Contraction Induced by Leukotrienes C4 and D4 and Antigen In Vitro. American Review of Respiratory Disease 146: 923-923.

21. Taniguchi Y, Tamura G, Honma M, Aizawa T, Maruyama N, et al. (1993) The effect of an oral leukotriene antagonist, ONO-1078, on allergen-induced immediate bronchoconstriction in asthmatic subjects. Journal of Allergy and Clinical Immunology 92: 507-512.
22. Irwin JJ, Shoichet BK (2005) ZINC- A Free Database of Commercially Available Compounds for Virtual Screening. Journal of Chemical Information and Modeling 45: 177-182.
23. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T (2011) Open Babel: An open chemical toolbox. Journal of Chem Informatics 3: 1.
24. Carpenter B, Hemsworth GR, Wu Z, Maamra M, Strasburger CJ, et al. (2012) Structure of the Human Obesity Receptor Leptin-Binding Domain Reveals the Mechanism of Leptin Antagonism by a Monoclonal Antibody. Structure 20: 487-497.
25. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, et al. (2004) UCSF Chimera- A visualization system for exploratory research and analysis. Journal of Computational Chemistry 25: 1605-1612.
26. Gasteiger J, Marsili M (1978) A new model for calculating atomic charges in molecules. Tetrahedron Letters 19: 3181-3184.
27. Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz KM, et al. (1995) A Second Generation Force Field for the Simulation of Proteins, Nucleic Acids, and Organic Molecules. Journal of the American Chemical Society 117: 5179-5197.
28. Halgren TA (1996) Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. Journal of Computational Chemistry 17: 490-519.
29. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2012) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews 64: 4-17.
30. Otero M, Lago RO, Lago F, Casanueva FF, Dieguez C, et al. (2005) Leptin, from fat to inflammation: old questions and new insights. FEBS Letters 579: 295-301.
31. Haakansson ML, Meister B (1998) Transcription Factor STAT3 in Leptin Target Neurons of the Rat Hypothalamus. Neuroendocrinology 68: 420-427.
32. Howard JK, Lord GM, Matarese G, Vendetti S, Ghatei MA (1999) Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. The Journal of Clinical Investigation 104: 1051-1059.
33. Das U (2001) Is obesity an inflammatory condition? Nutrition 17: 953-966.
34. Satapathy B, Panda PK, Mishra S, Pritam P (2014) Targeting of Leptin Protein to Treat the Complications in Obesity, An Insilico Drug Designning. Helix 3: 551-554.