Cure for Primary Dopaminergic Midbrain Neurons by GPR139 Agonists using Structure based Virtual Screening and Molecular Dynamics Simulation

[1,2]Aman Chandra Kaushik, [1]Deeksha Gautam, [1]Shakti Sahi

[1]School of Biotechnology, Gautam Buddha University, Greater Noida, Uttar Pradesh, India

[2]The Shraga Segal Dept. of Microbiology, Immunology and Genetics, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Email: amanbioinfo@gmail.com

Abstract

In various organisms, GPCR's are the mostly known cell surface receptors playing vital role among many interacting molecule during signal transduction and metabolic pathways. These are the super largest family which delivers signals from extracellular space to intracellular environment. GPCR'S having structural characteristics in terms of possessing seven transmembrane helices with distinct length of intra and extracellular loops. At both the loops varying terminal are found which usually distinguish the ligand role during the signal transduction pathways. GPCR's are involved in all regulating activities whether immune related or at physiological level in an organism. Through the human genome sequence project it has been reported that around 800 GPCR's sequence exists in human. These GPCR's found most effective physiological role in all peripheral organs and as well as in central nervous system. These also act as a multiple disease target. GPCR's mediate signals from the extracellular environment and then respond toward it to result in effective cellular response. Various ligands (outside signals) such as smaller interacting molecules, peptides (opoids, angiotensins, bradykinins, omatostatin, melanocortin), fatty acids, nitrogeneous substances, photons, proteins, amino acids, carbohydrates, ions and energy variable molecules harbour GPCR's. And then these ligands acknowledge endogeneous signals from the outer space of the cell. Due to the presence of different GPCR's it is not easy to identify the concerned natural ligand of it. So for further understanding of GPCR's, particular identification of endogeneous ligands is done. After knowing the ligand the particular GPCR is being drug targeted for the treatment of disease as they are 40-50% drug effective. GPCR share a common structural feature i.e. the presence of seven membrane spanning helices sharing three each intracellular and extracellular loops with an

intracellular carboxyl terminal and an extracellular amino terminal. Various differences in structure of GPCR can occur during the ligand binding, G protein coupling and interaction with other proteins. In Rhodopsin class of GPCR the basic structure of GPCR is verified by X-ray crystallography. Ligands acts as an extracellular stimulus for GPCR's and then brings physiological changes in organisms. GPR139 found most effective physiological role in all peripheral organs and as well as in central nervous system. In this study GPR139 targeted by virtually screened compounds which inhibit the Dopaminergic Midbrain Neurons. Molecular Dynamics simulation was performed for complex structure of GPR139 to validate binding affinity of compounds, and investigate active site fluctuation of complex structure.

Acknowledgements

We thank School of Biotechnology, Gautam Buddha University, Greater Noida, India.

References

1. L. A. Hu, P. M. Tang, N. K. Eslahi, T. Zhou, J. Barbosa, & Q. Liu. (2009). Identification of surrogate agonists and antagonists for orphan G-protein-coupled receptor GPR139, Journal of biomolecular screening.
2. A. Matsuo, S. I. Matsumoto, M. Nagano, K. H. Masumoto, J. Takasaki, M. Matsumoto, & Y. Shigeyoshi. (2005). Molecular cloning and characterization of a novel Gq-coupled orphan receptor GPRg1 exclusively expressed in the central nervous system, Biochemical and biophysical research communications, 331(1), 363-369.
3. D. E. Gloriam, H. B. Schiöth, & R. Fredriksson. (2005). Nine new human Rhodopsin family G-protein coupled receptors: identification, sequence characterisation and evolutionary relationship, Biochimica et Biophysica Acta (BBA)-General Subjects, 1722(3), 235-246.
4. D. K. Vassilatis, J. G. Hohmann, H. Li. F. Zeng, J. E. Ranchalis,, M. T. Mortrud, & G. A. Gaitanaris. (2003). The G protein-coupled receptor repertoires of human and mouse, Proceedings of the National Academy of Sciences, 100(8), 4903-4908.

5. S. Takeda, S. Kadowaki, T. Haga, H. Takaesu, & S. Mitaku. (2002). Identification of G protein-coupled receptor genes from the human genome sequence, FEBS letters, 520(1), 97-101.
6. U. Susens, I. Hermans-Borgmeyer, J. Urny, & H. C. Schaller. (2006). Characterisation and differential expression of two very closely related G-protein-coupled receptors, GPR139 and GPR142, in mouse tissue and during mouse development, Neuropharmacology, 50(4), 512-520.