IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2018; 7(2): 66-70 Demirel G.

Interaction Networks Of *GRM4* and Addiction-Related Genes

Goksun Demirel*

*Department of Pharmaceutical Toxicology, Faculty of Pharmacy Biruni Univesity

Abstract

Drug addiction is defined as a psychiatric disorder resulting in loss of control in substance consumption, despite all serious negative consequences. Addictive substances show effects by targeting the reward pathways of the brain, such as the nucleus accumbens, the ventral tegmental area ,the prefrontal cortex, and the hippocampus. Drugs of abuse can cause long-term adaptations in neuronal plasticity regulated by permanent changes in gene expression. Recent studies demonstrate that epigenetic regulation of gene expression plays an important role in neurogenesis, synaptic plasticity, and neurological disorders. MicroRNAs (miRNAs) are a class of 18-25 nucleotide non-coding sequences that are transcriptionally regulating gene expression. A miRNA is capable of modulating the expression of hundreds of genes by degrading mRNAs either by translational suppression or complement sequences in 3 'UTR.

Our bioinformatics studies have demonstrated that among the putative targets of mir-1202, *GRM4*. The *GRM4* gene is expressed in the brain and is involved in the process of glutamatergic, dopaminergic, GABAergic and serotonergic nerve conduction. *GRM4* gene and protein expression also have been previously reported to be associated with major depression in brain activity and association. In this study we used bioinformatics tools to screen for miRNAs related in drug addiction related regulatory genes network using STRING (http://string-db.org/) version 10,5. This study is important that potential common target genes of addiction related *GRM4* gene and help understand the underlying molecular pathways of addiction in association with those common target genes.

Keywords: *GRM4* gene, target genes, bioinformatic approaches

* Corresponding Author: Goksun Demirel. Biruni University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, 10. Yıl Caddesi Protokol Yolu No: 45, 34010, Istanbul, Turkey, Tel: +90- 212-4448276-1268, Fax: +90-212-4164646 e-mail: gdemirel@biruni.edu.tr

Introduction

Though levels of expression in genes related to glutamatergic system different brain regions which are releated limbic system have largely been studied in rodents, no comprehensive studies have been performed in human brain yet (1). Plenty of the evidence of addiction result from the instability in neuronal caution and inhibition, which is largely due to modifications in transposition of excitatory

IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2018; 7(2): 66-70 Demirel G.

glutamate and inhibitory gamma-aminobutyric acid GABA (2). Some addiction types which are like heavy alcohol consumption or cocaine use is known to result in widespread neuronal adaptations in limbic reward circuitry, including impairment in glutamate homeostasis (3). Altered glutamate-glutamine metabolism might either be a prognosticator for the progress of addiction or might be a stable effect of long-term consumption. (4). Chronic exposure to addictive drugs impress glutamate transporters together with ionotropic and metabotropic glutamate receptor availability and function (5).

'L-glutamate is the major excitatory neurotransmitter in the central nervous system and activates both ionotropic and metabotropic glutamate receptors. Glutamatergic neurotransmission is involved in most aspects of normal brain function and can be perturbed in many neuropathologic conditions. In figure 1 Tissue samples from 95 human individuals representing 27 different tissues in order to determine tissue-specificity of all protein-coding genes has been showed. (6) The metabotropic glutamate receptors are a family of G protein-coupled receptors, that have been divided into 3 groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group I includes *GRM1* and *GRM5* and these receptors have been shown to activate phospholipase C. Group II includes *GRM2* and *GRM3* while Group III includes *GRM4* (Figure 2), *GRM6, GRM7* and *GRM8*. Group II and III receptors are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities. Several transcript variants encoding different isoforms have been found for this gene.' (*GRM4* glutamate metabotropic receptor 4 (7).

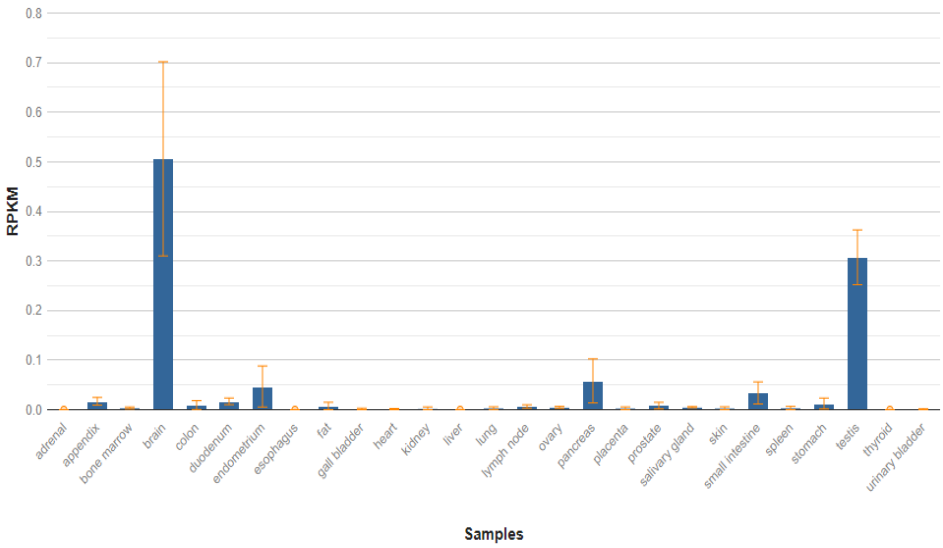

Figure 1: Tissue-specificity of all protein-coding genes

IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2018; 7(2): 66-70 Demirel G.

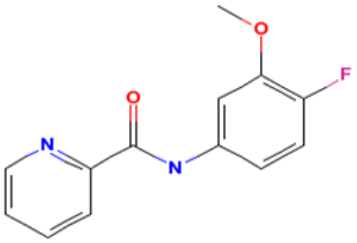

Figure 2 : 2D Structure of Modulation of Metabotropic Glutmate Receptor mGluR4: Human PAM Fold-Shift
https://pubchem.ncbi.nlm.nih.gov

Materials and Methods

Bioinformatics analyses

We previously identified the miRNA expression profiles of brain regions in MDMA user postmortem human brain tissues and matched controls. In this study we analyzed some results of our previously study interaction Networks Of *GRM4* and Addiction-Related Genes in genes related to glutamatergic neurotransmission.

We used a network propagation-based model (NP-method) to predict addiction-related genes (9). Predicted genes were enriched in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. In addition, by using STRING (http://string-db.org/) we found the Protein-Protein Interaction Networks (PPI) of common *GRM4* targets (8).

Results

We used bioinformatics tools to screen for GRM4 gene and drug addiction related regulatory networks (Figure 3 and Figure 4). As a result, we found eleven target genes of *GRM4* gene have an important role in the mesocorticolimbic system. String database result showed that target genes of *GRM4* involved in several biological processes which are drug-induced neuroplasticity and gene regulatory.

IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2018; 7(2): 66-70 Demirel G.

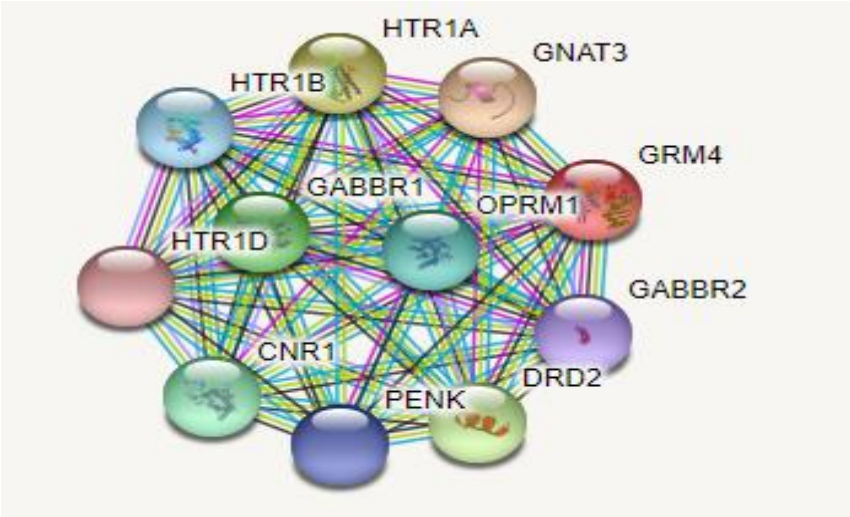

Figure 3: GRM4 gene Interaction Networks
(http://string-db.org/)

node1	node2	node1 accession	node2 accession	node1 annotation	node2 annotation	score
OPRM1	PENK	ENSP00000394624	ENSP00000324248	Opioid receptor, mu 1; Receptor for endo...	Proenkephalin; Met- and Leu-enkephalins...	0.967
GNAT3	PENK	ENSP00000381339	ENSP00000324248	Guanine nucleotide binding protein, alpha...	Proenkephalin; Met- and Leu-enkephalins...	0.900
GRM4	PENK	ENSP00000363296	ENSP00000324248	Glutamate receptor, metabotropic 4; G-pr...	Proenkephalin; Met- and Leu-enkephalins...	0.916
GABBR2	PENK	ENSP00000259455	ENSP00000324248	Gamma-aminobutyric acid (GABA) B rece...	Proenkephalin; Met- and Leu-enkephalins...	0.910
GABBR1	PENK	ENSP00000366233	ENSP00000324248	Gamma-aminobutyric acid (GABA) B rece...	Proenkephalin; Met- and Leu-enkephalins...	0.904
DRD2	PENK	ENSP00000354859	ENSP00000324248	Dopamine receptor D2; Dopamine recept...	Proenkephalin; Met- and Leu-enkephalins...	0.944
CNR1	PENK	ENSP00000358511	ENSP00000324248	Cannabinoid receptor 1 (brain); Involved i...	Proenkephalin; Met- and Leu-enkephalins...	0.932
HTR1D	PENK	ENSP00000313661	ENSP00000324248	5-hydroxytryptamine (serotonin) receptor...	Proenkephalin; Met- and Leu-enkephalins...	0.903
HTR1B	PENK	ENSP00000358963	ENSP00000324248	5-hydroxytryptamine (serotonin) receptor...	Proenkephalin; Met- and Leu-enkephalins...	0.912
HTR1A	PENK	ENSP00000316244	ENSP00000324248	5-hydroxytryptamine (serotonin) receptor...	Proenkephalin; Met- and Leu-enkephalins...	0.920
PENK	OPRM1	ENSP00000324248	ENSP00000394624	Proenkephalin; Met- and Leu-enkephalins...	Opioid receptor, mu 1; Receptor for endo...	0.967
GNAT3	OPRM1	ENSP00000381339	ENSP00000394624	Guanine nucleotide binding protein, alpha...	Opioid receptor, mu 1; Receptor for endo...	0.915
GRM4	OPRM1	ENSP00000363296	ENSP00000394624	Glutamate receptor, metabotropic 4; G-pr...	Opioid receptor, mu 1; Receptor for endo...	0.917
GABBR2	OPRM1	ENSP00000259455	ENSP00000394624	Gamma-aminobutyric acid (GABA) B rece...	Opioid receptor, mu 1; Receptor for endo...	0.909
GABBR1	OPRM1	ENSP00000366233	ENSP00000394624	Gamma-aminobutyric acid (GABA) B rece...	Opioid receptor, mu 1; Receptor for endo...	0.913
DRD2	OPRM1	ENSP00000354859	ENSP00000394624	Dopamine receptor D2; Dopamine recept...	Opioid receptor, mu 1; Receptor for endo...	0.926
CNR1	OPRM1	ENSP00000358511	ENSP00000394624	Cannabinoid receptor 1 (brain); Involved i...	Opioid receptor, mu 1; Receptor for endo...	0.948
HTR1D	OPRM1	ENSP00000313661	ENSP00000394624	5-hydroxytryptamine (serotonin) receptor...	Opioid receptor, mu 1; Receptor for endo...	0.909
HTR1B	OPRM1	ENSP00000358963	ENSP00000394624	5-hydroxytryptamine (serotonin) receptor...	Opioid receptor, mu 1; Receptor for endo...	0.910
HTR1A	OPRM1	ENSP00000316244	ENSP00000394624	5-hydroxytryptamine (serotonin) receptor...	Opioid receptor, mu 1; Receptor for endo...	0.913

Figure 4: Interactions in tabular form
*(*http://string-db.org/)

IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2018; 7(2): 66-70 Demirel G.

Discussion

In our previosuly study we examineted candidate miRNAs that played potential key roles in regulating MDMA addiction, we performed miRNA profiling of limbic regions in postmortem addicted individuals and postmortem control individuals brains. In this study we used bioinformatic tools for determined gene interactions about addicted releated genes. Bioinformatics approaches show that miRNAs can target the genes of specific pathways and generate miRNA-regulated gene networks (9). Clinical and epidemiological research suggests that addictions are associated with a wide range of psychiatric disorders (10). For the last decade, the concept of addiction has been stretched beyond substances to include addictions (11). There is some evidence that addiction and depression could share common biological and behavioral characteristics. Consistently, *GRM4* was up-regulated in depressed brains, whereas there was no difference between controls and depressed individuals with antidepressant history (12). Nevertheless, there was a difference in the expression of *GRM4* between depressed subjects with and without antidepressant history (13). Also in our study we determined *GRM4* up regulation in addicted brains. These results suggest that *GRM4* is associated with the pathophysiology of depression and addiction, and is a potential target for novel treatments.

References

1.Luscher C, Malenka RC. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron. 69(4): 650-663. 2011

2. McQuown SC, Wood MA. Epigenetic regulation in substance use disorders. Curr Psychiatry Rep. 12: 145-153. 2010

3. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci. 10(8):561-72. 2009

4. Thoma R, Mullins P, Ruhl D, et all. Perturbation of the glutamate-glutamine system in alcohol dependence and remission. Neuropsychopharmacology. 36(7):1359-65. 2011

5. Nestler EJ. Molecular mechanisms of drug addiction. Neuropharmacology. 47 Suppl 1: 24-32, 2004

6. Fagerberg L1, Hallström BM, Oksvold P, et all. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics. 2014 Feb;13(2):397-406. doi: 10.1074/mcp.M113.035600. Epub 2013

7. https://www.ncbi.nlm.nih.gov/gene/2914

8. Warde-Farley D, Donaldson SL, Comes O, Zuberi K, Badrawi R, Chao P, et al. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. Nucleic Acids Res. 38(Web Server issue):W214-20. 2010

9.Kawulok J, Deorowicz S. CoMeta: classification of metagenomes using k-mers. PLoS One. 10: e0121453, 2015

10. Varoa C, Murrua A, E Salagrea et all. Behavioral addictions in bipolar disorders: A systematic review. https://doi.org/10.1016/j.euroneuro.2018.10.012.

11. Grant JE, Potenza MN, Aviv Weinstein A et all. Introduction to Behavioral Addictions, The American Journal of Drug and Alcohol Abuse, 36:5, 233-241, 2010

12.Lopez JP, Fiori LM, Cruceanu C, Lin R, Labonte B, Cates HM, et al. MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. Nat Commun. 8: 15497. 2017

13.Lopez JP, Lim R, Cruceanu C et all. miR-1202 is a primate-specific and brain-enriched microRNA involved in major depression and antidepressant treatment. Nat Med.(20): 764-768. 2014