Utilization of NCIBI Tools MiMI and Cytoscape to Determine an Indirect Interaction Between Estrogen and Dopamine Receptor Sub-types in the Brain

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Abstract

Bipolar disorder (BPD) is a highly heritable, severe and chronic mental illness characterized by episodes of elation and high activity; alternating with periods of low mood and low energy. These symptoms are often complicated by the co-morbidity in people suffering with narcotics and alcohol abuse. Co-morbidity of BPD and substance abuse include activation of common neurological pathways. Literature individually suggests estrogen and dopamine receptor sub-types participate in the regulation of the neurological pathways common to BPD and drugs of abuse. In the brain, estrogen has been shown to modulate mood while abnormal dopamine receptor signaling is implicated in response to substance abuse use. Therefore, determination of any direct or indirect linkages between estrogen and dopamine receptor activation is necessary for further understanding the genetics behind BPD and substance abuse co-morbidity. In this study, we utilize the National Center for Integrative Biomedical Informatics (NCIBI) tools, Michigan Molecular Interactions (MiMI) and the Cytoscape MiMI Plugin (cytoscape) to demonstrate an indirect link between estrogen and dopamine receptor sub-types. MiMI allows users to explore all accessible databases of protein interactions, pathways and genes while cytoscape is an interactive visualization tool used for analyzing protein interactions and their biological effects.

Background / Significance

- Bipolar disorder is also known as manic-depressive illness [1]
- BP disorder is a brain disorder that causes unusual shifts in mood, energy, and activity levels, and affects an individuals ability to carry out day-to-day tasks [1]
- Substance abuse with alcohol or drug is very common amongst individuals with BP and serves as a means of self-medication.[1]
- Estrogen is associated with sex-specific effects on the dopamine receptor-containing neurons with respect to drug abuse and relapse in mice. [2]
- C_B1 cannabinoid receptor (CB_1)-transgenic mice demonstrate sex-specific effects on the D_4 dopamine receptor sub-type gene expression [3]
- MiMI and cytoscape were used to determine and generate visually an indirect genetic interaction between estrogen, dopamine and cannabinoid receptor sub-types.

Methods

Figure 1 Screen shots Panel A. MiMI is used to generate gene symbols used for cytoscape. Panel B. Demonstration of Cytoscape query once gene symbols are determined.

Results

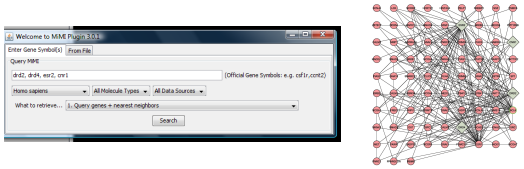

Figure 2 Screen shots: Panel A. Entry of genes and their nearest neighbors using cytoscape. Panel B. Generated visualization of genes and nearest neighbors by cytoscape.

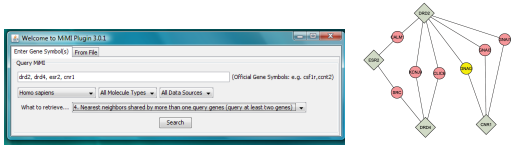

Figure 3 Screen shots: Panel A. Demonstrates how to query genes and their nearest neighbors shared by more than one gene in cytoscape. Panel B. Shows generated visualization of gene and nearest neighbors shared by more than one gene by cytoscape

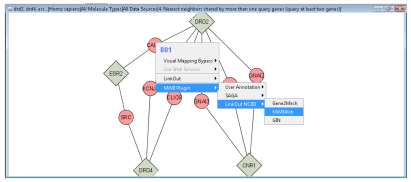

Figure 4: Screen shot demonstrates how to "Link Out" to MiMI and retrieve gene interactions, known pathways and supporting literature.

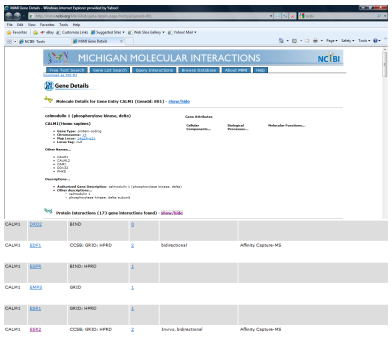

Figure 5 Screen shot: Interactions between a protein and an gene of interest as shown in MiMI, along with the number of supporting journal articles.

Results

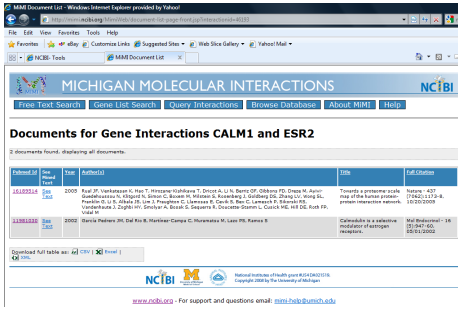

Figure 6 Screen shot: MiMI literature results for gene interaction between protein and gene of interest.

Conclusions

- The NCIBI tools were able to show an indirect genetic link between the dopamine and the estrogen receptor subtypes
- There was an indirect connection between the dopamine and the cannabinoid receptor subtypes.
- There was no one protein that connected the dopamine, estrogen and cannabinoid receptors directly, however there are several proteins that connect them indirectly
- There were no existing pathway models available for reference
- More extensive literature searches must be performed in order to determine experimental procedures that can be used to demonstrate the indirect connection.

References

1. http://www.nimh.nih.gov/health/publications/bipolar-disorder/complete-index.shtml
2. Zhang, Die; Yang, Sheng ; Yang, Chunhao; Jin, Guozhang; Zhen , Xuechu; Estrogen regulates responses of dopamine neurons in the ventral tegmental area to cocaine; Psychopharmacology (2008) 199:625–635
3. Gerald TM, Howlett AC, Ward GR, Ho C, Franklin SO. Gene expression of opioid and dopamine systems in mouse striatum: effects of CB_1 receptors, age and sex, Psychopharmacology (Berl). 2008 Jul;198(4):497-508

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