Talk 4.1

Integrated bioinformatics and molecular identification of cis-elements for dopamine-regulated gene expression

(NIDA R01-DA019362 FY 04)
Jiang-Fan Chen
Department of Neurology, Boston University School of Medicine

Zhiping Weng
Department of Biomedical Engineering and Bioinformatics Program, Boston University

Dopamine is an important neurotransmitter in CNS and contributes profoundly to a variety of motor and emotional behaviors. Dopaminergic dysfunction has been associated with several major neuropsychiatric disorders, ranging from drug addiction to schizophrenia to Parkinson's disease. To uncover the transcriptional regulatory mechanism underlying dopamine-regulated gene expression, we performed gene expression profiling in time-series manner (sampling up to 180 min at 30 min interval) by microarray after the treatment with amphetamine (2.5 mg/kg) and cocaine (25 mg/kg). Using algorithms for short time series microarray data ("STEM" and "EDGE"), we have refined amphetamine-regulated gene set. Further TF finding analysis using statistical algorithms ("Clover" and "Rover") and the algorithm with integrated phylogenetic features ("oPOSSUM) revealed that CREB as well as E47 are significantly over-represented in the promoter of amphetamine-regulated genes. CREB was identified by experimental as well as our bioinformatics analyses of dopamine regulated genes. E47 is a classic bHLH-type TF and directly interact with CREB-binding protein to enhance E47-mediated trans-activation of gene expression. The detection of statistical over-representation for both CREB and E47 in the subpopulation of amphetamine-regulated genes led us to propose that combinatorial regulation of the E47-CREB complex in amphetamine-regulated gene expression in the striatum. To seek further evidence for CREB role in dopamine regulated gene expression, we also evaluated the correlation of amphetamine-regulated genes with the gene set affected by CREB over-expression in mice. Using the Chi-square test, we observed that there was highly significant correlation between the gene sets by over-expression of CREB and the gene set by amphetamine, supporting that CREB is the potential regulator of amphetamine-regulated gene expression. Finally, we also examined possible role of histone modification and amphetamine action and gene expression. We provide *in vivo* experimental evidence that HDAC may interact with amphetamine at the levels of histone acetylation and transcription factor function (i.e. CREB phosphorylation and ΔFosB induction) to modify neuroplasticity associated with amphetamine behavioral sensitization. These results also lay the foundation for mapping histone acetylation sites across mouse genome in correlation with dopamine-regulated gene expression in mouse striatum by bioinformatics analysis which is currently underway.

Publications

1. Yu L, Haverty P, Mariani J, Schwarzschild MA, Weng Z, Chen J-F (2005) Egr-2-

mediated transcriptional regulatory network in striatum by genetic and pharmacological inactivation of the adenosine A_{2A} receptor as revealed by microarray and bioinformatics analyses. Physiology Genomics 23:89-102

2. Kalda A, Shen Y, Yu L, Ferrara J, Chen J-F (2006) Histone deacetylase inhibitors potentiate amphetamine behavioral sensitization and enhance striatal ΔFosB expression level by dual action of histones H3 and H4 hyperacetylation and extending CREB phosphorylation. (submitted to "Journal of Biological Chemistry")