
Integrated Bioinformatics and Molecular Identification of *cis*-Elements Responsible for Dopamine-Response Gene Expression

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Adenosine A_{2A} receptors (A_{2A}Rs) are colocalized with dopamine D2 receptors to exert profound modulatory effect on dopamine-mediated motor and emotional behaviors. As the first step toward our dissecting the molecular mechanism underlying dopamine-gene expression, we tested our microarray and bioinformatics tools to study gene expression profiles by genetic and pharmacological inactivation of A_{2A}Rs and inferred an A_{2A}R-controlled transcription network in the mouse striatum. A comparison between A_{2A}R KO-vehicle and WT-vehicle revealed 36 up-regulated genes that were partially mimicked by SCH58261 treatment, and 54 down-regulated genes that were not mimicked by SCH58261 treatment. We validated the A_{2A}R as a specific drug target for SCH58261 by comparing A_{2A}RKO-SCH and A_{2A}RKO-vehicle groups. The unique down-regulation effect of A_{2A}R KO was confirmed by comparing A_{2A}R KO-SCH and WT-SCH gene groups. The distinct striatal gene expression profiles induced by A_{2A}R KO and SCH58261 should provide clues to the molecular mechanisms underlying the different phenotypes observed after genetic and pharmacological inactivation of A_{2A}Rs. Bioinformatics analysis discovered that the Egr-2 binding sites are statistically over-represented in the proximal promoters of A_{2A}R KO-affected genes relative to the unaffected genes. This finding was further substantiated by the demonstration that Egr-2 mRNA level increased in the striatum of both A_{2A}R-KO and SCH58261-treated mice and that striatal Egr-2 binding activity in the promoters of two A_{2A}R KO-affected genes was enhanced in A_{2A}R KO mice as assayed by chromatin immunoprecipitation. Theses combined results strongly support the existence of an Egr-2-directed transcriptional regulatory network controlled by striatal A_{2A}Rs.

Project Website

http://www.bumc.bu.edu/Dept/ContentPF.aspx?PageID=8429&DepartmentID=60

Publications

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 (submitted)