Identification of genes affected by fetal alcohol exposure during brain development

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Abstract

Fetal alcohol exposure is the leading known cause of mental retardation in the western world. However, the mechanisms underlying alcohol-induced damage in fetal brain are largely unknown. The goal of this dissertation is to identify ethanol-responsive genes during brain development to provide more insights into the mechanisms. I chose a well-established animal model for all the studies in this dissertation. First, I demonstrated that this ethanol paradigm increased the mRNA of cellular retinol binding protein I (CRBP-1) in gestational day 13 (G13) brain and the incidence of apoptosis in G16 brain. Second, I identified 12 putative ethanol-responsive genes using mRNA differential display. After the quantitative analysis by Northern blot, *in situ* hyridization, western blot and relative quantitative RT-PCR, ribosomal protein S6 (rpS6), neuroendocrine-specific protein-A (NSP-A) and a novel gene were verified as ethanol-responsive genes. Third, I isolated 32 putative ethanol-responsive genes using cDNA microarray analysis. They encode proteins engaged in cell signaling, cell cycle regulation, metabolism, stress response and cell structure. Among all the putative genes, alcohol dehydrogenase 3 (Adh3) and glutathione S transferase pi 2 (GST pi 2) are previously known ethanol-responsive genes. ^ Additionally, bone morphogenetic protein receptor type IA (BMPR-IA) showed the largest change induced by ethanol, 2.1-fold, and the ethanol effect on its expression was confirmed by relative quantitative RT-PCR. Fourth, because NSP-A is also a thyroid hormone-regulated gene, I analyzed the expression of two other thyroid hormone-regulated genes, Oct-1 and Hes-1, in my ethanol-treated animal model. However, ethanol did not affect thyroid hormone regulation of these two genes in G16 cerebral cortex. Fifth, I examined the effects of ethanol on protein expression and phosphoralytion using two-dimensional (2D) electrophoresis and western blotting. Ethanol was shown not to robustly change the abundance of individual proteins, but may change the post translation modifications of some proteins during brain development, such as glycosylation. In conclusion, these studies systematically and thoroughly examined the effects of fetal alcohol exposure on gene expression during brain development. They provide useful insights for analyzing the complex pathways leading to CNS damage in the children born to mothers who drank heavily during pregnancy. ^

Subject Area

Molecular biology|Neurosciences

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