Genes to behavior and back again: Using genomics, genetics, and bioinformatics to study mechanisms of brain responses to drugs of abuse.

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Changes in brain gene expression are thought to be an important aspect of how exposure to ethanol and other drugs of abuse causes addiction. Identifying the genes involved in alcoholism and drug addiction, and the cognate mechanisms of action, are the major emphasis of our laboratory. We have used a combination of genetics, genomics and pharmacology, a process we refer to as "molecular triangulation", to identify brain region selective mRNA expression patterns related to ethanol-evoked behaviors. Intensive bioinformatics efforts are also used to identify potential functional correlations for expression patterns. Most of the work in our laboratory concerns acute responses to ethanol, cocaine or nicotine. Additional projects study more long-term behavioral responses such as sensitization and compulsive drinking. We use high-density oligonucleotide microarrays to profile brain region mRNA expression for 10-20,000 genes simultaneously. Prior work in the laboratory has developed improved methods for primary analysis of such microarray data.

A major portion of work on acute ethanol concerns studies on a variety of inbred mouse lines. The inbred mouse strains C57BL/6 (B6) and DBA/2J (D2) and recombinant inbred panels (BXD RI lines) derived from these progenitors have been widely used for behavioral, molecular and genetic studies on ethanol and other drugs of abuse. The inbred mouse strain DBA/2J (D2) has greater locomotor responses to acute ethanol and drink less than C57BL/6 mice (B6). Expression profiling of D2 and B6 nucleus accumbens, prefrontal cortex and ventral tegmental area identified strain-specific basal and acute ethanol-regulated patterns of gene expression. The ethanol responses in D2 and B6 mice differed to a remarkable degree with a 2 g/kg locomotor-activating dose of ethanol. A number of these genes were located in chromosomal regions for published quantitative trait loci for ethanol phenotypes. Overlaying ethanol-responsive gene patterns on expression networks derived for basal gene expression in the BXD RI panel was done using the WebQTL resource (www.webqtl.org). This hybrid "genetical genomics" approach identified groups of ethanol-responsive genes with basal expression linked to common chromosomal regions that, in some cases, have also been implicated in ethanol behavioral QTLs. Analysis of other genetic models, such as single gene null mutations, has confirmed or extended the association of select expression patterns with ethanol behaviors. Furthermore, bioinformatics tools for high-throughput biological pathway analysis, biomedical literature co-association analysis or promoter motif analysis identified testable functional/mechanistic groupings within the ethanol-responsive genes. Overall, these studies identify individual genes and gene networks that may have an important role determining acute behavioral responses to ethanol as well as possibly influencing ethanol drinking behavior.

Additional information regarding interests of the Miles laboratory can be found at our websites: http://www.brainchip.vcu.edu/ or http://www.vcu.edu/pharmtox/fac_bio/miles.htm.