Genetics, Drugs and Chips: Molecular Triangulation on CNS Plasticity

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Chronic exposure to ethanol or other addicting drugs causes long-lasting, deleterious behavioral responses such as tolerance, dependence, sensitization, and addiction. Addiction to drugs of abuse likely results from step-wise changes in the expression of specific genes at discreet locations in the brain. These changes in gene expression lead to altered function of networks of neurons, with resultant behavioral changes such as addiction. DNA microarrays allow parallel quantitative analysis of gene expression on a whole genome scale. We have used DNA microarrays to study expression of >10,000 genes simultaneously in mouse brain during exposure to drugs of abuse (cocaine, ethanol or nicotine). Currently, we are studying patterns of gene regulation following acute ethanol exposure that correlate with long-term behavioral responses. Different strains of mice show large differences in the expression patterns of genes regulated by these drugs. Some of these measured differences in expression are due to actual changes in the abundance of a particular messenger RNA (mRNA) but some are also due to differences between the DNA sequences of the genes in the mouse lines studied. These sequence differences are referred to as polymorphisms and might have important consequences for the function of the involved genes, and susceptibility of the particular mouse strain to becoming addicted. Furthermore, inbred lines, knockouts, gene delivery and pharmacological treatments are being used to correlate expression profiles with behavioral responses to acute ethanol.