Behavioral genomic and genetic analysis of chronic nicotine and withdrawal in mouse BXD strains.

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The molecular mechanisms underlying brain brain plasticity with chronic nicotine exposure and withdrawal are poorly understood. We have employed a mouse genetic model, the BXD inbred mouse panel, to identify genetic loci and candidate gene networks contributing to behavioral responses seen following chronic nicotine exposure and withdrawal. A total of 34 BXD strains and the progenitor C57BL/6J (B6) and DBA2/J (D2) strains have been studied using minipump subcutaneous delivery of nicotine (24 mg/kg/day) for seven days. Withdrawal was precipitated by mecamylamine (2 mg/kg) and mice were studied for somatic signs of withdrawal and anxiety-like effects in the elevated plus maze. Behavioral quantitative trait loci (QTL) were identified by interval mapping in the GeneNetwork online resource for behavioral and expression genetic analysis (www.genenetwork.org). In a separate study, nucleus accumbens tissue from B6 and D2 mice mice was analyzed for genomic responses to the same chronic nicotine exposure paradigm, using Affymetrix MTA microarrays to identify candidate genes contributing to behavioral responses to chronic nicotine. Behavioral QTL analysis identified a highly significant QTL for mecamylamine-induced somatic signs of withdrawal on Chr 14 (peak LOD=4.92, 1 LOD support interval 62-65 Mb) and anxiety-like behavior on Chr 9 (peak LOD=3.56, 1 LOD support interval 26.4-35.2 Mb). Genomic studies showed striking qualitative differences in responses to chronic nicotine and withdrawal in B6 vs. D2 mice. Co-analysis with gene expression results identified 6 candidate genes within the Chr 14 somatic signs QTL and 3 candidates within the Chr 9 anxiolytic-like QTL support intervals, as responding to chronic nicotine or withdrawal. Together, these studies have identified candidate genetic intervals and candidate genes contributing to the genetic diversity in behavioral responses to chronic nicotine and withdrawal. These results may contribute to our understanding of brain molecular mechanisms underlying nicotine dependence. *Supported by NIH R01 DA032246.*