Abstract

A primary public health concern regarding environmental chemicals is the potential for persistent effects from long-term exposure, and approaches to estimate these effects from short-term exposures are needed. Toluene, a ubiquitous air pollutant, exerts well-documented acute and persistent CNS-mediated effects from a variety of exposure scenarios, and so provides a useful case for determining whether its persistent effects can be predicted from its acute effects on the CNS. We recently reported that acute inhalation of toluene produced transcriptional effects in rat brain 18 h following a single, acute 6-h exposure to toluene. The goal of the present study was to determine whether these acute effects are also evident after long-term (sub-chronic) exposure to toluene, and thereby provide a mechanistic basis for predicting its persistent effects from short-term exposures. Male Long-Evans rats were exposed to toluene via inhalation (0, 10, 100, 1000 ppm, n=5/dose), 6h/day for 64 days, excluding weekends. The day following the final exposure, total **mRNA** was extracted from the cerebral cortex and striatum, and gene expression evaluated using Affymetrix arrays. Principal component analysis using all samples showed a clear discrimination of tissues, with striatum having more within-group variance than cortex. Differentially-expressed genes (DEGs) whose expression was altered by toluene were identified in each tissue by ANOVA followed by mapping to pathways. Analysis of striatum revealed 22, 57, and 94 significant DEGs for the 10 ppm, 100 ppm, and 1000 ppm doses, respectively, far fewer than the 3352 DEGS previously observed after acute exposure. In addition, the direction of change in the 57 DEGs common to both exposures differed between acute and sub-chronic exposure scenarios. Thus, relative to acute toluene exposure, sub-chronic exposure yielded both quantitative and qualitative differences in transcriptional response. Based on the current data, long-term gene expression **changes** after toluene inhalation cannot be readily predicted by acute responses.