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**Daily morphine exposure activates synaptogenesis and other neuroplasticity-related gene networks in the dorsomedial prefrontal cortex of male and female rats**

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We have found that greater anhedonia during withdrawal from repeated morphine exposure predicted resistance to opioid addiction as measured by morphine self-administration. As part of the NIDA Rat Opioid Genome Project, we are comparing High- and Low-Anhedonia rats to identify novel genomic loci associated with vulnerability to opioid addiction. In this preliminary study, we employed Next-Generation RNA-sequencing (RNA-seq), followed by quantitative chromatin immunoprecipitation (qChIP), to investigate changes in gene regulation in rat dorsomedial prefrontal cortex (dmPFC) after a series of daily morphine injections that produces robust locomotor sensitization, hyperalgesia, and anhedonia (5.0 mg/kg; 10 days). Compared to controls, 377 genes were differentially expressed in morphine-treated male rats and 409 genes in morphine-treated females, with a 35% overlap. 90% of differentially expressed genes (DEGs) were upregulated in both sexes. Functional annotation of these DEGs using the knowledge-based Ingenuity Pathway Analysis revealed activation in both sexes of canonical pathways involved in synaptic/intracellular signaling, including synaptogenesis, long-term potentiation, opioid signaling, dopamine-DARPP32 signaling and ephrin receptor signaling. FEV (necessary for serotonin synthesis and release) and ADORA2A (the adenosine 2a receptor gene) were implicated as key upstream regulators. A selection of genes with functions related to neuronal plasticity and intra-/inter-cellular signaling showed enrichment in their promoter regions of two activating histone modifications: pan-H3 acetylation and H3K4 trimethylation. Our results cohere with findings from previous studies based on *a priori* gene selection, but also reveal novel genes and molecular pathways that are upregulated by repeated morphine exposure and that may contribute to vulnerability to opioid addiction.