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Sex and brain region-specific gene expression and imprinting of nicotine sensitization and self-administration in rats inform GWAS findings of human smoking phenotypes

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Repeated nicotine exposure leads to sensitization (SST) and enhances self-administration (SA) in rodents. However, the molecular basis of nicotine SST and SA and their biological relevance to the mounting genome-wide association study (GWAS) loci of human addictive behaviors are poorly understood. Considering a gateway drug role of nicotine, we modeled nicotine SST and SA in F1 progeny of inbred rats (F344/BN) and conducted integrative genomics analyses. We unexpectedly observed male-specific nicotine SST and a parental effect of SA only present in paternal F344 crosses. Transcriptional profiling in the ventral tegmental area (VTA) and nucleus accumbens (NAc) core and shell further revealed sex- and brain region-specific transcriptomic signatures of SST and SA. We found that genes associated with SST and SA were enriched for those related to synaptic processes, myelin sheath, and tobacco use disorder or chemdependency. Interestingly, SST-associated genes were often downregulated in male VTA but upregulated in female VTA, and strongly enriched for smoking GWAS risk variants, possibly explaining themale-specific SST. For SA, we found widespread region-specific allelic imbalance of expression (AIE), of which genes showing AIE bias towards paternalF344 alleles in NAc core were strongly enriched for SA-associated genes and for GWAS risk variants of smoking initiation, likely contributing to the parental effect of SA. Our study suggests a mechanistic link between transcriptional changes underlying the NIC SST and SA and human nicotine addiction, providing are source for understanding the neurobiology basis of the GWAS findings on human smoking and other addictive phenotypes.