Adolescent Social Stress Results in Sex-Specific Transcriptional Reprogramming of The Medial Amygdala, A Critical Region for Sex Differences in Reward

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Adolescence, a time of heightened sensitivity to rewarding stimuli, is associated with vulnerability to psychiatric disorders. Male rodents that experience adolescent social isolation stress (SI) form stronger preferences for drugs of abuse. However, little is known about how females respond to SI. The medial amygdala (meAMY) is sexually dimorphic, develops during adolescence and is sensitive to SI. Our preliminary data suggest that SI reverses sex differences in reward behaviors and permanently reduces baseline sex differences (M>F) in neuronal projections from meAMY to ventral tegmental area (VTA). Across adolescent development (postnatal day (P)22, P32, P42 & P72), SI females show a male-typical developmental pattern in corticosterone and progesterone is reduced in SI adults (M & F). Given these peripheral and behavioral alterations, we tested the hypothesis that SI alters the meAMY transcriptome in a persistent and sex-specific manner. Mice were isolated or group housed (GH) from 22 - P42, then GH until ~P90. Transcriptome-wide changes in meAMY and VTA were investigated by RNA-seq after cocaine (acute/chronic) or saline. Sexually dimorphic genes in both regions were disproportionately affected by SI, with the greatest number of transcripts affected in the meAMY (Sex X SI: 869 genes). Hierarchical clustering revealed that SI reversed baseline sex differences in expression in both regions, similar to observed behavioral effects. Specifically, GH males cluster with SI females and vice versa for those sex X SI genes in the meAMY and VTA (276 genes). Cluster analysis also revealed that sex differences in response to chronic but not acute cocaine were reversed by SI, suggesting that meAMY to VTA projections are important for the regulation of sex differences in reward. Together, these data suggest that the meAMY plays an important role in sex differences in cocaine reward and SI disrupts sex-specific adolescent development of brain connectivity, transcription and endocrinology.

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