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HOT TOPICS

Critical roles for developmental hormones and genetic sex in stress-induced transcriptional changes associated with depression

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Major depressive disorder (MDD) is a devastating illness and the leading cause of disability worldwide [1]. Differences between men and women in the etiology and pathology of depression likely impact symptomatology, severity, and prevalence [2, 3]. Since depression prevalence remains higher in women across life stages and hormonal states, factors other than circulating gonadal hormones may contribute to these sex differences, including permanent organizational effects of gonadal hormones acting during sensitive developmental periods and/or genetic sex effects (i.e., XX/XY).

As genetic sex determines gonadal sex in standard laboratory mice, parsing the impact of developmental hormonal and genetic sex requires use of the unique Four Core Genotypes (FCG) mouse strain, in which gonadal sex determination is decoupled from sex chromosomes. In our study [4], we found males had lower depressive-like behavior than females. Since we used FCG mice, we were able to determine how both developmental gonadal hormone exposure and genetic sex independently contributed to this sex difference. We then used RNA-sequencing to examine potential molecular mechanisms driving sex differences in behavior within three nodes of mesocorticolimbic circuitry—prefrontal cortex (PFC), nucleus accumbens (NAc), and basolateral amygdala (BLA). We found significant sex differences in immune-related pathways that were driven by both developmental gonadal hormones and genetic sex. For example, genetic sex drove differences related to T- and B-cell signaling across brain regions. When we looked at the effect of stress on gene expression, we found very little overlap between males and females, consistent with recent findings by our group and others using human postmortem brains [5, 6]. For instance, in the BLA, stress altered the expression of dopamine- and serotonin-related genes in males, but EIF2 and mTOR signaling in females, both of which may be involved in stress-induced synaptic plasticity.

Additionally, we used an integrative network approach to probe for sex-specific brain circuits, gene modules, and upstream regulators of sex differences in stress vulnerability. Since MDD involves circuit-level disruption, examining the global impact of stress on molecular pathways is informative. One way to assess circuit-level disruption is to examine transcriptional coherence across brain regions. We found chronic stressinduced overlapping transcriptional changes between PFC and NAc in males and between BLA and NAc in females; both patterns were driven by genetic sex. Co-expression network analysis revealed gene modules that were oppositely affected by stress in males and females, including one module enriched for immune-related genes (Fcγ receptor-mediated phagocytosis). This was particularly interesting given our recent finding that men and women with MDD exhibit opposite changes in synapse- and immune-related genes [5]. We identified stress-specific hubs, including synapse-related genes (*Thbs1*, *Cadps2*, *Ntng1* in females; *Lnx2* in males), that are differentially expressed by sex, suggesting these genes may be drivers of sex differences in depression. *Papl*, previously identified within anxiety and neuroinflammation quantitative trait loci, is the only stress-specific hub in both sexes.

These results add to emerging literature identifying sex-dependent effects of stress on mood-related circuitry and highlight gene networks/pathways within specific brain regions that may contribute to sex differences in MDD.

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AUTHOR CONTRIBUTIONS

The authors contributed equally to the writing of this manuscript.

ADDITIONAL INFORMATION

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REFERENCES

1. WHO. The global burden of disease, 2004 update. 2008:1-146.
2. Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, et al. Gender differences in chronic major and double depression. J Affect Disord. 2000;60:1–11.

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3. Angst J, Dobler-Mikola A. Do the diagnostic criteria determine the sex ratio in depression? J Affect Disord. 1984;7:189–98.
4. Paden W, Barko K, Puralewski R, Cahill KM, Huo Z, Shelton MA, et al. Sex differences in adult mood and in stress-induced transcriptional coherence across mesocorticolimbic circuitry. Transl Psychiatry 2020;10:59.
5. Seney ML, Huo Z, Cahill K, French L, Puralewski R, Zhang J, et al. Opposite molecular signatures of depression in men and women. Biol Psychiatry 2018; 84:18–27.
6. Labonte B, Engmann O, Purushothaman I, Menard C, Wang J, Tan C, et al. Sex-specific transcriptional signatures in human depression. Nat Med 2017;23:1102–1111.