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Molecular Evidence of Sex-Specific Effects in Neonates with Prenatal Opioid Exposure

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Management of Neonatal Abstinence Syndrome (NAS) is designed to improve physiologic stability, length of stay, cost burden, and health outcomes. Males and females with NAS are treated the same despite the distinct clinical courses. Our pilot study showed dysregulated reward signaling in opioid-exposed than non-exposed males that correlated with feeding behavior, with no effects seen in females. Incorporating sex as a biological variable in NAS-related research is crucial to optimize outcomes. To understand the impact of sex, we analyzed the expression of select salivary hypothalamic and inflammatory genes in an independent validation cohort comprised of 31 opioid-exposed and 31 sex- and age-matched non-exposed neonates. Gene expression did not differ significantly between the groups. When stratified by sex, all neonates requiring pharmacotherapy were males. Opioid-exposed males also had a significantly greater expression of key reward gene *DRD2* than non-exposed males ($p< 0.01$). Although not significant, two-way ANOVA showed divergent expression of select genes in opioid-exposed males compared to females. Our findings provide molecular evidence of the sex effects of prenatal opioid exposure. The greater expression of *DRD2* and increased need for pharmacotherapy in opioid-exposed males confirms the findings from our prior study, suggesting dysregulated reward signaling is associated with the severity of NAS. The differential expression of genes in opioid-exposed males and females supports the need to incorporate sex as a biological variable in understanding and advancing science and public health measures for this vulnerable population.