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Integrated analysis of sex-specific regulation of RNA networks in the rat orbitofrontal cortex following heroin self-administration

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Opioids misuse accounts for >two thirds of drug overdose deaths in the US. Designing treatments to prevent opioid misuse requires an in-depth understanding of the neurobiological adaptations that the brain undergoes in response to opioids. A critical area involved in opioid seeking is the orbitofrontal cortex (OFC), which is activated in response to drug-associated cues, even following abstinence. Our lab used unbiased RNA sequencing in a rodent model of heroin self-administration (SA) to profile patterns of circular RNA (circRNA) and long noncoding RNA (lncRNA) regulation in the OFC following chronic heroin exposure, with the goal of identifying novel noncoding RNA mechanisms that are essential for drug-seeking behavior. CircRNAs are singled-stranded splice products with closed 5' and 3' ends that can act as microRNA (miRNA) sponges, modulate transcriptional events and interfere with RNA splicing and protein polypeptide synthesis. We demonstrate that heroin induces divergent patterns of regulation of each type of RNA in male and female animals. Additionally, we defined networks of circRNA:miRNA; circRNA:lncRNA and lncRNA:mRNA interactions that indicate the highly integrated manner in which these types of RNAs interact with one another following chronic heroin exposure. Lastly, we have functionally manipulated heroin-associated OFC circRNAs to demonstrate that regulation of a single circRNA in this critical brain region is sufficient to modulate heroin seeking behavior. This work is especially timely given the rising rates of opioid overdose deaths and highlights the value of further examining circRNA and lncRNA networks in addiction models to better understand the molecular consequences of opioid exposure.