

Name: Nithya Sarabudla, M.S.

Email: nithyas@wustl.edu

Opioid overdose death is associated with distinct patterns of differential gene expression in the preBotzinger complex

Previous gene expression studies have identified genes related to opioid overdose death (OOD) in addiction-relevant brain regions. However, no studies have yet characterized gene expression differences in the preBötzing (preBöt), despite the importance of this brain region in opioid-induced respiratory depression, the primary cause of OOD. Comparing gene expression in bulk preBot tissue of decedents who died of an opioid overdose (N = 42) to those who died of other causes (N = 40), we identified 27 significantly differentially expressed genes (DEGs; FDR-adjusted p-value < 0.05). Weighted Gene Co-expression Network Analysis (WGCNA) identified 94 co-expression modules across 41,537 expressed genes, five of which were significantly correlated with opioid overdose death status (p < 0.05). The most significantly associated module (r = 0.398, p = 0.0002), was enriched for neuroinflammatory signaling pathways including TNF, HIF-1, JAK-STAT, and NF- κ B signaling, with hub genes including STAT3 and SOCS3, consistent with active neuroinflammatory activation and hypoxic injury in the preBotC of opioid overdose cases. There was no evidence that DEGs were more associated with a genome-wide association study of opioid use disorder compared to other genes, suggesting these DEGs capture OOD-specific signals not captured in genetic studies of heavy opioid use. Only two of the DEGs we identified overlapped with the ~6,750 DEGs identified in a previously published snRNAseq experiment of opioid overdose death using tissue from the ventral midbrain, suggesting unique gene expression patterns in the preBöt compared to other brain regions. Our analyses suggest that opioid-induced expression changes in the brain's respiratory center that are distinct from those in addiction-relevant regions might serve as markers of OOD.

Authors:

Submitter: Nithya Sarabudla, Statistical Data Analyst, Washington University School of Medicine, St. Louis

Arpana Agrawal, PhD, Washington University School of Medicine

Emma Johnson, PhD, Washington University School of Medicine

Elliot Nelson, MD, Washington University School of Medicine