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Heroin overdose-associated transcriptional and epigenetic alterations in the orbitofrontal cortex concentrate in GABA interneurons and provide insight into cell type-specific regulatory response

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Opioid addiction remains a public health crisis and opioids cause more overdose deaths than any other drug of abuse in the United States. Therefore, there is an urgent need to uncover the biological basis of opioid addiction to guide prevention and develop novel treatments. Here we profiled transcriptional (RNA-seq) and epigenetic alterations (ATAC-seq, open chromatin regions; H3K27ac ChIP-seq, active promoters/enhancers) in the orbitofrontal cortex (OFC) from subjects who died of heroin overdose and control subjects. The data were obtained in the nuclei from three major brain cell types - MGE-derived inhibitory GABAergic neurons (GABA), excitatory glutamatergic neurons (Glu), and oligodendrocytes (OLIGs) that were separated from postmortem brains using fluorescent-activated-nuclear sorting. In both neuronal subtypes, heroin overdose led to decreased expression of multiple immediate early genes (*e.g.*, *FOS*, *NPAS4*). Overall, there were greater numbers of differentially expressed genes in GABA compared to Glu neurons or OLIGs. Compared to the other two cell types, GABAergic neurons also showed a large number of differentially acetylated H3K27ac peaks. Concordant changes in differentially accessible chromatin (ATAC-seq) and gene expression were observed in both neuronal subtypes, whereas no concordance was identified in OLIGs. Finally, we detected that delta-opioid receptor (*OPRD1*) had significantly higher expression in GABA compared to Glu neurons and OLIGs, whereas expression levels of the mu-opioid, kappa-opioid, and nociceptin receptors were lower compared to *OPRD1* and comparable between the neuronal subtypes. Our data suggest that the heroin-induced transcriptomic and epigenetic changes in the OFC occur predominantly in GABAergic neurons of the affected individuals.