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Transcriptomic changes in habenula following chronic fentanyl self-administration in rats

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A rise in deaths due to drug overdose has been driven by addiction to prescription analgesics such oxycodone, and the preponderance of the synthetic opioid fentanyl and fentanyl analogues. The habenula (Hb), a highly evolutionarily conserved epithalamic brain region, expresses high levels of μ-opioid receptors, which mediate the analgesic effects of opioids. The Hb modulates processing of reward and pain/aversive states through its connectivity with midbrain structures such as the dopaminergic ventral tegmental area (VTA), and the opioid receptor-rich interpeduncular nucleus (IPN). Furthermore, Hb circuit dysfunction is associated with alterations in reward-related behavior and responses to aversive or nociceptive stimuli. However, the molecular mechanisms mediating dysfunctions following chronic opioid use are unclear. Here, we subjected rats (n=8-11 per group) to an extended access fentanyl or saline self-administration (SA) paradigm consisting of short access sessions (2 hrs) followed by long access sessions (6 hrs) over 22-24 days during which rats showed escalating fentanyl intake. Brains were collected 60-90 min after the last SA session to measure gene expression changes associated with chronic fentanyl intake in the Hb as well as the amygdala using bulk RNA-sequencing. We found 88 (FDR < 0.05) differentially expressed genes in the Hb between saline and fentanyl SA rats. Chronic fentanyl SA induced distinct molecular changes in the rodent Hb compared to the amygdala. Results of this study provide new molecular insights into how Hb dysregulation contributes to opioid use disorder, which can be used to prioritize molecular targets for therapeutic development.