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Impact of neonatal opioid exposure on developmental trajectories of cortical GABAergic cell-types

Infants exposed to opioids in utero are at risk of developing Neonatal Opioid Withdrawal Syndrome (NOWS), marked by combination of acute somatic withdrawal symptoms. While opioid exposure in adulthood alters GABAergic transmission, how opioids affect the immature GABAergic system during development has remained unclear. We developed a mouse model of NOWS that delivers morphine throughout the entirety of gestation and for the first two postnatal weeks— a period that encompasses key developmental milestones of the developing GABAergic system. By profiling GABA-related gene expression across development, we uncover stage- and age-dependent alterations in cation-chloride cotransporters that appear at postnatal day 1 and persist into adulthood. At PND15, when mice experience spontaneous opioid withdrawal, we observe increased parvalbumin (PV) interneuron synapses and VGAT counts, with the most pronounced changes in the prelimbic cortex. To examine if these early-life changes produce persisting phenotypes, we assessed related behavioral alterations in adulthood. Morphine mice had a reduced threshold for seizure induction and a blunted sensitivity in response to benzodiazepines. To test lasting consequences, we assessed adult behavior and found a reduced seizure threshold and a blunted sensitivity to benzodiazepines in morphine-exposed mice. Collectively, these findings reveal that perinatal morphine exposure reprograms the developing GABAergic system, driving persistent molecular and behavioral changes into adulthood.

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