How prenatal opioid exposure impairs breathing in newborns

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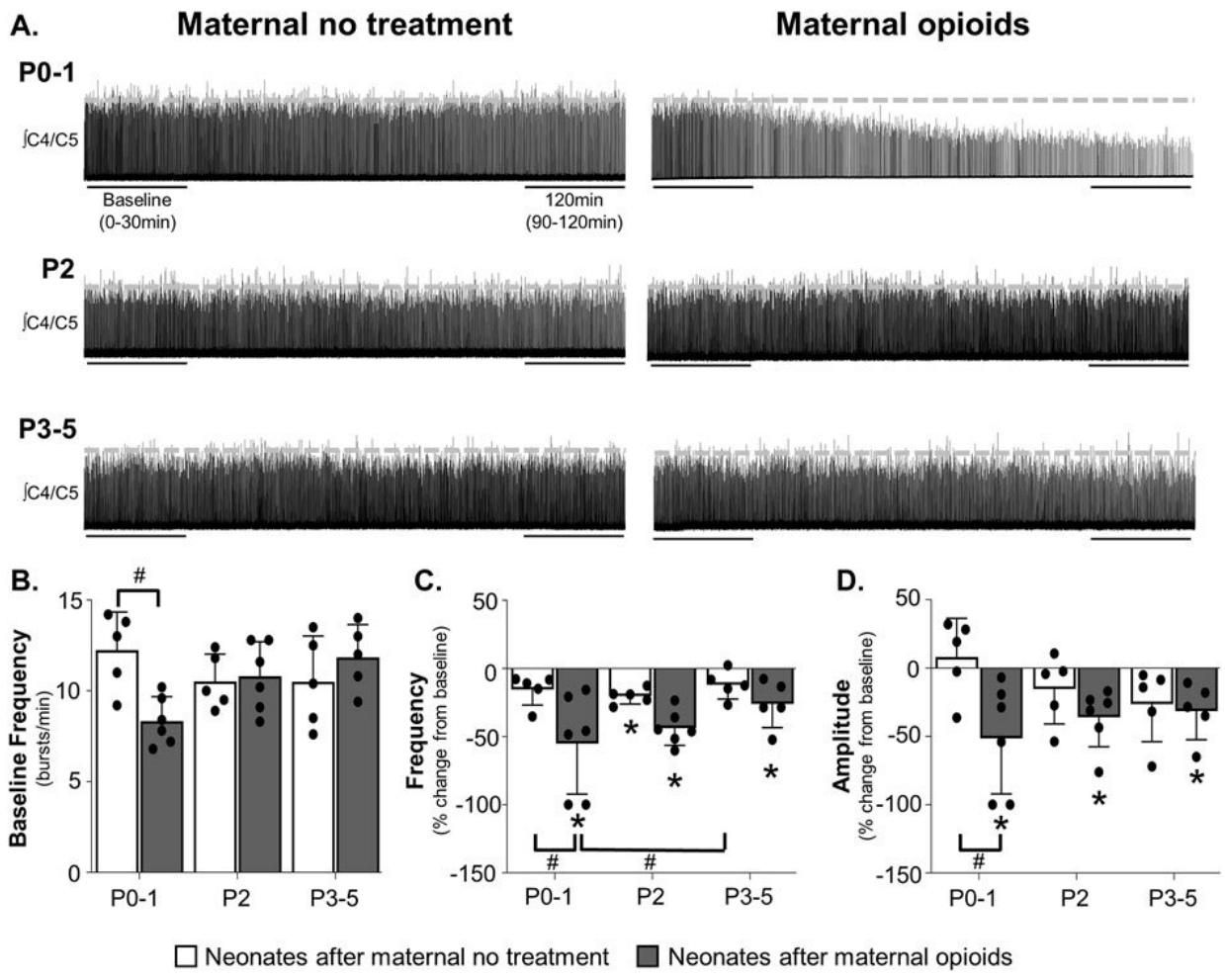

Maternal opioids age-dependently impair neural activity from isolated neonatal respiratory control networks. Representative neurograms **(A)** from isolated respiratory control networks show respiratory activity in neonatal brainstem-spinal cords were maintained in neonates after maternal no treatment at all ages and decreased in P0-1 neonates after maternal opioids. Baseline respiratory burst

frequencies [0–30 min, **(B)**] were similar in neonates after maternal no treatment (white bars) at all ages, reduced in P0-1 neonates after maternal opioids (gray bars), and unchanged in older (P2 and P3-5) neonates after maternal opioids. Respiratory burst frequencies **(C)** decreased from baseline in P2 neonates after maternal no treatment and in neonates after maternal opioids at all ages. Respiratory burst frequency decreased in P0-1 neonates after maternal opioids compared to P0-1 and P3-5 neonates after maternal no treatment. Respiratory burst amplitudes **(D)** were maintained in all neonates after maternal no treatment and decreased from baseline in all neonates after maternal opioids. Respiratory burst amplitudes decreased in P0-1 neonates after maternal opioids compared to P0-1 neonates after maternal no treatment (*p $^{\#}$p Frontiers in Physiology (2023). DOI: 10.3389/fphys.2023.1109754

Exposure to opioids in the womb affects the development of important circuits in the brain and spinal cord that control breathing, new University of Oregon research shows.

The study, led by Adrianne Huxtable in the UO's Department of Human Physiology and Institute of Neuroscience, was recently published in *Frontiers in Physiology*. Its findings could lead to better treatments and interventions for at-risk infants.

As opioid use has risen in the United States, so too has the number of infants exposed to the addictive drugs during pregnancy. Those babies often experience withdrawal symptoms after birth, and some experience longer-term health problems.

Huxtable's lab focuses on how the brain and spinal cord control breathing. Opioids slow breathing and heart rate, and opioid-exposed infants often have breathing difficulties, among other symptoms. But it's difficult to pick apart exactly how opioids affect the formation of the neural circuits that control breathing, Huxtable said, since exposure can

cause cascading effects on development.

"We know opioids can derail other aspects of neural development," said Huxtable, who is part of the College of Arts and Sciences. "We want to start to tease out whether these breathing deficits come from opioids at the beginning of development or if they are also shaping circuits later."

Researchers exposed pregnant rats to opioids around the time rhythmic respiratory activity begins in the fetus. This rhythmic activity, which is a relatively late-term development, is a prerequisite for breathing outside the womb. By the time it starts, many other key neural circuits have already formed.

Then, the team isolated parts of the breathing-related neural circuitry from the offspring and studied them in a dish for five days. Those neurons will continue to work outside the body, even though oxygen isn't being exchanged, Huxtable explained. Researchers found that opioids hung around in the nervous systems of neonatal rats exposed in the uterus, impairing respiratory control in the first few days after birth.

One area of interest was the primary respiratory rhythm generator, the part of the brainstem that keeps breathing steady without conscious thought. In most people who die from opioid overdoses, this rhythm generator is silenced, so scientists know the drugs affect that mechanism, Huxtable said.

In the experimental rats, the rhythm-regulating circuits were less sensitive to opioids given after birth, suggesting lasting changes from exposure during development.

But just how broad the developmental effects were within respiratory circuits was surprising, Huxtable said. The drugs' impact went far beyond the respiratory rhythm generator, impairing activity in many of

the neural circuits in the central nervous system that control breathing.

"The next step is narrowing down where within these central respiratory networks this is occurring, whether it's changes in neurons or support cells," Huxtable said. Her team also hopes to explore whether different opioids have similar effects.

More information: Sarah A. Beyeler et al, Maternal opioids age-dependently impair neonatal respiratory control networks, *Frontiers in Physiology* (2023). DOI: 10.3389/fphys.2023.1109754

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