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Caffeine prevents PGE1-induced disturbances in respiratory neural control

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Researchers from the Department of Pediatrics at Case Western Reserve University School of Medicine and University Hospitals Rainbow Babies and Children's Hospital presented results of a study that investigated

whether there are any deleterious effects of prostaglandin E1 (PGE1) treatment on breathing and whether these effects would be prevented via pre-treatment with caffeine.

PGE1 is a life-saving medication for infants with certain types of congenital heart disease, but can also cause respiratory complications such as apnea, which if severe enough may necessitate intubation. The study used an animal model to test whether pre-treatment with caffeine could prevent the PGE1-induced respiratory complications. Caffeine is commonly used in the neonatal intensive care unit to treat apnea of prematurity, and the lead authors (Lisa Mitchell, DO, and Peter M. MacFarlane, Ph.D.) proposed that caffeine could also have similar benefits in infants treated for congenital heart disease.

The study, called "Caffeine prevents prostaglandin E1-induced disturbances in respiratory neural control: therapeutic implications for infants treated for congenital heart disease," was presented as a platform discussion at the 2019 Pediatric Academic Societies Meeting in Baltimore.

Following a single injection of PGE1, whole-body plethysmography was used in baby rats to assess their ability to increase breathing (called the hypoxic ventilatory response, HVR) in response to an acute hypoxia challenge. In subsets of animals, rats received a subcutaneous injection of caffeine (5mg/kg, which has been shown to be an antagonist of adenosine receptors in the brain) one hour prior to PGE1. Brainstem regions containing respiratory control centers were removed and tested via RT-PCR for markers of inflammation (TNFα, IL-1β, IL-6, and iNOS) and microglia (Iba-1).

Two hours after PGE1 injection, the rats exhibited a significant alteration in the HVR, a finding suggestive of unstable breathing possibly via an undesirable disruption of CNS respiratory neural control

regions. Further supportive evidence of a CNS effect of PGE1 on breathing was the finding that PGE1 also decreased brainstem Iba-1 (a marker of microglia) mRNA expression. Microglia are the resident immune cells of the CNS and have previously been shown to modulate breathing, but this study is the first to show that they may play a role in mediating the respiratory disturbances associated with PGE1. Perhaps the most surprising finding was that pretreatment with caffeine prevented all the adverse effects of PGE1 on both breathing and Iba-1 expression. A more selective adenosine 2A receptor antagonist (MSX-3) had a similar beneficial effect.

Their conclusions: "We propose that PGE exerts adenosine-mediated effects on brainstem mechanisms of respiratory control, which may lead to destabilization of breathing in human infants undergoing treatment for congenital heart disease. Prostaglandin's effects could be mediated thorough microglia, and caffeine could be a convenient treatment to prevent respiratory instability in infants receiving PGE1 infusion."

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