PRENATAL ALCOHOL EXPOSURE EXAGGERATES NLRP3 INFLAMMASOME-DEPENDENT IMMUNE INTERACTIONS FOLLOWING MORPHINE TREATMENT THAT PARADOXICALLY INCREASES THE CHRONICITY OF PATHOLOGICAL PAIN IN MICE.

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In utero alcohol exposure can lead to Fetal Alcohol Spectrum Disorder (FASD) which can result in a range of neurobehavioral deficits. Prenatal Alcohol exposure (PAE) can lead to chronic central nervous system (CNS) immune dysfunction during adulthood. Our prior work has demonstrated that adult PAE rat offspring with minimal nerve injury develop pathological light touch sensitivity or allodynia due to aberrant peripheral and spinal glial-immune interactions resulting in increased levels of pain inducing proinflammatory cytokine, IL-1β. We suspect that PAE-related adaptations may "prime" CNS glial-immune cells to over-respond to subtle immune challenges through innate immune receptors, TLR4 and Nod-like receptor family pyrin domain containing 3 (NLRP3) signaling. Interestingly, morphine is known to be the standard opioid used as a pain therapeutic. In addition to signaling via μ-opioid receptor, recent literature suggests that morphine can activate glial TLR4 leading to NLRP3 inflammasome activation resulting in an increased production of mature IL-1β protein. These overlapping immune interactions from PAE and morphine lead us to hypothesize that morphine treatment following adult-onset peripheral nerve injury may paradoxically prolong allodynia in PAE offspring through an aberrant NLRP3 activation and if true, selectively blocking the NLRP3 inflammasome activity would reverse the morphine-prolonged allodynia in PAE mice. Our data suggest that morphine (10 mg/kg, 5 subsequent days) treatment in PAE mice with a minor nerve injury significantly increased the duration of allodynia, in comparison to nerve injured PAE mice without morphine treatment. We also confirmed that this morphine-induced prolongation of allodynia in PAE mice is sex-independent. Moreover, treatment with a small-molecule inhibitor of NLRP3, MCC950 (i.p. 10 mg/kg) resulted in full reversal of morphine induced allodynia with as soon as 90 minutes post-injection, compared to the vehicle treated mice. MCC950-mediated reversal of allodynia persisted at 24 hours post- injection. At this timepoint, pain-relevant brain regions and spinal cord tissues were collected. Our ongoing work is focused on evaluating differential expression of immune molecules related to the TLR4-NLRP3 pathway in the presence of morphine and PAE. These data provide evidence that in PAE and morphine interactions involve aberrant NLRP3 activation, which may be predictive of adverse responses to opioids intended to treat pain in individuals with FASD.

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