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Effect of dexpramipexole on neuropathic pain in prenatal alcohol exposed male and female subjects

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1. Introduction

- Neuropathic pain can be described as the result of damage caused to the somatosensory system manifested as a pathological sensitivity to light touch, clinically referred to as allodynia.
- Neuropathic pain is mediated, in part, by cytokines released from activated resident glial cells and peripheral immune cells that invade the central nervous system through a conversion of astroocytes to microglia.
- Our lab has previously demonstrated that prenatal alcohol exposure (PAE) is a risk factor for developing chronic neuropathic pain from very minor injuries to peripheral nerves of the somatosensory system that project to and communicate to spinal pain projection neurons.
- IL-1β is a potent pro-inflammatory cytokine that is elevated in spinal cords and peripheral immune cells from PAE offspring with either nerve damage or immune challenge, respectively.
- IL-1β is released by macrophages and to a lesser extent, T cells.
- Dexpramipexole ([β]-pramipexole) is an anionformer of [β]-pramipexole and has virtually none of the dopamine receptor binding activity that [β]-pramipexole exerts. However, given that dexpramipexole reduces caspase-3 activity and cell death, we speculated that dexpramipexole may exert anti-inflammatory properties on immune cells and glia.
- Therefore, we tested the hypothesis that administration of dexpramipexole will result in a decreased inflammatory response and reduced allodynia in PAE rats.
- To test this hypothesis, we administered an intrathecal (I.T., subarachnoid, peri-spinal) injection of dexpramipexole to determine if spinal glia and local immune cells could respond to dexpramipexole and lead to reversal of allodynia.
- In addition, we collected immune cells from the spleen (majority T-cells) and peritoneal cavity (PEC: macrophages/microphages), and stimulated them with lipopolysaccharide (LPS) alone, or in combination with dexpramipexole to determine whether dexpramipexole can decrease IL-1β protein levels.

2. Methods

- **Prenatal Alcohol Exposure Model:** Rat dams were provided Sac-sweetened alcohol (5%) or Sac-sweetened water for 4 hours/day during gestation (SBEs: ~60 mg/d). Offspring were acclimated to a 12:12 light cycle and remained in the colony room for ~4 months until the time of experimentation.
- **Habitation and Chronic Constriction Injury (CCI):** Rats were housed in the colony room for 4 months prior to the initiation of experiments. They were then habituated for a week for an hour a day. Chronic constriction injury model is a rat model of neuropathic pain based on a unilateral loose ligature of the sciatic nerve. Chronic constriction injury (CCI) consisted of a single loose ligature of the left sciatic nerve using 4–0.