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Development of Nociception by a direct way to modulate the nociceptive pathway at the spinal level, and to reduce pain perception in female rats with alcohol exposure

Introduction

Neuropathic pain can be described as the damage caused to the somatosensory system manifested as an increase in sensitivity to light touch, clonic referred to as allodynia. Prenatal alcohol exposure is a risk factor for developing allodynia via enhanced immune-inflammatory actions in the central nervous system (CNS) such as the spinal cord. Neuropathic pain is mediated by cytokines secreted from infiltrating peripheral immune cells to CNS and glial cells that reside within the CNS. Interleukin-1β (IL-1β) is a potent anti-inflammatory cytokine that inhibits the production of a variety proinflammatory cytokines and chemokines released by different types of immune cells such as T helper (Th1) and natural killer (NK) cells, and macrophages, which prevent further tissue damage. Interleukin-1β (IL-1β) is a potent cytokine that serves as a T cell and macrophage activator in response to inflammation and can further enhance inflammatory processes.

While pramipexole serves as a dopamine receptor agonist (D2/D3 receptors) used to reduce progressive movement disorders observed in Parkinson’s disease, dexpramipexole (t-enantiomer) is an enantiomer of (-)-pramipexole and has a very weak actions at the D2/D3 receptors. However, dexpramipexole reduces caspase-3 activation, and decreases cell death, suggesting that this compound may play a role in anti-inflammatory processes.

Prior unpublished data from our lab show that an i.v. injection of dexpramipexole reverses ongoing allodynia in non-PAE mice.

Further, we have observed that whereas control CCI rats display signs of tactile allodynia, the dexpramipexole group shows reduced tactile allodynia levels.

In the current experiments, we administered an i.v. injection to female rats to test whether dexpramipexole can also act directly on spinal glia and spinal immune cells to reverse allodynia.

In a parallel experiment, to test the possible anti-inflammatory effect of dexpramipexole on peripheral immune cells, cells were collected from the spleen because these cells include a large population of T cells.

In-vitro manipulation of splenocytes with an immune stimulator was performed to determine if treatment with dexpramipexole could elevate mRNA levels of IL-10 while simultaneously decreasing IFN mRNA levels.

Hypothesis

Effect 1: Injection of dexpramipexole will reduce allodynia in female rats and increase IL-10 mRNA while decreasing IFN mRNA levels from splenocytes.

Methods

Development of Sac and PAE rats:

Rat dams were provided Sac-sweated alcohol (5%) or Sac-sweated water for 4 hours/day during gestation (CECs: ~60 mg/d).

Habitation and Chronic Inflammation Injury (CCI):

Long-Evans Rats were housed in the counting room for 4 months prior to the initiation of experiments. They were then habituated for a week for an hour a day. Chronic injury-induced +CCI model is a rat model of neuropathic pain based on a unilateral loose ligature of the sciatic nerve. Chronic constriction injury consisted of a single loose ligation of the left sciatic nerve (L4-5).

Intraluminal (L) injection

Lightly anesthetized rats received a single i.t. injection via acute subarachnoid puncture with drug delivered via a sterile PE-10 tubing threaded 3 cm intrathecally to the spinal cord L5/S6 level. Intrathecal injections occurred on Day 10/11 post-surgery. Immediately following drug administration, tubing is removed, and rats are allowed to recover before being placed in their home cage. All rats recovered within 5 min of drug administration and resumed normal locomotor function prior to being placed back into their home cages.

Figure 1: Intrathecal dexpramipexole does not significantly reverse allodynia. Following CCI, female saccharin (SAC) rats develop a weak ipsilateral allodynia in the hindpaw, which was described as a 0% difference in sensitivity between stimulated and unstimulated sides. The right contralateral paw was used as control. The data show that dexpramipexole does not significantly affect allodynia in SAC rats, similar to vehicle saline.

Figure 2: Dexpramipexole induces greater production of IL-10 when stimulated with LPS in splenocytes from SAC treated rats but not in cells from PAE rats. Prenatal alcohol treated offspring revealed increased IL-10 production from dexpramipexole with LPS-stimulated compared SAC controls. These data suggest that spinal application of dexpramipexole fails to elevate IL-10 levels to achieve reversal of allodynia in females.

Figure 3: Dexpramipexole does not significantly reduce IFN mRNA in splenocytes from SAC rats nor from splenocytes from PAE when stimulated with LPS. Prenatal alcohol treated offspring did not reveal statistically significant difference in the production of IFN when treated with dexpramipexole.

Conclusions

Our female rat model of PAE and neuropathic pain shows that damage to the sciatic nerve results in clear susceptibility to developing neuropathic pain (allodynia). Furthermore, peripheral immune cells such as splenocytes (consisting predominately of T cells) from PAE rat offspring reveal a blunted anti-inflammatory response. In terms of the effectiveness of dexpramipexole, we can see that PAE offspring do not show significant reversal of allodynia after an i.t. injection. This could be because the dose used was too low, and larger doses may be required to reverse allodynia in these female rats. On the other hand, immune cells from culture oxPCR suggest that immune cells from PAE rats reveal a blunted anti-inflammatory response to dexpramipexole treatment, while immune cells from SAC controls robustly produce IL-10 in response to dexpramipexole. In splenocytes from either SAC or PAE rats, dexpramipexole did not significantly alter the proinflammatory T cell cytokine, IFNγ.

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Reference