SEX DIFFERENCES IN THE INVOLVEMENT OF MICROGLIA AND KCC2 IN NEUROPATHIC PAIN

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INTRODUCTION / AIM

Microglia-neuron signalling is integral in mediating pain hypersensitivity resulting from peripheral nerve injury in rodents. After nerve injury, activation of P2X4 receptors on microglia results in release of brain-derived neurotrophic factor, which acts on neurons to produce downregulation of the potassium chloride co-transporter KCC2. However, we recently demonstrated that microglia contribute to pain processing in male but not female mice. Thus, we wished to determine whether this sex difference also exists in rats and to further delineate the mechanisms which mediate pain hypersensitivity in females.

METHODS

Neuropathic pain was induced in mice and rats using spared nerve injury and the cuff model, respectively. Mechanical sensitivity was measured via von Frey fiber application.

RESULTS

First, we found that intrathecal injection of minocycline (300ug), which inhibits microglial functioning, alleviates pain hypersensitivity in male but not female rats. Second, we demonstrated that there is upregulation of p2rx4 after nerve injury in male rats only. Finally, we found that intrathecal injection of the KCC2 activator CLP290 (80ug) in mice reverses pain hypersensitivity in both sexes.

DISCUSSION / CONCLUSIONS

Our experiments indicate that the sex difference in microglia involvement in pain also occurs in rats. Furthermore, KCC2 contributes to pain hypersensitivity in both sexes despite a lack of microglial involvement in females. Thus, the spinal mechanisms mediating pain hypersensitivity appear to converge between the sexes at the neuronal level. Our findings highlight the importance of including female subjects in preclinical pain research.

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