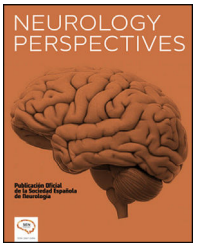
Neurology Perspectives 1 (2021) 242–243

NEUROLOGY PERSPECTIVES

www.journals.elsevier.com/neurology-perspectives



SCIENTIFIC LETTER

Role of microglia in the pathophysiology of neuropathic pain: Hormonal, neuroimmunological, and nociceptive differences by sex

Papel de la microglía en la fisiopatología del dolor neuropático: Diferencias hormonales, neuro inmunológicas y nociceptivas por sexo

L. Arce Gálvez, M.D. [a,*], **D.A. Mendez Vega, M.D.** [b]

[a] *Department of Physical Medicine and Rehabilitation, Universidad del Valle, Cali, Colombia*
[b] *Department of Gynecology and Obstetrics, Universidad Libre, Cali, Colombia*

Received 20 September 2021; accepted 25 September 2021
Available online 2 October 2021

Dear Editor,

It has been quite interesting to read the scientific letter by A. Alcantara Montero et al.[1] The role of different cell types, as well as receptors that may mediate the genesis of neuropathic pain and neuronal plasticity, is increasingly studied trying to define possible therapeutic interventions.

An interesting advance in understanding the role of glial cells in neuropathic pain is the neuroimmune characteristics concerning sex.[2] There are qualitative and quantitative sex differences in pain sensitization and analgesia; finding that highly prevalent pain syndromes such as fibromyalgia, arthritis, and migraine occur with a higher incidence in women.[2] Given the difficulty of human studies, animal models such as rodents have been used in an attempt to define transmission, conceptual models, and neuronal coding[2]; finding in chronic pain a greater sensitivity to nociceptive stimuli by females. Tactile allodynia is frequent in females, while hypersensitivity in context-dependent tonic pain is more frequent in males.[2]

These differences are based on the nociceptive and opioid analgesia threshold, which are generated from the gonadal hormonal organization in the gestational phase. It is known that fetal exposure to testosterone is necessary for the phenotype of decreased nociceptive sensitivity and increased analgesia to opioids, but it also generates pro-nociceptive events found more frequently in males.[3] Nociceptive and antinociceptive processes are found to vary with estrogenic exposure but are more dependent on the timing of the ovarian cycle,[2] where progestogens have a protective effect that may facilitate physiological changes in pregnancy, childbirth, and lactation.[2]

In the tissue changes generated by an injury, there is an immune cell response, where macrophages, neutrophils, T lymphocytes, and Schwann cells secrete communication factors with astrocytes, microglia, and oligodendrocytes of the central nervous system (CNS) to release mediators of sensitization to nociceptors. These changes at the glial level and in their adjacent neurons promote allodynia and hyperalgesia. In these processes, not only the p38 MAPK pathways of microglia are activated but also neurotransmitters such as glutamate, cytokines, chemokines, neuropeptides, bioactive lipids derived from cyclooxygenases and lipoxygenases, as well as the endocannabinoid system.[2] There are sex differences in the neuroimmune response that include glial cell-mediated reactions,[4] the number of immune cells, modifications for the immune response to

* **Corresponding author at:** Hospital Universitario del Valle, street 5 No 36-08, 112 building, 1 floor, Cali, Colombia.
E-mail address: leonardo.arce@correounivalle.edu.co (L. Arce Gálvez).

https://doi.org/10.1016/j.neurop.2021.09.004

gestation, epigenetic factors, and susceptibility to autoimmune diseases.[2] This generates nociceptive processes that are specific to men and women.

In men, spinal microgliosis generates allodynia mediated by factors such as p38, purigenic stimulation, tumor necrosis factor, macrophages, and fractalkine receptors, which act on tropomyosin kinase B receptors in dorsal horn neurons. In women, on the other hand, it is considered that allodynia mechanisms can be generated by the CD4 lymphocyte response at the central and peripheral levels.[5] Microglia have a predominant role in the genesis of neuropathic pain in men, but in women, they may be involved in mechanisms that modify adaptive immune mechanisms.[2] Microglial P2X7 in women is activated in arthritis, but not following nervous system injury; another important factor is progesterone-dependent neuroregulin-1 which produces a positive regulation of allodynia by modifying the production of interleukins (IL) 6,8 and 10, where IL-6 may be a protective factor in women for neuropathic pain.[2] There are less studied factors specific to women that may play an important role in the difference in the expression of neuropathic pain by sex, such as the dopaminergic receptors DRD1, DRD3 in the CNS, prolactin receptors in the sensory neurons, and the Gaba A receptor in the periaqueductal gray matter.[2]

We, therefore, consider the contribution of A. Alcantara Montero et al.[1] very valuable and we seek with this letter to include consideration of the hormonal, neuroimmunological, glial, and nociceptive pathway differences that exist between men and women, which will be an important point to be able to intervene effectively in people with neuropathic pain in the future.

Conflict of interest

We declare that we have no conflict of interest.

Funding

The authors did not receive funding to carry out this report.

References

1. Alcántara Montero A. Pacheco de Vasconcelos SR, Goicoechea García C.Neurol Perspect: Peñato Tarifa F. Role of microglia in the pathophysiology of neuropathic pain; 2021. https://doi.org/10.1016/j.neurop.2021.06.001.
2. Gregus AM, Levine IS, Eddinger KA, Yaksh TL, Buczynski MW. Sex differences in neuroimmune and glial mechanisms of pain. Pain. 2021;162.
3. Sorge RE, LaCroix-Fralish ML, Tuttle AH, Sotocinal SG, Austin J-S, Ritchie J, et al. Spinal cord Toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice. J Neurosci. 2011;31:15450–4. https://doi.org/10.1523/JNEUROSCI.3859-11.2011.
4. Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. J Neurosci Res. 2017;95:500–8. https://doi.org/10.1002/jnr.23831.
5. Sorge RE, Mapplebeck JCS, Rosen S, Beggs S, Taves S, Alexander JK, et al. Different immune cells mediate mechanical pain hypersensitivity in male and female mice. Nat Neurosci. 2015;18:1081–3. https://doi.org/10.1038/nn.4053.