

Sexual dimorphism of neuroimmune cells and its impact on the central nervous system: A special issue

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Abstract: Neuroimmune-related sex differences contribute to the complexity of neurological disorders, such as drug abuse, depression, and chronic pain. The collection of articles presented in this issue add to our understanding of sex as a critical biological variable in the study of psychiatric and neurological diseases.

Significance statement: Consideration of sex in the design and interpretation of study results is critical. Sex differences may warrant different treatment approaches for diseases in which sex or gender influences disease outcomes. The studies and reviews presented here examine the contribution of sexual dimorphism in the physiological responses and pharmacological treatments of neurological and psychiatric disorders.

Sex-dependent differences in neuroimmune cells have recently been recognized as a differentiating factor in physiological settings, including synapse remodeling and maturation and postnatal development. These differences have implications for gender-specific brain wiring and for the treatment of neurological and psychiatric diseases. This special issue of the journal showcases original research and reviews pertaining to the broad and intricate repertoire of neuroimmune-related sex differences and their impact on the central nervous system. Two ASPET symposia during the Experimental Biology conference in April 2019 focused on the biological manifestations of such differences. Presenters in the two symposia, one of them hosted by the authors of this introduction, provided the content included here.

The cells involved in immunoregulation of the CNS are an exciting line of research and a potential therapeutic target for neurological diseases. We start this issue with a review by Gopinath *et al.* (Gopinath *et al.*, 2020) outlining the roles of peripheral myeloid and neuroimmune cells in the healthy brain as well as their compromised contributions in the context of Alzheimer's and Parkinson's disease. Gustavo Martinez-Muniz and Susan K. Wood summarize recent preclinical and clinical studies that examine how stress induces inflammation and how inflammation may lead to depression (Martinez-Muniz and Wood). They also describe the sex differences in the immune response to stress, the role of antidepressant therapy on inflammation and the antidepressant-like effects of anti-inflammatory compounds. Alexandros G. Kokkosis and Stella E. Tsirka present recent evidence on the aberrant activation of neuroimmune cells and their impact on mental health disorders as a whole (Kokkosis and Tsirka, 2020). They examine the role of sex hormones, genetics, and environmental factors on the etiology of neuropsychiatric conditions. Following up on distinct neuropsychiatric susceptibilities, Paul W. Czoty and Michael A. Nader showcase their work on lofexidine and guanfacine, two alpha-2 adrenergic receptor agonists that have modest effects on reducing cocaine choice in male and female cynomolgus monkeys (Czoty and Nader, 2020).

Halievski *et al.* review past literature on sex-dependent differences in microglial P2X4R signaling, emphasizing how these differences might hinder proper treatment of chronic pain in both males and females (Halievski *et al.*, 2020).

Ewald *et al.* give us insight into the role of microglia in the modulation of the neuronal circuits that control breathing. Their work shows major transcriptomic differences in various microglial populations depending on their CNS location, as well as significant sex-dependent differences in gene expression in spinal cord microglia. Their findings may shed light on the cellular mechanisms responsible for the anatomical differences in breathing control seen in males and females (Ewald *et al.*, 2020). Finally, Maricedes Acosta-Martinez examines the role of estrogen receptors in the sex and age-dependent regulation of microglial function, using ischemic stroke as an example of a disease context where estrogen receptors shape the microglial response (Acosta-Martinez, 2020).

These articles point to our new understanding that neuroimmune-related sex differences play an important role in the physiological and pharmacological responses to neurological disorders. As additional reports become published describing such differences, it becomes increasingly evident that sex as a biological variable is indeed critical, and should be taken into account in the design and interpretation of study results. And such design may be even more complex when gender differences become accounted for as well. We hope to have provided an initial collection of important work being done in this area and to have shown how advances in this field might shape treatments for neurological and psychiatric disorders in the future.

Abbreviations: None needed

References

- Acosta-Martinez M (2020) Shaping microglia phenotypes through estrogen receptors: Relevance to sex-specific neuroinflammatory responses to brain injury and disease. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Czoty PW and Nader MA (2020) Effects of the Alpha-2 Adrenergic Receptor Agonist Lofexidine on Food-Cocaine Choice in Socially Housed Cynomolgus Monkeys. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Ewald AC, Kiernan EA, Roopra AS, Radcliff AB, Timko RR, Baker TL and Watters JJ (2020) Sex- and region-specific differences in the transcriptomes of rat microglia from the brainstem and cervical spinal cord. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Gopinath A, Collins A, Khoshbouei H and Streit W (2020) Microglia and other myeloid cells in CNS health and disease. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Halievski K, Ghazisaeidi S and Salter MW (2020) Sex-dependent mechanisms of chronic pain: A focus on microglia and P2X4R. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Kokkosis AG and Tsirka SE (2020) Neuroimmune mechanisms and sex/gender-dependent effects in the pathophysiology of mental disorders. *The Journal of pharmacology and experimental therapeutics*. [contributed article]
- Martinez-Muniz G and Wood S Sex differences in the inflammatory consequences of stress: Implications for pharmacotherapy. *The Journal of pharmacology and experimental therapeutics* in press (JPET/2020/266205). [contributed article]