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Themed Section: The Importance of Sex Differences in Pharmacology Research

EDITORIAL

The importance of sex differences in pharmacology research

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There still exists a sex bias in preclinical research where male subjects are primarily used. In this themed section of the British Journal of Pharmacology, we discuss why this problem exists and how it might contribute to translation and reproducibility issues in research. The articles here highlight sex differences in psychiatric disorders, addiction, dementias, metabolic diseases, and cardiovascular risk. The role of sex hormones, and inflammatory processes as mediators of the observed sex differences, is discussed. Given the variety of disorders highlighted in this issue that show sex differences, these articles underscore the importance of examining both sexes in research.

In 2014, the National Institutes of Health in the United States released policies stating that, for preclinical research to be funded, sex as a biological variable must be considered and single sex studies must be justified (Clayton & Collins, 2014). Similar policies are now being introduced by funding bodies around the world. The repercussions of a history of selectively studying males is not only the lack of knowledge but also the potential for harm when attempting to treat females with drugs developed and tested only in males. It has been acknowledged that some of the issues with translation and reproducibility that have plagued preclinical research may be driven by the inadequate inclusion of females or inadequate analysis of data to allow for sex-specific conclusions. Astonishingly, even when the disease of interest is a female-prevalent disorder, a male bias exists. Only 56% of the studies researching female-prevalent disorders reported which sex was used, and of these, only 12% included female animals or both sexes (Yoon et al., 2014). This problem is emphasized in the review by Kokras, Hodes, Bangasser, and Dalla (2019) in this issue. Here, they describe how compounds based on the hypothalamic–pituitary–adrenal (HPA) axis, that have potential as new therapeutic targets for depression have not translated successfully. Depression is twice as likely to occur in women, compared to men, and Kokras et al. (2019) propose that sex differences in the function of various HPA axis elements may well contribute to the failure of novel HPA axis-based drugs in clinical trials.

In a large study that consolidates the importance of sex, the International Mouse Phenotyping Consortium examined 10 institutes, 14,000 wild type, and over 40,000 mutant mice for 234 traits. They found that sex was often a significant source of variation and a modifier of treatment effects (Karp et al., 2017). In this issue, Karp and Reavey (2019) consider why the male bias exists and highlight reasons to include females in biomedical research. Notably, they provide a solution for changing the current standard practice of sex bias in preclinical research and the resistance to change. They suggest using organisational change theory as a tool to shape strategies needed at an individual and institute level to change the *status quo* and create a scientific environment that automatically implements sex sensitive approaches (Karp & Reavey, 2019). Encouragingly, since the introduction of policies to promote the consideration and inclusion of both sexes in preclinical research, a large number of papers, including original research and reviews, have been published highlighting significant sex differences. In this issue, we provide an up-to-date account on how sex influences disease processes, response to therapeutics, and therefore drug development.

Sex differences have been observed in many disorders, from psychiatric disorders including schizophrenia and anxiety, through to substance abuse, dementias, and even metabolic disorders such as cardiovascular disease and obesity, highlighting the need to consider sex in all realms of preclinical research. In this issue, Gogos, Ney, Seymour, Van Rheenen, and Felmingham (2019) describe the sex differences in prevalence, onset, symptom profiles, and disease outcome that are evident in three psychiatric disorders: **schizophrenia**, **bipolar disorder** and **post-traumatic stress disorder**. Likely candidates to explain these sex differences are gonadal hormones. The review by Gogos et al. (2019) details the clinical evidence that **oestradiol** and **progesterone** are dysregulated in females with these psychiatric disorders and concludes that low levels of oestradiol may increase the risk of disease development and worsen symptom severity. Interestingly, original research by Yoest, Cummings, and Becker (2019) provides evidence that oestradiol acutely and rapidly regulates **dopamine** release in females and dopamine reuptake in males in the nucleus accumbens shell. Post-traumatic stress disorder is a female-prevalent disorder characterised by impaired fear inhibition. Using mouse models of fear inhibition, Clark, Drummond, Hoyer, and Jacobson (2019) provide

evidence that sex differences influence processing of fear, but not safety-based behaviour in C57Bl/6J mice. Female mice exhibited decreased fear recall following conditioning but slower fear extinction, whereas the acquisition and recall of safety were not overtly influenced by sex (Clark et al., 2019).

Addiction vulnerability involves complex gene × environment interactions leading to a pathological response to drugs. Identification of the genes mediating these interactions is an important step in understanding the underlying neurobiology and in identifying potential targets for pharmacotherapy. Yet rarely have such analyses examined sex-specific influences. Bagley, Szumlinski, and Kippin (2019) demonstrated that sex was a significant factor that mediates the effects of early life stress on responsiveness to **cocaine**.

In this issue, Hornarpisheh and McCullough (2019) present a review on sex differences in neurodegenerative and neurovascular disease (**Alzheimer's disease**, cerebral amyloid angiopathy and stroke). They suggest that sex differences in brain structure, molecular and genetic markers, and cumulative oestrogen exposure are key risk factors for Alzheimer's disease, while sex differences in stroke may be driven by sex hormones, or differences in microglial function and in the immunoregulatory role of microRNAs. They also outline sex differences in the response to various approved pharmacological therapies for these dementias (Hornarpisheh & McCullough, 2019).

As discussed in this issue, sex differences are observed in disorders beyond the brain. Henstridge, Abildgaard, Lindegaard, and Febbraio (2019) review the literature on sex differences in metabolic disease and how this may be mediated by inflammatory pathways. Men have a higher risk of metabolic diseases, such as diabetes, compared to pre-menopausal women. This review outlines how oestradiol and sex-specific behaviours play a role in the observed sex differences in immune function, **metabolic syndrome**, various tissues relevant to inflammatory-related metabolic syndrome, and several pro- and anti-inflammatory cytokines (Henstridge et al., 2019). Arterial stiffness is an independent predictor of cardiovascular disease risk. The review by DuPont, Kenney, Patel, and Jaffe (2019) details evidence that there are sex differences in the time course of aging-related arterial stiffness and the associated cardiovascular disease risk which increases disproportionately in post-menopausal women. The authors focus on sex differences in vascular stiffness induced by aging, **obesity, hypertension** and sex-specific risk factors, as well as the impact of hormonal status, diet, and exercise on vascular stiffness (DuPont et al., 2019). The review by Taylor, Ramirez, and Sullivan (2019) examines sex differences in high-fat diet- and obesity-induced increases in blood pressure and vascular dysfunction, with a particular focus on the role of the immune system and inflammatory processes. They conclude that women have higher rates of obesity and are more susceptible to hypertension and vascular dysfunction due to a number of different factors, including dysregulation in the immune cell response and cytokine/adipokine profiles to promote inflammation (Taylor et al., 2019). Given the variety of mediators of metabolic disorders and vascular dysfunction that show sex differences, these reviews underscore the importance of examining both sexes in such studies.

In conclusion, the literature in this issue suggests that women may be more likely than men to suffer from certain diseases, depending on their hormonal (menopausal) status; yet females remain understudied. Further, the mechanisms underlying these disorders are unclear. Therefore, it is imperative that researchers do not exclude 50% of the population by selecting to examine only males. Repeatedly, the take-home message from the articles in this issue is that studying both males and females is necessary in all research, including cells, animals, and humans, that "the default position should be to automatically study both sexes and account for sex as a source of variation" (Karp & Reavey, 2019). Future studies require a more considered approach in regard to the mechanism(s) underlying a sex difference, be it (a) the presence of certain gonadal hormones, (b) sex chromosomes, and (c) sex-specific behaviours. As targeted, personalised medicine approaches should increasingly produce effective treatments for patients, developing treatments based on sex is a goal that is in reach.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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