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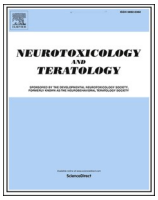

Introduction to sex differences in neurotoxic effects

Sex is the most prevalent and most essential genetic polymorphism in mammalian species. The great majority of physiological processes act in common in both sexes, but there are crucial differences: It is important that we as neuroscientists seek to understand them. The most evident sex differences in biology have to do with reproduction. However, there are many sex differences that are not directly related to reproduction in organs and organ systems including the liver, brain, immune system, and cardiovascular system. Clayton and Collins (2014) published a landmark article stating the rationale and requirement for the study of both females and males in NIH-sponsored studies, pointing out the myriad of conditions where sex differences in incidence and response to therapies have been identified, including multiple sclerosis, Parkinson's disease, schizophrenia, and stroke. Many neurodevelopmental disorders, such as Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Conduct Disorder, and Eating Disorders, also have striking sex differences in prevalence and in how they manifest and are diagnosed.

With regard to toxicology, gene x environment (GxE) interactions have been increasingly recognized as crucial for understanding who is most susceptible to harm by toxic exposure and why others are less vulnerable. Fortunately, developmental toxicology, and in particular neurodevelopmental toxicology, studies have a great and long history of studying sex differences. Thus, we have an abundant literature concerning sex differences throughout teratological research, particularly concerning differences between males and females in response to prenatal and neonatal toxicant exposure. Also important are sex differences in toxicant effects on neurobehavioral function later in development, including childhood, adolescence, and adulthood. Some sex differences in response to toxicants are expressed as a greater vulnerability of either males or females to toxicity, while other effects are expressed as toxicant-induced diminution of typical sex differences. Accordingly, *Neurotoxicology and Teratology* organized a Special Issue on the theme of "Sex Differences in Neurotoxic Effects" of exposure throughout the lifespan to environmental toxicants, drugs of abuse, and therapeutic drugs.

Articles in this special issue include a spectrum of approaches to discovering sex differences in neurotoxicity. Several focused on the neurotoxicity of exposures to drugs of abuse. Dow-Edwards (2020) provided a comprehensive review of the sex differences in the interactive effects of early life stress and the endocannabinoid system. Significantly, Dow-Edwards (2020) argued that the interactive effects of stress and the endocannabinoid system in males and females are not fully understood, including how use of exogenous cannabinoids may ameliorate the adverse mental health outcomes of early life stress. Stroud et al. (2020) showed that prenatal tobacco and marijuana co-exposure was significantly associated with sex-specific influences on infant cortisol stress response. As marijuana use becomes less taboo and more prevalent, these data emphasize the critical need to address and understand potential long-term impacts and interventions. Finally, Schuetze et al. (2020) examined sex-selective effects of autonomic functioning among prenatal cocaine-exposed kindergarten-aged children, and how that interacted with caregiving environment. It has long been known that psychosocial stress itself can produce adverse neurobehavioral effects in the offspring, particularly male offspring. Merced-Nieves et al. (2020) reported an association of prenatal maternal perceived stress with a sexually dimorphic measure of cognition in 4.5-month-old female infants. Because it coordinates stress behaviors and the perception of stress, disruption of the hypothalamic-pituitary-adrenal (HPA) axis is likely one path by which interactions between life events and substances of abuse induce adverse effects. Collectively, these papers emphasize that examining sex along with co-morbidities such as stress is crucial to understanding why disease manifestation differs across populations, sexes, and individuals.

Sex-selective effects on neurodevelopment and behavior are also seen following developmental exposure to environmental contaminants. In humans, Sears et al. (2020) found sex differences in the association between exposure to fly ash facilities, and resulting indoor contaminants, and cognitive control among children living near coal-fired power plants. Gillera et al. (2020) demonstrated sex-specific effects of perinatal FireMaster® 550 (FM 550) exposure on socioemotional behavior in prairie voles. Use of this species to probe the impact of chemical exposures on social traits is uniquely important because, unlike rats or mice, prairie voles are socially monogamous and display strong paternal and alloparental care. Finally, Wiersielis et al. (2020) reviewed how, following perinatal bisphenol A exposure, there are important sex-selective interactions of stress, anxiety, and depression that impact outcome. Thus, this review further highlights how intersectional factors such as early life chemical exposures and lifestyle factors in our "exposome" can shape disease risk in a sex-dependent manner.

When considering how "developmental exposure" is defined, the prenatal period is the most obvious and well-studied. However, emerging work is revealing how parental exposures might impact offspring. Most developmental neurotoxicology research has focused on the female parent because, in mammals, the offspring develops in the mother and maternal exposures are often readily conveyed to the developing offspring through disruption of maternal physiology. Offspring can also become exposed via lactation. More recently, it has become apparent that environmental exposures to the male parent can also have adverse effects on offspring neurobehavioral development. In rats, Hawkey et al. (2019) showed that paternal toxicant exposures before conception can cause long-lasting neurobehavioral effects in the

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offspring, and that these have differential expression in male and female offspring. Specifically, they showed that chronic paternal nicotine exposure can heighten locomotor hyperactivity and impaired habituation in their offspring, with some effects more pronounced in males. The need to understand how paternal exposures impact their future offspring remains a pressing need.

Similarly, peripuberty is a critically important, but often neglected, window of tremendous sexual differentiation and maturation and is thus a developmental window of heightened susceptibility to toxicants. Adolescence is a life stage when sex differences, including behavioral sex differences, become dramatically apparent. Significantly, some parts of the brain, including the hippocampus, cerebellum, and prefrontal cortex, continue their differentiation long after birth. Using a mixture of specialized mouse models, Jackson et al. (2020) showed the involvement of Sonic Hedgehog receptors in cerebellar overgrowth and sex-specific alterations in hippocampal and cortical development and in behavior in female mice. These kinds of sexually dimorphic neurodevelopmental pathways may help shed light on why only one sex may be susceptible to chemical or other exposures. Also in mice, Brown et al. (2020) found that supplemental taurine (which is found in many popular energy drinks) during adolescence and early adulthood has sex-specific effects on spatial learning and aspects of memory. Adolescence is also a sensitive timepoint for manifestation of earlier developmental neurotoxic exposures, particularly when an individual is challenged with a second "hit." Liberman et al. (2020) showed that, following gestational exposure to polychlorinated biphenyls, adolescent rats displayed sex-specific effects on neuroimmune and dopaminergic endpoints following an inflammatory challenge.

Finally, while it is ideal to avoid neurotoxic injury in the first place, it is also important to develop therapeutic treatments for attenuating neurotoxic injury for those already exposed. Using a classic valproic-induced neural injury paradigm in rats, Juybari et al. (2020) unfortunately found only limited success of resveratrol administration to attenuate neurotoxic injury. The development of sex- and age-appropriate therapeutic approaches to toxic exposures remains a critically pressing need.

While one of the functions of a special issue is to try to bring consensus to an area of investigation, the only consensus available at this juncture is that males and females do respond differently to a wide range of toxic insults. The mechanisms responsible for these wide-ranging differences seem to include a basic difference in the neurophysiology of the response to stress itself. McCarthy and Konkle (2005) reviewed many types of stressors and concluded that the sexes respond differently to different types of stressors at different developmental stages. Dow-Edwards (2020) presented sex differences in response to stress during prenatal and early postnatal life in the rat, while Merced-Nieves et al. (2020) detailed the sexually-dimorphic responses to gestational stress in infants. Two papers showed sex differences in the effects of drugs of abuse on infant stress and autonomic responses (Schuetze et al., 2020; Stroud et al., 2020). Interactions between the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis are substantial and can influence the physiological responses to a variety of toxic agents, bisphenol A being an obvious one (Wiersielis et al., 2020).

The paper by Liberman et al. (2020) began to address potential mechanisms, whereby the toxicant produced sex-dependent effects in the gene expression of neuroimmune function and this was found to vary in selected brain regions differentially by sex. But for most of the studies, there remains a large gap between the actions of the toxic agent and the neurophysiologic underpinnings for an alteration in behavior and the basis for the sex difference in the behavior.

We thank the authors who participated in this special issue by contributing their research and the readers for appreciating it. We look forward to continuing progress in discovering the importance of sex differences in neurotoxic response.

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