Sex differences in health and disease: brain and heart connections—a special issue

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The phenotypic manifestations of all physiological processes are routinely dictated by specific microenvironmental cues in the cell. As such, the well-recognized sex-based differences in many physiological responses and pathological outcomes should be in closed link to the unique role of sex steroid hormones, which ubiquitously target and freely enter all cell types in the body. Significantly, various impacts of the sex hormones, by both genomic and nongenomic actions, have been demonstrated in every level from gene expression to the whole intact animal models [3, 4, 9, 10, 14, 16, 25]. This special issue focuses particularly on the distinctive role of sex steroid hormones in two major organs, the brain and the heart, that are intimately connected, highly integrated, and often the major underlying mechanistic bases of most pathological conditions with emphasis on the issue of sex differences in health and disease. The articles compiled for this special issue were invited contributions from world leaders in their respective fields of research.

It has been more than a decade since the landmark clinical study on hormone replacement therapy in postmenopausal women has raised concerns about the many risks associated with the therapy [20]. The major concern was

the sharp increase in heart disease and death in the patients treated with a combined regimen of estrogen and progesterone. However, many studies in animal models have indicated the significant cardioprotective effects of both estrogen [5–7] and androgen [9, 25]. Despite the hypothesized significant role in myocardial function, how these steroid sex hormones perform the tasks responsible for the different outcomes are not yet well understood. Thus, several reviews in this issue have covered the context of sex differences in electrical signal and electrocardiography [22], in mechanical induction by excitation–contraction coupling [19], and in the energetics and metabolism of the heart [26]. Sex differences in cardiac adaptations to differential stresses either physiological, like conditions of exercise-induced cardiac hypertrophy [12] and nonischemic myocardial remodeling [15], or pathological, like ischemia–reperfusion injury [17], have also been included. Lastly, overview contribution of estrogen and estrogen receptors in cardiovascular oxidative stress is reviewed [1].

Mental health disorders and associated substance abuse are often comorbid with heart disease. Thus, several manuscripts in this issue focus on sex differences in emotion and anxiety [11], cognition and learning [2], alcohol abuse/withdrawal [21], and depression in association with cardiovascular disease [23]. Sex differences connecting the brain and heart are reinforced in the manuscripts of Gonzales [13] and Wilson [24] who describe the effects of sex hormones on the cerebral vasculature and recovery after stroke/ischemic injury. Lastly, the molecular aspects of sex differences are explored, especially pertaining to neurodevelopment and the epigenetics of sex steroid hormone action [8]. In addition, Pak et al. [18] provide an overview of the newly emerging field of regulatory microRNAs, with emphases on neurodevelopment, puberty, aging, and potential brain–heart connections. Together,

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these neuro-focused reviews integrate what is known about sex steroid hormones on brain function, while drawing pertinent correlates and extending these findings to the more recent novel discoveries in the heart and vasculature.

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