Genome and hormones: an integrated approach to gender differences in physiology

Over the course of the past decade, there has been a growing interest in gender/sex differences in basic physiological processes that lead to genetic differences in the presentation of human diseases. The importance of this topic is gaining recognition at a national level with the establishment of the Office of Women’s Health Research, the National Centers of Excellence in Women’s Health, federal guidelines for inclusion of women in clinical trials, and, in April of this year, a series of recommendations stemming from an Institute of Medicine Report entitled “Exploring the Biological Contributions to Human Health: Does Sex Matter?” which encourages interdisciplinary research on sex differences at cellular and systemic levels. The American Physiological Society has taken a leadership position in the area of gender physiology and has organized an interdisciplinary conference, entitled “Genome and Hormones: An Integrated Approach to Gender Differences in Physiology,” to be held October 18–20, 2001, in Pittsburgh, Pennsylvania.

This issue of the Journal of Applied Physiology introduces a three-month Highlighted Topics series focusing on gender differences in physiology. The current selection of mini-reviews focuses on hormonal aspects of gene regulation. In a mini-review entitled “Estrogen receptors: cell localization and physiology,” Dr. Ellis Levin, Vice-chair for Research at the University of California, Irvine, discusses new views regarding cellular localization of estrogen receptors and signaling pathways as they relate to specific functions in endothelial and breast cancer cells. In another mini-review entitled “Cardiovascular protective effects of 17β-estradiol metabolites,” Drs. Raghvendra Dubey of University Hospital of Zurich and Edwin Jackson from the University of Pittsburgh Medical Center discuss metabolism of 17β-estradiol. Endogenous metabolites of the hormone mediate physiological functions by receptor-dependent and receptor-independent pathways. Increasing evidence for membrane-associated cytosolic and nuclear estrogen receptors strengthens the concept for receptor-mediated rapid or nongenomic effects of hormones, in addition to the classical concept of gene regulation or genomic effects. Enzymes, which metabolize estrogen, have been identified in tissues other than those described as classical steroidogenic tissues. Because the various metabolites possess a spectrum of affinity for estrogen receptors, these compounds may provide cell specificity to the actions of hormones.

In the November issue of this series, the mini-reviews will provide summaries of two recent consensus papers related to human disease and adaptation. In the first mini-review entitled “Sex ratio and rheumatic disease,” Dr. Michael Lockshin, Director of the Barbara Volcker Center for Women and Rheumatic Disease at Cornell University and member of the panel of the Institute of Medicine Report, excerpts aspects of the report as related to sex ratio or female/male dominance in the presentation of rheumatic disease. Autoimmunity represents a prototypical class of diseases that have high female-to-male ratios. This mini-review critically evaluates evidence to distinguish between sex discrepancy of incidence and the severity of rheumatic disease. Both strengths and weaknesses of animal models used for the study of rheumatic disease are evaluated. Information presented in tabular form facilitates comparisons among the various experimental designs. Dr. Lockshin’s mini-review points out that studies are needed to explore how interactions among exposure to infectious agents, toxins, X or Y chromosome genetic modulators, and intrauterine influences contribute to sex differences in autoimmune and non-autoimmune diseases.

The second mini-review of the November issue, entitled “Gender issues related to space flight,” will focus on gender adaptation to the extreme environment of outer space. Dr. Deborah Harms, in collaboration with an expert panel from the NASA Johnson Space Center in Houston, Texas, summarizes a consensus paper related to gender-specific physiological changes and health issues among astronauts. Although, historically, investigations of physiological responses to microgravity have not been aimed at evaluating gender-specific responses, several have been identified. Cumulative data from space flights are reviewed as they relate to cardiovascular and renal physiology, endurance and exercise for extravehicular tasks, nutrition, osteoporosis, and reproduction. Specific areas are identified in which information regarding gender differences in physiological adaptation would impact policy-making decisions related to space flights in the future.

In the third mini-review of the November issue, entitled “Sex-based differences in gene expression,” Dr. Harry Ostrer, Director of the Human Genetics Program at New York University School of Medicine, reviews the molecular genetics of sex chromosomes. This
review includes a discussion of how the expression of X-linked genes in females and Y-linked genes in males as well as sex-limited gene expression could account for greater prevalence of certain diseases in women compared with men when regulated developmentally or hormonally. Analysis of individuals with and without genetic sex reversal, accompanied by genetic linkage and gene expression profiling, provides a means for distinguishing between genetic and hormonal causes of certain human diseases.

In the December issue, two mini-reviews will focus on gender differences in diagnostic and therapeutic interventions for cardiovascular and neurological disease. In a mini-review entitled “Pharmacogenetics of estrogen replacement therapy,” Dr. David Herrington and colleagues from the Center for Excellence in Women’s Health, Wake Forest University, will review new concepts of how gene polymorphisms for estrogen receptor α contribute to cardiovascular risks for elevated cholesterol and venous thrombosis. Included in this mini-review are data from the recently completed “Estrogen Replacement and Atherosclerosis” trial concerning drug-gene interactions related to high-density lipoprotein cholesterol. In the second mini-review entitled “Estrogen effects on the brain: an abundance of sites and molecular mechanisms,” Dr. Bruce McEwen, head of the Laboratory of Neuroendocrinology at Rockefeller University, will review the effects of estrogen on neuronal synapses. The question of whether estrogen replacement slows progression of neurological diseases associated with aging is controversial. This review will provide experimental evidence of how estrogen affects neuronal functions.

In summary, the study of sex differences is evolving into a mature science. This Highlighted Topics series features presentations of internationally recognized investigators discussing genetic and hormonal influences on physiological and pathophysiological processes. The Associate Editors and I hope that this series will promote interest and participation of scientists in the area of gender/sex differences in physiology. Physiologists have the unique ability to generate specific hypotheses that address molecular and integrative mechanisms and origins of sex differences using innovative, interdisciplinary approaches.

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*Journal of Applied Physiology*  
*October 2001, Volume 91*