Sex-based differences in physiology: what should we teach in the medical curriculum?

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Submitted 4 December 2006; accepted in final form 7 December 2006

Blair ML. Sex-based differences in physiology: what should we teach in the medical curriculum? Adv Physiol Educ 31: 23–25, 2007; doi:10.1152/advan.00118.2006.—An abundance of recent research indicates that there are multiple differences between males and females both in normal physiology and in the pathophysiology of disease. The Refresher Course on Gender Differences in Physiology, sponsored by the American Physiological Society Education Committee at the 2006 Experimental Biology Meeting in San Francisco, CA, was designed to provide teachers of medical physiology with the background necessary to include the most important aspects of sex-based differences in their curricula. The presentations addressed sex-based differences in the physiology and pathophysiology of the cardiovascular, musculoskeletal, and immune systems as well as the cellular mechanisms of sex steroid hormone actions on nonreproductive tissues. The slides and audio files for these presentations are available at http://www.the-aps.org/education/refresher/index.htm. This overview highlights the key concepts relevant to the topic of sex-based differences in physiology: why these differences are important, their potential causes, and examples of prominent differences between males and females in normal physiological function for selected organ systems.

There are marked differences between men and women in the incidence and expression of many major disease entities (8, 9). These sex-based differences in the pathophysiology of disease imply, in turn, that there are important underlying differences in physiological function. Despite the importance of this topic, sex-based differences in physiology are typically not systematically addressed either in physiology textbooks or in the medical physiology curriculum, with the obvious exception of reproductive physiology. For this reason, the American Physiological Society (APS) Education Committee elected to address this topic for the Refresher Course presented at the 2006 Experimental Biology Meeting in San Francisco, CA.

Until recently, most basic and clinical research either was performed exclusively in male subjects or included both sexes but did not differentiate between males and females in the data analysis. This reflected the broad assumption that there are minimal differences in the physiology and pathophysiology of males and females other than those that specifically involve the reproductive system. The potential complexities of controlling for the various phases of female reproductive cycle served as an additional deterrent for the inclusion of females in experimental design for both animal and human studies. During the period of 1977–1993, furthermore, women of reproductive age were required to be excluded from phase I clinical trials because of concerns about potential teratogenic effects. Since that time, there has been a progressively increasing emphasis on the inclusion of women in clinical trials as well as statistical analyses that specifically evaluate possible sex differences (8).

With the recent recognition of important sex-based differences in disease, there is now a burgeoning literature addressing sex-based differences in normal physiological function and effects of sex steroid hormones on the function of multiple organ systems (14). The goal of the Refresher Course symposium was to summarize our current state of knowledge of sex-based differences in three systems for which there are prominent differences between men and women: cardiovascular, musculoskeletal, and immune systems (3, 4, 7). In view of the fact that many sex-based differences are mediated by the actions of estrogens or androgens, the Refresher Course also presented an update on the genomic and nongenomic mechanisms of action of sex steroid hormones (20). The slides and audio files for these presentations are posted on the APS Refresher Course website http://www.the-aps.org/education/refresher/index.htm.

This overview highlights the key concepts relevant to the topic of sex-based differences in physiology: why these differences are important, their potential causes, and examples of prominent differences between males and females in normal physiological function for selected organ systems.

Sex-Based Differences in Human Disease

As noted above, there are important differences between men and women in the incidence and expression of many major disease entities. For example, 80% of patients with osteoporosis are women. The causes of osteoporosis are multifactorial and include genetic characteristics, exercise, dietary history, and the contributions of testosterone and estrogen to bone metabolism; the decline in estrogen production is one of the key factors that predisposes postmenopausal women to the development of osteoporosis (8).

Similarly, 80% of patients with autoimmune disease also are women, implying that sex steroid hormones and/or sex-linked genetic characteristics can profoundly alter immune system function (4). The discrepancy between sexes in the incidence of autoimmune disease is particularly dramatic for Hashimo-
to’s thyroiditis, which has a 10-fold greater incidence in women than in men; for Grave’s hyperthyroidism, which has a 7-fold greater incidence in women than in men; and for systemic lupus erythematosus, which has a 6-fold greater incidence in women than in men (2, 4, 5). There also are prominent sex-based differences in the incidence and expression of a wide range of mental illnesses, including depression, schizophrenia, posttraumatic stress disorder, and panic disorder. For example, depression is diagnosed two to three times more frequently in women than in men (8).

Conversely, heart disease has traditionally been thought to be predominantly a disease of men. In reality, this is not the case: heart disease is the leading cause of death in both women and men. However, the age of onset of coronary artery disease is, on average, roughly a decade later in women than in men. The incidence of heart disease in women increases markedly after menopause. While this strongly implies a cardioprotective role for estrogen, the role of estrogen in cardiovascular health is clearly not straightforward, as shown by the outcome of the Women’s Health Initiative (13, 19). It is important to recognize, however, that as striking as the difference in the age of onset of heart disease may be, it is only one facet of the difference between women and men in cardiovascular pathophysiology. There are, in addition, multiple sex-based differences in the symptoms, progression, comorbidities, and outcomes of heart disease that have important implications for the recognition and treatment of heart disease in women compared with men and that suggest widespread sex-based differences in the underlying physiology of the cardiovascular system. These differences are addressed in the accompanying article by V. Huxley (7).

Potential Causes of Sex-Based Differences in Normal Physiology and Disease

Sex-based differences in normal physiology, or in the predisposition to a specific disease, can be due to genetic differences, to the actions of the sex steroid hormones, or to an interaction between these factors.

The obvious genetic basis for sex-based differences lies in the fact that females have two X chromosomes but no Y chromosome, whereas males have a Y chromosome but only one X chromosome. There are genes on the Y chromosome that have no counterpart on X chromosomes, and, conversely, genes located on the X chromosome can, in some cases, be expressed at higher levels in females than in males. In addition, gene expression can be altered by sex steroid hormones (8).

The sex steroid hormones include androgens, estrogens, and progestins. Receptors for the sex steroid hormones are present in numerous nonreproductive tissues, including the heart, bone, skeletal muscle, vasculature, liver, immune system, and brain. As presented in the accompanying article by M. Weirman (20), these steroid receptors mediate their target tissue effects not only through their well-known genomic actions but by non-genomic effects as well. It is important to note that, although circulating androgen levels are higher in males than in females, and circulating estrogen/progestin levels are higher in premenopausal females than in males, both males and females produce estrogens, progestins, and androgens. Furthermore, estrogen and androgen receptors are present in nonreproductive tissues of both males and females and mediate physiological effects in both sexes. Indeed, some of the important physiological actions of circulating androgens, such as those on bone metabolism, are proposed to be mediated by the conversion of testosterone to estrogen in males by aromatase (20). The effects of testosterone on vascular tone also may be mediated in part by aromatase conversion to estrogen (13, 20).

One of the complexities of unraveling the contribution of steroid hormones to either normal physiology or disease is the changing role of these hormones across development. In utero, the sex hormones are critical for sex determination and differentiation, and gonadal steroid hormone levels and their contributions to physiological function undergo marked changes in the transitions from childhood to adolescence to adulthood. In women, there are the additional variables of the menstrual cycle, pregnancy, and menopause, and, in both women and men, testosterone levels decline with aging.

In addition to the contribution of genetic and gonadal steroid hormone effects to the pathophysiology of disease, it must also be recognized that societal factors can play a marked role in the incidence and expression of disease. Gender differences in lifestyle, daily environment, and healthcare can all make significant contributions to physical and mental health. These differences are present in all societies but play a particularly substantial role in certain cultures in developing nations. While this topic is beyond the scope of this overview, it is nonetheless an important contributing variable to the expression of sex-based differences in pathophysiology.

Sex-Based Differences in Normal Physiology

One consequence of differences in genetic attributes and circulating levels of sex steroid hormones is that there are structural/morphological differences between males and females. The differences between the sexes in body composition are well known: males typically have proportionately more muscle mass, more bone mass, and a lower percentage of body fat than women. These differences are, in a large part, the consequence of the well-documented effects of gonadal steroid hormones on skeletal muscle and bone metabolism and are reviewed in the accompanying article by M. Brown (3). What is less commonly recognized is that there are structural/morphological differences between adult males and females for many (if not all) organ systems that can have significant impact on physiological function (9). For example, sex differences in lung size have important consequences. Men have larger lungs, wider airways, and greater lung diffusion capacity than women, even when these values are normalized to height. An important consequence of this structural difference is that in contrast to healthy young men, maximal exercise capacity may be limited by pulmonary capacity in women, especially as they age (6).

There are well-defined differences in brain structure that result from fetal exposure to gonadal steroid hormones (11, 17). These morphological differences, in concert with the effects of sex steroid hormones on neuronal function, are proposed to support diverse nonreproductive differences between males and females such as differences in pain threshold and cognitive style and the greater glucocorticoid response to stressors exhibited by females compared with males (11). Receptors for sex steroids are found in multiple brain regions and mediate the effects both of circulating gonadal steroid hormones and of locally produced neuroactive steroids (12). Steroid receptors are abundantly located in brain regions in-
involved in autonomic regulation and thus have the potential to influence a wide range of homeostatic regulatory processes (18).

There are multiple differences between women and men in terms of their normal cardiovascular function. For example, men have significantly greater left ventricular mass and chamber size than women. Because the left ventricular ejection fraction is the same in both sexes (10), the stroke volume is larger in men than in women (7). Furthermore, there are sex-related differences in the expression of myosin isoforms in animal models, suggesting that there may be sex-based cardiac differences that are more complex than a simple difference in size (10). In addition, blood pressure regulation differs between sexes in several respects. Women have a lower resting blood pressure and higher resting heart rate and exhibit reduced tolerance to orthostatic stress and impaired venous return [see the accompanying article by V. Huxley (7)]. The electrocardiogram Q-T interval also is longer in women than in men (13), reflecting an underlying sex difference in the fundamental electrophysiological properties of the heart; consequently, the incidence of life-threatening arrhythmia (torsades de pointes) triggered by drugs that prolong ventricular repolarization is higher in women than in men (15). The development of sex differences in cardiovascular function typically shows a temporal correlation with developmental changes in sex steroid hormone levels. For example, sex differences in the heart rate and Q-T interval do not develop until adolescence (15). Similarly, while blood pressure is lower in premenopausal women than in men, blood pressure gradually rises in postmenopausal women to levels equivalent to those of men. Experimental studies (1, 7, 13, 16) have demonstrated widespread effects of sex steroid hormones on vascular tone as well as on lipid metabolism, hemostasis, and the regulation of fluid and electrolyte balance. However, while these documented actions of the sex steroid hormones undoubtedly contribute to the observed differences between men and women in both normal cardiovascular regulation and development of cardiovascular disease, the biological basis of these differences is complex and not yet fully understood.

Conclusions

The pronounced differences between men and women in the prevalence and presentation of multiple major diseases dictate that our students will be best prepared for the practice of medicine if their physiology curriculum prepares them to understand the basis of sex differences in pathophysiology. In this overview and the accompanying articles summarizing the 2006 Refresher Course presentations, we present key concepts that we propose should be included in a medical physiology curriculum.

REFERENCES