His and Her Physiology and Sex Hormones

By Margie Patlak*

It's not just the towels that need to be labeled his and hers—there are also his and her livers, neurons, immune systems, and a host of other differences between the sexes that are cropping up in the most unexpected places, researchers are finding. The latest additions to the *Men Are from Mars, Women Are from Venus* saga have important implications for the practice of both medicine and research, because they not only help explain why women or men are more prone to certain disorders, but also suggest that many treatments should be tailored according to sex.

Unlike the picture of sex differences that was painted with broad brush strokes in previous decades, recent findings reveal how the sexes diverge down to the level of genes and molecular pathways. The wealth of these more detailed findings reveal that sex hormones foster a wide range of different biochemical pathways in men and women throughout the body, affecting such processes as drug metabolism, injury response, and inflammation. That these hormones influence so many basic facets of physiology suggests we humans come in two distinct functional models, putting a whole new spin on sexual dimorphism. "There are surprisingly dramatic differences in physiology between the sexes in certain areas," said geneticist Aldons Lusis, Ph.D., of the University of California, Los Angeles. He was one of several experts who expressed their views to ***Endocrine News*** on this topic.

Sex Hormones' Role in Gene Expression

A few years ago, Dr. Lusis and his colleagues used microarray technology and mice to reveal sex differences in the expression of thousands of genes in liver, fat, and muscle tissues. In all these, more than half of the active genes were expressed to a different degree in male- versus female-derived samples. Strikingly, many of these differentially expressed genes had no obvious connection to X or Y chromosomes. This led Dr. Lusis to suspect that sex hormones were behind the differences.

He and his colleagues have now confirmed this suspicion in a study to be published in the March 2009 issue of ***Endocrinology.***[1] Researchers compared gene expres-

sion in the livers of various hormone-treated, castrated or ovariectomized mice, as well as genetically modified XX male and XY female mice. These comparisons revealed only modest effects due to sex chromosomes, apart from hormones, with most differential expression in liver genes deriving from sex hormones.

His and Her Drugs

Dr. Lusis's findings have particular relevance to drug metabolism. He found that some of the genes whose expression varied by sex in the liver code for cytochrome P450 enzymes. These proteins are responsible for metabolizing many drugs and toxins. This may explain noted differences in drug metabolism between men and women for such drugs as caffeine, erythromycin, cyclosporine, tirilazad, verapamil, and diazepam.

Because of metabolic differences, "the same drug given to a man and a woman may be handled differently in the two. This creates problems in determining the correct dose," declared Jeffrey Cossman, M.D., of the U.S. Food and Drug Administration (FDA) at a 2006 conference on sex differences co-sponsored by the FDA and the Society for Women's Health Research.

Drug dosages may have to be tailored by sex, and not just by size and weight, Dr. Lusis pointed out, because women aren't just small versions of men. Women also may be more prone to certain cancer-causing compounds in the environment because of how their livers process them.

But it's not only his and her drug *dosages* that may be needed, but also his and her *drugs*. The choice of drugs might have to depend on the patient's sex if the medicines work on specific disease-causing pathways that are not shared by men and women, pointed out neurologist Louise McCullough, M.D., Ph.D., director of stroke research and education at the University of Connecticut Health Center in Hartford. She and her colleagues discovered that neurons can follow two main pathways to their deaths following oxygen deprivation akin to that induced by a stroke. Surprisingly, "female neurons," derived from female rodents, appear to use one of these pathways predominantly, whereas male neurons prefer the other. This probably explains why an experimental drug that acted on just one of the pathways improved outcomes only in males.[2]

His and Her Cell Cultures

This finding illustrates the importance of testing experimental drugs in both male and female animals, and conducting in vitro experiments in male-derived and female-derived cell cultures (rather than using standard mixed cell cultures), Dr. McCullough indicated. "If you aren't aware of these sex differences, you won't analyze your studies properly," she said. Even removing rodents' gonads to avoid sex hormone effects or using embryonic or neonatal cell cultures does not eliminate all sex differences, possibly due to prenatal sex hormone exposure, or to genes on X or Y chromosomes with effects that are independent of circulating sex hormones.

Molecular pathways that diverge by sex aren't unique to neurons, but occur in many other cell types and tissues and appear to determine major responses in the body, such as the immune response to injury or infection. Both sexes produce the dozen-plus different T cell types and linked cytokines and regulators, but mounting evidence suggests that females lean more heavily on the antibody-laden Th2 immune response, whereas males tend toward a mostly cell-mediated Th1 response that fosters inflammation.

Sex Hormones Affect Immune Response

The opposite effects of estrogens and androgens, which can directly latch on to hormone receptors of immune cells, explain much of this divergent immune response, as revealed by both in vitro and in vivo studies. The balance of these hormones might elucidate why women are more susceptible to autoantibody-mediated disorders such as rheumatoid arthritis and lupus, postulated immunologist DeLisa Fairweather, Ph.D., of the Johns Hopkins Medical Institutions in Baltimore. In a recent review article in the *American Journal of Pathology*,[3] she noted that one study found that free estrogen levels in the synovial fluid of men with rheumatoid arthritis were twice those of men without the condition, and on par with those of women with rheumatoid arthritis.

But the influence of sex hormones on the immune system isn't all bad news for women. The pro-inflammation Th1 response in males tends to foster atherosclerosis and may explain, in part, why premenopausal women are protected to a large degree from coronary artery disease, suggested Doris Taylor, Ph.D., director of the University of Minnesota's Center for Cardiac Repair in Minneapolis. To assess the role that male or female immune cells have in fostering heart disease, Dr. Taylor and her colleagues injected atherosclerosis-prone male mice with bone marrow cells from females. After eating a high-fat diet for several months, these males had significantly less plaque on their heart arteries than either control males or males that received bone marrow cells from other males. The males with the female bone marrow also showed a heightened Th2 immune response, which tends to suppress inflammation.[4]

These recent findings reinforce the notion that what is good for the goose may not be good for the gander, and that sex differences are far more omnipresent in the body than originally thought. "You have to look before you can say there are no sex differences in basic processes," said Dr. McCullough. "No one really looked for these sex differences before. But now that we're looking, we're seeing them." ■

References

1. van Nas A, Thakurta DG, Wang SS, et al. Elucidating the role of gonadal hormones in sexually dimorphic gene co-expression networks. *Endocrinology;* in press.
2. Lange JT, McCullough LD. Pathways to ischemic neuronal cell death: are sex differences relevant? *J Transl Med,* 2008;6:33; published online June 23, 2008.
3. Fairweather DL, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. *Am J Pathol,* 2008;173:600–609.
4. Zenovich AG, Taylor DA. Atherosclerosis as a disease of failed endogenous repair. *Front Biosci,* 2008;13:3621–3636.