Endocrine Regulation of Exercise Substrate Utilization in Women Compared to Men

Barry Braun¹ and Tracy Horton²

¹Department of Exercise Science, University of Massachusetts, Amherst; and ²Center for Human Nutrition, Department of Pediatrics, University of Colorado Health Sciences Center, Denver

BRAUN, B., AND T. HORTON. Endocrine regulation of exercise substrate utilization in women compared to men. Exerc. Sport Sci. Rev. Vol. 29, No. 4, pp 149–154, 2001. During low to moderate intensity exercise, women utilize proportionally more lipid and less carbohydrate compared to men. Estrogen and progesterone may have direct effects on these differences by increasing lipolysis and/or constraining glucose production and utilization. Furthermore, sex steroids may have indirect effects through interactions with other hormones, especially catecholamines. Keywords: ovarian steroids, catecholamines, glucose metabolism, gender

INTRODUCTION

In the past ten years, it has been recognized that substrate utilization in men and women differs in several important ways, and these differences have been enumerated in several excellent reviews (14). How the sex differences are manifested, however, has not been elucidated as clearly. There is a general consensus that the hormonal environment, dominated by estrogen and progesterone in women and testosterone in men, plays a role in mediating sex differences in substrate metabolism. Nevertheless, the actual mechanisms by which these hormones directly or indirectly alter regulatory pathways are elusive.

Endocrine regulation of substrate utilization can occur at a number of points in metabolism. Such sites of regulation include substrate availability (via effects on storage of nutrients), mobilization from body tissue stores, uptake at the tissue site of utilization and, within the tissue itself, substrate trafficking between storage, oxidation and/or re-cycling (Figure 1). Metabolic demand and the internal and external environment at any given time modulate the overall effect of hormonal regulation on these processes. Of particular importance are metabolic stressors such as exercise, hypoglycemia, fasting, and hypoxia. Under these conditions, endocrine signals are vital to maintaining homeostasis.

REGULATORY THEMES COMMON TO MEN AND WOMEN

In the broad sense, substrate selection is not sex-specific under a variety of physiologic situations. In response to metabolic stressors such as exercise, but also during fasting, hypoglycemia, and hypoxia, there are characteristic changes in the pattern of substrate utilization and the counter-regulatory hormones. Endocrine changes include an increase in blood concentrations of catecholamines, glucagon, growth hormone, and cortisol. With exercise, insulin levels decline below the usual baseline. Acting in concert, the endocrine changes create a catabolic hormonal environment that results in fuel mobilization. In the early stages of exercise, utilization of muscle fuels (glycogen and muscle triglyceride) predominates, whereas blood-borne free-fatty acids (FFA), glucose, and amino acids contribute increasingly to fuel oxidation as submaximal exercise progresses. Increased endogenous glucose production during exercise is due to both greater hepatic glycogenolysis and gluconeogenesis. At the whole-body level, carbohydrate oxidation rises with the onset of exercise, but as the duration of exercise increases, there is a progressive rise in fat oxidation.

It is important to recognize that, although qualitatively similar, there are important quantitative differences in the relative utilization of the major energy substrates between the sexes. How the direct and indirect effects of the prevailing hormone environment serve to regulate those differences will be the focus of this review. In particular, we examine the ideas that, relative to men, carbohydrate is conserved in women, that this conservation is manifested mainly in response to metabolic stressors (using exercise as a primary

Address for correspondence: Barry Braun, Ph.D., Department of Exercise Science, Tumor Building, University of Massachusetts, Amherst, MA 01003 (E-mail: bbraun@excsci.umass.edu).
Accepted for publication: April 6, 2001.
0091-6601/01/04/149–154
Exercise and Sport Sciences Reviews
Copyright © 2001 by the American College of Sports Medicine

149
Figure 1. Potential sites for endocrine regulation of substrate utilization.

example), and that carbohydrate conservation is at least partly mediated by the female endocrine system.

IS CARBOHYDRATE CONSERVATION A PHYSIOLOGIC PRIORITY IN WOMEN?

A metabolic priority to conserve carbohydrate may be achieved in women by nonhormonal means, ie genetic imprinting in cells due to the presence of XX chromosomes. In addition, direct effects of the sex steroids could occur either via nuclear interaction and gene expression or nonnuclear effects on intracellular signaling. Alternatively, there may be indirect effects of the sex steroids via interactions with other endocrine hormones. Because the ovarian hormones are present in women and relatively absent in men, and because their concentrations can be experimentally manipulated, both naturally (menstrual cycle) and pharmacologically, most research to date has centered on the metabolic effects of estrogen and progesterone.

Role of the Ovarian Hormones

The continuum from amenorrhea through eumenorrhea (with its own variation during the follicular and luteal phases of the menstrual cycle), to pregnancy represents a wide spectrum of estrogen and progesterone levels (Figure 2). Increasing concentrations of estrogen and progesterone may serve to progressively reduce carbohydrate utilization in an almost dose-dependent manner (9). Although metabolic effects are often attributed to one or the other, the interactions between estrogen and progesterone, as observed during the luteal phase of the menstrual cycle and during pregnancy, are likely to be important (9). Most of the data addressing the effects of ovarian hormones on substrate metabolism are derived from in vitro studies and in vivo studies in animals. Estrogen alone has been repeatedly shown to increase the rate of adipose tissue lipolysis and hepatic very-low density lipoprotein (VLDL) triglyceride production, which could serve to make more lipid available as a potential fuel source or for re-esterification in other tissues (7,14). Progesterone, by decreasing endogenous glucose production (gluconeogenesis and glycogenolysis), may complement the lipid-mobilizing effect of estrogen to achieve carbohydrate conservation (9,14). In skeletal muscle, whereas estrogen administration alone increases insulin-mediated glucose transport, progesterone administration may oppose this action (9,13,14). The net effect on muscle glucose utilization may be determined by the relative concentrations of the two hormones. For example, in situations dominated by progesterone (eg pregnancy), muscle glucose utilization is minimized allowing blood glucose to be "shunted" to fetal tissues. In addition to their effects on blood glucose uptake, the combination of estrogen and progesterone may also indirectly reduce muscle glycogen utilization via alterations in the relative sensitivity of glycogenolytic and lipolytic pathways to catecholamines. Estrogen concentrations are elevated without a concomitant rise in progesterone during the follicular phase of the menstrual cycle, but, under normal physiologic conditions, progesterone is never elevated independently of estrogen. Unfortunately, much of the well-controlled research to date has focused on the effects of either estrogen or progesterone alone, which would minimize any additive or even synergistic effect the ovarian hormones might have in tandem.

To further obscure an accurate depiction of their regulatory actions, in the absence of any metabolic stress, the effects of normal variation in the ovarian hormones on substrate selection may be minimal. Under normal resting conditions, there are no differences in the rates of whole-body glucose or FFA turnover or oxidation when the follicular and luteal phases of the menstrual cycle are compared (1,14,15). Indeed, men and women do not differ in whole-body respiratory exchange ratio (RER) when they are compared at rest (11,14). In a normally menstruating female, the priority for carbohydrate conservation may not, therefore, be manifest until a metabolic stress is present, which potentially compromises glucose homeostasis.

Exercise: A Metabolic Stress Experienced in Everyday Life

During exercise, a wealth of data indicate that there are sex differences in whole-body fuel utilization (8,11,14). It is important to emphasize that the differences are consistently observed only when the study design has been carefully crafted with rigid control of preceding diet and exercise, matching of men and women for training status, and studying women in the same phase of their menstrual cycle. Under these conditions, and with women studied in the follicular phase of the menstrual cycle, women utilize proportionally
less carbohydrate and more lipid compared to men during exercise of mild to moderately high intensity (40%–70% \( V_{O_2}\max \)) (11,14). Because of the obligatory exponential increase in muscle glycogen utilization as exercise intensity increases to >75% \( V_{O_2}\max \), any substantive use of other fuel sources may be squelched, and thus, the sex gap in carbohydrate utilization diminished.

It seems logical to assume that differences between men and women in the sex steroids may be directly or indirectly mediating sex differences in exercise fuel metabolism. Because the normal menstrual cycle in females is characterized by fluctuations in estrogen and progesterone concentrations, this model can be used to examine the effects of the female sex steroids on exercise substrate utilization. Braun et al. (1) found no changes in whole-body fuel oxidation, glucose Ra or Rd when 16 women were studied in different phases of the menstrual cycle (mid to late follicular and mid luteal) during 45 min of exercise at 50% \( V_{O_2}\max \). In contrast, Zderic et al. (15), reported lower whole-body carbohydrate oxidation, glucose Ra and Rd in 6 women studied during exercise performed in the luteal versus early follicular phase of the menstrual cycle. The difference was observed with exercise at 90% lactate threshold (LT; 52% \( V_{O_2}\peak \), 25 min) but not at 70% LT (42% \( V_{O_2}\peak \), 25 min). There were no obvious differences in the subject characteristics, hormonal profile, or stable isotope methods between the 2 studies, and it is presently unclear why these studies had different results.

Estrogen has been administered to estrogen naive subjects (amenorrheic women or men) in order to minimize confounding variables and extract the independent role of circulating estrogen levels on exercise substrate utilization. Estrogen administration decreased exercise glucose flux but had no effect on whole-body carbohydrate oxidation or muscle glycogen utilization (2,14). In contrast, when men and women (in the follicular phase of the menstrual cycle) were compared during exercise, the rate of muscle glycogen utilization and whole-body carbohydrate oxidation was lower in women (14). Taken together, the results from these studies imply that the presence of estrogen alone can lower blood glucose utilization. Because males and females also differ with respect to muscle glycogen utilization and whole-body carbohydrate oxidation, factors other than plasma estrogen levels (eg differences in progesterone, testosterone and the catecholamine response to exercise) must be mediating the sex differences in exercise substrate utilization.

As previously described, the physiological effects of estrogen appear to be modulated by the concurrent presence of progesterone. Studies in vitro show that estrogen alone stimulates lipolysis. It is also likely that estrogen effects hepatic glucose production, particularly in combination with progesterone (and potentially other progesterone derivatives including androgens). Maximal glucose sparing may thus be observed with both an elevation in estrogen and progesterone, particularly when carbohydrate and glucose requirements are significantly elevated (as during exercise, hypoglycemia, or hypoxia).

**Is Testosterone Important By Virtue Of Its (Relative) Absence?**

It is possible that the low level of testosterone in females (at least relative to males) facilitates the conservation of carbohydrate. Exactly how this might work, mechanistically, is unclear because there are few data available to address the question. Certainly the sex-based difference in elevated testosterone levels is largely responsible for the greater muscle mass in men compared to women. Thus, during exercise at least, the ratio of the most metabolically active tissue (muscle), to one of the least metabolically active tissues (fat) is much lower in women. This anatomical difference could be viewed as a form of carbohydrate conservation, in that there is a smaller quantity of energy-consuming tissue in women and a smaller muscle mass in which to store glycogen. To allow for these sex-based differences in absolute total and lean body mass, it is conventional to express substrate production and utilization rates, as well as glycogen storage, relative to the whole-body or lean body mass. When expressed this way, sex differences in substrate utilization with metabolic perturbations persist, which suggests that the ratio of fat and lean tissue do not explain the sex differences. Careful study of the effects of testosterone on the glycogenolytic and lipolytic pathways will likely yield provocative and potentially important new data.

**DIRECT VERSUS INDIRECT EFFECTS OF THE SEX STEROID HORMONES**

The presence of cell surface receptors, in what would traditionally be considered nontarget tissues for estrogen and progesterone, are beginning to be identified. These have been isolated in adipose tissue and muscle, and these cell receptors are capable of intracellular signaling (14). Thus, changes in circulating levels of estrogen and progesterone that occur rapidly and those that occur over a period of days could affect substrate utilization directly. For example, with exercise, there is a significant increase in estrogen and progesterone concentrations, more so in women than in men (11). Whether these acute changes in circulating sex steroids can directly impact substrate mobilization and/or utilization is not currently known. It is hoped that future work will expand our knowledge in this area.

Indirect effects of the sex steroids can be manifested through interactions with other endocrine hormones. These interactions could be via alterations in (1) hormone production and/or secretion, (2) hormone receptor type and/or density on target cells, or (3) variations in cell signaling (increased or decreased sensitivity to hormones). Although work in these areas is in its infancy, a strong candidate to explain at least part of the increased exercise fat utilization in women is a sex-based difference in the impact of the catecholamines on carbohydrate versus lipid metabolism.

**Sex Differences in the Catecholamine Response to Exercise and Other Metabolic Stressors**

A possible interaction between the ovarian hormones and the endocrine system may be manifested in response to sym-
pathetic activation. Although the focus of this discussion is exercise, it is important to note that the observations made with respect to the endocrine responses are also observed with other metabolic stresses, emphasizing the biological imprinting of a sex-specific response. During exercise, hyperinsulinemia, hypoglycemia, hypoxia, and cold exposure, there is a lower catecholamine response in women, i.e., blood levels of epinephrine and norepinephrine do not rise as much as they do in men (5,11,14). Concurrently, a lower muscle sympathetic activity has been observed during exercise and during hypoglycemia (14). Despite this lower catecholamine response, and lower muscle sympathetic activation, women have a similar or greater level of lipolysis (4,5,11) but lower rates of glucose production and utilization compared to men (4,5). These data suggest that women may be more sensitive to the lipolytic action of catecholamines, while maintaining a similar level of sensitivity to glycogenolysis and possibly glucose production. The lower catecholamine response may facilitate a decreased reliance on blood glucose and/or muscle glycogen in glucose conservation.

An enhanced lipolytic response to a given catecholamine concentration in females seems paradoxical given that adipose tissue stores in men are distributed more abdominally and viscerally than in women. Visceral and abdominal adipose tissue is considered more lipolytically sensitive than gluteal and femoral adipose tissue. Hence, it seems logical that males would have higher rates of lipolysis during metabolic stress due to their greater visceral fat mass and higher catecholamine concentrations. Other factors, therefore, may be interacting with the catecholamines to enhance lipolysis in women, including differences in the distribution and/or activation of α- and β-adrenergic receptors (antilipolytic and lipolytic, respectively). High levels of estrogen in women could also interact with their lower sympathetic activation to alter intracellular signaling in the direction of enhanced lipolysis. Alternatively, it may be intramuscular stores of triglycerides (IMTG) that are more sensitive to the lipolytic actions of catecholamines in females. These possibilities require future exploration.

To further complicate the picture, it has been reported that, at rest, norepinephrine or epinephrine alone does not stimulate lipolysis differently in men and women (12), nor does estrogen replacement have any effects in postmenopausal women. However, these experimental manipulations are very different from the metabolic stressors previously discussed. In these highly controlled experiments, the circulating levels of either norepinephrine or epinephrine are manipulated without the homeostatic response from the other arm of the sympathoadrenal system. Under usual physiological conditions, is it the combination of epinephrine and norepinephrine required to elicit the sex difference in substrate flux? Is such an effect of the catecholamines only observed when there is an increase in energy requirements (exercise), or when blood glucose is compromised (hypoglycemia), or when oxygen delivery is attenuated (hypoxia)? Although the results from controlled studies of single hormones are vital to understanding how the system might be regulated, all researchers recognize that there is an interaction between the different endocrine hormones and that studying one in isolation will not fully reflect the complete physiologic mechanism.

Other counter-regulatory hormones could play a role in mediating the sex-based differences in substrate flux in response to exercise and other metabolic stressors. Another common theme between exercise, fasting, and hypoglycemia is the lower glucagon response in females relative to males (4,5,14). Because glucagon increases hepatic glucose production, this observation is concordant with the lower glucose flux rate in females during fasting and hypoglycemia. There has been no direct comparison of exercise glucose flux between the sexes, at least under well-controlled conditions. Therefore, it is not yet possible to deduce a role for glucagon in mediating sex-based differences in exercise glucose utilization. The effects of the other counterregulatory hormones, i.e., cortisol and growth hormone are, however, not evident and require further clarification (11,14).

Blood Flow: Sex-Based Differences?

The apparent sex difference in lipolytic sensitivity could potentially be explained simply by sex-based differences in adipose tissue blood flow in response to metabolic perturbation. If, under these circumstances, women maintained a higher blood flow to the subcutaneous adipose tissue, contact between circulating catecholamines (or other hormones and factors) and adipocytes would be increased. In addition, enhanced blood flow might allow greater drainage of glycerol and FFA into the general circulation. Indeed, estrogen has been shown to increase nitric oxide production and thus vasodilation (3). Whether this would be specific to adipose tissue perfusion, or a generalized effect on the entire vasculature, is not known.

GREATER RELIANCE ON FAT: LIPOLYTIC PUSH OR CARBOHYDRATE CONSTRAINT PULL?

From a mechanistic viewpoint, an unanswered question concerns which of two possible forces drives the shift to greater fat use and less carbohydrate use in women. Does the enhanced ability to mobilize and utilize fat as an energy source, in response to exercise, displace carbohydrate oxidation (a lipolytic push)? Or, does a limited capacity to utilize carbohydrate leave a deficit that is filled by the increased fat availability (carbohydrate constraint pull)? The evidence for and against each of these two scenarios (Figure 3) is considered next.

Lipolytic Push

In considering the first scenario, and at the simplest level, there are significant differences in the body stores of potential substrates (lipid, glycogen, and protein) between men and women. These are dictated by the changes in the sex steroids occurring at puberty that result in a greater lean tissue mass in men, a greater percent body fat in women, and the characteristic male and female differences in body fat distribution.

Can greater lipid stores in women explain greater fat oxidation?

It has been suggested that the greater subcutaneous body fat in women may promote increased lipid utilization by
a) Lipolytic push: Decrease in carbohydrate utilization is secondary to the direct and/or indirect effects of estrogen and progesterone to enhance lipolysis and lipid utilization.

\[
\text{Elevated estrogen and progesterone} \xrightarrow{\text{cellular/metabolic factors}} \text{increased sensitivity to catecholamines} \rightarrow \text{lipid utilization} \rightarrow \text{less CHO utilization}
\]

b) Carbohydrate constraint pull: Estrogen and progesterone have direct and/or indirect effects to decrease hepatic production/muscle utilization of carbohydrate with enhanced lipolysis a consequence of the constraint on carbohydrate availability.

\[
\text{Elevated estrogen and progesterone} \xrightarrow{\text{cellular/metabolic factors}} \text{less CHO utilization} \rightarrow \text{lipolysis and/or lipid utilization}
\]

Figure 3. Lipolytic push versus carbohydrate constraint pull?

virtue of a larger pool of substrate (14). This has indeed been cited as a reason for the common observation that during submaximal exercise, women derive a greater proportion of their energy expenditure from lipid, relative to men. However, data show no significant correlation between body fat levels and either resting or exercise lipid oxidation across gender and a range of body fat levels (11,14). These results suggest that other lipid sources may be important as energy reservoirs in women, including IMTG, and/or circulating triglyceride (derived endogenously from liver secretion or exogenously from meal absorption). It has been suggested that IMTG concentrations are higher in women than in men, (14) but whether the increased concentration per se raises the capacity for females to mobilize and utilize IMTG is not known.

Lipid mobilization

It is likely that the absolute quantity of fat stores is less important than the ability to access them, ie, lipolytic capacity and lipid mobilization. Recently, longitudinal exercise training data in women have shown that, despite no significant changes in body fat, exercise-trained women oxidized more lipid, post-versus pre-training, at either the same absolute or relative workload (65% \(V_{\text{O2 max}}\) or below) (8,10). These results confirm previous observations in males showing a greater lipolytic capacity post-training, independent of adipose tissue stores. Interestingly, in males, the increased lipid utilization post-training is only evident during exercise at the same absolute, but not relative, intensity (8). In women, the source of the increased lipid oxidation after training is controversial. Using tracer-determined measurements of FFA oxidation and utilization, one study reported a greater contribution of circulating FFA to whole-body fat oxidation (8), whereas another study found the increased lipid oxidation was due to a greater utilization of IMTG and/or circulating triglycerides (10). Further work is needed to corroborate either of these findings and to explore how hormonal mechanisms drive the different training responses in men and women.

It is not known whether changes in the estrogen and progesterone levels in women, for example during the menstrual cycle, during oral contraceptive use, or during pregnancy, affect the balance between utilization of circulating FFA versus nonadipose tissue derived FFA such as IMTG or circulating triglycerides. It is hoped that future work will expand our knowledge in this area.

Other factors that could promote lipid utilization in women

As noted above, increased blood flow to peripheral adipose tissue, especially during exercise or other metabolic stresses, could increase FFA removal and delivery to tissues for utilization in women. At the cellular level, there are a number of points at which the metabolism of FFA’s could differ between the sexes including, in women, a greater FFA uptake, greater formation of long chain fatty acyl Co-A within cells, greater transport of long chain fatty acyl Co-A into the mitochondria (greater CPT-1 activity), and a greater capacity for mitochondrial and peroxisomal \(\beta\)-oxidation. The only data available to date suggest that there is no sex difference in CPT-1 activity, whereas females have been reported to have a greater capacity for \(\beta\)-oxidation relative to men in one study (14). These areas are fruitful avenues for further exploration.

Carbohydrate Constraint Pull

An alternative view is that ovarian hormones confer some form of constraint on carbohydrate utilization. Thus, almost
by default, cells are obligated to utilize more lipid to satisfy their energy requirements. Consistent with this hypothesis is the operation of a reverse Randle cycle. The reverse Randle cycle proposes that glucose availability and metabolism is the primary determinant of the pattern of substrate utilization within tissues as opposed to vice versa, that is, the original Randle hypothesis. Hence, the ovarian hormones may exert effects via one or more of the following mechanisms: decreasing circulating glucose availability for utilization by lowering glucose Ra, decreasing noninsulin-mediated glucose uptake, reducing intracellular glucose phosphorylation, decreasing glycogen mobilization, and decreasing glycolytic capacity.

PROMISING AREAS FOR FUTURE STUDY: A LOOK AHEAD

Some facet of femaleness, at least part of which is rooted in endocrine factors, appears to confer a homeostatic advantage in the ability to adapt to changes in metabolic status. In the future, many of the important questions related to this idea will be best addressed using a two-pronged approach. Genetic modifications in which individual components of the cellular machinery are removed or overexpressed are most likely to shed light on basic mechanisms by which the sex steroid hormones manifest sex differences in metabolic regulation (eg recent work using mice deficient in the peroxisome proliferator-activator receptor-α to show that estrogen administration greatly attenuates the profound hypoglycemia in males). At the same time, in vivo experiments in men and women will be necessary to test the new hypotheses generated by the animal and in vitro studies to determine the physiological relevance to humans. Will sex differences in hormonal regulation of substrate metabolism mandate sex-specific regimes (exercise, diet, pharmacological agents) for disease prevention and treatment? Should the dietary recommendations for male and female athletes be sex specific? Questions such as these, which require systematic study at both the cellular and whole-organism level, promise to guide a cornucopia of new research in the area of the endocrine regulation of fuel utilization in women and men.

References