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EDITORIAL REVIEW

Evaluation of gender differences in physiology: an introduction

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The overall theme of the current section is an evaluation of gender differences in physiology. Cognizant of the broad scope of the topic, we will limit this to muscle physiology and whole body energy and macronutrient metabolism. Given the massive increase in strain placed upon a physiological system in response to physical exercise, the articles will focus mostly on exercise as a major theme to illustrate gender differences in physiology.

An understanding of the physiology of exercise has broad implications for many pathological states. For example, exercise is an established therapeutic and evaluation modality in coronary artery disease, while the metabolic changes with exercise are somewhat analogous to short-term starvation, being a common state in institutionalized patients.

For years there has been evidence of a gender bias in bio-medical research [1,2]. This became apparent upon review of the large clinical studies that evaluated cardiovascular disease medications in the 1960s and 1970s [3]. As a result of this gender bias, agencies such as the National Institute of Health in the United States mandated that equal numbers of males and females be included in bio-medical research. As a result of increased awareness, this bias may be less apparent, however there are still several examples of its continued presence [1,2].

In the area of exercise physiology, the area was largely ignored, perhaps due to early work suggesting that there were no gender differences in metabolism or muscle morphology [4,5]. At a practical level, most of the current recommendations for exercise training and nutrition have been derived from studies that contained primarily or exclusively male participants [6–9]. One of the most graphic examples of gender bias comes form the fact that women were not allowed to compete in the Olympic marathon until 1984. While the reasons for an inherent gender bias in the physiology literature are likely multifactorial, the need to control for menstrual cycle and the perception that females may be less willing to undergo invasive procedures such as muscle biopsies have been cited anecdotally by some researchers. In reality, it has been our experience in recent years that females are in fact more willing to volunteer for studies involving muscle biopsies and other minor procedures.

This gender bias is even more poignant given recent evidence that has shown that females may in fact be better suited to ultra-endurance sports compared with males [10]. A 'field' study matched males and females for performance times at the 56 km distance and found that the females outperformed the males at the 90 km distance [10]. Regression analysis has shown that males outperform females at distances up to $\sim$42 km, with an increasing performance advantage for females above an intercept of 66 km [10]. Another group reported that equally trained males and females performed similarly at 42 km, yet the females outperformed the males at the 90 km distance [11].

The mechanism behind the aforementioned performance observations may relate to metabolic substrate selection, differences in muscle oxidative stress or damage, or even differences in thermo-regulation. In carefully controlled studies examining metabolic substrate selection during exercise, it has been consistently demonstrated that females utilize proportionately more lipid and less carbohydrate and protein than males (see Table 1 and the review by Tipton (pp. 493–498)). It is interesting that the gender dimorphism in substrate selection only becomes apparent under physiological stress for there is good evidence from studies using large numbers of participants that under resting conditions, the aforementioned gender differences are not apparent [12]. Individual articles evaluate potential gender differences and the role of sex hormones in macronutrient selection (fat, carbohydrate and protein). The paper by Blaak (pp. 499–502) focuses on the differences in fat utilization. The review by Tipton also considers the issue regarding gender differences in muscle mass and the response of muscle protein turnover to resistance exercise. The potential for gender differences in muscle strength and neuronal input during the aging process and the possible role of sex hormones are both evaluated by

Table 1. Summary of studies where whole body substrate metabolism was reported in males and females

Reference	Subjects	Exercise	RER (mean)
Costill *et al.* (1979) [4]	12 F, T 12 M, T	60 min run @ 70% VO_{2max}	F = 0.83 M = 0.84
Froberg and Pedersen (1984) [34]	7 F, T 7 M, T	to exhaustion @ 80 + 90% VO_{2max}	F = 0.93 M = 0.97
Blatchford *et al.* (1985) [35]	6 F, T 6 M, T	90 min walk @ 35% VO_{2max}	F = 0.81 M = 0.85
Tarnopolsky *et al.* (1990) [22]	6 F, T 6 M, T	15.5 km run @ ~65% VO_{2max}	F = 0.876 M = 0.940
Phillips *et al.* (1993) [21]	6 F, T 6 M, T	90 min cycle @ 65% VO_{2max}	F = 0.820 M = 0.853
Tarnopolsky *et al.* (1995) [23]	8 F, T 7 M, T	60 min cycle @ 75% VO_{2max}	F = 0.892 M = 0.923
Tarnopolsky *et al.* (1997) [20]	8 F, T 8 M, T	90 min cycle @ 65% VO_{2max}	F = 0.893 M = 0.918
Horton *et al.* (1998) [32]	13 F, T + U 14 M, T + U	120 min cycle @ 45% VO_{2max}	F = 0.84 M = 0.86
Freidlander *et al.* (1998) [31]	17 F, UT→T 19 M, UT→T	60 min cycle @ 45 and 65% VO_{2max}	F = 0.885 M = 0.932
Romijn *et al.* (2000) [36]	8 F, T 5 M, T	20–30 min cycle @ 65% VO_{2max}	F = 0.81 M = 0.81
McKenzie *et al.* (2000) [30]	6 F, UT→T 6 M, UT→T	90 min cycle @ 65% VO_{2max}	F = 0.889 M = 0.914
Davis *et al.* (2000) [33]	8 F, UT 8 M, UT	90 min cycle @ 50% VO_{2max}	F = 0.92 M = 0.92
Goedecke *et al.* (2000) [37]	16 F, T 45 M, T	10 min cycle @ 25, 50 and 75% VO_{2max}	F = 0.90 M = 0.92
Rennie *et al.* (2000) [38]	6 F, UT→T 5, M UT→T	90 min cycle @ 60% VO_{2max}	F = 0.893 M = 0.945
Carter *et al.* (2001) [19]	8 F, UT→T 8 M, UT→T	90 min cycle @ 60% VO_{2max}	F = 0.847 M = 0.900
Mean	135 F 162 M		F = 0.869 (0.04) M = 0.900 (0.04)*

Values are mean (SD). For longitudinal training studies, the pre/post rides are all collapsed across time for each gender. A, active; F, females; M, males; T, trained; U, untrained; U→T, longitudinal training study; T + U, trained and untrained in same study. RER = respiratory exchange rate. *Significant gender difference ($P < 0.05$).

Doherty (pp. 503–508). Although much of the focus of this section is on human studies, there is much that has been found in animal studies [13–17]. As a result, two of the reviews will focus primarily on animal models of muscle damage/oxidative stress (Tiidus, pp. 509–513) and substrate selection during exercise (Campbell and Febbraio, pp. 515–520).

From a practical perspective, there are many issues that must be considered when conducting gender comparative studies. First, the average female has a higher percentage of body fat (~5–10%) and lower muscle mass compared with the average male [18–23]. Therefore, it is important to express indicators of fitness (i.e. maximal aerobic capacity, VO_{2max}) relative to fat-free mass, as a between-gender comparison based upon absolute VO_{2max} would lead to the selection of females who are heavier than the males. Sparling (pp. 000–000) has also suggested gender matching consideration and assessment of habitual activity in the year before testing [24]. Cureton presents a convincing argument for comparing the genders based upon training history for trained individuals, and VO_{2max} expressed relative to lean mass in untrained individuals [25]. In between-gender comparison studies, it is best to match the groups based upon assessment of both training history and VO_{2max} expressed relative to lean body mass (ml O_2/kg LBM/min). This matching approach takes into account both the genetic (VO_{2max} potential) and environmental (training state) factors contributing to VO_{2max}, and expresses them relative to the mass of metabolically active tissues.

An additional issue in studies using athletes is the importance of testing at an exercise intensity at/or below 75% of VO_{2max} (<65% for non-athletes) such that potential differences in lactate threshold between the groups do not influence the results [26]. Using the above-mentioned selection criteria, we have found that the lactate threshold is about 80% for well-trained males and females (males = 79.4 ± 1.4%; females = 80.1 ± 2.7%) [21]. To overcome the issue of inter-group differences in fitness, a longitudinal approach can be taken to studies where untrained people are placed on a set exercise program to ensure equality of training.

Another critical factor to consider in gender comparative studies is the phase of the menstrual cycle and

whether or not the females are having regular menses (eumenorrhea) versus amenorrhea or oligo-amenorrhea. During the follicular phase of the menstrual cycle (approximately the first 14 days after the onset of menses) the estradiol concentration starts at levels comparable to males and then increases until ovulation (which marks the onset of the luteal phase). During the luteal phase of the menstrual cycle the concentrations of both estrogen and progesterone are markedly elevated until a rapid drop at the onset of menses to start another cycle ($\sim$28 days in total).

The menstrual cycle has a significant effect on a number of physiological variables including thermogenesis and metabolism. The onset of the luteal phase is marked by an increase in basal body temperature of about 0.5°C and this is used as a non-invasive method to determine luteal phase onset. During the luteal phase of the menstrual cycle there is a slightly higher muscle glycogen concentration [27] and plasma glucose kinetics are also altered [28]. Protein oxidation during exercise is also higher during the luteal phase of the menstrual cycle [29]. These are just a few examples of the importance to control for menstrual cycle in any gender comparative studies.

When menstrual cycle, diet and training are considered in the matching criteria, there appears to be a higher lipid oxidation and lower carbohydrate and amino acid oxidation in females compared with males during endurance exercise [19,21–23,29–33]. When one includes all of the reports comparing men and women during endurance exercise (including those that reported no gender differences) the 'meta-analysis' still shows that females oxidize more lipid and less carbohydrate and protein compared with males during endurance exercise (Tables 1 and 2).

In spite of the increased awareness of gender differences in physiology, this area is far from being resolved. The focus of this issue on gender differences in physiology is meant to provide an awareness of the major issues in the field such that future studies further explore these differences and ultimately provide gender specific recommendations based upon the results of careful research.

Table 2. Summary of substrate utilization in several studies (see Table 1) directly comparing males and females

Subjects	RER	CHO (%)	FAT (%)	PRO (%)
n = 135 F	0.869 (0.04)	56 (10)	41 (9)	2 (2)
n = 162 M	0.900 (0.04)*	66 (9)*	28 (8)*	6 (3)*

Values are mean (SD). *Gender difference ($P < 0.05$). RER = respiratory exchange rate; CHO = carbohydrate; PRO = protein.

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