ACTA PHYSIOLOGICA

Acta Physiol 2014, **210,** 768–789

REVIEW

Sex differences in human fatigability: mechanisms and insight to physiological responses

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Received 4 June 2013,
revision requested 29 July 2013,
revision received 4 November 2013,
accepted 8 January 2014
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Abstract

Sex-related differences in physiology and anatomy are responsible for profound differences in neuromuscular performance and fatigability between men and women. Women are usually less fatigable than men for similar intensity isometric fatiguing contractions. This sex difference in fatigability, however, is task specific because different neuromuscular sites will be stressed when the requirements of the task are altered, and the stress on these sites can differ for men and women. Task variables that can alter the sex difference in fatigability include the type, intensity and speed of contraction, the muscle group assessed and the environmental conditions. Physiological mechanisms that are responsible for sex-based differences in fatigability may include activation of the motor neurone pool from cortical and subcortical regions, synaptic inputs to the motor neurone pool via activation of metabolically sensitive small afferent fibres in the muscle, muscle perfusion and skeletal muscle metabolism and fibre type properties. Non-physiological factors such as the sex bias of studying more males than females in human and animal experiments can also mask a true understanding of the magnitude and mechanisms of sex-based differences in physiology and fatigability. Despite recent developments, there is a tremendous lack of understanding of sex differences in neuromuscular function and fatigability, the prevailing mechanisms and the functional consequences. This review emphasizes the need to understand sex-based differences in fatigability to shed light on the benefits and limitations that fatigability can exert for men and women during daily tasks, exercise performance, training and rehabilitation in both health and disease.

Keywords central fatigue, fibre types, gender, metabolism, peripheral fatigue, women.

Men and women differ in anatomy and physiology, which results in marked sex differences in neuromuscular performance and fatigability. In general, the skeletal muscles of men are larger and some muscles possess a greater proportional area of metabolically and functionally faster muscle fibres (Type II) than that of women [e.g. (Simoneau & Bouchard 1989, Staron *et al.* 2000, Porter *et al.* 2002, Roepstorff *et al.* 2006)] due to sex-related differences in human skeletal muscle gene expression and interactions with sex-specific hormones (Roth *et al.* 2002, Welle *et al.* 2008, Maher *et al.* 2009, Liu *et al.* 2010). Consequently, the whole muscles of men are usually stronger and more powerful than that of women. When contractions are sustained or repeated, however, as they are during exercise, rehabilitation and many daily activities, the relative reduction in force and power can differ between men and women when performed

 doi: 10.1111/apha.12234

at the same relative intensity of contraction. This activity-induced reduction in force or power is known as muscle fatigue (Gandevia 2001, Enoka & Duchateau 2008, Kent-Braun *et al.* 2012) or fatigability (Kluger *et al.* 2013). In this review, the terminology is used interchangeably. Muscle fatigue develops soon after the onset of sustained physical activity and can occur despite continued and successful performance of submaximal exercise. However, if the submaximal task is maintained, task failure will eventually occur. Multiple mechanisms contribute to the force and power decrements and range from an inadequate activation of the motor cortex to impairment of the contractile proteins within skeletal muscle fibres; however, the dominant mechanism is specific to the process that is stressed the most (Gandevia 2001). While motor performance is ultimately limited by the output of the muscle, limitations in both activation within the central nervous system and muscle can lead to fatigability and a decrement in performance of maximal and submaximal tasks in both men and women.

Despite recent developments in our understanding of the mechanisms of muscle fatigue [e.g. (Gandevia 2001, Enoka & Duchateau 2008, Kent-Braun *et al.* 2012)], there is still a tremendous lack of knowledge and appreciation of sex-based differences in fatigability and the prevailing mechanisms under different task conditions. This is, in part, because of the historical and current bias of studying proportionally more males than females in both human and animal-based physiology (Anonymous 2010, Kim *et al.* 2010, Zucker & Beery 2010, Beery & Zucker 2011, Cahill 2012, Miller 2012) and the presumption that sex differences in fatigability do not exist. This review will provide a framework to understand the importance of sex differences in fatigability and its relevance for rehabilitation, training and daily function. The review will highlight the following: (i) known sex differences in fatigability for different task conditions, and (ii) some of the physiological differences between men and women that may explain the sex differences in fatigability.

Sex differences in muscle fatigue are task specific

Two experimental approaches have emerged over the last 20 years that, together, provide valuable insight into the mechanisms for the sex differences in fatigability. The *classic* approach is to measure the physiological mechanisms during maximal contractions performed by men and women before, during and after fatiguing exercise. A *functionally relevant* approach has been to vary the task requirements and environment of a fatiguing contraction in order to stress different sites (or the same site at a different rate) within the neuromuscular system (Hunter *et al.* 2004a, Enoka & Duchateau 2008). This second approach is based on the concept that muscle fatigue is specific to the demands of the task (Enoka & Stuart 1992), and this specificity can differ for men and women because of sex-related differences within the neuromuscular system (Hunter 2009). Hence, the sex difference in fatigability and the rate limiting mechanisms can differ, for example, according to the contraction type, speed and intensity, the involved muscle group, environmental conditions and state of arousal. Following are examples of how the magnitude of the sex difference in fatigability can differ between single limb isometric, shortening and lengthening contractions and multiple sprint exercise. In general, while much has been learned about sex differences in fatigability during isometric contractions over the last 20 years, less is known about the sex differences in fatigability during dynamic performance.

Single limb contractions

Isometric contractions. There can be large sex differences in muscle fatigue for isometric fatiguing contractions, especially for some muscle groups. In general, women are less fatigable than men for isometric sustained and intermittent contractions performed at the same relative intensity for several muscle groups, including the elbow flexors, finger flexors, adductor pollicis, back extensors, dorsiflexors, knee extensors and respiratory muscles [e.g. (Maughan *et al.* 1986, Fulco *et al.* 1999, Hunter & Enoka 2001, Hunter *et al.* 2002, 2006b, 2009, Clark *et al.* 2003, Russ & Kent-Braun 2003, Guenette *et al.* 2010)] (Fig. 1a). Some muscle groups, such as the ankle dorsiflexors, demonstrate less of a sex difference in fatigability than the elbow flexor muscles (Kent-Braun *et al.* 2002, Hunter *et al.* 2008, Avin *et al.* 2010), and for the elbow extensor muscles, there is no sex difference for a sustained contraction (Dearth *et al.* 2010). The explanation for the differences in the magnitude of the sex difference between muscle groups likely involves a combination of muscular mechanisms which include contractile properties, fibre type proportion and perfusion. These mechanisms are addressed in the second part of the review. Those muscle groups that exhibit the largest sex differences in fatigability, for sustained isometric contractions also tend to show associations between strength and fatigability (e.g. elbow flexors and knee extensors) (Maughan *et al.* 1986, Hunter & Enoka 2001, Avin *et al.* 2010). Further, the sex difference in muscle fatigue is diminished as the contraction intensity increases for some of these muscles

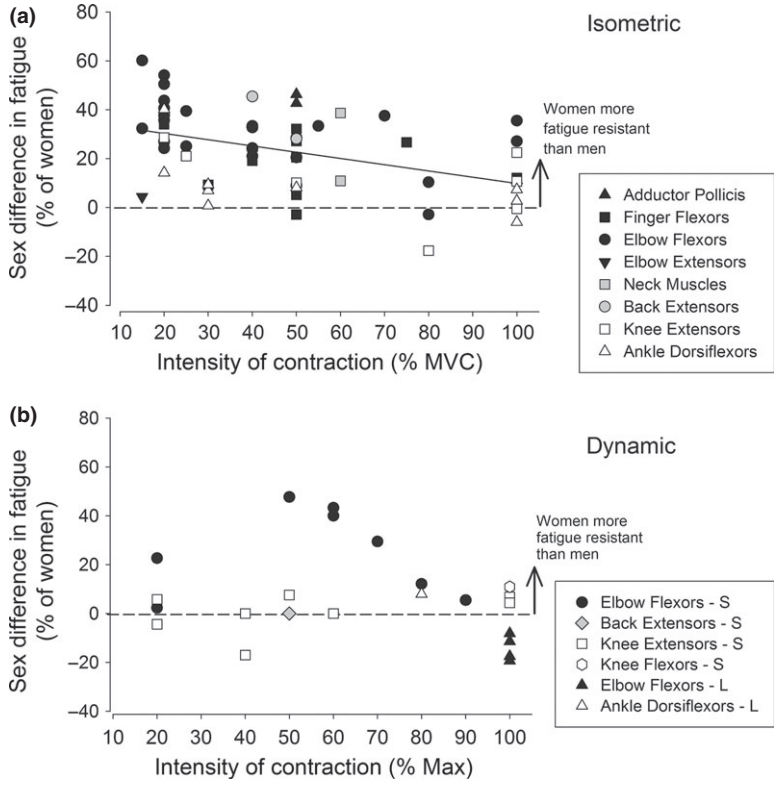

Figure 1 Sex differences in muscle fatigue for voluntary isometric contractions (a) and dynamic contractions (b). Represented are mean data from 59 studies: 43 isometric contraction studies (a) and 16 dynamic contraction studies (b) that assessed muscle fatigue in men and women for various muscle groups. Plotted in both panels is the difference between the mean fatigue index or time to task failure of the men and women (as a percentage of the women's value) within a study as a function of the contraction intensity of the fatigue task. In both panels, upper limb muscles are in closed symbols and lower limb muscles represented in open symbols. Back and neck muscles are represented as grey symbols. (a) Sex differences in muscle fatigue for sustained and intermittent isometric fatiguing contractions are plotted. Most data points are above the line, indicating women are more fatigue resistant than men for most muscle groups. There was a significant negative relation between the relative contraction intensity and the magnitude of the sex difference for the isometric contractions when all muscle groups are included ($r^2 = 0.20$, $P < 0.05$). (b) Sex differences in muscle fatigue for shortening (S) and lengthening (L, triangle-up symbols) contractions are plotted. There was no relation between contraction intensity and the sex difference for dynamic contractions, although data from two studies for the elbow flexor muscles (between 50–90% max) showed a significant negative relation ($r^2 = 0.97$) for shortening contractions. There are more data points than number of stated studies because some studies involved multiple contraction types or intensities.

(Maughan *et al.* 1986, West *et al.* 1995, Yoon *et al.* 2007). These observations provide insight into the role of strength-associated mechanisms and blood flow as potential mechanisms for the sex difference in muscle fatigue, especially at lower intensity contractions (see blood flow section).

Comparison of fatigability in men and women during sustained vs. intermittent isometric contractions demonstrates the reliance of the sex difference in fatigability on the details of the task. For example, men (who are usually stronger) have a briefer time to failure than women for the elbow flexor muscles (Hunter & Enoka 2001, Hunter *et al.* 2004a, Yoon *et al.* 2007). For men and women who were matched for strength, however, there was no sex difference in the time to failure of a sustained submaximal contraction (Hunter *et al.* 2004b), indicating a strength-related mechanism contributed to the longer time to task failure. In contrast, the strength-matched women were able to perform an intermittent isometric task until failure almost three times longer than the strength-matched men (23.5 vs. 8.6 mins) (Hunter *et al.* 2004c). The major difference between the fatiguing tasks is that the muscle is more perfused during the intermittent contraction than the sustained contraction. Comparison of these studies with the elbow flexor muscles suggests that the mechanisms responsible for the sex difference in fatigability for an intermittent task (i) differ from those responsible for the sex difference in fatigue during sustained isometric

contractions and (ii) were independent of the absolute strength exerted by the men and women. More studies are needed to understand the magnitude and cause of the sex difference in fatigability during intermittent isometric tasks for many muscle groups (e.g. elbow extensor muscles). Comparisons with sustained contractions would also provide valuable insight into whether or not isometric contractions that are often prescribed in early rehabilitation need to be prescribed differently for men and women under different task conditions and for specific muscles.

A functionally relevant strategy that provides insight into the influence of environment during a submaximal isometric fatiguing contraction is shown with experiments that have varied the cognitive demand and arousal (stress) imposed during a submaximal fatiguing task in men and women (Yoon *et al.* 2009b) (Fig. 2). Women typically exhibit greater physiological responses to stress-inducing events than men, such as increased cognitive demand or unpredictable electric shocks to the back of the hand (Christou *et al.* 2004, Kajantie & Phillips 2006). Sex differences in response to a stressor include different brain activation strategies (Wang *et al.* 2007) and reduced steadiness (larger force fluctuations) during light-load contractions (Christou *et al.* 2004). Further, when a cognitive stressor was imposed during performance of a fatiguing contraction sustained at 20% of maximal voluntary contraction (MVC), the time to failure was reduced for men (8.6%), but more so for women (27.3%) compared with their control fatiguing contraction that involved no imposed stressor (Yoon *et al.* 2009b) (Fig. 2). The cognitive stressor involved performance of a mental-math task (counting backwards in increments of 13), which increased levels of reported anxiety and stress as well as salivary cortisol levels. Heart rate and blood pressure were also elevated, which increased cardiac work. The increased fatigability was not due to differences in the ability of young men and women to perform the mental math, nor mental distraction (Yoon *et al.* 2009b) (Fig. 2). This was corroborated by subsequent experiments that showed that when stress was induced in young men and women with unpredictable, but brief, electric shocks to the back of the hand of the non-exercising arm, the women exhibited larger reductions in the time to failure relative to control conditions compared with men (T. Yoon and S. K. Hunter, unpublished data) (Fig. 2, Study 4).

The cause of the stress-induced increase in fatigability in the women is not fully understood. For the cognitive stressor experiments with the elbow flexor muscles, strength-related mechanisms may, in part, be responsible for the sex difference in the reduction in time to failure. There was an association between the initial maximal strength and the reduction in the time to failure when the cognitive stressor was imposed, and comparison of strength-matched men and women

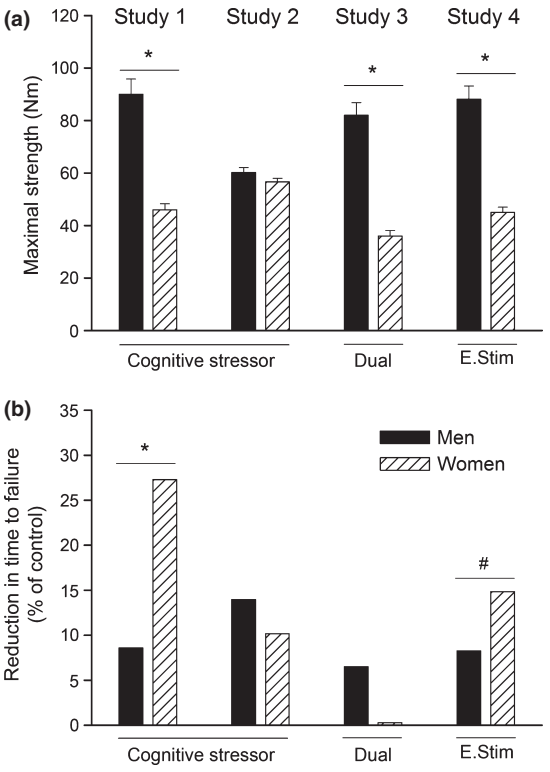

Figure 2 Summary of findings from four studies showing the influence of increased arousal on time to task failure of a fatiguing isometric contraction (20% MVC until failure) with the elbow flexor muscles in young men and women. In each study, two sessions were performed. A fatiguing contraction with no imposed stressor (control) and an experimental session where one of the following were imposed during the contraction: a difficult mental-math task (counting backward by 13, cognitive stressor), easy mental math (dual) or brief electric shocks to the back of the non-exercising hand (E. Stim). (a) Shown is the maximal voluntary isometric strength performed prior to the fatiguing contraction by young men and young women. (b) Shown is the relative reduction in time to task failure (between the control and experimental contraction, i.e. the Stressor, Dual task or E. Stim) for each study. Women had greater reductions than men for the cognitive stressor (study 1, $n = 20$) (Yoon *et al.* 2009b); but not when matched for strength (study 2, $n = 10$) (M. L. Keller-Ross, H. M. Pereira, J. Pruse, T. Yoon, B. Schlinder-DeLap, K. A. Nielson and S. K. Hunter, submitted). Study 3 showed minimal changes in time to failure when the subjects performed easy mental math (Dual, $n = 20$) (Yoon *et al.* 2009b). Reductions in time to failure were observed when the arousal was induced with unpredictable brief electric shocks to the back of the hand during the contraction (Study 4, E.Stim, $n = 20$) (T. Yoon and S. K. Hunter, unpublished data). $^{*}P < 0.05$ between men and women, $^{\#}P = 0.07$ although, not included in the results, are two women who failed to complete the fatiguing contraction because of increased levels of anxiety.

indicated a similar reduction in the time to task failure for the sexes (Yoon *et al.* 2009b, M. L. Keller-Ross, H. M. Pereira, J. Pruse, T. Yoon, B. Schlinder-DeLap, K. A. Nielson and S. K. Hunter, submitted) (Fig. 2). The increased fatigability with exposure to the cognitive stressor in the elbow flexor muscles may involve altered perfusion via stress-induced changes in sympathetic activation of muscle that has greater effects in people who are weaker and therefore have a more perfused muscle at the start of low-force sustained contractions. Other mechanisms, however, also likely contribute to the sex difference in fatigability in response to a stressor because there was no association between initial strength and the time to failure ($r = -0.09$) for experiments that induced stress with the electric shocks (T. Yoon and S. K. Hunter, unpublished data). Furthermore, the sex effect may only be relevant to the low-force contractions. Fatigability was greater when a stressor was imposed during a sustained contraction at 50% MVC and an intermittent maximal task with the handgrip muscles with no sex differences reported (Bray *et al.* 2008, 2012). More studies are required to determine the mechanism for the stress-induced increase in muscle fatigability for different muscle groups and task conditions, and the susceptibility of women.

Shortening contractions. The sex difference for dynamic fatiguing contractions has been studied less than isometric contractions, but the findings indicate that women are either less fatigable than men or that the sex difference in fatigability is diminished (Fig. 1b). Women were less fatigable than men for a protocol of 30 maximal dynamic contractions with the knee extensor and knee flexor muscles at a relatively constant speed of 3.14 rad s^{-1} (180 deg s^{-1}) (Pincivero *et al.* 2003): the magnitude of fatigue was explained by the initial maximal torque, because stronger subjects (men) exhibited greater fatigue (decline in maximal torque). Similarly, the time to task failure was longer for women than for men (9.7 ± 5.5 min vs. 6.1 ± 2.1 min respectively) for a dynamic task that required the participant to lift and lower a load equivalent to 20% of MVC force for as long as possible (1 contraction every 3 s) (T. Yoon and S. K. Hunter, unpublished data). These studies indicate that women exhibited less fatigue than men for dynamic fatiguing contractions that assessed fatigability as either the time to task failure or as a loss of maximal torque when the velocity of contraction was relatively controlled. The intensity of the dynamic contraction, however, can alter the sex difference in fatigability because, as the load progressively increased between 50 and 90% of one repetition maximum (1RM), the sex difference lessened (Maughan *et al.* 1986). For these studies, women were less fatigable than men for dynamic contractions.

The sex difference in fatigability of some dynamic tasks, however, can be diminished by and dependent on the contraction speed (Clark *et al.* 2003, Pincivero *et al.* 2004, Senefeld *et al.* 2013, Taipale & Hakkinen 2013). For example, despite women having a longer time to task failure than men with the back extensor muscles for an isometric contraction sustained at 50% of maximal strength (28% difference), there was no sex difference in the number of repeated shortening contractions performed at 50% of maximal strength until failure (24.3 vs. 24.0 repetitions) (Clark *et al.* 2003). Furthermore, there was no sex difference in the relative reduction in velocity and power for a task that required the young men and women to contract their elbow flexor and knee extensor muscles as quickly as possible with a load equivalent to 20% of their maximal isometric strength over approx. 4.5 min (Senefeld *et al.* 2013). In contrast, the decline in MVC from initial values that were measured immediately following the dynamic exercise in this study was significantly greater for the men than for the women for the knee extensor muscles (17.8 ± 2.8 vs. 10.4 ± 2.3%), but similar for the elbow flexor muscles. Although a sex difference in fatigability was not apparent during the dynamic task, men experienced greater relative reductions in maximal force than women at the end of the dynamic task with the knee extensor muscles. The decline of maximal force is due to fewer high-force cross-bridges and/or less force per cross-bridge, but reductions in maximal velocity contractions are related to the speed of cross-bridge cycling and calcium kinetics in the fibre [see (Kent-Braun *et al.* 2012) for review]. Greater insight into sex differences in the rate limiting mechanisms of dynamic contractions could be gained from experiments that fatigue human single fibres during shortening contractions *in vitro*. The implications of these findings for clinicians and scientists assessing fatigability of dynamic contractions in men and women are important because the mode of measurement chosen to assess fatigability may not reveal the underlying force decrements and potential differences between the sexes.

Lengthening contractions. Many dynamic contractions involve lengthening of the muscle fibres while they are activated; this is also known as eccentric activation. Examples of such tasks include lowering an object with the elbow flexor muscles with the arm in the sagittal plane or walking down a set of stairs so that the quadriceps muscles are activated while lengthening. A lengthening contraction is able to generate more force within the muscle fibre and, hence, greater muscle torque than

maximal isometric and shortening contractions (Duchateau & Baudry 2013, Herzog 2013). Prior to fatiguing exercise, the sex difference in peak torque during a lengthening contraction is less than the sex difference in torque for a shortening contraction at the same velocity of contraction, although the mechanism is not fully understood [e.g. (Seger & Thorstensson 1994, Lindle *et al.* 1997)]. Further, voluntary activation is less during maximal lengthening contractions than shortening contractions prior to fatigue (Duchateau & Baudry 2013), with no apparent differences between men and women (Spurway *et al.* 2000).

A bout of repeated lengthening contractions will elicit muscle fatigue and also muscle damage, the latter of which results in delayed onset muscle soreness (DOMS) (Clarkson & Hubal 2002). Muscle damage involves ultrastructural muscle fibre damage and inflammatory responses (Clarkson & Hubal 2002). The initial loss of force due to muscle fatigue vs. damage is difficult to differentiate, because both potentially reduce force generating capacity, but via different mechanisms. Fatigability of muscle is usually resolved within hours, while muscle damage can impair force generation for up to 7 days. Muscle damage, however, can increase fatigability of the elbow flexor muscles (Heroux & Gandevia 2013, Semmler *et al.* 2013), although whether sex differences exist is not known. In contrast to the animal model (Tiidus & Enns 2009, Enns & Tiidus 2010), maximal force reductions after repeated lengthening contractions in humans is either similar for men and women (Rinard *et al.* 2000, Hubal *et al.* 2008, Hubal & Clarkson 2009, Power *et al.* 2010), or women have greater losses of force than men (Sayers & Clarkson 2001, Sewright *et al.* 2008) (Fig. 1b). Recently it was shown that women have slower recovery of power and rates of force development compared with men after 150 maximal lengthening actions performed at 60 deg.s^{-1} with the ankle dorsiflexor muscles (Power *et al.*, 2013). A possible confounder is that women have lower pain thresholds than men (Fillingim *et al.* 2009, Racine *et al.* 2012), and pain will influence motor output and fatigability (Prasartwuth *et al.* 2005, Martin *et al.* 2008, Semmler *et al.* 2013). Pain and muscle damage from lengthening contractions also alter voluntary activation (Prasartwuth *et al.* 2005). Thus, sex differences in muscle fatigue with lengthening contractions may be masked by the pain accompanying muscle damage, which can influence men and women differently. Insight into any potential sex differences in fatigability could be gained by comparing the fatigability of lengthening contractions of men and women after several sessions of training or pre-conditioning (Chen *et al.* 2012). Because fatiguing lengthening contractions are important in optimizing muscle hypertrophy during strength training and rehabilitation programmes (Roig *et al.* 2009), addressing sex differences in fatigability may reveal information that is relevant to individualizing such programmes.

Multiple sprint exercise

The reduction in maximal power during, and in recovery from sprint exercise on a cycle ergometer with multiple repeats, indicates that, in general, men experience greater reductions in power than women (Esbjornsson-Liljedahl *et al.* 2002, Billaut & Smith 2009, Billaut & Bishop 2012). [See (Billaut & Bishop 2009) for review.] In each study, men were approx. 30% more powerful than women for the knee extensors (Esbjornsson *et al.* 2006, 2012, Billaut & Smith 2009). The difference in decline in power between men and women with multiple high-intensity sprints of short duration was associated with the initial power (Billaut & Bishop 2012). Consequently, when men and women were matched for initial power, there was no sex difference in the reduction in power (Smith & Billaut 2012). More mechanistic studies are needed to determine the role that maximal power plays in the difference in fatigability with multiple sprint exercise. Although the relative reduction in power is not always significantly different between men and women [e.g. (Esbjornsson *et al.* 2006, 2012, Smith & Billaut 2012)], several of these studies have revealed sex differences in muscle and whole-body metabolism that would likely have functional consequences for multiple sprint exercise of longer durations than several minutes. One functional consequence is that while men exert greater absolute power and speed than women, women recover more quickly than men (Laurent *et al.* 2010).

Mechanisms for sex differences in muscle fatigue

Sex differences in physiology and anatomy contribute to differences between men and women in muscle function and fatigability, although there are other non-physiological factors that may also contribute and are addressed towards the end of this review.

Physiological mechanisms

Following are mechanisms from physiological sources that potentially contribute to the sex difference in muscle fatigability and task specificity (Fig. 3).

Muscle mass and strength differences. For some muscle groups and tasks, a greater initial strength is associated with increased fatigability, indicating the involvement of a strength-related mechanism

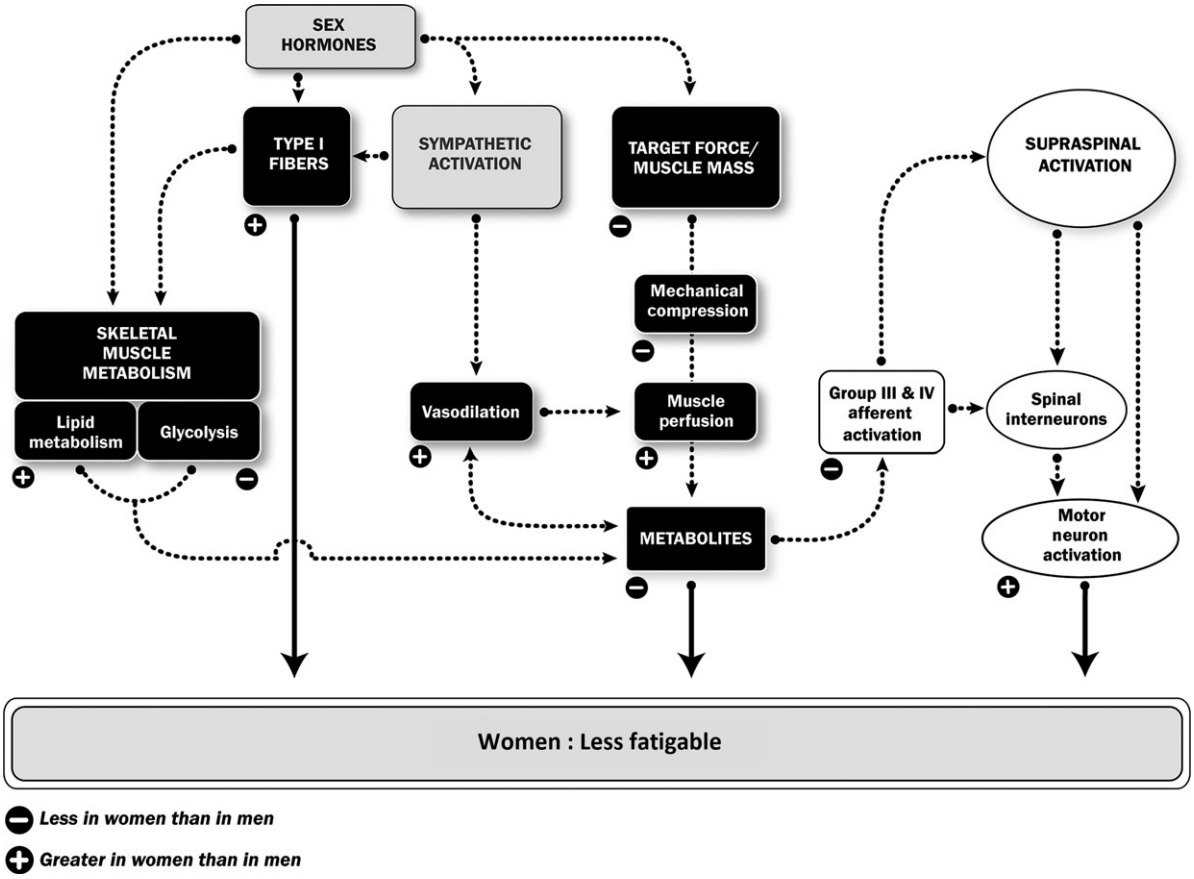

Figure 3 Potential physiological mechanisms for the sex difference in muscle fatigability (or time to task failure). The figure shows those potential mechanisms that can contribute to women being more fatigue resistant than men. The strength of a potential mechanism will vary with the task conditions so that one dominant mechanism does not fully explain the sex difference in performance of a fatiguing contraction. A negative sign indicates that the physiological variable or process is less in women than in men, whereas a positive sign indicates it is greater in women than in men. Ultimately, the differences in fatigue between men and women can be due to differences in (i) motor neurone activation, (ii) contractile function of the activated fibres and (iii) the magnitude of metabolites accumulating that interfere with contractile function. These mechanisms are stipulated with the large arrows. Black boxes indicate processes within the muscle, white boxes are processes in the nervous system, and the grey are hormonal and sympathetic actions.

(Maughan *et al.* 1986, West *et al.* 1995, Hunter & Enoka 2001, Hunter *et al.* 2004a, 2006a,b, Avin *et al.* 2010). Men are usually stronger than women because they have a larger skeletal muscle mass (Miller *et al.* 1993, Lindle *et al.* 1997, Ivey *et al.* 2000, Welle *et al.* 2008). The relative sex difference in muscle mass and strength is greater for some muscle groups than others, such as the elbow flexor muscles and finger flexors compared with the knee extensor and dorsiflexor muscles (Miller *et al.* 1993, Russ & Kent-Braun 2003, Hunter *et al.* 2006b, Senefeld *et al.* 2013). Because men and women are able to voluntarily activate their muscles to similar, and near maximal levels during a maximal voluntary isometric contraction (MVC) in the upper (Miller *et al.* 1993, Hunter *et al.* 2006a, Yoon *et al.* 2007) and lower limb (Russ & Kent-Braun 2003) prior to a fatiguing task, there are usually minimal reported sex differences in specific strength (i.e. force/unit of muscle). Thus, subsequent fatiguing contractions are usually performed at similar relative intensities for men and women, and any sex difference in fatigability therefore is not because women activate relatively less muscle than men at the start of a fatiguing task. The sex difference in strength is mainly due to larger diameter muscle fibres in the men than in the women for both upper and lower limb muscles, and probably not due to any sex difference in the number of fibres (Miller *et al.* 1993).

The larger absolute differences in muscle mass and greater forces exerted during a fatiguing contraction for men compared with women can have mechanical and metabolic consequences during fatiguing exercise, some of which are highlighted in Fig. 3 and the following sections. Consequently, for some tasks, greater

  doi: 10.1111/apha.12234

fatigability of men compared with women is a direct result of men exerting greater absolute force during the contraction (see blood flow section). In other instances, the sex difference in fatigability is associated with the greater strength exerted by men, but is not the primary cause for the sex difference [e.g. (Hunter *et al.* 2006a)]. For other tasks, such as the intermittent isometric contraction, the sex difference in muscle fatigue is independent of strength differences [e.g. (Fulco *et al.* 1999, Hunter *et al.* 2004c)]. Comparing men and women of the same absolute strength can determine the role of absolute strength in the observed sex differences in fatigue, but is not always easy to achieve given that, for most muscle groups, the majority of men are stronger than women.

Blood flow and muscle perfusion. Reduced blood supply to an active muscle will result in accelerated muscle fatigue and earlier task failure because of the reduced oxygen delivery to the muscle and rapid accumulation of metabolites that interfere with the contractile function (Russ & Kent-Braun 2003, Clark *et al.* 2005). Accumulated metabolites may further accelerate fatigue by increasing peripheral afferent feedback and inhibitory inputs to the motor neurone pool and further limit voluntary activation (Gandevia *et al.* 1996). Differences in muscle perfusion between men and women contribute to a sex difference in muscle fatigue and performance, but this mechanism is specific to certain tasks and muscle groups (Russ & Kent-Braun 2003, Hunter *et al.* 2004b, Clark *et al.* 2005, Parker *et al.* 2007, Thompson *et al.* 2007, Saito *et al.* 2008). In general, women may have greater muscle perfusion than men for some muscle groups, due to a difference in mechanical compression onto the feed arteries during low-force sustained isometric contractions [e.g. (Hunter & Enoka 2001)], a sympathetically mediated difference in vasodilation (Ettinger *et al.* 1996, Hogarth *et al.* 2007, Parker *et al.* 2007), and greater capillarization of the muscle bed. The contribution of each of these mechanisms to any sex difference in fatigability is task and muscle group dependent.

During low-to-moderate force sustained isometric contractions, when the muscle is not fully occluded (Barnes 1980, Sadamoto *et al.* 1983), blood flow can be more restricted for men than women at the same contraction intensity. This is because men are typically stronger than women and therefore exert more intramuscular pressure onto the feed arteries (Hunter *et al.* 2006b, 2009) (Fig. 3). Thus, when men were stronger than women for the elbow flexor muscles and handgrip muscles, the time to failure of women was longer than the men (Hunter & Enoka 2001, Hunter *et al.* 2004a, 2006b, Yoon *et al.* 2007), but similar when the sexes were matched for strength (Hunter *et al.* 2004b, 2006b). Accordingly, the metaboreflex [increase in mean arterial pressure due to activation of sensory fibres by muscle metabolites (Kaufman & Hayes 2002)] was greater during the isometric contractions for the men compared with the women, and associated with greater fatigue in the men (Hunter & Enoka 2001). For high-intensity sustained contractions, when the blood flow is similarly occluded for men and women, the difference in fatigability between men and women is reduced relative to that for low-force contractions for some muscle groups (Maughan *et al.* 1986, West *et al.* 1995, Yoon *et al.* 2007) (Figs 1 and 3). Under these isometric conditions, the absolute target force and resultant blood flow appear to be the primary causes for the differences in fatigability between men and women.

There are also widespread sympathetic-mediated actions on skeletal muscle (Joyner & Halliwill 2000, Roatta & Farina 2010), and sex differences in these actions potentially alter muscle fatigue of men and women. For example, a sex difference in sympathetic-mediated actions can influence muscle perfusion and may promote a sex difference in fatigability. Possibilities include sex differences in muscle sympathetic nerve activity at rest and during contraction (Ng *et al.* 1993, Hogarth *et al.* 2007) and β_2 adrenergic receptor-mediated vasodilation. β_2-receptors are localized with greater density on type I fibres than type II (Roatta & Farina 2010). Women have greater type I fibre area than men in some muscles (see fibre type section) and therefore possibly greater β_2 adrenergic receptor-mediated vasodilation than men during exercise (Fig. 3). Although the interactions are not fully understood, the balance of vasoconstriction and vasodilation potentially alters the net perfusion of the active muscle, and thus, muscle fatigability in men vs. women. These altered interactions could be responsible for the greater fatigability during low-force contractions when arousal is increased (Yoon *et al.* 2009b).

Greater vasodilatory responses of feed arteries to the skeletal muscle of women may also allow them to offset muscle fatigue during dynamic contractions compared with men. For example, vasodilatory responses of the femoral artery during dynamic knee extensor exercise were greater in women than in men (Parker *et al.* 2007). These responses were not dependent on strength. Greater vasodilatory responses in women would promote increased muscle perfusion, less accumulation of metabolites and potentially offset the rate of muscle fatigue relative to men. Further studies are required to understand the contribution of these sex differences in vasodilation to fatigability.

Last, perfusion can also depend on capillarization of skeletal muscle. There is a higher density of capillaries per unit of skeletal muscle (measurements

made from muscles biopsies) in the vastus lateralis of women than men (Roepstorff *et al.* 2006), due to a greater proportional area of type I fibres. Such differences will increase muscle perfusion in the women relative to men. In contrast, capillary density within the fibres of the tibialis anterior muscle was similar for both sexes, although less in type II fibres than type I (Porter *et al.* 2002). The lack of differences in capillary density of the tibialis anterior fibres between men and women is consistent with a smaller sex difference in muscle fatigue in that muscle relative to other muscles (Avin *et al.* 2010).

Collectively, evidence indicates that women have greater muscle perfusion than men during exercise at the same relative intensity, which potentially explains some of the sex differences in muscle fatigability. However, the cause for the altered blood flow will differ with the details of the task, such as whether the contraction is sustained or intermittent.

Contractile properties. Sex-based differences in muscle fibre types, their size, number, contractile properties and metabolism will influence muscle function and fatigability. Several studies show that less muscle fatigue in women was associated with slower contractile properties measured from contractions evoked by electrical and transcranial magnetic stimulation (TMS) (Hunter *et al.* 2006a, Wust *et al.* 2008, Keller *et al.* 2011). For example, young women demonstrated less muscle fatigue at the end of 2 min of electrically evoked intermittent contractions (1 s on at 30 Hz; 1 s off) of the quadriceps muscles than young men (30 ± 10% vs. 38 ± 11% reduction respectively) (Wust *et al.* 2008). Lower initial peak rates of relaxation (slower muscle), which occurred in the women, were associated with less muscle fatigue at the end of the electrically evoked fatiguing contraction (Wust *et al.* 2008). Similarly, for the elbow flexor muscles, greater muscle fatigue exhibited by men compared with women during voluntary maximal and submaximal isometric fatiguing contractions was associated with faster peak relaxation rates (measured from contractions evoked with TMS, during an MVC) (Hunter *et al.* 2006a, Keller *et al.* 2011). For example, by the end of the six sustained MVCs (22 s duration each) with the elbow flexor muscles, young men exhibited greater absolute and relative reductions in torque (65 ± 3% of initial MVC) than young women (52 ± 9%) (Fig. 4) (Hunter *et al.* 2006a). Supraspinal fatigue that was assessed with TMS, increased similarly for the men and women. The motor evoked potential (MEP, EMG response to TMS) increased to similar levels for the men and women, and the superimposed twitch torque (elicited with TMS during an MVC) was also similar for both sexes, indicating no sex difference in neural mechanisms. The sex difference in muscle fatigue, however, was attributed to muscular (peripheral) mechanisms because the reduction in the amplitude of the estimated resting twitch was greater for the men (59%) than for the women (27%). Furthermore, the men had faster relaxation rates than women at baseline and the muscle slowed more during the fatigue task in the men (53% from initial values) compared with the women (22% from initial values) (Fig. 4). Together, these studies with the knee extensor and elbow flexor muscles underscore the involvement of contractile mechanisms contributing to the sex differences in muscle fatigue in several large muscle groups. Comparison of several studies, however, indicates that the contribution of muscular mechanisms to the sex difference in fatigability varies across muscle groups. There is less of a sex difference in the ankle dorsiflexors (Russ & Kent-Braun 2003, Russ *et al.* 2005) than the elbow flexors and knee extensors (Hunter *et al.* 2006a, Martin & Rattey 2007, Wust *et al.* 2008). In general, the tibialis anterior muscle (primary ankle dorsiflexor) has a greater proportion of slow type I fibres than the elbow flexor and knee extensor muscles (Johnson *et al.* 1973, Simoneau & Bouchard 1989, Porter *et al.* 2002), possibly limiting the expression of any sex differences in contractile fatigability.

Fibre types. Skeletal muscles of men and women are comprised primarily of a combination of type I, type IIA and type IIX fibres that are named based on the primary myosin heavy chain composition of the fibre, but whose metabolic, Ca^{2+} kinetics and functional contractile properties are generally coupled with the behaviour of the myosin proteins (Schiaffino & Reggiani 2011). Hence, type II fibres, classified according to the dominant myosin isoform, have faster calcium kinetics, generate greater power, faster shortening velocities and relaxation and are more fatigable than type I fibres (Schiaffino & Reggiani 2011). While these categories are convenient for analysis, in reality there is a continuum of fibre properties based on a combination of myosin heavy and light chain isoforms, polymorphic expression of protein isoforms, metabolic potential and Ca^{2+} handling properties (Ingalls 2004). Furthermore, co-expression of myosin heavy chain isoforms within a fibre is not unusual (Klitgaard *et al.* 1990, Williamson *et al.* 2000, Caiozzo *et al.* 2003). Ultimately, the functional properties differ across the broad spectrum of fibre types. Because there are sex differences in the proportional area of fibre types within some muscles, the functional properties and fatigability of whole muscles can differ between men and women.

There is considerable evidence that women have a greater proportional area of the 'slow' type I fibres

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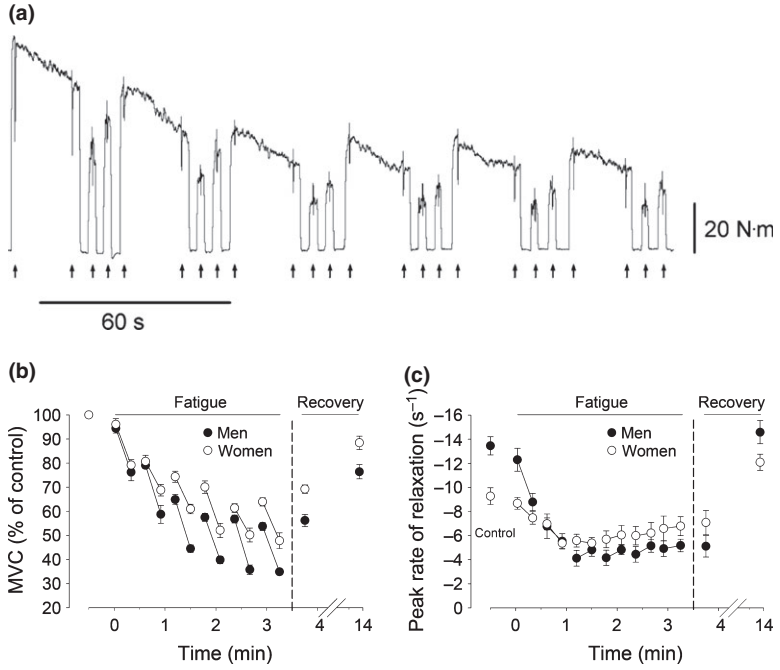

Figure 4 Young men (n = 9) and young women (n = 8) performed an isometric fatiguing protocol with the elbow flexor muscles. The protocol involved 6 × 22 s maximal voluntary contractions (MVC) with submaximal contractions at 60 and 80% MVC before, after and between the sustained MVCs. (a) Representative torque data of a male subject. Arrows at the bottom of the panel show the timing of transcranial magnetic stimuli (Stim). (b) MVC torque (mean ± SEM) relative to baseline control values for the men (closed circles) and women (open circles) during, and in recovery from, the fatiguing task. Relative torque is shown at the start and end of each sustained 22-s MVC, and during brief MVCs at the start and end of 10-min recovery. The men exhibited larger reductions in torque than the women during the intermittent fatiguing contractions (65 vs. 52%). (c) Peak relaxation rate of muscle measured from the fall in force immediately after the superimposed twitch during the MVC. Plotted are the mean (±SEM) from the five brief control MVCs, and then values at the start and end of each 22-s maximal contraction, and for a brief MVCs at the start and end of recovery. Peak relaxation rate became slower for both men and women as the muscle became more fatigued and then recovered within the 10-min. However, the men had greater reductions in the peak relaxation rate than the women ($P < 0.05$). Note that the y-axis is inverted. Larger negative numbers indicate faster relaxation. Adapted from (Hunter *et al.* 2006a).

than men in several key muscles that are important to locomotion and daily function (Simoneau & Bouchard 1989, Esbjornsson-Liljedahl *et al.* 1999, Staron *et al.* 2000, Carter *et al.* 2001b, Porter *et al.* 2002, Roepstorff *et al.* 2006, Welle *et al.* 2008) (Fig. 5). Most studies also show that men have larger fibres than women across most of the fibre types with proportionally larger cross-sectional area (CSA) of type II fibres in the tibialis anterior, vastus lateralis and biceps brachii (Alway *et al.* 1989, Simoneau & Bouchard 1989, Staron *et al.* 2000, Carter *et al.* 2001b, Porter *et al.* 2002). Hence, young women have smaller muscles that possess a greater proportional area of the type I fibre compared with men.

The muscle fibre properties and morphology of men and women are due to sex-related differences in human skeletal muscle gene expression and an interaction with sex-specific hormones (Roth *et al.* 2002, Welle *et al.* 2008, Maher *et al.* 2009, Liu *et al.* 2010). While genetic factors play an important role in determining variation in muscle fibre properties between men and women, specific genes are still being identified and further study is needed. Certainly, metabolically slower and more fatigue-resistant fibres in women compared with men promote a sex difference in muscle fatigability. Greater insight into the sex differences in muscle fatigability can be gained by *in vitro* experiments of contractile properties and fatigability of various fibre types obtained from muscle biopsies of men and women. Several studies have shown that there are limited differences in the peak force, power and shortening velocity of single fibres (chemically skinned) between men and women relative to cell size (Krivickas *et al.* 2001, 2006, Trappe *et al.* 2003). Valuable information into sex differences in fatigability would be gained by including both men and women in single fibre studies.

Consistent with a sex difference in fibre properties, there is some evidence that the calcium (Ca^{2+}) kinetics of the sarcoplasmic reticulum is slower in women

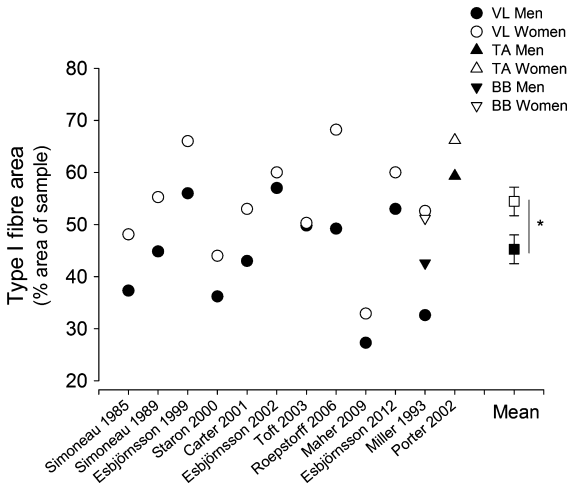

Figure 5 Type I fibre area (%, proportional area) of skeletal muscle histochemically analysed for myosin ATPase activity from muscle biopsy samples of vastus lateralis (VL), tibialis anterior (TA) and biceps brachii (BB) in young men (closed symbols) and women (open symbols) that were sampled in the same study. Shown are the mean proportional areas of the men and women in each of the 12 studies (Simoneau *et al.* 1985, Simoneau & Bouchard 1989, Miller *et al.* 1993, Esbjornsson-Liljedahl *et al.* 1999, 2002, Staron *et al.* 2000, Carter *et al.* 2001b, Porter *et al.* 2002, Toft *et al.* 2003, Roepstorff *et al.* 2006, Maher *et al.* 2009, Esbjornsson *et al.* 2012). The mean (±SEM) per cent area of type I fibres of all the muscles from the 12 studies is plotted on the right side. Women had greater type I fibre area (%) than men ($P < 0.05$).

compared with men. Analysis of muscle biopsy samples before and after sprint exercise showed that young women have a 24% lower maximal rate of sarcoplasmic reticulum Ca^{2+}ATPase activity than men (Harmer *et al.* 2014) (Fig. 6). Slower Ca^{2+}ATPase activity and Ca^{2+} uptake into the sarcoplasmic reticulum is associated with slower rates of relaxation and muscle mechanics (Gollnick *et al.* 1991). Type II fibres have approx. threefold higher Ca^{2+}ATPase activity and twofold higher calcium uptake than type I fibres (Li *et al.* 2002). Also, a significant relationship exists between the proportional area of type II fibres and Ca^{2+}ATPase activity (Madsen *et al.* 1994, Hunter *et al.* 1999). Although this is the first study to directly compare the calcium kinetics in the skeletal muscle of men and women (Harmer *et al.* 2014), the values reported for men and women are similar to reports of Ca^{2+}ATPase activity of men and women reported as separate cohorts (Booth *et al.* 1997, Hunter *et al.* 1999, Ortenblad *et al.* 2000, Thom *et al.* 2001, Li *et al.* 2002) (Fig. 6). The lower Ca^{2+}ATPase activity in the muscle of young women is not due to a less active muscle, because Ca^{2+}ATPase activity was not altered after a 12-week high resistance strength training programme (Hunter *et al.* 1999) or 10 days of immobilization (Thom *et al.* 2001). Thus, the sex difference in Ca^{2+}ATPase activity of the sarcoplasmic reticulum is consistent with women possessing a slower and more fatigue-resistant skeletal muscle profile than men. Studies comparing the calcium regulation of single fibres from the skeletal muscle of men and women are needed. Determining associations with fatigability *in vitro* and *in vivo* would provide valuable information into the contribution of Ca^{2+} kinetics to the sex difference in fatigability.

Skeletal muscle metabolism. Sex-based differences in muscle fibre type and contractile properties have consequences for the skeletal muscle metabolism during dynamic and isometric fatiguing contractions in men and women. During high-force isometric fatiguing contractions with the tibialis anterior (ankle dorsiflexors), men exhibited greater *in vivo* glycolysis, estimated from magnetic resonance spectroscopy of muscle, than women, with no sex differences in creatine kinase flux or oxidative capacity (Russ *et al.* 2005). During high-intensity single and multiple sprints with the lower limb, men and women exhibit differences in metabolic pathways of quadriceps muscles. For example, in response to sprint exercise, women exhibited less increase in blood lactate concentration (Esbjornsson-Liljedahl *et al.* 1999), a smaller reduction in ATP and less accumulation of its breakdown products, IMP and inosine than men, especially in type II fibres (Esbjornsson-Liljedahl *et al.* 2002). These metabolic sex differences within a muscle are likely related to the greater proportional area of type I fibres in women compared with men (Esbjornsson *et al.* 1993, Esbjornsson-Liljedahl *et al.* 1999, Roepstorff *et al.* 2006, Maher *et al.* 2009), demonstrating the central contribution of skeletal muscle metabolism to the sex differences in fatigability. Despite differences in muscle metabolism between men and women during short duration isometric and single or multiple sprint exercise, a sex difference in muscle fatigue is not always observed [e.g. (Russ *et al.* 2005, Esbjornsson *et al.* 2012)], indicating that, for those tasks, other rate limiting mechanisms were more important during the fatiguing exercise. Metabolic sex differences may influence men and women during longer duration high-intensity exercise.

During whole-body moderate-to-high intensity endurance exercise, women also oxidize more fat and less carbohydrate than men when compared at the same relative intensity of exercise (Horton *et al.* 1998, Carter *et al.* 2001a, Mittendorfer *et al.* 2002, Roepstorff *et al.* 2002, 2006). Some of these differences originate from skeletal muscle metabolism, because women demonstrate a larger capacity for lipid metabolism than men,

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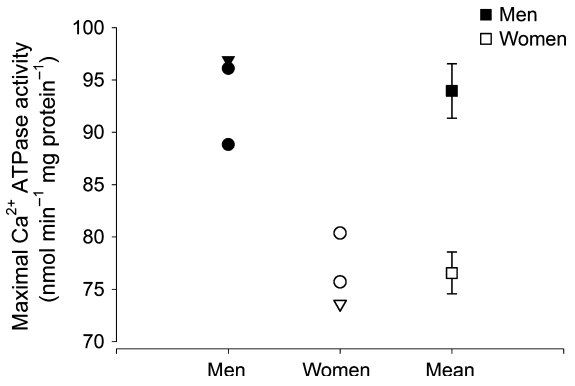

Figure 6 Maximal rates of sarcoplasmic reticulum Ca^{2+}ATPase activity for whole muscle homogenates (obtained via needle biopsies of the vastus lateralis) of young men (n = 27) and women (n = 31) at rest. Men are represented in the closed symbols and women in the open symbols. Data plotted as circles are from four different studies that examined men only (Booth *et al.* 1997, Li *et al.* 2002) and women only (Hunter *et al.* 1999, Thom *et al.* 2001). The triangles are men and women in the same study (Harmer *et al.* 2014). The mean (±SEM) of the men and women from all the studies are plotted on the right side of the figure (squares) showing that men have faster maximal Ca^{2+}ATPase activity than women.

including greater mRNA levels of muscle lipoprotein lipase, membrane fatty acid transport protein-1, FAT/CD36 protein levels, and citrate synthase, irrespective of training status and age (Binnert *et al.* 2000, Kiens *et al.* 2004). Lipid metabolism in skeletal muscle of women is related to the presence of oestrogen (17-estradiol, E2) (Maher *et al.* 2010). Collectively, these studies demonstrate that the sex differences in skeletal muscle properties during, and in recovery from, moderate- and high-intensity exercise may contribute to less muscle fatigue and faster recovery of force and power in women compared with men.

Voluntary activation and the role of the central nervous system. Activation of the motor neurone pool during voluntary contraction involves integration of synaptic inputs from descending pathways, spinal interneurones and peripheral afferent feedback (Enoka 2012). The challenge during a fatiguing contraction is to maintain adequate and optimal voluntary activation as spinal and supraspinal centres modulate the changing muscle conditions during maximal and submaximal tasks (Enoka 2012). Sex differences in voluntary activation and ultimately motor output during fatiguing exercise will arise if the synaptic inputs from descending pathways, spinal interneurones and peripheral afferent feedback differ between men and women.

Descending inputs from cortical centres that affect motor performance potentially differ between men and women because there are widespread sex differences in brain physiology, anatomy and functional activation throughout the lifespan (Becker *et al.* 2005, Hodes 2013, Koolschijn & Crone 2013). In general, during non-fatiguing motor tasks and comparable motor performance, such as finger tapping or preparation to reach, women tend to show greater activation levels of ipsilateral and bilateral cortical areas than men when assessed with functional magnetic resonance imaging (fMRI), which estimates the blood oxygenation level dependent (BOLD) as a correlate of neural activity in the brain (Lissek *et al.* 2007, Gorbet *et al.* 2010). Men, however, exhibited greater activation (fMRI signals) of subcortical areas, such as the basal ganglia (Lissek *et al.* 2007). Little is known about brain activation patterns during fatiguing tasks in men compared with women. A significant challenge is to determine the functional significance of these sex-based differences in the brain activity during motor control tasks and fatiguing exercise.

At rest, there are minimal sex differences in motor cortical input–output properties characterized with the MEP in healthy young men and women (Pitcher *et al.* 2003). During contraction, one method to assess adequacy of voluntary activation within the central nervous system involves stimulating the nervous system during maximal efforts at either the muscle or motor neurone (Merton 1954, Belanger & McComas 1981, Gandevia 2001). Similarly, adequacy of voluntary drive to the motor cortex can be estimated with a transcranial magnetic stimulus during voluntary contractions (Todd *et al.* 2003, 2004). Any observed increase in the increment in force evoked by a superimposed stimulation at the muscle or cortex during the voluntary contraction implies a failure of voluntary drive at one or more sites proximal to the site of stimulation. During brief maximal efforts, men and women are able to similarly activate and drive their motor cortex during upper limb maximal efforts before fatiguing exercise (Hunter *et al.* 2006a, Keller *et al.* 2011, Molenaar *et al.* 2013). Similarly, there is no sex difference in voluntary activation of the elbow flexor muscles (Miller *et al.* 1993, Yoon *et al.* 2007) and ankle dorsiflexor muscles (Russ & Kent-Braun 2003). Hence, during brief maximal efforts in a non-fatigued and healthy muscle, there appears to be minimal sex differences in neural drive to skeletal muscles when assessed with these techniques.

During fatiguing exercise, there is often a failure of voluntary activation by both men and women. A failure in voluntary activation during maximal efforts means that the level of neural drive to the muscle is less than optimal because either the motor units were not all recruited voluntarily, or they were discharging at rates that were not high enough to maximize the

force capacity of the muscle (Gandevia 2001). This fall in voluntary activation is sometimes referred to as central fatigue. Supraspinal fatigue is a component of central fatigue and is attributable to suboptimal output from the motor cortex (Gandevia 2001). It is seen as an exercise-related fall in voluntary activation measured with cortical stimulation. Despite women sustaining a low-force isometric contraction with the elbow flexor muscles for a longer duration than the men, the sexes demonstrated a similar reduction in voluntary activation at task failure for superimposed stimulations at the muscle (14% decline) (Yoon *et al.* 2007) and the motor cortex (14% decline to ~79%) (Keller *et al.* 2011). Comparison of these results indicates that a reduction in voluntary drive during the maximal contraction at task failure is due to a failure to generate output from the motor cortex in both men and women. Men and women also had similar levels of voluntary activation (assessed with TMS) at the end of six 22-s sustained maximal contractions (approx. 77% for both sexes), despite the men exhibiting greater decrements in maximal force than the women (Hunter *et al.* 2006a). The greater fatigue exhibited by the men than the women was explained by muscular mechanisms (Fig. 4). Thus, there was no sex difference in central and supraspinal fatigue at the end of the low- and high-force isometric fatiguing contractions sustained with the elbow flexor muscles, despite greater fatigue exhibited by the men.

For lower limb exercise, however, greater fatigability of men than women during maximal contractions was associated with a larger loss of voluntary activation (Russ & Kent-Braun 2003, Martin & Rattey 2007). Men, for example, had greater decrements in maximal force and voluntary activation than women when assessed with peroneal nerve stimulation during intermittent maximal contractions with the ankle dorsiflexor muscles (Russ & Kent-Braun 2003). Similarly, men had larger reductions in knee extensor force during a sustained maximal contraction (100 s) than women (24 vs. 16%), and this difference was associated with the larger reductions in voluntary activation in men than in women (22 vs. 9%) when assessed with evoked contractions elicited at the femoral nerve (Martin & Rattey 2007). It is unknown whether this sex difference is universal for submaximal tasks or dynamic contractions.

The fatigue-related reduction in voluntary activation can be increased by peripheral afferent feedback and is possibly greater for men than for women in lower limb muscles (Russ & Kent-Braun 2003). The firing of group III and IV muscle afferents, for example, is sensitive to ischaemia and metabolite accumulation associated with fatigue and pain (Martin *et al.* 2008, Kaufman 2011, Murphy *et al.* 2011). Their effect on increased excitation of motor neurone output with fatigue is not fully understood, but they depress cortical excitation in response to pain [e.g. (Martin *et al.* 2008)]. At the spinal cord, they can excite or inhibit motor neurones, and this may depend on the muscle group (extensors vs. flexors) and whether the excitation is from pain or metabolites [see (Martin *et al.* 2006, 2008)]. Excitation of group III and IV afferents however, appears to result in a net decrease of motor unit discharge rates and impaired voluntary activation [e.g. (Woods *et al.* 1987, Gandevia 2001, Martin *et al.* 2006, 2008, Dideriksen *et al.* 2010, Amann 2012, Rossman *et al.* 2012)], although evidence for their actions is indirect in humans. Higher intramuscular pressure in stronger muscles, or sex differences in muscle metabolism and accumulation of metabolic by-products, (Ettinger *et al.* 1996, Russ *et al.* 2005), may lead to a greater discharge of group III and IV muscle afferents in men than in women during similar intensity exercise. While it is possible that excitation of group III and IV afferents and their actions in the central nervous system in some muscle could reduce voluntary activation differently in men and women, more direct evidence is needed to support their role.

A loss of voluntary activation during maximal tasks, however, may not represent the impairments or sex differences in voluntary activation that occur during submaximal fatiguing tasks. Comparison of submaximal isometric fatiguing tasks that are similar in intensity but differ in the load compliance, for example (force vs. position task) [e.g. (Hunter *et al.* 2002, 2008, Madeleine *et al.* 2002, Maluf *et al.* 2005, Yoon *et al.* 2009a, Rudroff *et al.* 2010)], suggests that the limitations during submaximal contractions are probably more related to loss of activation rather than the capacity of muscle to develop maximal force or power (Enoka 2012). The difference between the force and position task involves greater activation of gamma motor neurones, increased excitation of muscle spindles and Ia afferent feedback to correct deviations of limb position, and differential modulation of pre-synaptic Ia inhibition for the position task (Enoka *et al.* 2011). Men and women have similar reductions in time to failure for a position task compared with a force task in upper and lower limb muscles (Hunter *et al.* 2003, 2005, 2008), indicating that deficits in activation and the involved Ia afferent spinal networks during a position task are likely similar for men and women.

Because inputs from descending pathways and the periphery are modulated in the spinal cord, any sex-related differences in modulation at this level will influence the motor output. While these inputs may differ between men and women for some tasks and

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muscles (e.g. greater group III and IV input to spinal centres by men under some task conditions), it is not clear whether spinal modulation differs between the sexes once the inputs are received. While one study indicated no sex differences in electrophysiological indices [Hoffmann reflex (H-reflex)] of spinal excitability for the lower leg muscles at rest (Christie *et al.* 2004), another showed recurrent inhibition was greater in the men than in the women at rest for motor neurone pools of the soleus muscle (Johnson *et al.* 2012). The lack of sex differences in response to the position task vs. force task, however, would suggest that modulation is similar in spinal excitability that involves Ia afferent inputs. Whether there is a sex difference in recurrent inhibition or other indices of spinal excitability, that are modulated differently for men and women during fatiguing tasks is not known.

Menstrual cycle and reproductive hormone fluctuations. There is no clear evidence that monthly fluctuations in hormones associated with the menstrual cycle will substantially alter fatigability and contractile function in young women at moderate environmental temperatures (Janse de Jonge 2003). Initial reports suggested that women were stronger (greater specific tension), but also exhibited increased fatigability and slowing of relaxation in mid-cycle when oestrogen levels were high (Sarwar *et al.* 1996). More recent and well-controlled studies, however, indicate there are minimal differences across the menstrual cycle in strength and fatigability (Ettinger *et al.* 1998, Janse de Jonge *et al.* 2001, Friden *et al.* 2003, Hoeger Bement *et al.* 2009a). Furthermore, we have repeatedly found no association between the day of menstrual cycle and strength or fatigability of isometric fatiguing contractions (Hunter *et al.* 2004a,c, 2006b, 2009, Keller *et al.* 2011). While differences in muscle sympathetic activity may be greater during the late follicular phase (mid-cycle when oestrogen levels were high) than the luteal phase, there were no differences in metabolite accumulation (H^+ and H_2PO^{-4} concentrations) during isometric fatiguing contractions (Ettinger *et al.* 1998).

Whole-body substrate utilization during endurance exercise can be influenced by menstrual cycle phase and use of oral contraceptives (Tarnopolsky 2008). The effects of altered substrate utilization on performance, however, are small, and the fluctuations in metabolism during the menstrual cycle are relatively small compared with the larger differences between men and women (Casazza *et al.* 2002, 2004, Suh *et al.* 2003, Devries *et al.* 2006, Tarnopolsky 2008, Fu *et al.* 2009). Menstrual cycle phase may, however, be more important to performance during longer duration exercise in hot and humid conditions. Time to exhaustion for submaximal exercise on a cycle ergometer (60% of maximal oxygen consumption and >60 mins duration) was reduced, and heart rate, ventilation and perceived exertion greater for young women during the luteal phase (days 19–25 of the cycle) compared with follicular (days 1–5) during hot, humid conditions, but not during temperate conditions (Janse *et al.* 2012). Hence, menstrual cycle may influence long-duration fatiguing exercise in hot and humid conditions.

The long-term reductions in reproductive hormones associated with age provide an opportunity to determine their influence on fatigability and function in both men and women. The sex difference in fatigability with advanced age is generally reduced (Hunter 2009), although the role of the hormonal reductions is not entirely clear. Despite the possible anticatabolic effects of hormone replacement therapy on skeletal muscle in older women and men (Brown 2008, Greising *et al.* 2009, Ronkainen *et al.* 2009, Ahtiainen *et al.* 2012, Qaisar *et al.* 2013), a limited number of studies to date indicate there are minimal differences in fatigability and endurance in older women on hormone replacement therapy compared with those who are not (Cheng *et al.* 2003, Finni *et al.* 2011). More, well-designed human studies are required to understand and clarify the effects of reproductive hormonal reductions on muscle fatigue and the possible impact of hormone replacement therapy for both men and women.

Beyond physiology

There are several sociological factors that potentially mask a true understanding of the sex-based differences in performance and fatigability. They not only contribute to a lack of knowledge of the female response during fatiguing motor tasks but distort the sex differences that may exist and attributed to physiology alone. These factors include (i) the experimental bias of under-reporting non-significant differences between men and women, (ii) the past and present sex bias reporting the physiology and function of predominantly males in both human and animal studies, and (iii) sex differences in physical activity levels.

An accurate understanding of the sex differences in performance and fatigability due to physiology alone can be limited because of the sampling bias of studying lower numbers of females than males in animal and human laboratory experiments (Anonymous 2010, Kim *et al.* 2010, Zucker & Beery 2010, Beery & Zucker 2011, Cahill 2012, Miller 2012). The assumption that the underlying mechanisms of fatigability apply to one sex only is limiting; every cell in

the human body has a sex which potentially impacts function (Miller 2012). Generally, women are underrepresented in biomedical research studies (Kim *et al.* 2010), and this is also true in the fatigability literature. Fatigability is the foundation of neuromuscular adaptations during training and rehabilitation, but information on the female response is lacking. More studies are needed that examine neuromuscular function and fatigability that include both men and women, and also are statistically powered to determine whether sex differences exist. In cases where both men and women were previously included in data sets that are already published, re-examining the data for sex differences, where power is sufficient, may reveal new findings.

In general, women tend to be less active than men (Bassett *et al.* 2010), and this difference may promote sex differences in muscle performance and fatigability. Certainly, large reductions in activity and activation of a limb result in muscle atrophy and impaired muscle function for both men and women (Narici & de Boer 2011, Hackney & Ploutz-Snyder 2012). There is some, but limited, evidence that sex differences in muscle function and fatigability exist after a period of disuse (L. Ploutz-Snyder, S. Bloomfield, D. Bemben, S. Hunter, S. Smith and K. Templeton, in review). For example, women demonstrated greater decrements in strength (isometric and dynamic) compared with men after 7 days of lower limb unloading (Deschenes *et al.* 2009, 2012), although the susceptibility to fatigability was not examined. Further, 4 weeks of disuse of elbow flexor muscles resulted in large reductions in muscle strength and paradoxically an increased time to failure of a low-force fatiguing contraction (Semmler *et al.* 2000) but more so in women than in men (Semmler *et al.* 1999). While sex differences may exist in response to large reductions in muscle activity (e.g. casting or unloading models), little is known about the more subtle, but daily, and long-term reductions in physical activity on muscle function and fatigability in men and women. Physical activity levels therefore need to be controlled and reported in studies to expose the sex differences due to physiology alone.

Relevance to clinical populations, training and rehabilitation

Understanding sex-based differences in muscle fatigue across different maximal and submaximal tasks and the prevailing mechanisms is relevant to designing best strategies and practices (i) for training and rehabilitation, (ii) to offset limitations in sports performance and in daily tasks for some older and clinical populations, and (iii) to address sex differences in pain often observed during and after fatiguing contractions. Muscle fatigability, for example, is a primary vehicle for promoting overload and the subsequent adaptation of the neuromuscular system that results in improved muscle performance in both men and women (Staron *et al.* 1991, Fiatarone *et al.* 1994, Hunter *et al.* 1999, Adams *et al.* 2004, Munn *et al.* 2005, Burd *et al.* 2012). Because there are sex differences in muscle fatigue and the contributing mechanisms, then neuromuscular adaption and optimal training regimens that adopt different contraction types will differ between men and women. In the push for greater individualization of medicine and rehabilitation, and more emphasis on genomics (Bouchard 2012), the sex of the individual and the fundamental presence of XX or XY chromosome pairs in each cell is surely one of the basic individual differences that need to be considered (Miller 2012). One potent example is osteoarthritis, which increases in incidence with age but has greater prevalence and severity in women than in men across all ages (Boyan *et al.* 2012, 2013). Strength and endurance training that rely on fatiguing exercise can be beneficial to treatment and offset pain; however, whether there are sex differences in the response to different exercise regimens is not known (Golightly *et al.* 2012). The assumption that rehabilitation based on fatiguing exercise at relative intensities after injury or neuromuscular disorder should be similar for men and women is inappropriate, until it is otherwise known.

Fatigability can also limit exercise performance, ergonomic tasks and daily activities, especially for older men and women and people with chronic disease or disability [e.g. (Sjogaard *et al.* 2010, Skurvydas *et al.* 2011, Vedsted *et al.* 2011)]. For example, women exhibit less fatigue than men for maximal sustained contractions in healthy populations due to a more fatigue-resistant muscle of the women (Bilodeau *et al.* 2001, Hunter *et al.* 2006a). However, this sex difference was diminished in the quadriceps of people with multiple sclerosis. Both men and women with multiple sclerosis demonstrated large and similar decrements in voluntary activation and similar changes in fatigue within the muscle when assessed with evoked contractions using electrical stimulation (Skurvydas *et al.* 2011). Thus, the mechanisms contributing to sex differences in muscle fatigue in healthy men and women differed to those contributing to fatigue in people with multiple sclerosis. Multiple sclerosis is one of many chronic diseases that results in muscle atrophy and weakness, leading to greater muscle fatigue that can limit daily activities of living.

Despite women being less fatigable than men during many fatiguing tasks, women can experience greater perception of pain during exercise, and there are sex differences in pain perception before and after exercise

(Fillingim *et al.* 2009, Racine *et al.* 2012). The sex differences in fatigability interactions with increased pain during fatiguing exercise (Ge *et al.* 2005, Falla *et al.* 2008, Johansen *et al.* 2013), and the potential for exercise to decrease pain in healthy and clinical populations (Hoeger Bement *et al.* 2008, 2009b, 2011) deserves greater attention. Understanding the mechanisms involved in sex differences in muscle fatigue will provide information for targeted strategies to offset fatigability and pain that differ between men and women.

Conclusions

Fatigability is the foundation for effective training and rehabilitation, but also limits performance during exercise and daily tasks for some populations. However, there is a superficial understanding of the origins of the sex differences in fatigability under different task conditions, and the responsible physiological mechanisms. This is in part due to the predominance of male only studies in the physiology, fatigability and exercise training literature, and the false assumption that sex differences do not exist. There is a clear need for more high-quality and well-designed studies to examine sex differences in muscle fatigability and performance under differing task conditions. Progress towards a true understanding of the sex differences in fatigability and the involved mechanisms will promote more tailored and effective strategies to enhance neuromuscular adaptations or offset muscle fatigue in both men and women.

Conflict of interest

I have no conflict of interest.

The author thanks Mr Jeffrey Rainwater for his contribution to Fig. 3.

Funding

Funding was provided by the National Institute of Health, USA (R15AG039697).

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