



# The good and the BAT of metabolic sex differences in thermogenic human adipose tissue

Michaela Keuper<sup>\*</sup>, Martin Jastroch

Department of Molecular Biosciences, The Wenner-Gren Institute, The Arrhenius Laboratories F3, Stockholm University, SE-106 91, Stockholm, Sweden

## ARTICLE INFO

### Keywords:

Sex  
Gender  
Adipose tissue  
WAT  
BAT  
Obesity  
Metabolism  
Mitochondria  
UCP1  
Adipocytes

## ABSTRACT

Thermogenic adipose tissue, which comprises classical brown and beige adipose tissue, has the ability to improve systemic metabolism. Its identification in adult humans has fostered extensive investigations on the therapeutic value to counteract obesity and metabolic disorders. Sex and gender differences of human thermogenic adipose tissue, however, are still understudied despite their importance for personalized treatment options. Here, we review studies reporting human sex differences of thermogenic adipose tissue and related potential improvements of systemic energy metabolism. An increasing body of evidence suggests higher prevalence, mass and activity of thermogenic adipose tissue in women, but the consequences for metabolic disease progression and mechanisms are largely unknown. Therefore, we also discuss observations on sex-specific adipose metabolism in experimental mouse and rat studies that may assist to establish molecular mechanisms and instruct future investigations in humans.

## 1. Introduction

Although the prevalence of obesity and associated comorbidities is increasing in both men and women, the clinical manifestations of the disease vary between the genders (Lemieux et al., 1993). For instance, men are at greater risk of visceral obesity, despite having less body fat than women (Bergman et al., 2007). As a consequence, men are also at greater risk of developing and dying from obesity-related comorbidities such cardiovascular diseases (Song et al., 2014) whereas women retain a metabolically healthier phenotype as they gain weight (van Vliet-Ostapchouk et al., 2014). In contrast, however, women with established diabetes are at greater risk to die from disease-associated complications such as heart failure (Ohkuma et al., 2019). Thus, it is inevitable that therapeutic treatment options are tailored to gender or sex. Sex is defined as unambiguous genetic evidence for male or female, and the term 'sex' is also used in experimental animal studies, although this is mainly based on anatomical characteristics. In clinical studies, one refers mostly to 'gender' when this is solely based on the patient's statement. We simplify the use of 'sex' and 'gender' in this review by using 'sex' for animal studies and we refer to 'gender' in human studies.

In the recent years, brown adipose tissue (BAT) and browning of white adipose tissue (WAT) have become attractive therapeutic targets to increase energy expenditure, thereby clearing excessive nutrients

from circulation to combat obesity and its associated metabolic disorders. Although the developmental origins of brown and beige adipocytes are still a matter of debate (de Jong et al., 2020; Kajimura and Spiegelman, 2020), both are generally considered thermogenic, energy-combusting cells. Brown/beige adipocytes mainly use mitochondrial uncoupling protein 1 (UCP1) to short-circuit the proton motive force and accelerate substrate oxidation, supported by a molecular network that enables increased substrate delivery and energy turnover. Activating thermogenic metabolism in BAT and WAT may therefore improve several parameters of metabolic health in humans. For example, individuals with high BAT activity display elevated blood levels of high-density lipoprotein (HDL) cholesterol, and lower levels of glycated hemoglobin (Hb1Ac), glucose and FFA/triglycerides (Matsushita et al., 2014; Ouellet et al., 2011; Wang et al., 2015). Studies in laboratory mice established causality and molecular mechanisms, showing that activating BAT and browning pathways of WAT in the cold improve glucose and lipid homeostasis (Bartelt et al., 2011; Chondronikola et al., 2016). The majority of experimental studies in mice, notably with a few exceptions, use only one sex, mainly males, to avoid high individual numbers and twice the cost. Males are preferred for simplicity, omitting confounding parameters such as the estrus cycle. There are, however, obvious downsides by omitting one of the sexes that will eventually result in knowledge gaps for optimal therapeutic impact

<sup>\*</sup> Corresponding author.

E-mail address: [michaela.keuper@su.se](mailto:michaela.keuper@su.se) (M. Keuper).

<https://doi.org/10.1016/j.mce.2021.111337>

Received 22 October 2020; Received in revised form 17 May 2021; Accepted 25 May 2021

Available online 29 May 2021

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on male and female patients concerning BAT function, browning potential of WAT depots and the consequences on systemic metabolism. To form the biomedical basis for better personalized treatment options, it will become crucial to collect knowledge on molecular and functional sex/gender differences. Thus, discovering sex differences of thermogenic adipose tissue is a timely topic.

In contrast to WAT mass, BAT prevalence and activity correlate negatively with age and obesity (Saari et al., 2020; Saito et al., 2009; Yoneshiro et al., 2011) and may be of limited importance for the therapy of adult obesity and metabolic disorders. Therefore, we also discuss sex differences in WAT metabolism and the browning process. This mini-review covers the current knowledge on sex-specific parameters that affect BAT/WAT function and energy dissipation (heat production), including innervation, adrenergic receptors, thermogenic gene programming, lipolysis, vascularization, mitochondrial and UCP1 function. In many excellent reviews, the role of sex hormones (e.g., estrogen, progesterone and testosterone) are comprehensively discussed as important regulators of BAT and WAT metabolism (Kaikaew et al., 2021; Law et al., 2014; Quarta et al., 2012). Therefore, we omitted extensive discussion on sex hormone-related differences in this review to avoid redundancy. Also, we do not cover the impact of ethnicity on BAT function, which has been reviewed previously (Merkestein et al., 2014) and has not yet extensively integrated gender differences. In short, whether ethnic differences in metabolic disease progression can be linked to BAT, is not yet resolved. Previous studies suggested differences in BAT volume between Asian and Caucasian patient cohorts (Bakker et al., 2014), which result in minor, but not striking differences in BAT activity (Boon et al., 2019; Nahon et al., 2020). Currently, there are neither molecular nor genetic clues supporting ethnic differences of human BAT.

## 2. Gender differences in systemic lipid metabolism

Metabolically active adipose tissue will impact in particular systemic lipid metabolism. At the systemic level, women display higher net lipid oxidation under resting conditions (Tran et al., 2010). When energy demand increases (e.g. during physical activity), women also increase the contribution of fat oxidation to total energy expenditure more than men (Tarnopolsky, 2008; Venables, 2004). During epinephrine infusion to stimulate lipolysis, higher levels of circulating fatty acids are observed in women, indicating increased adrenergic sensitivity and recruitment of fat oxidation as compared to men (Schmidt et al., 2014). The notion that fat mass contributes more to resting metabolic rate in women (Nookaew et al., 2013) further supports the idea of gender-specific adipose metabolism, possibly by mitochondrial function as speculated by others (Norheim et al., 2019).

## 3. Gender differences in human BAT prevalence

Intriguingly, an early report using PET/CT scans had already visualized gender differences in the prevalence of human BAT, showing that 10.5% of the female scans ( $n = 443$ ) were BAT-positive, versus only 2.9% of the male scans ( $n = 462$ ) (Cohade et al., 2003). A later study estimated the likelihood of possessing substantial amounts of BAT as three times higher in women versus men (Cypess et al., 2009). Not only does the prevalence of BAT appear to be higher in women in many studies (Cohade et al., 2003; Cronin et al., 2012; Hany et al., 2002; Persichetti et al., 2013), but there is also an indication of its increased metabolic activity and mass in female subjects (Pfannenberger et al., 2010). Notably, the majority of reports claim higher BAT prevalence in women (Table 1), while only a few studies found no significant gender effects using multivariate analyses (Ouellet et al., 2011). PET/CT scanning data, however, have to be taken with some caution as only BAT activity is detected, which is affected by several factors such as ambient and outdoor temperature, season, diet, medications, time of day, and in women, by estrus cycle variations. As a number of scans have been

**Table 1**

Reported gender differences in the prevalence of neck/supraclavicular brown adipose tissue in several human studies.

Study	number of scans	positive scans (%)			Ratio women/men
		total	men	women	
Cohade et al. (2003)	1017	13.7–4.1	2.9	10.5	3.6
Yeung et al. (2003)	863	2.3	0.3	2.0	6.7
Truong et al. (2004)	845	1.8	0.5	1.3	2.6
Kim et al. (2008)	1495	2.8	1.2	4.7	3.9
Cypess et al. (2009)	1972	5.4	3.1	7.5	2.4
Au-Yong et al. (2009)	3614	4.6	2.8	7.2	2.6
Cronin et al. (2012)	6867	4.3	2.7	5.9	2.2
Persichetti et al. (2013)	8004	3.5	1.8	4.9	2.7
Wei et al. (2015)	1550	3.5	0.9	2.6	2.9

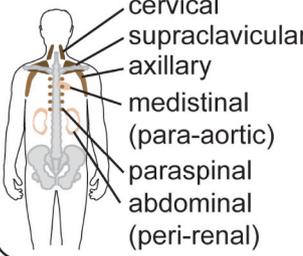
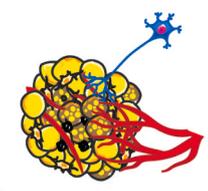
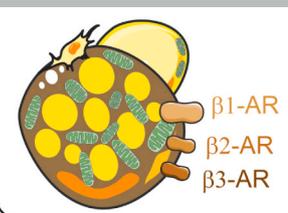
analyzed retroactively for the presence of BAT, many of these key details have not been recorded and are thus unknown. Presumably, these scans were taken from patients at room temperature without maximizing BAT activity with cold exposure. Thus, the prevalence of BAT with only 0.3–13.7% positive PET/CT scans (Table 1) may represent an underestimation, and the high variation (e.g. in calculated tissue mass ranging between 0.5 and 170 g (Cypess et al., 2009)) may not only be due to inter-individual differences. Current efforts aim to standardize the PET/CT analysis (e.g. (Pardo et al., 2017)) for better accuracy of human BAT quantities and activity to allow comparisons under different physiological and pathophysiological conditions.

### 3.1. The anatomical distribution of human BAT

No major gender difference in the anatomical distribution of BAT has been reported so far, contrasting WAT, which usually is located more in the subcutaneous region around hip and thighs in women, while men usually develop more visceral WAT in the abdominal part. The BAT depots of both genders are mainly located in six regions: cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal (Fig. 1). The supraclavicular region is the most common location for the detection of active BAT via PET/CT scan, with a prevalence of about 60–94% in BAT-positive individuals (Lee et al., 2010; Leitner et al., 2017; Ouellet et al., 2011; Persichetti et al., 2013). The sum of supraclavicular, cervical and axillary deposits accounts for 60% of total BAT volume and 69% of total BAT activity (Leitner et al., 2017). Some data suggest that women possess more capacity to increase BAT mass and activity. This is based on the right-skewed distribution of BAT mass and activity in women vs. men, showing a median total mass of 12.3 g in women adding cervical, supraclavicular, and superior mediastinal BAT (range: 1.1 g–170.0 g), and 11.6 g in men (range: 0.5 g–42.0 g) (Cypess et al., 2009). As stated in the previous section, the high variation in BAT mass may not only be due to inter-individual differences, but a result of non-standardized methods and unknown factors. Contrary to these studies, a very recent study claims no gender difference of relative BAT amount and glucose uptake (Fletcher et al., 2020). The authors report on similar BAT distribution with the exception of the superficial dorsocervical depot, a remnant of the interscapular BAT of human newborns and small mammals, which was significantly ( $P = 0.02$ ) more prevalent in women (found in 6 of 12) as compared to men (found in 1 of 12) (Fletcher et al., 2020).

## 4. Sex differences in BAT

Rodent BAT is very well-characterized and sex differences are

BODY	HUMAN DATA?	PARAMETER
	✓	<b>anatomical distribution</b>
	✓	<b>prevalance</b> ↑
		<b>deactivation of thermogenesis under caloric restriction</b> ↑
	✓	<b>temperature threshold for activation</b> ↑
TISSUE	HUMAN DATA?	PARAMETER
	(✓)	<b>innervation</b> ↑
	(✓)	<b>vascularization</b> ↑
		<b>adrenergic control of blood flow</b>
		<b>lipid composition</b>
CELL	HUMAN DATA?	PARAMETER
	(✓)	<b>browning potential</b> ↑
		<b>adrenergic receptor expression</b> ↑ ?
	(✓)	<b>sensitivity to <math>\beta</math>-adrenergic stimulation</b> ↑
	(✓)	<b>lipolytic response</b> ↑
ORGANELLE	HUMAN DATA?	PARAMETER
<b>MITOCHONDRIA</b> 		<b>cristae height and density</b> ↑
	(✓)	<b>UCP1 levels</b> ↑
<b>NUCLEUS</b> 	(✓)	<b>expression levels of mitochondria-related and thermogenic genes</b> ↑

**Fig. 1.** BAT parameters impacted by sex differences.

The figure summarizes data on sex differences in adipose tissue, with a focus on human BAT, from the systemic level (body) to the organelle. Parameters reported in rodent models with gender/sex differences (purple font) or without evidence for gender/sex differences (green font). Red arrows indicate whether the parameter is higher or lower in females compared to males. Check marks indicate that human data are available for BAT or only for WAT (in brackets).

documented for several parameters, such as the thermogenic response, adrenergic signaling, morphology, and expression levels of thermogenic genes including UCP1. In humans, gender differences for many of these parameters have been reported and are discussed in the following sections.

#### 4.1. Vascularization

To supply nutrients and oxygen, and to distribute heat to the remainder of the body, vascularization and the regulation of blood flow are two central components for BAT thermogenesis during cold exposure (Xue et al., 2009). Thus, both of these parameters are important measures when studying BAT activity quantitatively in the context of sex/gender differences. Sex differences in vascularization were mostly studied in WAT. For example, the perigonadal fat of female mice showed higher angiogenesis upon diet-induced obesity (Rudnicki et al., 2018). Vascular endothelial growth factor-A (VEGFA), the master regulator of angiogenesis, is dynamically regulated in murine adipocytes by, e.g. estradiol (Fatima et al., 2017). Gender differences may also exist in humans, given reports on endothelial cells of women showing higher capacity to form capillary-like tubes *in vitro* (Lorenz et al., 2015) and to proliferate and migrate (Addis et al., 2014). Furthermore, sex hormones

mediate gender differences in the responsiveness of vascular tone to adrenergic activation (Riedel et al., 2019). Collectively, these data strongly suggest sex/gender differences in vascularization and the regulation of blood flow in BAT upon cold and obesity in mice and humans. While these differences would likely affect the impact of BAT on systemic energy metabolism, direct studies addressing sex-specificity and its physiological consequences are still missing.

#### 4.2. Adrenergic activation

Adrenergic signaling, the major signaling pathway to activate BAT thermogenesis, has been reported as sex-specific in rodents, as brown adipocytes of female rats are more sensitive to  $\beta$ -adrenergic stimulation (Rodríguez-Cuenca et al., 2002). In humans, however, adrenergic innervation of BAT has not yet been explicitly investigated for sex differences, but these are supported by elevated adrenergic responses of systemic lipolysis in women (Schmidt et al., 2014). The gender difference in systemic lipolysis likely derives from adipose tissue, as it persists *ex vivo* in isolated subcutaneous adipocytes, even in the absence of sex hormones (Lofgren et al., 2002). The reason for sex-specific sensitivity of adrenergic stimulation is not entirely understood. While some suggest the lower ratio of  $\alpha$ 2/ $\beta$ 3-receptor signaling in female adipocytes of rats

and men as the underlying mechanism (Rodríguez-Cuenca et al., 2002; Schmidt et al., 2014), others doubt the importance of canonical  $\beta$ 3-signalling in human BAT per se. Instead, other authors highlight the importance of  $\beta$ 1-receptors, which are expressed without gender differences (Riis-Vestergaard et al., 2019), or  $\beta$ 2-receptors without stating gender specificity (Blondin et al., 2020). Notably, guinea pigs activate BAT independent of  $\beta$ 3-receptors (Himms-Hagen et al., 1995), suggesting variation in  $\beta$ -signaling even among rodents.

Taken together, further studies are needed to delineate sex-specific adrenergic receptor expression and signaling.

#### 4.3. Flexibility

The process of BAT activation and deactivation in response to physiological stress appears to be more flexible in female rodents. In response to caloric restriction, female rats deactivate facultative thermogenesis to a higher degree than males, thereby better protecting the mass of metabolic organs (Valle et al., 2005, 2007). During pregnancy and lactation, BAT in female rodents is deactivated and atrophied (Abelenda and Puerta, 1987; Frontera et al., 2005; Trayhurn and Wusteman, 1987). The downregulation of BAT thermogenesis is best explained as the consequence of heat dissipation limits to prevent overheating, given that milk production is a highly energetic and thermogenic process (Król and Speakman, 2019). In contrast, the degree of deactivation may be higher in male mice during pathological conditions such as obesity: males of the leptin-deficient ob/ob mouse model show pronounced lipid accumulation ('whitening') in BAT during aging, paralleled by decreased expression of tyrosine hydroxylase and a higher degree of peripheral neuropathy, strongly suggesting decreased innervation (Blaszkiewicz et al., 2019).

Thus, at least in rodent models, the higher plasticity and flexibility of female BAT activity may be retained longer during obesity and aging.

#### 4.4. Mitochondrial and molecular biology

BAT of female rats shows higher mitochondrial density and cristae height (Justo et al., 2005; Rodríguez-Cuenca et al., 2002). To the best of our knowledge, similar gender differences in the morphology of BAT mitochondria are unknown in humans.

The master regulator of non-shivering thermogenesis and energy wasting is UCP1. Several animal studies report higher UCP1 abundance in females as compared to males. For example, female rats express more UCP1 protein than males at room temperature, while UCP1 decreases to similar low levels at 28 °C, which was interpreted as sex-specific temperature thresholds of BAT activation (Quevedo et al., 1998), possibly caused by differences in body size or thermoneutral zones. Similarly, female mice of the C57Bl/6J strain display increased UCP1 protein levels at room temperature (Grefhorst et al., 2015), but other mouse strains, which have not been systematically analyzed in this review, may differ. Although not explicitly shown, similar regulation may be found in humans, where sexual dimorphism of thermic, metabolic and cardiovascular responses to cold exposure (Graham, 1988), as well as cold sensation (Yasui et al., 2007) have been reported. In general, women seem to display more cold sensation and may have to activate thermogenesis at higher temperatures than men (Kaikaew et al., 2018). If higher BAT activation at room temperature (Table 1) explains higher prevalence of BAT-positive PET scans in women, differential gender effects of cold sensation require consideration in PET/CT scans of human BAT.

On high-fat diets, female rats show higher expression of selected thermogenic genes in BAT (Valle et al., 2005). This is further supported by comparative proteomic analysis of BAT from female vs. male rats, which revealed several sex differences upon diet-induced obesity, including different protein levels of UCP1 and other proteins that have been implicated in thermogenesis, such as creatine kinase (CK), glycerol kinase (GyK), and fatty acid synthase (FAS) (Choi et al., 2011). Together,

these rodent data support an overall higher thermogenic capacity of BAT in females. Similar human data have yet to be reported, but higher UCP1 mRNA levels were found in subcutaneous (Nookaew et al., 2013) and perirenal WAT of females (van den Beukel et al., 2015). Notably, however, higher UCP1 mRNA levels in *ex vivo* differentiated perirenal adipocytes from women did not translate into higher protein levels and did not result in higher uncoupled respiration, suggesting no profound functional effect of increased UCP1 mRNA (van den Beukel et al., 2015). Adding to sex-specific mRNA and protein expression pattern in BAT, the lipid composition of murine BAT is sex-specific, with more pronounced differences in BAT than in gonadal or subcutaneous WAT, as judged by lipidomic approaches (Hoene et al., 2014). Collectively, the available data so far support sexual dimorphisms at the functional level, with female brown adipocytes displaying improved mitochondrial function and metabolism.

### 5. Sex differences in WAT browning and metabolism

BAT mass and activity declines with age and weight gain, reducing the potential for treatment of obesity and metabolic disorders such as cardiovascular diseases (Saito et al., 2009; Yoneshiro et al., 2011). Furthermore, the capacity of BAT for thermoregulation and/or energy wasting diminishes during obesity in both the basal and the cold-stimulated state (Saari et al., 2020). Thus, the stimulation of WAT metabolism or browning of WAT represents an alternative, possibly even more promising avenue. The term 'browning' of WAT is currently not well-defined, but involves metabolic remodeling that promotes higher metabolic activity and energy turnover, including the appearance of multilocular adipocytes, the increased expression of thermogenic and mitochondria-related genes, particularly UCP1 expression. There are several descriptions of sex differences for browning parameters and for WAT metabolism, in general which we discuss in the following two paragraphs and that may offer potential for sex-specific targets in obesity therapy.

#### 5.1. Browning of WAT

Rodent studies suggest higher capacity for browning in females. The gonadal WAT (gWAT) of female mice shows enhanced browning upon methionine-choline deficient diets (Lee et al., 2016) or  $\beta$ 3-adrenergic activation (Kim et al., 2016). Despite lower  $\beta$ 3-adrenergic receptor mRNA levels in gWAT of female mice, tyrosine hydroxylase levels are higher, suggesting more innervation of gWAT under normal chow feeding and housing temperatures of 23 °C (Kim et al., 2016). With age, the decreased innervation of subcutaneous WAT shows signs of sexual dimorphism in the leptin-deficient ob/ob mouse. Female ob/ob mice develop less neuropathy and possess higher levels of the nerve growth factor BDNF (brain-derived neurotrophic factor) (Blaszkiewicz et al., 2019). Recently, a comprehensive analysis comparing global gene expression across >100 inbred mice strains strongly corroborated higher UCP1 expression in WAT of female mice (Norheim et al., 2019). This study also associated the increased UCP1 expression in gonadal WAT of female mice with metabolically healthier phenotypes, whereas in males, UCP1 expression positively correlated with higher fat mass accumulation and insulin resistance. Gonadectomy was instrumental to demonstrate that gonadal hormones are not the main causal factors for sex-specific gene expression profiles in adipose tissue, contrasting findings in the liver, which showed reversible effects of gonadal hormones on sex-specific gene expression (Norheim et al., 2019). The authors of this study suggested that mitochondrial function in adipose tissue is a key factor that underlies sex differences in metabolic phenotypes (Norheim et al., 2019).

In women, the evidence for higher browning potential of WAT depots is seen in preadipocytes from perirenal fat depots (van den Beukel et al., 2015). Coherently, the notion of higher browning capacity in WAT of women is supported by higher UCP1 mRNA in subcutaneous WAT

(Nookaew et al., 2013).

## 5.2. WAT metabolism

The gender-dependent differences in glucose and lipid homeostasis of human adipose tissue (Varlamov et al., 2015) are reflected at the cellular level, as adipocytes isolated from subcutaneous and visceral regions show gender-specific differences in basal and norepinephrine-stimulated lipolysis (Lofgren et al., 2002; Lönnqvist et al., 1997). The idea of gender differences in mitochondrial oxidative metabolism of white adipocytes is supported by some molecular evidence, seen as higher expression of oxidative phosphorylation-related genes in females, which appears to be independent of fat distribution and sex hormones (Nookaew et al., 2013). At the functional level, mitochondria-related sex differences were already shown for other organs, such as the brain, heart and blood cells (Ventura-Clapier et al., 2017). Recently, we reported on gender-specific differences in the mitochondrial activity of subcutaneous preadipocytes from obese donors, demonstrating higher and more efficient mitochondrial activity in women as compared with BMI- and age-matched men (Keuper et al., 2019). The manifestation of gender differences in adipocyte energy metabolism is in particular significant during obesity. Basal and stimulated lipolytic rates are higher in obese women vs. obese men, while no significant gender differences are found in non-obese subjects (Lofgren et al., 2002). Furthermore, weight-reduction may modulate the lipolytic capacity of adipocytes in a gender-specific manner (Kolehmainen et al., 2002). Triglyceride synthesis rates in subcutaneous WAT of obese women are found to be higher than in obese men (Edens et al., 1993).

Despite lipid metabolism, several studies also suggest regulation of glucose homeostasis in adipose tissue of rodents and humans in a sex/gender-dependent manner (Kolehmainen et al., 2002; Lundgren et al., 2008; Macotela et al., 2009). Adipocytes from female mice are more insulin-sensitive (Macotela et al., 2009). In obese women vs. obese men, insulin-stimulated maximal glucose uptake into adipocytes is higher (Foley et al., 1984). Coherent with these findings, we demonstrated gender-specific differences in human preadipocyte bioenergetics in the response to insulin and glucose (Keuper et al., 2019), demonstrating that changes of mitochondrial function by insulin can be uncovered *in vitro*. Whether these differences also exist in brown and beige adipocytes, has yet to be elucidated.

## 6. Concluding remarks

There is an increasing body of evidence from experimental rodent models and patients, that sex differences in BAT and WAT metabolism ultimately contribute to gender differences in systemic and substrate metabolism (Kolehmainen et al., 2002; Lönnqvist et al., 1997; Lundgren et al., 2008; Macotela et al., 2009; Tarnopolsky, 2008; Tran et al., 2010; Venables, 2004).

The role of the immune system in controlling energy metabolism is not discussed in-depth in this review, despite its marked potential to impact BAT biology in a sex-specific manner. Several publications support the importance of the immune-metabolism-axis for BAT/WAT energy turnover and WAT browning in mice and humans (Camell et al., 2017; Fischer et al., 2017; Keuper et al., 2017; Nguyen et al., 2011; Omran and Christian, 2020; Pirzgalska et al., 2017; Wu et al., 2011). The sex-specific nature of inflammatory processes throughout life has been well-established (Casimir et al., 2018), in particular for the obesity-associated chronic low-grade inflammation of adipose tissue in mice (Medrikova et al., 2012; Singer et al., 2015). WAT inflammation is lower in female mice when analyzing, for instance, the infiltration and accumulation of macrophages in so called crown-like structures around dying adipocytes in both gonadal and subcutaneous WAT after 35 weeks on a high-fat diet (Medrikova et al., 2012). In humans, many studies support a gender-specific relationship between inflammation and metabolic diseases (Bo et al., 2005; Canello et al., 2006; ter Horst et al.,

2020; Thorand et al., 2007), further emphasizing translational potential to study mechanistic links between the immune system and BAT/WAT metabolism in a sex-dependent manner.

The role of sex hormones in control of systemic thermoregulation is discussed comprehensively elsewhere, as they are the main drivers of sex-specific BAT/brown adipocyte parameters (Fig. 1) (Rodríguez-Cuenca et al., 2007). Sex hormones are able to modify responsiveness to adrenergic signaling (Monjo et al., 2003), partially through the central nervous system (Labbe et al., 2015), and control the browning capacity of WAT (Kim et al., 2016).

Our understanding of the sex-specific parameters in BAT, which are driven independent of sex hormones, derives mostly from mouse models, which indicate a significant contribution of the sex chromosomes. In mouse models with increased X chromosome number, such as the Klinefelter syndrome model (XXY), positive effects on adiposity progression and fat mass were found (Chen et al., 2012, 2013), possibly complementing the effects of gonadal hormones. To the best of our knowledge, no study has focused on the effects of sex-chromosomal differences in BAT mass or activity yet. Interestingly, large-scale single-nucleotide polymorphism (SNP)-based GWAS and whole exome sequencing have started to unravel the contribution of genomic and epigenomic sex-differences in human adipose tissue. A recent review highlights that 50% of central obesity loci have significant, but poorly understood, sexual dimorphism, with most loci imposing stronger effects in women (Lumish et al., 2020).

With the existing studies, it transpires that sex differences in various adipose tissue parameters persist or even increase during obesity (e.g. lipolytic capacity, vascularization, and expression of thermogenic genes). Thus, sex as confounding parameter of BAT/WAT function should be considered for effective obesity therapies. The impact of environmental stressors such as obesity may impact BAT/WAT physiology depending on sex. A recent study even suggest that sex-specific impacts of BAT are epigenetically transmitted to offspring (Sun et al., 2018). Mice exposed to cold before conception develop offspring with higher UCP1 expression in BAT and subcutaneous WAT, resulting in increased systemic energy expenditure. Interestingly, the phenotype is paternally, but not maternally transmitted (Sun et al., 2018).

Most studies have considered only one sex, but the number of pre-clinical studies considering the impact of sex differences is steadily increasing. There is, however, still unprecedented potential to explore a promising field of sex differences that may assist future therapeutic interventions in both women and men.

## Acknowledgments

We thank Michael Gaudry for editing our manuscript. MK is supported by the Åke Wiberg Stiftelse (M19-0276) and MJ is supported by the Novo Nordisk Research foundation (NNF20OC0059646).

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