Sex-dependent Thermogenesis, Differences in Mitochondrial Morphology and Function, and Adrenergic Response in Brown Adipose Tissue*

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Gender-related differences in brown adipose tissue (BAT) thermogenesis of 110-day-old rats were studied by determining the morphological and functional features of BAT. The adrenergic control was assessed by studying the levels of $\beta_2$- and $\alpha_2A$-adrenergic receptors (AR) and by determining the lipolytic response to norepinephrine (NE) and isoproterenol (ISO). Norepinephrine ($\beta_2$-, $\beta_2$- and $\beta_2$-AR agonist) and CGP12177A (selective partial $\beta_2$-AR agonist but $\beta_2$- and $\beta_2$-AR antagonist) together with post-receptor agents, forskolin and dibutyryl cyclic AMP. The female rats that had higher oxygen consumption showed higher UCP1 content, a higher multilocular arrangement, and both longer cristae and higher cristae dense mitochondria in BAT indicating heightened thermogenic capacity and activity; this picture is accompanied by a more sensitive $\beta_2$-AR to norepinephrine signal (EC$_{50}$ 10-fold lower for CGP12177A) and a lower expression of $\alpha_2A$-AR than male rats. Taken together, our results support the idea that the BAT hormonal environment could be involved in the control of different elements of lipolytic and thermogenic adrenergic pathways. Gender dimorphism is both at receptor (changing $\alpha_2A$-AR density and $\beta_2$-AR affinity) and post-receptor (modulating the links involved in the adrenergic signal transduction) levels. These changes in adrenergic control could be responsible, at least in part, both for the important mitochondrial recruitment differences and functional and morphological features of BAT in female rats under usual rodent housing temperatures.

Adaptive thermogenesis constitutes a critical component of energy expenditure, playing an important role in obesity and response to cold, particularly in rodents (1). Within this overall response, brown adipose tissue (BAT) is the main effector of non-shivering thermogenesis, with UCP1 as the principal mediator (2, 3). UCP1 is an inner-membrane mitochondrial protein whose function is to uncouple the respiratory chain from ATP synthesis by dissipating the proton gradient generated by the respiratory chain as heat (4).

Activity and expression of UCP1 is under adrenergic control. The main physiological regulator of BAT thermogenesis is norepinephrine (NE), released by sympathetic terminals that densely innervate this tissue, which promotes thermogenesis activation in two ways. First, adrenergic stimulation promotes BAT differentiation increasing the UCP1 expression (2, 5), mitochondrial biogenesis (5, 6), and cellular proliferation of brown adipocytes (7, 8), reviewed in Lafontan et al. (9). Second, adrenergic stimulation increases release of FFA, which are positive UCP1 modulators (11, 12), supporting the concept that lipolysis represents the flux-generating step controlling BAT respiration (10).

The effects of catecholamines on thermogenic and lipolytic activity are mainly mediated by adrenergic receptors (9). In adipocytes, the $\beta$-adrenoreceptors ($\beta_1$-AR, $\beta_2$-AR, and $\beta_3$-AR), positively coupled to adenyl cyclase, co-exist with $\alpha_2$-AR, negatively coupled to adenyl cyclase (11). In rodents, $\beta_3$-AR is quantitatively the most abundant of adrenoreceptors in brown adipocytes (12) and is the most important adrenoreceptor coupled to the induction of UCP1 synthesis (13, 14); it is also the predominant receptor to mediate agonist-induced lipolysis in adipocytes (15, 16). However, it has been well established that the $\alpha_2\beta_3$-AR balance is key in the regulation of thermogenesis and lipolysis by modulating the net adrenergic signal response in the adipocyte (17).

Gender dimorphism in energy metabolism has been established, and in particular some differences have been found in brown adipose tissue thermogenic capacity (18–20). On the other hand, it is known that there is a positive correlation between the energy metabolism of a tissue and the general morphological features of the mitochondria of this tissue, such as the number and size of mitochondria and also the surface area and cristae density (cristae length per mitochondrial area) (21).

Thus, this study was designed to investigate further gender dimorphism in BAT thermogenesis and its adrenergic control and also to analyze whether the gender differences in thermogenic capacity and activity correspond to particular mitochondrial morphological features.

1. AR, adrenergic receptor; FFA, free fatty acids; COX, cytochrome-c oxidase.

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1 The abbreviations used are: BAT, brown adipose tissue; NE, norepinephrine; $\beta_2$cAMP, dibutyryl cyclic AMP; UCP1, uncoupling protein.
**Sex-dependent Thermogenesis**

**EXPERIMENTAL PROCEDURES**

**Animals**—110-Day-old Wistar rats, 32 female and 32 male rats (supplied by CRIFFA, Barcelona, Spain), were randomized into the following four studies: BAT parameters, indirect calorimetry, electron microscopic analysis, and lipolytic determination. They were housed in group cages (2 rats/cage) at 22 °C, with a 12-h light and 12-h dark cycle (lights on at 08:00 h), with free access to water and food.

**Indirect Calorimetry**—Oxygen consumption and carbon dioxide production were assessed with a Power Lab analyzer (ADInstruments Pty Ltd., Australia). Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured independently in four experiments (14 male and 14 female rats) by open circuit respirometry (flow rate 1 liter/min). VO₂ and VCO₂ were adjusted for mass (ml/min/kg or g/min kg⁻¹). A separate value for respiratory quotient (RQ = VCO₂/VO₂) was calculated. Animals were allowed to become acclimated for 30 min before data collection was initiated, which was continued for 2 h before the beginning of the 12-h light cycle. Room temperature was maintained at 22 °C. Data recordings were made every 120 s and were averaged over the entire collection period.

**Sacrifice and Isolation of Samples**—All animals (8 male and 8 female rats) were killed by decapitation at the start of the light cycle. The interscapular BAT depot was dissected and weighed. The BAT was then homogenized in HEPES/sucrose buffer (250 mM sucrose, 1 mM HEPES, 0.2 mM EDTA) with a Teflon/glass homogenizer. Homogenate was used for total protein content, cytochrome oxidase (COX; EC 1.9.3.1) activity determination, and Western blot analysis. Protein concentration was measured by the method of Lowry et al. (22). COX activity was measured using a spectrophotometric method (23); DNA was measured using the diphenylamine acid method (24), and the triglyceride content was measured using the Folch extract (25) and determined with a Sigma chemical kit (triglycerides triglyceride (INT)²₀).

**Preparation of Isolated Adipocytes and Lipolysis Assay**—Brown adipocytes were isolated from BAT of each rat (7 male and 7 female rats) by modification of the method of O’Donnell and Horwitz (55). Cell counts were performed with an improved Neubauer hemocytometer. Adipocyte activity was performed by incubating isolated adipocytes (125,000 cells/ml) at 37 °C in a shaking bath in 0.5 ml of KRB buffer (modified with 4% bovine serum albumin, 10 mM glucose, 250 units/ml penicillin, and 250 μg/ml streptomycin) in the presence of various concentrations of lipolytic agents under an atmosphere of 5% CO₂ in O₂, and then incubated for 60 min in a 37 °C shaking (45 rpm) water bath. The lipids and concentrations used in this study are as follows: norepinephrine (β₁-, β₂-, and α₁-AR agonist), isoproterenol (β₁-, β₂-, and α₁-AR antagonist), isoprenaline (β₁- and β₂-AR agonist) and CGB12177A (selective partial β₂-AR agonist but β₁- and β₂-AR antagonist), forskolin (stimulating adenylyl cyclase) from 10⁻⁹ to 10⁻⁴ M, and dibutylryl cyclic AMP (stimulating protein kinase A) from 10⁻⁸ to 10⁻⁶ M. After 60 min of incubation, the reaction was stopped in an ice-water bath for 30 min to allow the adipocytes to separate from the buffer, and aliquots (200 μl) of each solution were then taken to determine the glycerol content, as an index of lipolysis. The glycerol content of the deproteinated supernatant was determined enzymatically with a Sigma chemical kit (triglyceride GPO-Trinder number 337).

**Western Blot for UCP1 and Adrenergic Receptors (α₂-AR and β₁-AR)—**Varying amounts of BAT total protein of homogenate (15 μg for UCP1 and 25 μg for adrenergic receptor) were fractionated by SDS-PAGE (12% polyacrylamide for UCP1 and 9% polyacrylamide for adrenergic receptors) according to Laemml (26) and electrotransferred onto nitrocellulose filter as described elsewhere (27). Staining with Pon- nendorf and Horwitz (55). Cell served as the matrix for adipocytes, and can be quantified by calculating the area of BAT in relation to the total area.

**Electron Microscopic Analysis**—For electron microscopic examination, BAT was carefully removed and placed in ice-cold fixative buffer (2.5% glutaraldehyde in 0.2 M tris hydroxymethyl aminomethane buffer, pH 7.2) for 6 h. The specimens were then washed four times in 0.2 M trihydrated sodium cacodylate buffer and postfixed (1% OsO₄) for 2 h. The fixed pellets were dehydrated in graded acetone stages, stained with 2% uranyl acetate overnight, and embedded in Spurr’s resin. Ultrathin sections for electron microscopy, about 50 nm thick, were stained with saturated lead citrate solution and examined by a Hitachi H-600 electron microscope at 75 kV. Transmission electron micrographs were obtained at magnifications of ×2,500 for locularity analysis and ×15,000 for mitochondrial analysis.

For morphometric studies, scanning and transmission electron micrographs were analyzed by Scion Image and Zeiss KS-100 software. In the case of locularity evaluation, the analysis was performed randomly in a double-blind test; sections (three from each animal) were independently graded (by five people) for degree of multilocularity. In the case of mitochondrial morphology, the analysis was performed randomly from 340 mitochondria from three animals per group.

**Materials**—All enzymes, substrates, and coenzymes were obtained from Sigma. Antibody for UCP1 was obtained from Alpha Diagnostic International (San Antonio, TX), and antibodies for β₁-AR and α₁-AR were from Santa Cruz Biotechnology, Inc. (Norepinephrine bitartrate salt, isoproterenol bitartrate salt (isoprenaline), forskolin, dibutylryl cyclic AMP, bovine serum albumin (fraction V), and Clostridium histolyticum collagenase (1 mg/ml) were from Sigma. CGB12177A was obtained from Research Biochemicals International. Reagents for glycerol determination and routine chemicals used were from Sigma, Panreac (Spain), Amersham Biosciences, and CTK (Spain).

**Statistical Analysis**—The lipolytic activity was expressed as a percentage stimulation over basal lipolysis levels. All agonists caused a concentration-dependent stimulation of glycerol release, which reached a plateau at the highest agonist concentrations. Dose-response curves for agonists and the differences between male and female rats in the maximal capacity and EC₅₀ differences were fitted with nonlinear regression analysis for sigmoidal curves using GraFit computer program (R. J. Leatherbarrow, version 4, Eirishtac Software Ltd.). This data processing allowed us to calculate the maximal stimulation of the glycerol release induced by each agonist, and EC₅₀ was used as an affinity value. Likewise the differences between male and female rats in the maximal capacity and EC₅₀ values were obtained with the same program. The level of probability was set at p < 0.05 as statistically significant.

With respect to body and tissue weights, COX activity, protein, DNA, triglyceride content and oxygen consumption, adrenergic receptor levels, basal lipolysis, and morphometric analysis, differences between groups were assessed by Student’s t test. The analysis was performed with SPSS 10.0 for Windows. The level of probability was set at p < 0.05 as statistically significant.

**RESULTS**

**Characteristics of BAT in Male and Female Rats**—Previous studies (19, 20) have clearly demonstrated that female rats show a lower threshold temperature for cold-induced thermogenic response, showing a higher thermogenic capacity at 12 °C, than male rats. This was confirmed by the present study.

In order to establish further the characterization of this response, some BAT parameters were obtained in female and male rats (see Table I). Female rats showed clear signs of BAT recruitment compared with males; their BAT depot represented a higher percentage of total body mass (47% with respect to males) showing marked BAT hypertrophy with a
lower DNA content and higher triglyceride and protein content. The greater amount of protein has been attributed to an increase of mitochondrial protein (20).

Although there was no significant difference in specific COX activity (IU/mg protein) between genders (see Table II), female rats had a higher COX activity per g of tissue (38% with respect to males). The UCP1 levels (per mg of protein) were higher in female rats (representative Western blots are given in Fig. 1), but the difference did not reach statistical significance. Nevertheless, the levels of UCP1 per g of tissue were 70% higher (statistically different) in female rats than male rats. In the same way, the UCP1 content corrected per Kg 

As commented previously, the α2/β3-AR balance is key in the regulation of thermogenesis and lipolysis in BAT by modulating the net adrenergic signal response. It has been established that a lower α2/β3-AR ratio would lead to a greater thermogenic and lipolytic activity and vice versa (18, 29, 30). In this study, the protein levels of α2AR were lower in female than male rats, ~50% (representative Western blot is given in Fig. 1). With respect to β3-AR protein levels, there were no differences between genders. However, considering the levels of α2AR and β3-AR per g of tissue, the profile was modified, with female rats showing higher values of β3-AR and slightly lower values of α2AR. Thus, the lower α2AR/β3-AR ratio in female rats supports the fact that under low adrenergic stimulation they show a higher thermogenic capacity than males.

Respirometry—Considering the gender differences in BAT thermogenic capacity, it was interesting to study whether this feature was found in BAT energy expenditure. Because global oxygen consumption is held to correlate positively with BAT oxygen consumption (31), the whole animal O2 consumption, CO2 release, and RQ value were measured (see Table III). Female rats showed a higher O2 consumption than males; this increase was on the order of 30%. In accordance with this increase, the values of CO2 released also reached higher levels in female rats. In this way, female rats had a higher energy expenditure than males. The RQ showed no significant differences between genders.

Histological Analysis in BAT—In addition, in order to evaluate further whether the findings commented above (concerning thermogenic features of brown adipose tissue in both sexes) were reflected in particular histological characteristics, a whole tissue histological study was performed. Thus, female BAT showed a more shaped multilocular brown adipocyte structure, i.e. numerous small lipid droplets dispersed in the cytoplasmic space around a central nucleus (see Fig. 2). This picture is characteristic of the greater thermogenic activation situation of this tissue (32), indicating that female rats showed an increased thermogenic activity in BAT compared with male rats.

Mitochondrial Morphometric Study in BAT of Male and Female Rats—Because mitochondria do not always have the same distribution or the same morphological or biochemical features varying in several physiological situations (33), the mitochondrial morphometric parameters were also studied in order to analyze the existence of gender-related differences. Thus, the area, perimeter, cristae length, and cristae density were measured (see Table IV). Female rats showed a greater size of mitochondria than males: larger area (20%), longer perimeter (10%), greater cristae length (42%), and higher mitochondrial cristae density (14%) than male rats. In Fig. 3, representative photographs of BAT mitochondria from male and female rats can be observed. It is possible to appreciate that female BAT had bigger mitochondria and a greater amount of cristae.

Gender Differences in Lipolytic Activity in Isolated Brown Adipocyte Cells—It is well established that catecholamines secreted from the sympathetic nerves in BAT promote mitochondrial biogenesis (7), general recruitment (37, 38), and thermogenesis (34). At this point several questions may arise. The first is whether the gender differences in the morphology and function of BAT are due to a distinct NE release in this tissue. Along these lines, gender-related differences in sympathetic outflow in BAT have been established; thus, McDonald et al. (35) demonstrated that 6-month-old 26 °C housed female rats show a higher sympathetic activity on BAT by measuring NE turnover. Furthermore, estradiol treatment has been shown to restore sympathetic nervous system activity and outflow in BAT of ovarioctomized rats (36). Second, the sympathetic signaling to BAT is not necessarily a full indicator of thermogenic responsiveness, suggesting in this way that differences with respect to signal transduction could also be involved in thermogenesis activity in BAT (37, 38). In order to go further into this issue, functional effects of different adrenoreceptor agonists were studied: norepinephrine (β1, β2, and α2-AR agonist), isoproterenol (β1- and β2-AR agonist), and CPG12177A (selective partial β2-AR agonist but β1- and β2-AR antagonist), in isolated brown adipose
cells from female and male rats. Thus, the EC$_{50}$ value and maximal lipolytic capacity as a percentage of basal lipolysis are compiled in Table V.

Isolated adipocytes from female and male rats showed no differences in basal lipolysis. All agonists stimulated lipolysis in a concentration-dependent pattern.

In male adipocytes the potency rank for agonists was isoprenaline > norepinephrine > CGP12177A. In female adipocytes the potency rank was isoprenaline > CGP12177A > norepinephrine. In the latter, norepinephrine gave a greater maximal effect, whereas in male rats it was only a partial agonist with approximately 66% intrinsic activity. In the latter, this would point to the higher presence of an inhibitory effect, due to $\alpha_{2A}$-AR and $\beta$-AR, as a full agonist in the case of females, showing approximately 99% intrinsic activity with respect to the isoprenaline maximal effect, whereas in male rats it was only a partial agonist with approximately 66% intrinsic activity. In the latter, this would point to the higher presence of an inhibitory effect, due to $\alpha_{2A}$-AR. In addition, the results obtained when increasing doses of NE were tested in the presence of RS79945 (a $\alpha_{2A}$-AR antagonist) point to the inhibitory effects of $\alpha_{2A}$-AR being more important in male rats than in females (data not shown). The lower $\alpha_{2A}$-AR pool in female rats could contribute, at least in part, to the observed gender-dependent variations in BAT thermogenic and lipolytic response.

It is also worth noting that the affinity of $\beta_3$-AR to its agonist CGP12177A is more than 1 order of magnitude higher in female than in male rats, without any gender differences in $\beta_2$-AR functional receptor pool (determined by the maximal capacity value). These data suggest that under low physiological NE concentrations, the $\beta_2$-AR of female rats would be more activated.

On the other hand, several links in the lipolytic and thermogenic pathway should also be considered when it comes to establishing adrenergic signal response differences. Thus, both forskolin, which mimics nonspecific $\beta$-agonist effects and the combined effects of adenylyl cyclase-coupled receptors, and Bt$_c$CAMP, which mimics the effects of protein kinase A-interacting factors, were used in adipocytes isolated from male rats. The maximal stimulation was obtained with Bt$_c$CAMP, which was higher in males than females (see Table VI), whereas there were no differences in forskolin-induced response. These data suggest that all the links involved in the adrenergic signal transduction pathway could be important to establish gender dimorphism in the control of thermogenesis and lipolysis.

### DISCUSSION

In this paper, gender differences in the thermogenic response, adrenergic control pathway, and morphology of BAT in 110-day-old rats have been reported.

Female rats had a higher energy expenditure than males such as can be concluded from the oxygen consumption values. Likewise, there was a clear sign of BAT thermogenesis activation; their BAT depot represented a greater percentage of total body mass, with marked BAT hypertrophy, a higher multilocular arrangement of lipid droplets, greater UCP1 levels, and a lower COX/UCP1 ratio.

The gender dimorphism observed in the thermogenic capacity and activity was accompanied by differences in mitochondrial morphological features. Thus, the female rats, more thermogenically activated, showed larger and more active mitochondria (greater mitochondrial size, longer cristae, and higher cristae density) in comparison with males; these parameters are considered as an index of functional activity of mitochondria (39). This increased size of mitochondria and greater number of cristae per mitochondrion in BAT have been reported under different conditions like cold exposure, which stimulates the activity of BAT (40, 41), reflecting their role in heightened metabolic activity during thermogenesis, but never before had gender-dependent differences in morphological features been established.

As far as the signal transduction pathway of the thermogenic activation is concerned, gender differences have been found for different adrenoreceptor protein levels, which might contribute to explaining, at least in part, the gender differences in thermogenic and lipolytic parameters. In this study, female rats expressed lower levels per mg of protein of $\alpha_{2A}$ than males, with no observed gender differences in $\beta_3$-AR levels, thus the $\alpha_{2A}$/ $\beta_3$-AR ratio was double in male rats than females. Therefore, the results obtained in this paper could help to understand that under low adrenergic stimulation (22 °C usual rodent housing temperature), female rats have a higher thermogenic response than males. Thus, in females, this lesser presence of $\alpha_{2A}$-AR, a receptor with high affinity for catecholamines and clearly involved in the inhibition of lipolysis (14), could be responsible for the higher thermogenic activity due to a lower inhibitory effect on thermogenic and lipolytic signal transduction pathway. Moreover, BAT of female rats has a more sensitive $\beta_3$-AR to NE signal (EC$_{50}$ 10-fold lower for CGP12177A), leading to a higher signal for lipolytic and thermogenic activation with identical levels of NE.

One of the causes for these gender differences in thermogenic

### Table IV

**Effects of gender on the mitochondrial morphometric parameters in BAT**

The data represent the mean ± S.E. from 340 mitochondria of 3 animals per group and were analyzed by Student’s t test. Significant differences ($p < 0.05$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area ($\mu$m$^2$)</td>
<td>0.51 ± 0.01</td>
<td>0.62 ± 0.02$^a$</td>
</tr>
<tr>
<td>Perimeter ($\mu$m)</td>
<td>2.77 ± 0.04</td>
<td>3.03 ± 0.04$^a$</td>
</tr>
<tr>
<td>Cristae length ($\mu$m)</td>
<td>7.37 ± 0.22</td>
<td>10.5 ± 0.35$^a$</td>
</tr>
<tr>
<td>Cristae density ($\mu$m$^{-1}$)</td>
<td>15.9 ± 0.29</td>
<td>17.1 ± 0.29$^a$</td>
</tr>
</tbody>
</table>

$^a$ Values shown are females versus males.

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FIG. 2. Representative mitochondrial images of IBAT of male and female Wistar rats. White line represents 1 μm.

FIG. 3. Representative interscapular brown adipose tissue electronic microscopy images of male and female rats. White line represents 10 μm.
Effect of gender on adrenergically stimulated lipolytic activity of isolated fat cells from interscapular brown adipose tissue of male and female rats.

Data are means ± S.E. of 7 animals per group. The lipolytic activity was expressed as a percentage of stimulation over basal lipolysis. Maximal action over basal lipolysis, EC₅₀, and significant differences were obtained using the GraFit computer program.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EC₅₀ (nM)</th>
<th>Maximal capacity (nmol glycerol/10⁶ cells × 1 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>627 ± 131</td>
<td>563 ± 239</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>2.0 ± 1.0</td>
<td>12.0 ± 10⁶</td>
</tr>
<tr>
<td>CGP12177A</td>
<td>3887 ± 1494</td>
<td>122 ± 61¹</td>
</tr>
<tr>
<td>Basal lipolysis (nmol glycerol/10⁶ cells × 1 h)</td>
<td>65.4 ± 6.7</td>
<td>52.6 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>658 ± 38</td>
<td>638 ± 28</td>
</tr>
</tbody>
</table>

¹ Values shown are females versus males.

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REFERENCES


CONCLUSIONS

Taken together, our results support the idea that brown adipose tissue hormonal environment could be involved in the different elements of lipolytic and thermogenic adrenergic pathway activation. Gender dimorphism is both at receptor (changing α₂A-AR density and β₁-AR affinity) and at postreceptor (modulating the links involved in the adrenergic signal transduction) levels. These changes in the adrenergic control could be responsible, at least in part, both for the important mitochondrial recruitment differences and functional and morphological features of BAT in female rats under usual rodent housing temperature (22 °C), a more activated BAT with a higher multilocular arrangement, greater mitochondrial machinery (bigger mitochondria and higher cristae density), and finally a higher thermogenic capacity and activity.
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