The capacity for oestrogen to influence obesity through brown adipose tissue thermogenesis in animal models: A systematic review and meta-analysis

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Summary
Pharmacological interventions to aid weight loss have historically targeted either appetite suppression or increased metabolic rate. Brown adipose tissue (BAT) possesses the capacity to expend energy in a futile cycle, thus increasing basal metabolic rate. In animal models, oestrogen has been implicated in the regulation of body weight, and it is hypothesized that oestrogen is acting by modulating BAT metabolism. A systematic search was performed, to identify research articles implementing in vivo oestrogen-related interventions and reporting outcome measures that provide direct or indirect measures of BAT metabolism. Meta-analyses were conducted where sufficient data were available. The final library of 67 articles were predominantly in rodent models and provided mostly indirect measures of BAT metabolism. Results of this review found that oestrogen's effects on body weight, in rats and possibly mice, are likely facilitated by both metabolic and appetitive mechanisms but are largely only found in ovariectomized models. There is a need for further studies to clarify the potential effects of oestrogen on BAT metabolism in gonad-intact and castrated male animal models.

KEYWORDS
Animal models, brown adipose tissue, oestrogen, thermogenesis

1 | INTRODUCTION

The pathogenesis of obesity can be largely explained by an imbalance between caloric intake and caloric outflow,1 but the underlying mechanisms are far more complex. Among the contributing factors that remain unresolved are the influence of metabolic rate, physiological perception of satiety, and neurohormonal control of feeding behaviour.2 The focus of this review is on one of these influencing factors, metabolic rate, and how it is modulated by brown adipose tissue (BAT) activity. A paucity of BAT in adult humans has been correlated to development of obesity in later life.2 During typical physiological activity, BAT uses energy to produce heat (rather than ATP), as part of thermoregulatory cold-defense.3 BAT is also exploited by the body to increase energy expenditure after a meal, even if temperatures are above the thermoneutral zone, as part of the physiological response known as

ABBREVIATIONS: AR, adrenergic receptor; BAT, brown adipose tissue; BPA, bisphenol A; GLP1, glucagon-like protein 1; GPER, G protein-coupled oestrogen receptor; NR3A1, oestrogen receptor alpha; NR3A2, oestrogen receptor beta; OVX, ovariectomized; RER, respiratory exchange ratio; UCP1, uncoupling protein 1; VMH, ventromedial hypothalamus.

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diet-induced thermogenesis.\(^4\) Additionally, increased BAT activity increases insulin sensitivity (improving glucostasis)\(^5\) and stimulates BAT cell proliferation.\(^4\) Therefore, therapies that increase BAT activity in humans could (a) increase metabolism—potentially leading to weight loss, (b) improve glucose tolerance—decreasing risk of diabetes mellitus type II, and (c) increase BAT mass—creating a positive cycle that will ultimately reduce obesity and metabolic syndrome comorbidities. With these observations in mind, it would seem desirable to target and activate BAT and exploit it as an anti-obesity therapy.

There exist some experimental interventions that, in rodents, stimulate or restore BAT activity.\(^6\) Experiments have implicated oestrogen as a key modulator of BAT activity.\(^7\) Female rats seemingly gain weight when endogenous oestrogen is removed (by ovariectomy), and subsequent weight gain is attenuated upon the administration of exogenous oestrogen.\(^7\) Ovariectomy is a commonly used, experimental, animal model for investigating postmenopausal weight gain. Given oestrogen’s capacity to attenuate weight gain in this animal model, it is therefore promising in its application to humans. Postovariectomy weight gain can be alleviated in animals, by administering exogenous oestrogen either peripherally via intravenous (IV) injection or to the central nervous system (CNS) via intracerebroventricular (ICV) injection.\(^7\) Additionally, weight gain, similar to that observed following ovariectomy, can be reproduced by oestrogen receptor knockout (ER-KO). Knockout of either the nuclear receptor oestrogen receptor alpha (NR3A1), or the G protein-coupled oestrogen receptor (GPER), elicits weight gain.\(^8\)

Thus, the research question is whether decreased oestrogen levels will reduce BAT thermogenesis (Figure 1). Measures used to quantify BAT thermogenesis include uncoupling protein 1 (UCP1) expression, sympathetic discharge to BAT, and BAT responsiveness to norepinephrine.\(^7\)\(^9\) These outcome measures are of interest because UCP1 facilitates thermogenesis in BAT by uncoupling the proton gradient in mitochondria, sympathetic discharge to BAT releases norepinephrine thereby stimulating thermogenesis, and the sensitivity of BAT to norepinephrine influences the efficacy of sympathetic discharge to BAT. Decreased BAT thermogenesis could also be less directly inferred from outcome measures such as decreased oxygen consumption/decreased energy expenditure (because BAT thermogenesis contributes to oxygen consumption and energy expenditure by the futile cycle), increased body weight (as changes in energy expenditure can manifest as changes in body weight), or increased respiratory exchange ratio (RER). Because the primary substrate of BAT is free fatty acids, this may be reflected in the RER.

While the effect of oestrogen on metabolism, mostly in female rodents, has been the subject of a number of experimental papers\(^7\)\(^10\)\(^11\) and narrative reviews,\(^12\)\(^13\)\(^14\) a systematic review and/or meta-analysis has never been conducted. The purpose of this systematic review and meta-analysis is to definitively characterize the effect of oestrogen on metabolism in animal models and to compare any potential differences between genders and species.

![FIGURE 1](image)

### 2 | METHODS

#### 2.1 | Search strategy and identification of studies

Three databases were searched (EMBASE, Web of Science, and PubMed), from the earliest date available to 28 February 2019. A subject heading and keyword search was conducted using three concepts (oestrogen, energy homeostasis, and CNS), which were combined using the AND Boolean operator. Synonyms within each concept were combined using the OR Boolean operator (Appendices S1 and S2). The results were imported into EndNote X8 (Thompson Reuters, USA). Articles were screened using selection criteria (Table 1) initially by title alone, by one reviewer (W.S.). Screening by abstracts was then
performed by two independent reviewers (W.S. and C.K. or J.R.). Any differences in opinion on inclusion were discussed until consensus was reached.

2.2 | Intervention

Interventions needed to modulate oestrogen levels (eg, ovariectomy [OVX] and administration of exogenous oestrogen) or oestrogen signalling (eg, ER-KO). Studies were not excluded based on whether oestrogen levels/signalling were increased or decreased.

2.3 | Outcomes

The outcomes needed to include a measure of BAT activity or whole body metabolism in some form as outlined in Figure 1. Temperature, BAT sympathetic nerve discharge, body weight, and indirect calorimetry were all accepted outcome measures. Food intake was considered relevant, even though it is not a measure of metabolism, since it allows some inference as to whether a change in body weight was driven by appetite or a change in metabolic rate. Hence, food intake data were collated only if a measure of body weight was also included in the study.

2.4 | Research design

The article needed to be a research article containing in vivo experiments (exclusively in vitro studies, and reviews were excluded). Articles were not excluded on the basis of gender, sample size, or animal age.

2.5 | Data extraction

Data extraction was completed by one author (W.S.) and checked by second author (C.K. or J.R.). Data pertaining to population, study design, description of intervention, and outcome measures were extracted and compiled in a spreadsheet. Where data were not provided numerically, it was estimated based on graphs presented. If data were not presented numerically or graphically, authors were contacted to request data.

2.6 | Quality analysis

Article quality, in terms of risk of bias, was assessed with the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool. This tool was adapted from the Cochrane risk of bias tool, specifically for animal intervention studies. SYRCLE’s risk of bias tool uses a total of 10 items to assess selection, performance, detection, attrition, and reporting biases. Each of the 10 items was scored as low, high, or unclear risk of bias. Articles were not excluded from this review on the basis of quality. The quality of articles was used to inform the weight to give each set of results when collating and interpreting data.

2.7 | Data synthesis

Data for outcome measures that were reported in sufficient detail were then transferred to Review Manager Version 5.3 (RevMan) for meta-analysis. Due to a mixture of various scales being reported to measure the same outcome, standard mean difference (SMD) with 95% confidence interval (CI) was used to calculate effect sizes. In order to incorporate heterogeneity among studies, a random effects model was used. Additionally, the $I^2$ value was used to assess heterogeneity. An $I^2$ value of 100% was considered completely heterogeneous. Values of 75%, 50%, and 25% indicated high, moderate, and low heterogeneity, respectively. Articles were grouped by the population characteristics, and the outcome measures of interest were recorded (Table 2). Species- and sex-specific meta-analyses were performed in order to identify any potential species or sexual dimorphisms.

| TABLE 1 | Study selection criteria |
|---------|--------------------------|
| Criteria | Determined by |
| Must contain concept of energy homeostasis | Outcomes |
| Must contain concept of oestrogen | Intervention |
| Must be a research article | Research design |
| Must be a mammalian species | Research design |
| Must contain at least one outcome measure of metabolic change (only feeding insufficient) | Outcomes |
| Must be in English | |

| TABLE 2 | Populations and variables for comparison by meta-analysis |
|---------|-----------------|
| Population | Treatment Groups | Outcome Measures |
| OVX female rats | Control | Body weight (change from baseline in grams) |
| OVX female mice | Experimental | Body weight (final in grams) |
| Intact female rats | | Body weight (percentage change from baseline) |
| Intact female mice | | |
| Intact male mice | | |
3 | RESULTS

3.1 | Yield

A total of 10,008 articles were identified through database searches (Figure 2). Of these, 2,913 were duplicates. Citation tracking and reference checking yielded 13 additional articles. Inclusion/exclusion criteria (Table 1) were applied to the titles of 7,108 articles and as a result, 6,196 articles were excluded. The inclusion/exclusion criteria (Table 1) were then applied to the abstracts of the remaining 912 articles, resulting in 812 articles being excluded. One hundred articles underwent full-text screening, and of these, 67 were included in this review. Articles excluded during full-text screening and reasons for exclusion can be found in Appendix S3.

3.2 | Characteristics of included studies

Of the 67 studies in the final library, 35 used mice, 27 used rats, four used guinea pigs, and three used Syrian hamsters (Appendix S4). Forty-nine of the included studies used only females, five used only males, while 12 used both males and females. One article did not report the gender of the animals used. Of the studies using females, a large proportion (39 articles) used ovariectomy as a part of their experimental design. Body weight was the most common outcome.
measure reported (61 articles), closely followed by food intake (47 articles).

3.3 | Quality

For items 1, 3, 4, 5, 6, and 7 in the SYRCLE’s risk of bias tool,15 the majority of articles were deemed to have an unclear risk of bias because relevant information was not reported (Appendix S5). Of the 67 included studies, 28 (41.8%) did not adequately address incomplete outcome data, five (7.5%) did not adequately generate their allocation sequence, four (6.0%) were not “free of other problems that could result in a high risk of bias,” three (4.5%) used groups that were not similar at baseline or not adjusted for confounders, three (4.5%) were not free of selective outcome reporting, and two (3.0%) did not adequately conceal group allocation (Appendix S5).

3.4 | Effect of oestrogen in ovariectomized females

Of the included studies, five studies performed ovariectomy, with no subsequent oestrogen administration, as the experimental group.28,38,39,66,73 Of these five studies, three reported a significant increase in the body weight of mice and rats subsequent to ovariectomy,28,66,73 and two reported no significant change in the body weight of rats and Syrian hamsters.28,39 Several studies also implemented ovariectomy, followed by administering exogenous oestrogen, or an oestrogen analogue. Nineteen single studies,7 utilizing oestrogen supplemented ovariectomized rodents as the experimental group, could not be included in the meta-analysis (Appendix S4). Of these five studies, three reported a significant increase in sympathetic nerve activity to BAT in the oestrogen treated group. While MacKay et al11 indicated a significant increase in energy expenditure following administration of bisphenol A (BPA) to male mice. One additional study11 reported no significant change to energy expenditure in female mice. Four studies reported a decrease in body weight, upon administration of exogenous oestrogen in mice23,31,43 and rats,59 while four reported no significant difference in body weight between treatment groups in mice11,18,45 and rats.19

In the six studies that investigated the effects of exogenous oestrogen in male mice and rats,11,20,27,45,50,70 two reported a decrease in body weight, upon administration of exogenous oestrogen in mice22,31,43 and rats,59 while two others reported no significant difference in body weight between treatment groups in mice.11,45 The study of Miyawaki

TABLE 3

| Study or Subgroup | Control | Mean | SD | Total | Mean | SD | Total | Std. Mean Difference | IV, Random, 95% CI |
|-------------------|---------|------|----|-------|------|----|-------|---------------------|-------------------|
| 1.1.1 Rat Body Weight (change from baseline, g) | | | | | | | | | |
| Gray 199373 | 9.8 | 5.9 | 9 | 5 | 8.7 | 7.6 | 8 | 10.3% | -2.17 [-3.45, -0.88] |
| Nishimura 201471 | 16 | 6.3 | 10 | 37 | 6.3 | 10 | 9.7% | -3.12 [-4.33, -1.90] |
| Pantazaki 201010 | 2 | 1.4 | 12 | 39 | 11.8 | 12 | 10.0% | -3.54 [-4.83, -2.25] |
| Heterogeneity: Tau² | 0.05; CH² = 2.20; df = 2 (P = 0.33); I² = 0% | | | | | | | ||
| Test for overall effect: Z = 7.02 (P = 0.00001) |

1.1.2 Rat Body Weight (final, g)

| Study | Control | Mean | SD | Total | Mean | SD | Total | Std. Mean Difference | IV, Random, 95% CI |
|-------|---------|------|----|-------|------|----|-------|---------------------|-------------------|
| Liang 200270 | 217 | 8.4 | 8 | 24 | 8.4 | 8 | 9.1% | -2.67 [-4.12, -1.22] |
| Nishimura 201471 | 205 | 9.5 | 10 | 24 | 9.5 | 10 | 9.2% | -3.31 [-5.01, -1.61] |
| Marjani 201445 | 243 | 11.6 | 15 | 26 | 11.6 | 12 | 13.6% | -1.42 [-2.24, -0.61] |
| Pedersen 200121 | 206 | 43.3 | 8 | 26 | 33.2 | 8 | 11.2% | -1.79 [-2.76, -0.82] |
| Richard 198622 | 203.6 | 15.8 | 8 | 267.5 | 13 | 8 | 7.8% | -4.18 [-6.11, -2.24] |
| Rodrigues 201471 | 314.9 | 77.2 | 6 | 369.2 | 22 | 6 | 9.4% | -1.88 [-3.13, -0.62] |
| Tsi 201010 | 272 | 7.3 | 6 | 353 | 14.7 | 6 | 3.1% | -6.43 [-9.77, -3.10] |
| Zhang 201610 | 250 | 17.8 | 5 | 293 | 7.3 | 5 | 6.7% | -3.13 [-5.16, -1.11] |
| Heterogeneity: Tau² | 0.28; CH² = 23.51; df = 10 (P = 0.009); I² = 57% | | | | | | | ||
| Test for overall effect: Z = 5.39 (P = 0.00001) |
| Total (95% CI) | 96 | 97 | 100.0% | -2.73 [-3.40, -2.06] |
| Heterogeneity: Tau² | 0.69; CH² = 23.51; df = 10 (P = 0.009); I² = 57% | | | | | | | ||
| Test for overall effect: Z = 7.97 (P = 0.00001) |
| Test for subgroup differences: CH² = 0.17; df = 1 (P = 0.68); I² = 0% |

FIGURE 3  Effect of oestrogen (experimental) on attenuation of body weight gain between ovariectomized female rats

The findings of the meta-analysis were not devoid of the obvious species differences seen in the meta-analysis (Appendix S4, Figures 3 and 4). Of these individual studies, 15 reported a significant attenuation of weight gain in the oestrogen-supplemented group,15 three reported no significant difference in body weight,19,46,67 and one study reported an increase in body weight.77

A meta-analysis could only be conducted when sufficient studies administered exogenous oestrogen post ovariectomy and reported body weight outcomes. Results of the meta-analyses suggest that exogenous oestrogen attenuated weight gain, in ovariectomized rats (Figure 3). However, no significant attenuation was observed in ovariectomized mice (Figure 4).

3.5 | Effect of oestrogen in gonad-intact females and males

Several studies reported on the effects of exogenous oestrogen, or an oestrogen analogue, in gonad-intact mice and rats. Nine single studies that could not be included in the meta-analysis analysed the effect of oestrogen in gonad-intact animals (Appendix S4).15 Batista et al20 indicated reduced heat production in mice compared with the control group. In contrast, MacKay et al13 indicated a significant increase in energy expenditure following administration of bisphenol A (BPA) to male mice. One additional study11 reported no significant change to energy expenditure in female mice. Four studies reported a decrease in body weight, upon administration of exogenous oestrogen in mice23,31,43 and rats,59 while four reported no significant difference in body weight between treatment groups in mice11,18,45 and rats.22

In the six studies that investigated the effects of exogenous oestrogen in male mice and rats,11,20,27,45,50,70 two reported a decrease in body weight, upon administration of exogenous oestrogen in mice22,31,43 and rats,70 while two others reported no significant difference in body weight between treatment groups in mice.11,45

1References 7, 19, 29, 32, 33, 37, 41, 46, 49, 52, 54, 57, 60, 62, 64, 67, 71, 77, 78.
2References 5, 10, 46, 76, 80.
3References 7, 29, 32, 33, 37, 41, 49, 52, 54, 57, 60, 62, 64, 71, 78.
4References 11, 18, 22, 23, 31, 43, 45, 50, 59.
et al.\(^{30}\) was the only article that reported an increase in body weight in mice.

The results of the meta-analyses for mice and rats for this intervention suggest that oestrogen had no significant effect on body weight in either gonad-intact female mice and rats (Figure 5\(^{**}\)) or male mice (Figure 6\(^{††}\)).

### 3.6 | Oestrogen receptor knockout

Multiple studies used ER-KO animals. Most frequently, NR3A1 was knocked out, with nine studies implementing this as their intervention. Although a meta-analysis could not be conducted, eight of the nine studies report an increase in body weight in both males and females subsequent to NR3A1-KO.\(^{15}\) Liver-specific NR3A1-KO animals demonstrated no significant change in body weight relative to wild type.\(^{21}\)

\(^{**}\)References 26, 30, 40, 42, 59, 72, 81.

\(^{††}\)References 30, 40, 68, 72, 81.
Only one study used oestrogen receptor beta knockout (NR3A2-KO) mice, and reported a decrease in body weight for the experimental group, but failed to report the sex of the animals used. One additional study used G protein-coupled oestrogen receptor knockout (GPER-KO) mice and reported a significant increase in body weight for both males and females in the experimental group.

3.7 | Appetite

Meta-analysis analysing the effect of oestrogen in ovariectomized rats and mice identified a relatively consistent and significant reduction of food intake in oestrogen supplemented ovariectomized rats, but not mice (Figure 7).

4 | DISCUSSION

This review identified that data directly related to BAT thermogenesis are limited as are studies reporting indirect measures of metabolic rate. Exogenous oestrogen trended to increase metabolic rate and BAT thermogenesis, although a meta-analysis could not be performed since studies did not report on similar outcome measures. Exogenous oestrogen administration, to ovariectomized rodents, attenuated weight gain and increased metabolic rate in rats and possibly mice. Administration of exogenous oestrogen to gonad-intact females yielded more varied data than ovariectomized animals. Gonad-intact male rats and mice chronically administered with exogenous oestrogen also weighed less than control animals. Changes in body weight could not be accounted for solely by metabolic mechanisms; it would appear that changes in feeding were also contributing to modulation of body weight.

Results from the meta-analysis and individual studies not included in the meta-analysis identified that ovariectomy causes weight gain, which can be negated by administration of exogenous oestrogen (Figures 3 and 4). Data pertaining to whether exogenous oestrogen elicits weight loss in gonad-intact females contained more discrepancies. These discrepancies for gonad-intact animals were also observed in our meta-analysis (Figure 5) and the individual studies that could not be included in the meta-analysis.

Although the ratio of studies reporting weight loss to those reporting no weight loss, in gonad-intact males and females appear to be similar, the physiological mechanisms behind these observations may not be the same. A previous study analysing the direct effects of sex hormones on BAT identified that oestrogen modulated the expression of adrenergic receptors (ARs) in BAT, such that β3-AR mRNA and protein were up-regulated, and α2A-AR mRNA and protein were down-regulated. This resulted in a larger and more prolonged response to sympathetic activation by norepinephrine. Therefore, in gonad-intact females, metabolic response to oestrogen may have a ceiling effect that exogenous oestrogen cannot overcome. The converse was observed upon administration of testosterone; β3-AR mRNA and protein were down-regulated, and α2A-AR mRNA and protein were up-regulated, leading to smaller and shorter responses to sympathetic activity evoked norepinephrine. Therefore, in gonad-intact males, the expression ratio of ARs may result in the BAT being more resistant to sympathetic activation.

While metabolic data from individual studies, collected in this review, contained discrepancies, greater weight can be placed on more direct measures, as alluded to in Figure 1 and in our assessment of risk of bias. Nerve recording, as performed by Martinez de Morentin et al,7 was assessed to have a low risk of bias under every item for which there was sufficient information.
(Appendix S5). This study reported increased activity along the nerve branch that innervates interscapular BAT (iBAT nerve), following administration of exogenous oestrogen in ovariectomized animals. This provides strong evidence that exogenous oestrogen increases sympathetic nerve drive to BAT, via oestrogen’s effects in the CNS.

Both BAT metabolism and appetite are being modulated by the CNS via the intracellular adenosine monophosphate-activated protein kinase (AMPK) signalling pathway, in the hypothalamus. Specifically, metabolism seems to be mediated by neurons in the ventromedial hypothalamus (VMH), while feeding is controlled by neurons of the arcuate nucleus (ARC). Selective knockout of NR3A1 in hypothalamic pro-opiomelanocortin (POMC) neurons (which suppress feeding behaviour) leads to increased feeding and weight gain. Additionally, selective knockout of NR3A1 in neurons coexpressing steroidogenic factor-1 (SF1) demonstrated reduced BAT thermogenesis as measured by UCP1 expression in BAT. These data suggest that the activation of distinct populations of NR3A1-expressing cells in the brain are involved in body weight and metabolic regulation. However, not all details of this signalling pathway are clear. Findings in this review suggest that the GPER and NR3A1 are involved in oestrogen-mediated metabolic changes.

Further elucidation of the receptors and signalling pathway for oestrogen-mediated changes in metabolism is of great clinical relevance. For instance, there is a correlation between menopause and increased prevalence of the metabolic syndrome. While hormone-replacement therapy has been implicated in alleviating aspects of the metabolic syndrome in postmenopausal women, this therapy has also been associated with an increased incidence of breast cancer, stroke, and pulmonary embolism. Selectively targeting the oestrogen-BAT axis (via CNS pathways) might allow alleviation of the metabolic syndrome in postmenopausal women.

Oestrogen seemingly has the capacity to stimulate BAT thermogenesis, in ovariectomized female rats and possibly mice. This increase in thermogenesis, along with appetite suppression, appears to attenuate postovariectomy bodyweight gain. Although these observations are relatively well supported in ovariectomized animal models, the effects of exogenous oestrogen in gonad-intact male and female rodents are less robust.

5 | STRENGTHS AND LIMITATIONS

The systematic nature of our search strategy reduced the likelihood of missing relevant articles. To our knowledge, a meta-analysis has not been performed to investigate the metabolism modulating effects of oestrogen in animal models. Meta-analyses increase statistical power beyond that available in a single study. This is exemplified in Figure 4, where studies with seemingly clear but contrasting outcomes can be consolidated. Few studies reported similar direct outcome measures of BAT metabolism and therefore were unable to be included in the meta-analysis. Limited studies from the final library could be included in a meta-analysis, usually because n values were reported as a range rather than discrete values for each group. There were also deficits in reporting sufficient detail for accurate assessment of risk of bias that may have influenced the final findings presented in this review.

6 | CONCLUSION

Oestrogen seems to have the capacity to stimulate BAT thermogenesis, in ovariectomized female rats and possibly mice. This increase in thermogenesis, along with appetite suppression, appears to attenuate postovariectomy bodyweight gain. Although these observations are relatively well supported in ovariectomized animal models, the effects of exogenous oestrogen in gonad-intact male and female rodents are less robust.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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REFERENCES

1. Schwartz MW, Seeley RJ, Zeltser LM, et al. Obesity pathogenesis: An endocrine society scientific statement. Endocr Rev. 2017;38:267-296.
2. Wang Q, Zhang M, Xu M, et al. Brown adipose tissue activation is inversely related to central obesity and metabolic parameters in adult human. PLoS ONE. 2015;10:13.
3. Kajimura S, Seale P, Spiegelman BM. Transcriptional control or brown fat development. Cell Metab. 2010;11:6.

†††References 8, 35, 36, 51, 56, 61, 65, 74, 75.
4. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Am J Physiol. 2004;84:82.

5. Brinton RD, Retterberg JR, Yao J. Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol. 2014;35:23.

6. Correa SM, Newstrom DW, Warne JP, et al. An estrogen-responsive module in the ventromedial hypothalamus selectively drives sex-specific activity in females. Cell Rep. 2015;10:13.

7. Martínez de Morentín PB, Gonzalez-García I, Martíns L, et al. Estradiol regulates brown adipose tissue thermogenesis via hypothalamic AMPK. Cell Metab. 2014;20:41-53.

8. Davis KE, Carstens EJ, Irani BG, Gent LM, Hahner LM, Clegg DJ. Sexually dimorphic role of G protein-coupled estrogen receptor (GPER) in modulating energy homeostasis. Horm Behav. 2014;66:196-207.

9. Rodríguez AM, Palou A, Monjo M, Roca P. Direct effects of testosterone, 17β-estradiol, and progesterone on adrenocortical regulation in cultured brown adipocytes: potential mechanism for gender-dependent thermogenesis. Endocrinology. 2003;144:4923-4930.

10. Saito K, He YL, Yang YJ, et al. PI3K in the ventromedial hypothalamic nucleus mediates estrogenic actions on energy expenditure in female mice. Sci Rep. 2016;6.

11. MacKay H, Patterson ZR, Khazali R, Patel S, Tsirilin D, Abizaid A. Organizational effects of perinatal exposure to bisphenol-A and diethylstilbestrol on arcuate nucleus circuitry controlling food intake and energy expenditure in male and female CD-1 mice. Endocrinology. 2013;154:1465-1475.

12. Lopez M, Tena-Sempere M. Estradiol and brown fat. Best Pract Res Clin Endocrinol Metab. 2016;30:527-536.

13. Liu X, Shi H. Regulation of estrogen receptor α expression in the hypothalamus by sex steroids: implication in the regulation of energy homeostasis. Int J Endocrinol. 2015;2015:17.

14. Lopez M, Tena-Sempere M. Estrone and the control of energy homeostasis: a brain perspective. Trends Endocrinol Metab. 2015;26:11.

15. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.

16. Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327:557-560.

18. Al-Qahtani SM, Bryzgalova G, Valladolid-Acebes I, et al. 17β-Estradiol suppresses visceral adipogenesis and activates brown adipose tissue-specific gene expression. Horm Mol Biol Clin Investig. 2017;29:13-26.

19. Bartness TJ, Wade GN. Effects of interscapular brown adipose tissue denervation on body weight and energy metabolism in ovariectomized and estradiol-treated rats. Behav Neurosci. 1984;98:674-685.

20. Batista TM, Alono-Magdalena P, Vieira E, et al. Short-term treatment with bisphenol-A leads to metabolic abnormalities in adult male mice. PLoS One. 2012;7:e33814.

21. Benedusi V, Della Torre S, Mitro N, et al. Liver ERα regulates AgRP neuronal activity in the arcuate nucleus of female mice. Sci Rep. 2017;7.

22. Benoit V, Valette A, Mercier L, Meignen JM, Boyer J. Potentiation of epinephrine-induced lipolysis in fat cells from estrogen-treated rats. Biochem Biophys Res Commun. 1982;109:1186-1191.

23. Bless EP, Yang J, Acharya KD, et al. Adult neurogenesis in the female mouse hypothalamus: estradiol and high-fat diet alter the generation of newborn neurons expressing estrogen receptor α. eNeuro. 2016;3:E77-E116.

24. Borgquist A, Meza C, Wagner EJ. Role of neuronal nitric oxide synthase in the estrogenic attenuation of cannabinoid-induced changes in energy homeostasis. J Neurophysiol. 2015;113:904-914.

25. Byerly MS, Al Salayta M, Swanson RD, et al. Estrogen-related receptor β deletion modulates whole-body energy balance via estrogen-related receptor γ and attenuates neuropeptide Y gene expression. Eur J Neurosci. 2013;37:1033-1047.

26. Carrillo B, Collado P, Díaz F, Chowen JA, Perez-Izquierdo MA, Pinos H. Physiological and brain alterations produced by high-fat diet in male and female rats can be modulated by increased levels of estradiol during critical periods of development. Nutr Neurosci. 2017;22:1-11.

27. Cederoth CR, Vinciguerra M, Kuhne F, et al. A phytoestrogen-rich diet increases energy expenditure and decreases adiposity in mice. Environ Health Perspect. 2007;115:1467-1473.

28. Chen Y, Heiman ML. Increased weight gain after ovariectomy is not a consequence of leptin resistance. Am J Physiol Endocrinol Metab. 2001;280:E315-E322.

29. Cheng H, Isoda F, Mobbas CV. Estradiol impairs hypothalamic molecular responses to hypoglycemia. Brain Res. 2009;1280:77-83.

30. Dubuc PJ. Effects of estrogen on food intake, body weight, and temperature of male and female obese mice. Proc Soc Exp Biol Med. 1985;180:468-473.

31. Finan B, Yang B, Ottaway N, et al. Targeted estrogen delivery reverses the metabolic syndrome. Nat Med. 2012;18:1847-1856.

32. Fontana R, Della Torre S, Meda C, Longo A, Eva C, Maggi AC. Estrogen replacement therapy regulation of energy metabolism in female mouse hypothalamus. Endocrinology. 2014;155:2213-2221.

33. Gonzalez-García I, Contreras C, Estevez-Salgueiro A, et al. Estradiol regulates energy balance by ameliorating hypothalamic ceramide-induced ER stress. Cell Rep. 2018;25:413.

34. Gray JM, Schrock S, Bishop M. Estrogens and antiestrogens--actions and interactions with fluphenazine on food-intake and body-weight in rats. Am J Physiol. 1993;264:R1214-R1218.

35. Handgraaf S, Riant E, Fabre A, et al. Prevention of obesity and insulin resistance by estrogens requires ERα activation function-2 (ERαAF-2), whereas ERαAF-1 is dispensable. Diabetes. 2013;62:4098-4108.

36. Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, Cooke PS. Increased adipose tissue in male and female estrogen receptor-α knockout mice. Proc Natl Acad Sci USA. 2000;97:12729-12734.

37. Jeffery GS, Peng KC, Wagner EJ. The role of phosphatidylinositol-3-kinase and AMP-activated kinase in the rapid estrogenic attenuation of cannabinoid-induced changes in energy homeostasis. Pharmaceuticals. 2011;4:630-651.

38. Jones AP, McElroy JF, Cnic L, Wade GN. Effects of ovariectomy on thermogenesis in brown adipose tissue and liver in Syrian hamsters. Physiol Behav. 1991;50:41-45.

39. Kemnitz JW, Glick Z, Bray GA. Ovarian hormones influence brown adipose tissue. Pharmacol Biochem Behav. 1983;18:563-566.

40. Krumm EA, Patel VJ, Tillery TS, et al. Organophosphate flame-retardants alter adult mouse homeostasis and gene expression in a sex-dependent manner potentially through interactions with ERα. Toxicol Sci. 2017;162:212-224.

41. Lazzarini SJ, Wade GN. Role of sympathetic-nervous in effects of estradiol on rat white adipose-tissue. Am J Physiol. 1991;260:R47-R51.

42. Liang YQ, Akishita M, Kim S, et al. Estrogen receptor β is involved in the anorectic action of estrogen. Int J Obes. 2002;26:1103-1109.

43. Litvak SA, Wilson JL, Chen W, et al. Estradiol prevents fat accumulation and overcomes leptin resistance in female high-fat diet mice. Endocrinology. 2014;155:4447-4460.

44. Luo J, Sladek R, Carrier J, Bader JA, Richard D, Giguere V. Reduced fat mass in mice lacking orphan nuclear receptor estrogen-related receptor α. Mol Cell Biol. 2003;23:7947-7956.

45. MacKay H, Patterson ZR, Abizaid A. Perinatal exposure to low-dose bisphenol-A disrupts the structural and functional development of the hypothalamic feeding circuitry. Endocrinology. 2017;158:768-777.
46. Mamounis KJ, Hernandez MR, Margolies N, Yasrebi A, Roepeke TA. Interaction of 17β-estradiol and dietary fatty acids on energy and glucose homeostasis in female mice. Nutr Neurosci. 2017;21:715-728.

47. Mamounis KJ, Yang JA, Yasrebi A, Roepeke TA. Estrogen response element-independent signaling partially restores post-ovariectomy body weight gain but is not sufficient for 17 beta-estradiol's control of energy homeostasis. Steroids. 2014;81:98-98.

48. Marangoz PB, Silva LECM, Rorato R, Gomiero Alves P, Antunes-Rodrigues J, Elias LLK. Oestradiol modulates the effects of leptin on energy homeostasis by corticotrophin-releasing factor type 2 receptor. J Neuroendocrinol. 2014;26:796-804.

49. Martinez de Morentin PB, Gonzalez-Garcia I, et al. Pregnancy induces resistance to the anorectic effect of hypothalamic melanocyte-COA and the thermogenic effect of hypothalamic AMPK inhibition in female rats. Endocrinology. 2015;156:947-960.

50. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H, Perinatal and postnatal exposure to bisphenol A increases adipose tissue mass and serum cholesterol level in mice. J Atheroscler Thromb. 2007;14:245-252.

51. Musatov S, Chen W, Pfaff DW, et al. Silencing of estrogen receptor α in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. Proc Natl Acad Sci USA. 2007;104:2501-2506.

52. Negro M, Santos AT, Barthem CS, et al. A change in liver metabolism but not in brown adipose tissue thermogenesis is an early event in ovariectomy-induced obesity in rats. Endocrinology. 2014;155:2881-2891.

53. Nishimura Y, Mabuchi K, Takano A, et al. S-equol exerts estradiol-like anorectic action with minimal stimulation of estrogen receptor-α in ovariectomized rats. Front Endocrinol. 2017;8.

54. Nunez AA, Kannan K, Giesy JP, Fang J, Clemens LG. Effects of bisphenol A on energy balance and accumulation in brown adipose tissue in rats. Chemosphere. 2001;42:917-922.

55. Pantaleau TU, Mousovich F, Rosenthal D, Padron AS, Carvalho DP, Costa VMCD. Effect of serum estradiol and leptin levels on thyroid function, food intake and body weight gain in female Wistar rats. Steroids. 2010;75:638-642.

56. Park CJ, Zhao S, Glidewell-Kenney C, et al. Genetic rescue of non-classical ERα signaling normalizes energy balance in obese ERα-null mutant mice. J Clin Investig. 2011;121:604-612.

57. Pedersen SB, Bruun JM, Kristensen K, Richelsen B. Regulation of UCP1, UCP2, and UCP3 mRNA expression in brown adipose tissue, white adipose tissue, and skeletal muscle in rats by estrogen. Biochem Biophys Res Commun. 2001;288:191-197.

58. Puerta ML, Abelenda M, Nava MP, Fernandez A. Reduced noradrenaline responsiveness of brown adipocytes isolated from estradiol-treated rats. Can J Physiol Pharmacol. 1993;71:858-861.

59. Puerta ML, Nava MP, Abelenda M, Fernandez A. Inactivation of brown adipose tissue thermogenesis by oestradiol treatment in cold-acclimated rats. Pflugers Arch. 1990;416:659-662.

60. Qiu J, Bosch MA, Tobias SC, et al. A G-protein-coupled estrogen receptor is involved in hypothalamic control of energy homeostasis. J Neurosci. 2006;26:5649-5655.

61. Ribas V, Nguyen MT, Henstridge DC, et al. Impaired oxidative metabolism and inflammation are associated with insulin resistance in ERα-deficient mice. Am J Physiol Endocrinol Metab. 2010;298:E304-E319.

62. Richard D. Effects of ovarian hormones on energy balance and brown adipose tissue thermogenesis. Am J Physiol. 1986;250:R245-R249.

63. Rodrigues MFC, Ferreira FC, Silva-Magosso NS, et al. Effects of resistance training and estrogen replacement on adipose tissue inflammation in ovariectomized rats. Appl Physiol Nutr Metab. 2017;42:605-612.

64. Roepeke TA, Bosch MA, Rick EA, et al. Contribution of a membrane estrogen receptor to the estrogenic regulation of body temperature and energy homeostasis. Endocrinology. 2010;151:4926-4937.

65. Roepeke TA, Yasrebi A, Villalobos A, Krumm EA, Yang JA, Mamounis KJ. Loss of ERα partially reverses the effects of maternal high-fat diet on energy homeostasis in female mice. Sci Rep. 2017;7:6381.

66. Rogers NH, Perfield JW 2nd, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. Endocrinology. 2009;150:2161-2168.

67. Schneider JE, Palmer LA, Wade GN. Effects of estrous cycles and ovarian steroids on body weight and energy expenditure in Syrian hamsters. Physiol Behav. 1986;38:119-126.

68. Stout MB, Steyn FJ, Jurczak MJ, et al. 17α-Estradiol alleviates age-related metabolic and inflammatory dysfunction in male mice without inducing feminization. J Gerontol A Biol Sci Med Sci. 2017;72:3-15.

69. Tsai YC, Lee YM, Lam KK, Wu YC, Yen MH, Cheng PY. The role of hypothalamic AMP-activated protein kinase in ovariectomy-induced obesity in rats. Menopause. 2010;17:1194-1200.

70. Vogel H, Wolf S, Rabasa C, et al. GLP-1 and estrogen conjugate acts in the supramammillary nucleus to reduce food-reward and body weight. Neuropharmacology. 2016;110:396-406.

71. Wade GN, Powers JB. Taioxifen antagonizes the effects of estradiol on energy balance and estrous behavior in Syrian hamsters. Am J Physiol. 1993;265:E555-R562.

72. Wang HH, Zhou CL, Lv M, et al. Prenatal high estradiol exposure induces sex-specific and dietyrably reversible insulin resistance through decreased hypothalamic INS. Endocrinology. 2018;159:465-476.

73. Witte MM, Resuehr D, Chandler AR, Mehl K, Otveron JM. Female mice and rats exhibit species-specific metabolic and behavioral responses to ovariectomy. Gen Comp Endocrinol. 2010;166:520-528.

74. Xu P, Cao X, He Y, et al. Estrogen receptor-α in medial amygdala neurons regulates body weight. J Clin Investig. 2015;125:2861-2876.

75. Xu Y, Nendugadi TP, Zhu L, et al. Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metab. 2011;14:453-465.

76. Yasrebi A, Rivera JA, Krumm EA, Yang JA, Roepeke TA. Activation of estrogen response element-independent ERα signaling protects female mice from diet-induced obesity. Endocrinology. 2017;158:319-334.

77. Yonezawa R, Wada T, Matsumoto N, et al. Central versus peripheral impact of estradiol on the impaired glucose metabolism in ovariectomized mice on a high-fat diet. Am J Physiol Endocrinol Metab. 2012;303:E445-E456.

78. Zhang R, Su D, Zhu W, et al. Estrogen suppresses adipogenesis by inhibiting S100A16 expression. J Mol Endocrinol. 2014;52:235-244.

79. Zhang Z, Liu J, Veldhuis-Vlug AG, et al. Effects of chronic estrogen administration in the ventromedial nucleus of the hypothalamus (VMH) on fat and bone metabolism in ovariectomized rats. Endocrinology. 2016;157:4930-4942.

80. Zhu LR, Yang YJ, Xu PW, et al. Steroid receptor coactivator-1 mediates estrogenic actions to prevent body weight gain in female mice. Endocrinology. 2013;154:150-158.

81. Akter MH, Yamaguchi T, Hirose F, Osumi T, Perilipin, a critical regulator of fat storage and breakdown, is a target gene of estrogen receptor-related receptor α. Biochem Biophys Res Commun. 2008;368:563-568.

82. Madden CJ, Morrison SF. Brown adipose tissue sympathetic nerve activity is potentiated by activation of 5-hydroxytryptamine (5-HT) 1A/5-HT7 receptors in the rat spinal cord. Neuropharmacology. 2008;54:487-496.

83. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Arterioscler Thromb Vasc Biol. 2004;24:e13-e18.

84. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006;8:538-554.
85. Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet (London, England). 2002;360:942-944.

86. Klaver M, Dekker M, de Mutsert R, Twisk JWR, den Heijer M. Cross-sex hormone therapy in transgender persons affects total body weight, body fat and lean body mass: a meta-analysis. Andrologia. 2017;49:e12660.

87. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011;164:635-642.

88. Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. European Journal of Endocrinology. 2014;170:809-819.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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