Glucocorticoids suppress brown adipose tissue function in humans: A double-blind placebo-controlled study

Moe Thuzar FRACP1,4 | Weikiat Phillip Law FRANZCR2,4 | Jeyakantha Ratnasingam MD1 | Christina Jang MD1,4 | Goce Dimeski PhD3,4 | Ken K. Y. Ho MD1,4

1Department of Endocrinology & Diabetes, Princess Alexandra Hospital, Brisbane, Australia
2Department of Molecular Imaging, Princess Alexandra Hospital, Brisbane, Australia
3Chemical Pathology, Princess Alexandra Hospital, Brisbane, Australia
4School of Medicine, University of Queensland, Brisbane, Australia

Correspondence
Ken Ho, Centres for Health Research, Level 7, Translational Research Institute, 37 Kent Street, Brisbane, Queensland 4102, Australia.
Email: k.ho@uq.edu.au

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Aim: To investigate the effect of glucocorticoids on brown adipose tissue (BAT) function in humans.

Materials and methods: In a randomized double-blind cross-over design, 13 healthy adults underwent 1 week of oral prednisolone treatment (15 mg/d) and placebo with an intervening 2-week wash-out period. BAT function was assessed in response to cooling (19°C) and to a standardized meal, by measuring fluoro-deoxyglucose (FDG) uptake using positron emission tomography-computed tomography and skin temperatures overlying the supraclavicular (SCL) BAT depots using infrared thermography. Postprandial energy and substrate metabolism was assessed by indirect calorimetry.

Results: During cooling, prednisolone significantly reduced BAT FDG uptake (standardized uptake value, SUV max, 6.1 ± 2.2 vs 3.7 ± 1.2; P < .05) and SCL temperature (−0.45 ± 0.1 vs −1.0 ± 0.1°C; P < .01) compared to placebo. Postprandially, prednisolone significantly blunted the rise in SCL temperature (+0.2 ± 0.1 vs −0.3 ± 0.1°C; P < .05), enhanced energy production (+221 ± 17 vs +283 ± 27 kcal/d; P < .01) and lipid synthesis (+16.3 ± 3.2 vs +23.6 ± 4.9 mg/min; P < .05). The prednisolone-induced reduction in SCL temperature significantly correlated with the reduction in FDG uptake (r = 0.65, P < .05), while the increase in energy production significantly correlated with the increase in lipogenesis (r = 0.6, P < .05).

Conclusion: Prolonged exposure to glucocorticoid suppresses the function of human BAT. The enhancement of energy production and lipogenesis in the face of reduced dissipation of energy as heat suggests that glucocorticoids channel energy towards fat storage after nutrient intake. This is a novel mechanism of glucocorticoid-induced obesity.

KEYWORDS
brown adipose tissue, brown fat, glucocorticoids, humans, lipid, lipogenesis, metabolism, obesity, regulation, thermogenesis

1 | INTRODUCTION

Glucocorticoids are widely used to treat many immune and inflammatory conditions. Obesity is a common adverse effect of glucocorticoid excess.1 The mechanism of glucocorticoid-induced obesity is poorly understood, but is probably multifactorial. There is evidence that glucocorticoids stimulate differentiation of preadipocytes into mature white adipocytes2,3 and appetite.4,5 In animals, glucocorticoids impair brown adipose tissue (BAT) function, predisposing them to obesity.6-8 There is a paucity of information on the effect of glucocorticoids on BAT function in humans. We have previously demonstrated in vitro that glucocorticoids inhibit the response of cultured human brown adipocytes to adrenergic stimulation.9 Ramage et al. have recently reported that glucocorticoids acutely stimulate BAT function,10 an effect that is against the obesogenic effect of glucocorticoids.

BAT protects against hypothermia and obesity by dissipating energy as heat in response to cold exposure and food intake. This thermogenic property is conferred by uncoupling protein-1 (UCP1) which uncouples substrate oxidation from ATP synthesis.11 It was
previously believed that, in humans, BAT was present only during infancy. However, over the last decade, there is strong evidence that functional BAT persists and is highly prevalent in adult life.12–16 There is also cumulating evidence that BAT plays a significant role in energy and substrate metabolism.17

Energy is produced from the oxidation of substrates to sustain mammalian life.18 Chemical energy (ATP) and heat are 2 different forms of energy that constitute the total energy produced during substrate oxidation; ATP is the energy form useful to perform body functions,18 while heat is the energy wasted in the presence of active UCPs.19 Changes in either or both forms influence total energy production. Cold exposure and food intake stimulate energy production. In the case of cold exposure, increased thermogenesis from UCP-rich tissues such as BAT mostly accounts for the increase in total energy production.19 In contrast, the stimulation of energy production following a meal arises from a combined contribution from BAT thermogenesis and the energy required for processing and storage of nutrients.19–22 Total energy production is usually quantified by indirect calorimetry, based on gas exchange.18 In order to specifically determine the thermogenic contribution after a meal, an independent method for assessing heat is required. Infrared thermography is a valuable and reliable method for assessing the thermogenic activity of human BAT, both in vitro23,24 and in vivo.25–29

In this randomized double-blind placebo-controlled cross-over study, we investigated the effect of treatment with prednisolone for 1 week on BAT function, with a focus on its thermogenic contribution to postprandial metabolism in humans by combining metabolic imaging, infrared thermography and indirect calorimetry.

2 MATERIALS AND METHODS

2.1 Subjects

A total of 13 healthy adults (6 men, 7 women; mean ± SEM age, 28 ± 2 years; BMI, 24 ± 1 kg/m²) participated in the study. Subjects were recruited via local advertisements (Table S1). Inclusion criteria were: age, 18 to 40 years; BMI, 18 to 30 kg/m²; absence of medical conditions; absence of regular medications; non-pregnant status; non-smoker; alcohol intake ≤14 standard drinks/week; ability to maintain stable diet and activity throughout the study; absence of plans for prolonged (>1 week) travel throughout the study; normal blood pressure and pulse rate; normal results on blood screening (fasting glucose, thyroid function, full blood count, renal and liver function); and ability to provide informed consent. The study was approved by the Institutional Human Research Ethics Committee, and written informed consent was obtained from all subjects.

2.2 Study design

This was a randomized, double-blind, placebo-controlled cross-over study, involving 1 week each of oral prednisolone treatment (15 mg once daily at ~0700–0800 AM) and matching placebo with an intervening 2-week wash-out period (Figure 1A). Study assessments were conducted over 2 consecutive days at the end of each treatment, in temperature-controlled rooms (19°C) (Figure 1B). BAT metabolic activity was assessed by FDG-PET-CT scan. BAT thermogenic response to cold and to meal intake was assessed by measuring skin temperatures overlying the supravacular (SCL) BAT depots using infrared thermography. Postprandial energy and substrate metabolism was assessed after a standardized mixed meal by indirect calorimetry and blood tests. Subjects were advised to avoid exercise and alcohol for 24 hours prior to study assessment and to avoid coffee on the days of study assessment.

2.3 Randomization and masking

Research staff (2 individuals) not involved in the study prepared numbered medication envelopes, each containing 2 bottles (1 bottle containing active study medication and 1 bottle containing placebo, marked as treatment 1 or 2) using 1:1 randomization (half of the packs containing placebo as treatment 1 and half containing active medication as treatment 1), and kept the list of treatment sequences in a locked cabinet. Blinded investigators randomly assigned the pre-packed medication envelopes to participants and recorded the envelope numbers in a study log. Participants and investigators were masked to the treatment assignment sequence throughout the study.

2.4 FDG-PET-CT scan

Subjects fasted for at least 5 hours, changed to standard hospital gowns and rested comfortably in a recliner chair in an air-conditioned room cooled to 19°C for a total of 3 hours prior to the PET-CT scan. 75 MBq (2 mCi) of 18F-FDG was injected intravenously after 2 hours of cooling. Scanning was performed at 1 hour after FDG injection, using a Biograph mCT 128 PET-CT scanner (Siemens Healthcare, Erlangen, Germany) in 3-dimensional list mode for 30 minutes in 1 bed position covering the skull base to the aortic arch. PET and CT image datasets were reconstructed in axial, coronal and sagittal planes with a slice thickness of 4 mm. All attenuation-corrected images were analysed by WPL and MT using syngo.via software (Siemens Healthcare). BAT metabolic activity was measured as standardized uptake value corrected for body weight (SUVmax), and BAT volume (cm³) was quantified by autocontouring the 3-dimensional regions of interest in the SCL areas, with visual fat attenuation on CT images and FDG uptake above a set SUV threshold (SUV ≥ 2).

2.5 Infrared thermography (IRT)

To assess BAT thermogenic response, an infrared imaging camera (FLIR B425, 3.1Mpixel, FLIR Systems Australia Pty Ltd, Melbourne, Australia) was used to acquire thermal images of the anterior neck and upper chest regions as previously described.29 Subjects were seated upright, and the camera was positioned with a tripod, at 1 m from the subject at the level of the neck.29 Images were taken at 0, 1 and 2 hour(s) of cooling before PET-CT scanning, and at 0, 1 and 2 hour(s) after ingestion of a standardized meal (n = 11) (Figure 1B). Baseline temperature measurement for the cold exposure study was taken at 23 to 24°C, and that for the meal study was taken after 60 minutes in the temperature-controlled room at 19°C.
Thermogenic response to the meal was assessed under the same temperature-controlled conditions as for the FDG-PET study. Using FLIR Research IR Professional Analysing Software (Version 1.2, Wilsonville, Oregon), mean skin temperatures overlying the SCL fossa were analysed for each image by placing circles with 2-cm margins, centred immediately above the mid-clavicle points. Skin temperature of an area devoid of BAT, just to the left of the mid-sternum of the chest, was also measured as control.

2.6 | Indirect calorimetry

Resting metabolic rate (RMR) and substrate metabolism were quantified after an overnight 10-hour fast by indirect calorimetry using a metabolic monitor (ParvoMedics, Sandy, Utah), which was calibrated against standard gases before each study, as previously described.20,31 Subjects rested for 30 minutes in a supine position in the temperature-controlled room (19°C) before measuring RMR over 20 minutes. Meal-induced energy production rate was measured at 30 to 60 minutes and at 90 to 120 minutes after a standardized meal. Energy production rates (EPR), carbohydrate oxidation (Cox) and fat oxidation (Fox), and lipid synthesis rates (LSR) were calculated using the equations described by Ferrannini18 and Frayn32 as follows:

\[
\text{EPR (kcal/d)} = [3.91 \text{VO}_2 \text{ litre/min} + 1.10 \text{VCO}_2 \text{ litre/min} - 3.34 \text{N}] \times \text{1440}
\]

\[
\text{Cox (mg/min)} = \{4.55 \text{VCO}_2 \text{ litre/min} - 3.21 \text{VO}_2 \text{ litre/min} - 2.87 \text{N}\} \times \text{1000}
\]

\[
\text{Fox (mg/min)} = \{1.67 \text{VO}_2 \text{ litre/min} - 1.67 \text{VCO}_2 \text{ litre/min} - 1.92 \text{N}\} \times \text{1000}
\]

\[
\text{LSR (mg/min)} = \{1.67 \text{VCO}_2 \text{ litre/min} - 1.67 \text{VO}_2 \text{ litre/min} + 1.92 \text{N}\} \times \text{1000}
\]

where N = 0.14 × body weight kg/1440.

2.7 | Blood tests

Blood samples were collected at fasting, 60 and 120 minutes post meal. Sample tubes were placed in ice immediately after collection, centrifuged and aliquoted within 4 hours of collection. The aliquots of plasma/serum were then stored at ~80°C and batch testing was performed at the end of the study. Because of the cool environment, difficulties were encountered in obtaining sufficient paired samples from all subjects. Paired measurements were able to be obtained for adrenocorticotrophic hormone (ACTH) in 10, glucose in 7, free fatty acid (FFA) in 8, insulin in 6 and noradrenaline (NA) in 4 subjects. Glucose was measured by the glucose oxidase method (Beckman Coulter Diagnostics, USA), FFA by the spectrophotometric method (Randox Laboratories, UK, catalogue No. FA 115), ACTH and insulin by immunoassay (Immulite 2000, Siemens Diagnostics, USA), and NA by high
2.8 | Standardized meal

For the meal study, subjects consumed a mixed meal drink (Ensure plus, Abbott Nutrition; 237 mL; 355 kcal consisting of 56% carbohydrate, 29% fat, 15% protein) within 5 minutes, followed by a small amount of water.

2.9 | Statistical analysis

Statistical analysis was performed using IBM SPSS Software Version 23. Data were determined for normality and analysed by pair-wise or repeated measures ANOVA and post-hoc parametric or non-parametric methods as appropriate. Correlations were assessed using Pearson’s correlation. Data are presented as mean ± SEM or median (25th-75th centiles). P values less than .05 were considered statistically significant.

3 | RESULTS

Plasma ACTH was undetectable (< 10 ng/L) in all participants during prednisolone treatment as compared to 21 ± 2.3 ng/L during placebo (P < .01), confirming that participants adhered to treatment.

3.1 | BAT metabolic activity

The metabolic activity of SCL BAT depots was quantified by FDG-PET-CT after a pre-cooling period of 3 hours at 19°C. Compared to placebo, mean SCL BAT activity was significantly lower during prednisolone treatment (SUV_{max} 6.1 ± 2.2 vs 3.7 ± 1.2; P = .049) (Figure 2). The effect was more pronounced in a subgroup of 4 subjects with highly active BAT (SUV > 10), in whom the mean activity fell by 52.2 ± 12.8% (17.1 ± 1.9 to 8.4 ± 2.6; P = .015). There was no significant difference in SCL BAT volume between placebo and prednisolone treatment (44 ± 22 vs 30 ± 16 cm³; P = .13) nor in the effect of prednisolone on BAT activity between males and females (ΔSUV = 1.0 ± 1.7 vs −3.7 ± 2.0; P = .17).

3.2 | BAT thermogenic response

The thermogenic response of BAT was assessed by measuring skin temperatures overlying the SCL BAT depots at 0, 1 and 2 hours of cooling (19°C), and after a standardized mixed meal drink (Ensure plus).

During the 2 hours of cooling, SCL skin temperature (averaged for left and right SCL) decreased (Table 1). The magnitude of decrease was significantly greater during prednisolone treatment (P < .01) (Figure 3A), indicating that prednisolone suppresses the thermogenic response of BAT to cooling.

Postprandially, SCL skin temperature rose during placebo, but fell during prednisolone treatment (P < .02) (Figure 3B) (Table 1), suggesting that prednisolone inhibits the thermogenic response of BAT to a meal.

### TABLE 1  Skin temperatures and energy metabolism measurements during placebo and prednisolone treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Prednisolone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hr</td>
<td>1 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>SCL temp (°C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooling</td>
<td>33.4 ± 0.2</td>
<td>33.0 ± 0.2</td>
<td>32.9 ± 0.2</td>
</tr>
<tr>
<td>Meal</td>
<td>33.1 ± 0.1</td>
<td>33.3 ± 0.1</td>
<td>33.3 ± 0.1</td>
</tr>
<tr>
<td>Chest temp (°C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooling</td>
<td>31.9 ± 0.1</td>
<td>31.1 ± 0.2</td>
<td>31.1 ± 0.3</td>
</tr>
<tr>
<td>Meal</td>
<td>31.5 ± 0.2</td>
<td>31.9 ± 0.2</td>
<td>31.9 ± 0.3</td>
</tr>
<tr>
<td>EPR (kcal/d)</td>
<td>1445 ± 93</td>
<td>1665 ± 95</td>
<td>1600 ± 85</td>
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<tr>
<td>Lipid synthesized (mg)*</td>
<td>0 [0–0]</td>
<td>0 [0–129]</td>
<td>0 [0–28]</td>
</tr>
</tbody>
</table>

Abbreviations: EPR, energy production rate; SCL, supraclavicular. Results are expressed as mean ± SEM. P values are for time x treatment interaction using repeated measures ANOVA. EPR and amount of lipid synthesized over 30-minute periods were measured in response to a standardized liquid mixed meal.

* Data expressed as a median [25th-75th percentile] and were analysed using the Friedman test (n = 12).
3.3 Relationship between metabolic and thermogenic response

To ascertain whether the temperature response to the meal is attributed to BAT, we first compared meal-induced SCL temperature changes between subjects who were PET-positive and those who were PET-negative (defined using SUV threshold of 2) during the placebo phase. Before the meal, the mean SCL temperature was not significantly different between PET-positive and PET-negative subjects (33.2°C ± 0.2°C vs 33.0°C ± 0.1°C; P = .2). After the meal, the mean SCL temperature rose to a significantly higher level in PET-positive than in PET-negative subjects (33.6°C ± 0.1°C vs 33.0°C ± 0.1°C; P = .01). This observation provides evidence that SCL temperature changes reflect heat produced from underlying BAT depots that are metabolically active.

The reduction in SCL temperature induced by prednisolone at 1 hour after the meal correlated positively with the reduction in BAT metabolic activity on FDG-PET-CT (r = 0.65, P = .03). On the other hand, the changes in skin temperatures of the control chest area during cooling (P = .1) and after the meal (P = .3) did not differ significantly between placebo and prednisolone treatment (Table 1). The mean temperatures after the meal were significantly different between the SCL and chest regions (P = .036) during placebo and prednisolone treatments. Thus, prednisolone specifically reduced SCL but not chest skin temperature, indicating that SCL temperature changes were unlikely to be the result of factors such as changes in skin blood flow or subcutaneous tissue thickness. Together, these results provide strong evidence that prednisolone inhibits the thermogenic activity of BAT.

3.4 Postprandial energy production and substrate metabolism

After determining that prednisolone reduced the dissipation of energy as heat from BAT, we next analysed the effect of prednisolone on total energy production and substrate metabolism in response to the mixed meal using indirect calorimetry and blood tests. In the fasting state, the serum FFAs level was significantly higher (0.32 ± 0.07 vs 0.44 ± 0.05 mmol/L; P = .04) during prednisolone treatment, consistent with known metabolic effects of glucocorticoids.33,34 Mean serum glucose concentration was not significantly different (4.7 ± 0.2 vs 5.2 ± 0.3 mmol/L; P = .07) between placebo and prednisolone treatments. The mean RMR, Fox and Cox did not differ significantly between placebo and prednisolone treatment.

After the meal, energy production increased and FFAs and Fox fell, while glucose concentration and Cox rose, as expected during both treatments. Prednisolone caused a greater postprandial increase in EPR (P < .01) (Figure 4A) (Table 1), fall in Fox (∆16.3 ± 3.2 vs
−23.7 ± 4.9 mg/min; \(P = .03\)) and rise in Cox (+80.2 ± 9.7 vs +110.5 ± 16.1 mg/min; \(P = .01\)). The mean insulin concentration during prednisolone treatment (21.8 ± 7 mU/L) was approximately 50% higher than that with placebo (14 ± 2.9 mU/L); however, the difference was not statistically significant (\(P = .06\)). Among the 13 subjects, 8 (62%) displayed a respiratory quotient (RQ) >1, indicative of lipogenesis, at some stage after the meal during prednisolone treatment, compared to 3 with placebo (\(P = .047\)). The amount of lipid synthesized over each of the 30 minutes at baseline, 1 and 2 hour(s) was quantified (Table 1). The data from 1 subject was excluded because of wide fluctuations caused by unstable gas exchange. The increase in LSR at 1 hour after the meal was significantly higher (\(P = .03\)) during prednisolone treatment (Figure 4B). The increase in EPR correlated significantly with the enhancement in LSR induced by prednisolone (\(r = 0.6, P = .02\)) (Figure 4C). These results indicate that the rise in EPR after the meal likely reflects the energy required for lipid synthesis, and that prednisolone drives the energy towards storage, while reducing the wastage as heat after nutrient intake.

### 3.5 | Catecholamines

As the sympathetic nervous system (SNS) plays a central role in stimulating the activity of BAT and thermogenesis,\(^{11}\) we explored whether the SNS is involved in the modulation of BAT activity and thermogenesis by glucocorticoids. We measured plasma NA concentrations during the meal study. There was no significant difference in baseline fasting levels between the placebo and prednisolone treatments. In the 4 subjects from whom paired blood samples were obtained during the meal, plasma NA level rose uniformly during placebo treatment at 1 and 2 hour(s) (+1 ± 0.5 and +0.65 ± 0.36 nmol/L, respectively). In contrast, plasma NA fell uniformly during prednisolone treatment at these time points (-0.63 ± 0.3 nmol/L and -1.3 ± 0.4 nmol/L, respectively). This observation suggests that the suppression of BAT function by glucocorticoids may be mediated, in part and indirectly, by the SNS.

### 4 | DISCUSSION

This randomized, double-blind, placebo-controlled, cross-over study provides strong evidence for a novel pathophysiological role of BAT in glucocorticoid-induced adiposity in humans. Our key findings are: (1) prednisolone treatment for 1 week markedly inhibited the metabolic (FDG-PET) and thermogenic activity (IRT) of BAT in response to cooling and to a meal, and (2) postprandially, the inhibition of BAT function is accompanied by enhanced propensity for lipid synthesis.

The current findings extend our in vitro observation that dexamethasone attenuates the stimulation by isoprenaline of UCP1

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**FIGURE 4** Effect of glucocorticoids on energy metabolism after a mixed meal. Prednisolone enhanced meal-induced energy production rate (EPR)\(^a\) (A) and lipid synthesis rate (LSR)\(^b\) (B). There was a significant positive relationship between prednisolone-induced increases in EPR and LSR after the meal\(^c\) (C). Results are expressed as mean ± SEM. \(^aP < .05, \(^{**}P < .01\) using repeated measures ANOVA, \(^{b}paired t\)-test and \(^c\)Pearson’s correlation \((n = 12)\)
uptake. We, therefore, employed I R T o a s s e s B A T h e r m o g e n e s i s.

because of the competing effect of meal-derived glucose with FDG

FDG-PET cannot be used to assess BAT response to nutrients

bution of BAT to energy metabolism in response to nutrient intake.

study was to determine the effect of glucocorticoids on the contri-

ecting nutrient energy as heat. There fore, an important aim of our

FIGURE 5

Schematic representation of the components of energy production after a meal and the effect of glucocorticoids. The total energy

produced after a meal comprises 2 components: 1) the energy required for nutrient processing and storage, and 2) the energy dissipated as heat

by uncoupling protein (UCP) containing tissues such as brown adipose tissue (BAT). Glucocorticoids enhance total energy production after a

meal, increasing proportionately the component for storage as fat while suppressing the component of wastage as heat.

expression and oxygen consumption in human brown adipocytes.9

Our findings are in line with the results of animal studies. In rodents, glucocorticoids reduce the expression of UCP16 and tissue respons-

siveness to adrenergic and cold stimulations.1,35 On the other hand, depletion of glucocorticoids by adrenalectomy36,37 or inhibition of

their action by mifepristone, a glucocorticoid receptor antagonist,38,39 stimulates BAT and reduces weight gain.

In contrast, Ramage et al.10 recently reported that glucocorticoids acutely enhanced BAT function in humans over and above the stimu-

latory effect of acute cold exposure, an observation that cannot explain the obesogenic effect of glucocorticoids. FDG uptake and

skin temperatures overlying SCL BAT increased after 2 doses of pred-

nisolone administered over 12 hours. In our study, glucocorticoids inhibited BAT activity after 1 week. It is probable that the effect of

glucocorticoids on BAT is time-dependent. Indeed, in in vitro studies of brown adipocytes, cortisol stimulated UCP1 expression in the first

24 hours but inhibited this after 48 hours.10 In a retrospective analy-

sis of patients undergoing PET-CT, the investigators also observed active BAT to be less prevalent among patients undergoing chronic

glucocorticoid treatment.10 These observations collectively point to a

time-dependent dominant inhibitory effect of glucocorticoids on BAT.

Glucocorticoids may act directly or indirectly on BAT. Gluco-

corticoids bind to both glucocorticoid (GR) and mineralocorticoid

(MR) receptors.9 Our in vitro study employing dexamethasone, a

selective agonist for GR, suggests a direct action on GRs.9 This is

supported by another in vitro finding that MR antagonists did not

affect the inhibition of BAT by cortisol.10 In vivo, BAT is regulated

mainly by the SNS via the release of NA,11 and there is evidence that

plasma NA concentration is a good indicator of SNS activity.41

The post-prandial fall in NA during prednisolone treatment, in con-

trast to the rise observed during placebo treatment in the 4 sub-

jects, suggests that glucocorticoids may also act indirectly via the

SNS to suppress BAT. However, given the limited number of blood

samples, this preliminary finding needs to be confirmed in future

studies.

BAT protects animals against diet-induced obesity by dissipat-

ing nutrient energy as heat. Therefore, an important aim of our

study was to determine the effect of glucocorticoids on the contri-

bution of BAT to energy metabolism in response to nutrient intake.

FDG-PET cannot be used to assess BAT response to nutrients

because of the competing effect of meal-derived glucose with FDG

uptake. We, therefore, employed IRT to assess BAT thermogenesis.

We found that prednisolone inhibited the postprandial rise in tem-

perature overlying the SCL BAT depots, and the prednisolone-

induced reduction in SCL temperature response highly correlated with a parallel reduction in the BAT FDG uptake. In addition, signi-

ficient changes in temperatures during prednisolone therapy

occurred for skin overlying the SCL BAT depots but not over a

control chest area. Together, these findings provide strong evi-

dence that glucocorticoids inhibit the thermogenic response of

BAT to both cooling and meal intake.

We next assessed whole body energy and substrate metabolism

in response to a meal. Prednisolone enhanced the EPR following a

meal. The energy produced after a meal consists of 2 components,

(1) chemical energy (ATP) for processing and storage of ingested

nutrients and (2) heat energy dissipated by UCP-rich tissues such as

BAT18,19 (Figure 5). As heat dissipation was reduced by prednisolone,

it is probable that the increase in EPR stems from the first compo-

nent. In a study comparing the EPR between the oral and intravenous

administration of equi caloric nutrient loads, Vernet et al. concluded

that the cost of digestion and absorption was negligible.42 On the

other hand, the energy cost of storage is high, amounting to 24% of

the energy content of glucose for conversion to fat.20 From indirect

calorimetry, we found strong evidence that prednisolone enhanced

postprandial lipid synthesis as indicated by an RQ >1.18,32 The magni-

tude of lipogenesis correlated positively with the increase in EPR.

Our findings are consistent with those of in vitro studies demonstrat-

ing stimulation of lipogenesis by glucocorticoids in the presence of

insulin,43,44 and of others reporting similar relationships between

postprandial EPR and lipogenesis11,22 in humans. The collective evi-

dence indicates that the greater EPR observed during prednisolone

treatment is largely explained by the energy requirement for lipogen-

esis (Figure 5).

Meal intake is a physiological process during which the nutrient

ingested is processed for storage. When BAT is activated, part of the

nutrient energy is wasted as heat, a process stimulated by the

SNS,45,46 which probably represents a protective mechanism against

the development of obesity during times of energy surplus. Our

results suggest that glucocorticoids dampen postprandial energy

wastage as heat, while promoting deposition as fat by suppression of

the SNS activity and BAT function.

The meal-induced increase in EPR is commonly referred to as

diet-induced thermogenesis (DIT). Employing separate methods to

assess energy metabolism and heat, we have shown that the meal-

induced increase in EPR measured by indirect calorimetry does not

FIGURE 5 Schematic representation of the components of energy production after a meal and the effect of glucocorticoids. The total energy

produced after a meal comprises 2 components: 1) the energy required for nutrient processing and storage, and 2) the energy dissipated as heat

by uncoupling protein (UCP) containing tissues such as brown adipose tissue (BAT). Glucocorticoids enhance total energy production after a

meal, increasing proportionately the component for storage as fat while suppressing the component of wastage as heat.
necessarily represent thermogenesis. The use of the term ‘DIT’ to describe the energy produced after a meal can be conceptually misleading, because thermogenesis infers energy dissipated as heat. Our findings, along with those of others,\textsuperscript{21,22} show that EPR after a meal is affected by the anabolic fate of nutrients such as lipogenesis. Reporting the meal-induced increase in EPR as an enhancement of ‘DIT’ would have conveyed, incorrectly, that glucocorticoids stimulate heat dissipation, a desirable metabolic outcome favouring weight loss. In fact, glucocorticoids inhibited thermogenesis, increasing the proportion of nutrient energy for lipid synthesis.

Our observations shed light on the long-standing controversy concerning a pathogenic role of ‘DIT’ in obesity.\textsuperscript{47,48} As the meal-induced EPR or ‘DIT’ quantified by indirect calorimetry can vary, depending on contributions from its 2 components, differences in ‘DIT’ between individuals may not necessarily reflect corresponding differences in heat dissipation after the same meal. It is conceivable that the assumed attribution to thermogenesis by indirect calorimetry underlies the controversial evidence surrounding the role of ‘DIT’ in obesity.

There is increasing evidence that BAT contributes significantly to adiposity and substrate metabolism in humans.\textsuperscript{17} Increase in BAT activity has led to fat loss of approximately 0.7 kg over 6 weeks,\textsuperscript{49} amounting to approximately 6 kg over 12 months, and improvements in glycaemic status\textsuperscript{50} and insulin sensitivity over 4 to 6 weeks.\textsuperscript{51,52} The observed 50% reduction in BAT activity induced by 15 mg/d prednisolone may translate into a gain in fat mass of approximately 3 kg per year. This is metabolically significant and clinically relevant, given the widespread use of glucocorticoids and the rising tide of obesity in all communities, and the fact that the dose is in the range commonly used in clinical practice.

In summary, 1-week treatment with prednisolone suppresses BAT metabolic activity and thermogenesis, while stimulating meal-induced energy production and lipogenesis. We conclude that prolonged exposure to glucocorticoids suppresses human BAT function, diverting energy from dissipation as heat towards storage as fat after nutrient intake. Our findings suggest a role of BAT in the interplay between heat and nutrient metabolism in the regulation of energy balance. We provide novel mechanistic insights into the obesogenic effect of glucocorticoids, underscoring the metabolic importance of BAT in human energy metabolism.

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Conflict of interest
The authors have no conflicts of interest to disclose.

Author contributions

ORCID
Ken K. Y. Ho http://orcid.org/0000-0002-2508-9588

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