

Effect of beta-adrenergic stimulation on whole-body and abdominal subcutaneous adipose tissue lipolysis in lean and obese men

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Abstract

Aims/hypothesis Obesity is characterised by increased triacylglycerol storage in adipose tissue. There is in vitro evidence for a blunted beta-adrenergically mediated lipolytic response in abdominal subcutaneous adipose tissue (SAT) of obese individuals and evidence for this at the whole-body level in vivo. We hypothesised that the beta-adrenergically mediated effect on lipolysis in abdominal SAT is also impaired in vivo in obese humans.

Methods We investigated whole-body and abdominal SAT glycerol metabolism in vivo during 3 h and 6 h [$^2\text{H}_5$]glycerol infusions. Arterio–venous concentration differences were measured in 13 lean and ten obese men after an overnight fast and during intravenous infusion of the non-selective beta-adrenergic agonist isoprenaline [$20 \text{ ng (kg fat free mass)}^{-1} \text{ min}^{-1}$].

Results Lean and obese participants showed comparable fasting glycerol uptake by SAT (9.7 ± 3.4 vs $9.3 \pm 2.5\%$ of total release, $p=0.92$). Furthermore, obese participants showed an increased whole-body beta-adrenergically mediated lipolytic response versus lean participants. However, their fasting

lipolysis was blunted [glycerol rate of appearance: 7.3 ± 0.6 vs $13.1 \pm 0.9 \mu\text{mol (kg fat mass)}^{-1} \text{ min}^{-1}$, $p < 0.01$], as was the beta-adrenergically mediated lipolytic response per unit SAT [Δ total glycerol release: 140 ± 71 vs $394 \pm 112 \text{ nmol (100 g tissue)}^{-1} \text{ min}^{-1}$, $p < 0.05$] compared with lean participants. Net triacylglycerol flux tended to increase in obese compared with lean participants during beta-adrenergic stimulation [Δ net triacylglycerol flux: 75 ± 32 vs $16 \pm 11 \text{ nmol (100 g tissue)}^{-1} \text{ min}^{-1}$, $p=0.06$].

Conclusions/interpretation We demonstrated in vivo that beta-adrenergically mediated lipolytic response is impaired systematically and in abdominal SAT of obese versus lean men. This may be important in the development or maintenance of increased triacylglycerol stores and obesity.

Keywords Adipose tissue · Arterio–venous differences · Beta-adrenergic stimulation · Catecholamines · Glycerol · In vivo · Lipolysis · Obesity · Triacylglycerol

Abbreviations

ATBF	adipose tissue blood flow
FFM	fat free mass
FM	fat mass
R_a	glycerol rate of appearance
SAT	abdominal subcutaneous adipose tissue
TAG	triacylglycerol
TTR	tracer/tracee ratio

Introduction

Obesity is characterised by excess fat storage in adipose tissue, in the form of triacylglycerol (TAG). A blunted fat mobilisation, due to decreased adipose tissue lipolysis,

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might be an important factor contributing to the development or maintenance of the expanded adipose tissue mass in obesity. Fasting lipolysis per unit of lean body mass has been reported to be increased in obesity, whereas a decrease is reported when expressed per unit of fat mass (FM) [1]. The hormonal regulation of lipolysis is still under debate. There is strong evidence from *in vitro* and *in vivo* studies for the existence of lipolytic resistance to catecholamines in obese individuals. Blunted whole-body catecholamine-induced lipolysis has been shown *in vivo* in obese persons [2, 3]. This impaired lipolysis did not improve after weight reduction [4]. Furthermore, a decreased lipolytic response to catecholamines is a feature of childhood-onset obesity [5, 6] and is also present in adipocytes from first-degree relatives of obese persons [7]. These observations suggest that catecholamine resistance of lipolysis may be an important early, and perhaps primary factor, in the development of obesity. *In vitro* catecholamine resistance of lipolysis was reported in subcutaneous adipocytes of men and women with upper-body obesity, in relation with a decreased cell surface density of β_2 -adrenoceptors [8]. We hypothesised that beta-adrenergically mediated lipolytic response at the whole-body and abdominal subcutaneous adipose tissue (SAT) level is impaired *in vivo* in obese persons. If so, this might contribute to the increased fat storage in this adipose tissue depot.

To obtain an accurate estimation of lipolysis, state-of-the-art [$^2\text{H}_5$]glycerol tracer methodology in combination with the measurement of arterio-venous concentration differences across abdominal SAT was used. Obese and lean male control participants were investigated after an overnight fast and during catecholamine stimulation using the non-selective beta-adrenergic agonist isoprenaline. The primary outcome measures of the present study were glycerol rate of appearance (R_a) and glycerol exchange across abdominal SAT. A methodological issue that arises when determining local adipose tissue glycerol release is the possibility that adipose tissue may also take up small amounts of glycerol [9]. A pilot study was performed to determine the time period required to obtain a steady-state in glycerol enrichment in both arterialised and venous blood draining from adipose tissue, since a lack of isotopic equilibration may explain previous discrepant findings on glycerol uptake [10].

Methods

Participants

Three lean (two women and one man; BMI < 25 kg/m²) participants took part in a pilot experiment, during which [$^2\text{H}_5$]glycerol enrichment was measured for 6 h to determine the time required for obtaining an isotopic steady-

state. Thirteen lean (BMI < 25 kg/m²) and ten obese (BMI \geq 30 kg/m²) non-smoking normotensive men participated in the actual SAT lipolysis study, during which [$^2\text{H}_5$]glycerol was infused for a 3 h period. Clinical characteristics of the participants are summarised in Table 1. Body weight and body density were determined after an overnight fast, as previously described [11]. All participants were in good health as assessed by their medical history, free of any medication and spent no more than 3 h/week in organised sports activities. The Medical Ethical Committee of Maastricht University approved the study protocol and all participants gave their written informed consent before participating in the study.

Experimental protocol

Pilot study The time course in [$^2\text{H}_5$]glycerol enrichment was determined in order to identify when steady-state levels were achieved ($n=3$). Glycerol enrichment was measured in arterialised blood and blood draining the abdominal SAT (adipose vein) during primed (3 $\mu\text{mol/kg}$) constant infusion for 6 h of [$^2\text{H}_5$]glycerol (0.20 $\mu\text{mol kg}^{-1} \text{min}^{-1}$). Blood samples were taken simultaneously from the two sites, both at baseline before the start of the tracer infusion (t_0 min), and at ten time points during glycerol infusion (t_{60} , t_{90} , t_{120} , t_{150} , t_{180} , t_{210} , t_{240} , t_{330} , t_{345} , t_{360} min).

Whole-body and SAT lipolysis study Glycerol enrichment and exchange across abdominal SAT were investigated during primed (3 $\mu\text{mol/kg}$) constant infusion of [$^2\text{H}_5$]glycerol for 3 h (0.20 $\mu\text{mol kg}^{-1} \text{min}^{-1}$). Following a 120 min baseline period, isoprenaline was infused at a rate of 20 ng [kg fat free mass (FFM)]⁻¹ min⁻¹ for 60 min. During the experiment, heart rate was recorded continuously by means of a three-lead ECG. When heart rate increased by more than 40 beats per min or in the event of ECG irregularities, isoprenaline infusion was stopped ($n=2$, one lean and one obese participant). Before the start of the tracer infusion an arterialised blood sample was taken for background enrich-

Table 1 Clinical characteristics of the participants

	Lean ($n=13$)	Obese ($n=10$)
Age (years)	43 \pm 3	54 \pm 3
BMI (kg/m ²)	23.0 \pm 0.5	31.9 \pm 0.6 ^a
FM (kg)	15.2 \pm 0.8	32.4 \pm 1.2 ^a
WHR	0.91 \pm 0.01	1.01 \pm 0.01 ^a
Systolic blood pressure (mmHg)	126 \pm 3	137 \pm 4
Diastolic blood pressure (mmHg)	77 \pm 2	85 \pm 3
HOMA-IR	1.8 \pm 0.2	3.4 \pm 0.3 ^a

Values are mean \pm SEM

^a $p < 0.05$ obese vs lean

HOMA-IR, homeostatic model assessment of insulin resistance

ment. Blood samples were also taken simultaneously from the arterialised and adipose vein at three baseline time points (t_{90} , t_{105} and t_{120} min) and at three time points during the last 30 min of isoprenaline infusion (t_{150} , t_{165} and t_{180} min). Adipose tissue blood flow (ATBF) was monitored continuously using the ^{133}Xe washout technique [12]. ATBF results have been published previously in another context [13].

Clinical methods

All participants were asked to refrain from drinking alcohol and to perform no strenuous exercise for 24 h before the study. Participants came to the laboratory by car or bus at 08:00 hours after an overnight fast. Three cannulas were inserted before the start of the experiment. Arterialised venous blood was obtained through a 20-gauge cannula inserted retrogradely into a superficial dorsal hand vein. The hand was warmed in a hotbox, which was maintained at 60°C to achieve adequate arterialisation [14]. In the same arm, a second cannula was inserted in a forearm antecubital vein for the infusion of [$^2\text{H}_5$]glycerol tracer and the non-selective beta-adrenergic agonist isoprenaline at a rate of 20 ng (kg FFM) $^{-1}$ min $^{-1}$. At this infusion rate, plasma isoprenaline concentrations are comparable in lean and obese participants [3]. Finally, the veins on the anterior abdominal wall were identified by means of a fibre-optic light source. In order to obtain adipose tissue venous blood, a 10 cm 22-gauge catheter (Central venous catheter kit Seldinger technique; Becton Dickinson, Alphen aan den Rijn, the Netherlands) was introduced anterogradely over a guide wire into one of the superficial veins and threaded towards the groin, so that its tip lay just superior to the inguinal ligament [15]. This method provides the drainage from the adipose tissue of the abdomen, uncontaminated by muscle drainage and with only a minor contribution from skin [15]. The adipose vein was kept patent by continuous saline (9 g/l NaCl) infusion at a rate of 80 ml/h. The participants rested in a supine position for the duration of the study.

Analytical methods

A small portion of blood was used to measure oxygen saturation (%HbO $_2$) and ensure adequate arterialisation (ABL510; Radiometer, Copenhagen, Denmark). Blood was collected in tubes containing EDTA and immediately centrifuged for 10 min at 1,000g, 4°C. The plasma was removed for enzymatic colorimetric quantification of NEFA (NEFA C kit; Wako, Neuss, Germany), glycerol (Boehringer, Mannheim, Germany) and TAG (Sigma, St Louis, MO, USA) on a centrifugal spectrophotometer (Cobas Fara; Roche Diagnostica, Basel, Switzerland). Plasma glucose concentra-

tion (ABX Diagnostics, Montpellier, France) was measured on an automated spectrophotometer (Cobas Mira; Roche Diagnostica). Plasma insulin was measured with a double antibody radioimmunoassay (Linco Research, St Charles, MO, USA). Insulin sensitivity was assessed by the homeostasis model assessment index for insulin resistance, calculated from fasting glucose and insulin [16]. Packed cell volume was measured using a microcapillary system (Hirschmann Laborgeräte, Eberstadt, Germany).

Isotope enrichment

To determine isotopic enrichment of glycerol, samples first were derivatised. Acetone (1 ml) was added to 150 μl plasma and each tube was vortexed for 2 min and centrifuged for 20 min at 17,500g, 4°C. The supernatant fraction was transferred to a clean tube and dried under nitrogen at 37°C and derivatised by adding 80 μl ethyl acetate (cat. no. 45765; Sigma-Aldrich, Seelze, Germany) and 80 μl heptafluorobutyric acid anhydride (cat. no. 63164; Pierce Biotechnology, Rockford, IL, USA). The tubes were vortexed for 2 min and incubated for 1 h at 70°C. Samples were then rotated end over end for 5 min at 25°C and evaporated under nitrogen at room temperature. Ethyl acetate (70 μl) was added before injection into the GC-MS (Finnigan MAT 252, Bremen, Germany) for measurement of glycerol enrichment. Stable isotope enrichment was analysed by selectively monitoring the mass to charge ratio (m/z) of molecular ions 253 and 257 for glycerol [17].

Calculations

The net exchange (flux) of metabolites across abdominal SAT was calculated by multiplying the arterio-venous concentration difference of metabolites by adipose tissue plasma flow. Plasma flow was calculated as ATBF \times (1–packed cell volume), with packed cell volume expressed as a fraction. A positive net flux indicates net uptake from plasma, whereas a negative net flux indicates net tissue release.

The expected adipose vein enrichment, in case of no glycerol uptake, was calculated as arterialised enrichment multiplied by arterialised glycerol concentration divided by the measured adipose vein enrichment.

The R_a of glycerol was calculated according to the following steady-state equation:

$$R_a \left(\mu\text{mol kg}^{-1} \text{min}^{-1} \right) = \text{TTR}^{-1} \times F$$

where TTR is tracer/tracee ratio and F is the isotope infusion rate ($\mu\text{mol kg}^{-1} \text{min}^{-1}$).

The fractional extraction (fract) of glycerol across abdominal SAT was calculated by dividing the arterio-venous concentration difference of [$^2\text{H}_5$]glycerol by the

arterialised [$^2\text{H}_5$]glycerol concentration. Abdominal SAT total glycerol uptake was calculated as follows:

abdominal SAT total glycerol uptake

$$= \text{fract} \times (\text{glycerol}_{\text{art}}) \times \text{ATBF}$$

where the units are $\text{nmol} (100 \text{ g tissue})^{-1} \text{ min}^{-1}$; ($\text{glycerol}_{\text{art}}$) is arterialised glycerol concentration ($\mu\text{mol/l}$); and ATBF is in $\text{ml} (100 \text{ g tissue})^{-1} \text{ min}^{-1}$. Abdominal SAT total glycerol release was calculated from the formula:

abdominal SAT total glycerol release

$$= \text{abdominal SAT net glycerol flux} \\ - \text{abdominal SAT total glycerol uptake}$$

Statistical analysis

Baseline fasting values and changes (Δ beta-adrenergic stimulation to baseline) were compared between groups (obese vs lean) using Student's unpaired *t* test. Statistical calculations were performed with SPSS for Macintosh (version 11.0; SPSS, Chicago, IL, USA). Data are presented as mean \pm SEM. A value of $p < 0.05$ was considered statistically significant.

Results

Characteristics

Obese participants had significantly higher BMI, FM, waist to hip ratio, fasting circulating TAG and insulin concentrations than their lean counterparts (Tables 1 and 2).

Tracer/tracee ratio

In the pilot experiment, the tracer/tracee ratios (TTR) obtained during a 6 h [$^2\text{H}_5$]glycerol infusion after an overnight fast

were examined ($n=3$). Arterialised and adipose vein TTR reached a steady-state after 1 h of infusion (Fig. 1). Mean values are presented, as all participants ($n=3$) showed the same pattern. The measured adipose vein enrichment was consistently lower than the expected enrichment, implying uptake of glycerol by adipose tissue. In the actual SAT lipolysis experiment (3 h [$^2\text{H}_5$]glycerol infusion), TTR also reached a steady-state after 1 h and remained stable during isoprenaline infusion. Data in lean and obese men were comparable (data not shown).

Circulating metabolites

Beta-adrenergic stimulation with isoprenaline increased arterialised TAG concentrations in obese participants, while in lean participants TAG concentrations decreased during isoprenaline infusion (Table 2). Thus, the change in arterialised TAG concentrations from baseline to isoprenaline was different between obese and lean participants (Δ TAG obese vs lean, 100 ± 37 vs $-45 \pm 22 \mu\text{mol/l}$, $p < 0.05$; Table 2).

Furthermore, beta-adrenergic stimulation increased arterialised NEFA and glycerol concentrations in lean and obese participants. The beta-adrenergic mediated increase in arterialised NEFA (Δ NEFA 454 ± 68 vs $271 \pm 46 \mu\text{mol/l}$, $p < 0.05$) and glycerol concentration (Δ glycerol 40 ± 8 vs $15 \pm 5 \mu\text{mol/l}$, $p < 0.05$) was more pronounced in obese than in lean participants (Table 2), suggesting a higher whole-body lipolytic response in the former. Indeed, beta-adrenergic stimulation increased whole-body glycerol R_a in lean and obese participants (Table 2), this increase tending to be higher in the obese group (Δ glycerol R_a obese vs lean: 172 ± 19 vs $109 \pm 13 \mu\text{mol/min}$, $p = 0.07$; Table 2). Expressed per unit of FM, fasting glycerol R_a was significantly reduced in obese compared with lean participants ($p < 0.05$; Table 2). Interestingly, the beta-adrenergically mediated increase in glycerol R_a per unit of FM was significantly blunted in obese participants [Δ glycerol R_a per unit FM: 5.4 ± 0.9 vs $7.7 \pm 1.5 \mu\text{mol} (\text{kg FM})^{-1} \text{ min}^{-1}$, $p < 0.05$] (Table 2), sug-

Table 2 Circulating (arterialised) metabolite levels during baseline (fasting) and isoprenaline infusion in lean and obese participants

	Lean		Obese	
	Baseline ($n=13$)	Isoprenaline ($n=10$)	Baseline ($n=10$)	Isoprenaline ($n=7$)
TAG ($\mu\text{mol/l}$)	701 \pm 66	648 \pm 64	1,464 \pm 190 ^b	1,667 \pm 217 ^a
NEFA ($\mu\text{mol/l}$)	661 \pm 41	942 \pm 53	638 \pm 42	1,124 \pm 82 ^a
Glycerol ($\mu\text{mol/l}$)	102 \pm 5	118 \pm 7	106 \pm 4	147 \pm 10 ^a
Glycerol R_a ($\mu\text{mol/min}$)	199 \pm 12	311 \pm 28	220 \pm 15	391 \pm 30
Glycerol R_a /FM [$\mu\text{mol} (\text{kg FM})^{-1} \text{ min}^{-1}$]	13.1 \pm 0.9	20.9 \pm 1.6	7.3 \pm 0.6 ^b	12.9 \pm 1.1 ^a
Glucose (mmol/l)	5.3 \pm 0.1	5.4 \pm 0.1	5.5 \pm 0.2	5.4 \pm 0.1
Insulin (pmol/l)	50 \pm 4	74 \pm 6	94 \pm 7 ^b	167 \pm 16 ^a

Values are mean \pm SEM

^b $p < 0.05$ baseline obese vs lean; ^a $p < 0.05$ change (Δ) from baseline obese vs lean using unpaired Student's *t* test

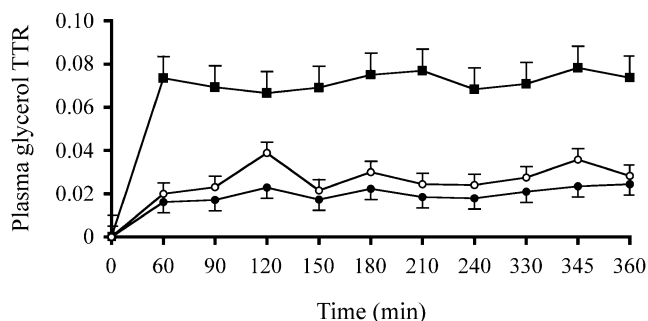


Fig. 1 Plasma glycerol TTR during 6 h primed constant infusion of [$^2\text{H}_5$]glycerol ($n=3$) in arterialised blood (squares) and blood draining from abdominal SAT (adipose vein; black circles). White circles, expected adipose vein enrichment. The measured adipose vein enrichment was consistently lower than the expected enrichment

gesting a blunted lipolytic response per unit of FM in obese participants.

Finally, beta-adrenergic stimulation increased arterialised insulin concentrations in lean and obese participants (Table 2). This increase in circulating insulin levels was significantly higher in obese than in lean participants (Δ insulin 62 ± 13 vs 25 ± 4 pmol/l, $p < 0.05$; Table 2).

Abdominal SAT lipolysis

Glycerol uptake by abdominal SAT was observed in lean and obese participants after an overnight fast (Fig. 2a). Fractional extraction of [$^2\text{H}_5$]glycerol from the circulation

(lean vs obese, 16.6 ± 4.5 vs $13.9 \pm 6.7\%$) and total glycerol uptake expressed relative to total glycerol release were very small (lean vs obese, 9.7 ± 3.4 vs $9.3 \pm 2.5\%$ of total release) with no significant difference between lean and obese participants ($p=0.74$ and $p=0.92$, respectively). Adipose tissue total glycerol uptake increased during beta-adrenergic stimulation in lean and obese participants, but this increase was not significantly different between groups [Δ total glycerol uptake obese vs lean, 4 ± 9 vs 21 ± 5 nmol (100 g tissue) $^{-1}$ min $^{-1}$, $p=0.15$] (Fig. 2a). The increased total glycerol uptake during beta-adrenergic stimulation appeared to be partly explained by the increase in ATBF ($r=0.633$, $p < 0.05$).

Fasting net glycerol and NEFA release across abdominal SAT were comparable between lean and obese participants (Table 3). Beta-adrenergic stimulation increased net NEFA and glycerol release across abdominal SAT to a greater extent in lean than in obese participants, although changes were not significantly different between groups (Table 3). In line with these findings, the beta-adrenergically mediated increase in total glycerol release across abdominal SAT was blunted in the obese group [Δ total glycerol release obese vs lean, 140 ± 71 vs 394 ± 112 nmol (100 g tissue) $^{-1}$ min $^{-1}$, $p < 0.05$] (Fig. 2b), suggesting a blunted lipolytic response per unit of abdominal SAT in obese participants. Finally, obese men tended to show an increased net TAG flux across abdominal SAT during beta-adrenergic stimulation [Δ net TAG flux obese vs lean, 75 ± 32 vs 16 ± 11 nmol (100 g tissue) $^{-1}$ min $^{-1}$, $p=0.06$] (Table 3).

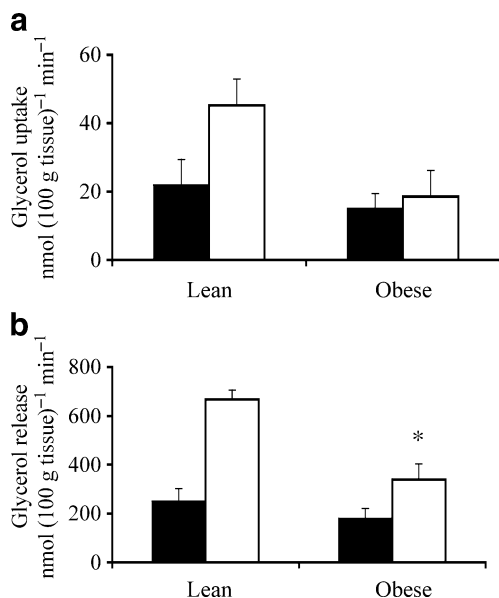


Fig. 2 Total glycerol uptake (a) and release (b) across abdominal SAT after an overnight fast (black bars) and during beta-adrenergic stimulation (white bars) in obese vs lean participants during 3 h [$^2\text{H}_5$]glycerol infusion. Values are mean \pm SEM. * $p < 0.05$ for change (Δ) from baseline obese vs lean

Discussion

The present study was designed to investigate in vivo whole-body and abdominal SAT lipolysis in obese and lean men. To our knowledge, this is the first study to show in vivo that obese participants have a blunted beta-adrenergically mediated lipolytic response per unit of adipose tissue.

Methodological considerations

A point of discussion with studies on glycerol uptake and release using tracer methodology is the infusion time of the labelled glycerol. In previous studies, the infusion time was relatively short (1–3 h), raising the question of whether equilibration between labelled glycerol and the adipose tissue glycerol pool is complete or not [9, 10]. We investigated glycerol enrichment during a 3 h and 6 h period of [$^2\text{H}_5$]glycerol infusion. Steady-state levels in labelled [$^2\text{H}_5$]glycerol were achieved in arterialised and adipose vein enrichment after 1 h and remained constant for the subsequent 5 h. Thus, our data support the use of a relatively short infusion time (1 h) for study of glycerol metabolism.

Table 3 Blood flow and net SAT fluxes during baseline (fasting) and isoprenaline infusion in lean and obese participants

	Lean		Obese	
	Baseline (n=13)	Isoprenaline (n=10)	Baseline (n=10)	Isoprenaline (n=7)
ATBF [ml (100 g tissue) ⁻¹ min ⁻¹]	2.2±0.2	6.3±1.2	1.4±0.2 ^a	3.6±0.6
Net SAT fluxes [nmol (100 g tissue) ⁻¹ min ⁻¹]				
TAG	25±8	43±17	34±29	113±62
NEFA	-780±160	-2,101±371	-486±101	-1,824±667
Glycerol	-229±49	-640±148	-211±51	-486±128
Glucose	53±49	-69±151	-143±96	-677±632

Values are mean±SEM

A positive net flux indicates net uptake from plasma, whereas a negative net flux indicates net tissue release

^a*p*<0.05 baseline obese vs lean using unpaired Student's *t* test

Glycerol uptake

The present data show a slight glycerol uptake by abdominal SAT of lean and obese participants. Glycerol uptake was not significantly different between lean and obese participants. Uptake and dilution of [²H₅]glycerol across abdominal SAT has been shown previously during 1 h [9] of tracer infusion. In this study, the dilution of the labelled glycerol was consistently greater than expected from the measured net release of glycerol, indicating significant uptake of glycerol by adipose tissue. In line with this study, we observed a two- to fivefold higher glycerol enrichment in arterialed than in venous blood draining adipose tissue. The observed enrichment in venous blood was universally lower than that predicted from the net addition of glycerol to venous blood. This indicates that an exchange must occur between enriched glycerol in the blood and the unenriched non-esterified glycerol pool in adipose tissue. In contrast, some studies were unable to detect significant uptake of glycerol by adipose tissue after 1 h of tracer infusion [10]. The reason for this apparent discrepancy remains to be elucidated. It should be mentioned that glycerol uptake is low in human adipose tissue as is the activity of the enzyme glycerol kinase [18]. This enzyme is responsible for the phosphorylation of glycerol into glycerol 3-phosphate, making it available for re-esterification.

Abdominal SAT lipolytic response to beta-adrenergic stimulation

A blunted isoprenaline-induced increase in total glycerol release per unit abdominal SAT was observed in obese men, indicating that in vivo beta-adrenergic mediated lipolytic response in abdominal SAT of obese participants is blunted. Our data are consistent with evidence of catecholamine resistance in vitro and in situ in obese individuals [2–4], in children with obesity [5, 6] and also in relatives of obese individuals [7]. Defects in catecholamine signal transduc-

tion have been observed at the β₂-adrenoceptor level and further downstream or directly involving hormone-sensitive lipase [8, 19–22]. However, from our experiments it is not possible to determine at which level the observed defect is located. Interestingly, catecholamine resistance has been observed in adipose tissue of first-degree relatives of obese participants [7] and persists after weight reduction [4], suggesting that catecholamine resistance may be a primary defect in obesity. Furthermore, plasma insulin concentrations may play an important role in regulating lipolysis [23]. Therefore, we cannot fully rule out the possibility that the blunted lipolytic response per unit adipose tissue mass that we observed is a secondary phenomenon, due to the higher degree of hyperinsulinaemia during beta-adrenergic stimulation in obese compared with lean participants. However, this explanation seems unlikely, since a blunted in situ lipolytic response in abdominal SAT of obese women was still observed when the confounding influence of hyperinsulinaemia had been excluded using a pancreatic hormonal clamp [2].

In contrast to the present study, two in situ microdialysis studies performed in men found that the increase in interstitial glycerol during isoprenaline administration did not differ between lean and obese individuals [24, 25]. A possible explanation for this is that in microdialysis studies interstitial glycerol is used as a measure of lipolysis. Since glycerol is taken up by adipose tissue, interstitial glycerol concentration may not reflect the overall rate of lipolysis. Rather, it may be the net result of TAG and glycerol metabolism, thus reflecting net glycerol turnover [26].

Whole-body beta-adrenergically mediated lipolytic response

Whole-body lipolytic response during isoprenaline infusion tended to be higher in obese participants. This was reflected by a higher increase in circulating NEFA and glycerol concentrations during beta-adrenergic stimulation in obese

than in lean participants. Expressed per unit of FM, beta-adrenergically mediated lipolysis (glycerol R_a) was significantly lower in obese than in lean men. This suggests that the increased whole-body beta-adrenergically mediated lipolytic response in obese individuals is directly linked to the increased adipose tissue mass, as has been shown before in upper body obese women [2]. Increased release of NEFA into the circulation increases NEFA delivery to the liver, resulting in increased hepatic VLDL-TAG output and hence increased circulating TAG levels during beta-adrenergic stimulation, as was observed in our obese participants. The control of whole-body lipid metabolism is, to a large extent, dependent on the efficient regulation of lipid metabolism in adipose tissue and the liver. Moreover, hepatic VLDL-TAG is a precursor of TAG stored in adipose tissue [27, 28]. Consequently, a greater VLDL-TAG delivery to adipose tissue and greater lipoprotein lipase-mediated hydrolysis might explain the tendency towards increased positive TAG flux across abdominal SAT of obese participants during beta-adrenergic stimulation. Our observation is in agreement with a study by Samra et al. [29] showing an increased rate of action of lipoprotein lipase during epinephrine infusion. These in vivo findings are in contrast with in vitro studies showing that lipoprotein lipase expression and activity are suppressed by epinephrine [30, 31]. Future studies are needed to elucidate whether an increased TAG flux across SAT might contribute to the increased TAG storage in adipose tissue of obese participants.

Conclusion

The present study demonstrates in vivo that obese men have a blunted beta-adrenergically mediated lipolytic response in abdominal SAT. Therefore, a blunted lipolysis during beta-adrenergic stimulation may be an important factor in the development or maintenance of increased TAG stores and obesity.

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Duality of interest statement The authors declare that there is no duality of interest associated with this manuscript.

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