Success to increase postprandial blood flow in subcutaneous adipose tissue is associated with tissue resistance to adrenergic stimulation


Abstract

Aims. – Adequate adipose tissue blood flow (ATBF) is essential for its metabolic and endocrine functions. From a metabolic point of view, sufficient increases in ATBF after meals permits full storage of excess energy into fat, thus protecting other tissues against the toxic effects of fatty acids and glucose spillover. It was previously shown that postprandial increases in ATBF are blunted in obese and insulin-resistant subjects, and that much of the postprandial ATBF response is the result of β-adrenergic activation. Examination of previously recorded data on postprandial ATBF responses revealed an underlying heterogeneity, with postprandial ATBF being largely unresponsive to food stimuli in a substantial proportion of normal weight healthy people (low responders). Our study tests the hypothesis that this unresponsive pattern is due to resistance to β-adrenergic stimulation in adipose tissue.

Methods. – Five responders and five low responders were selected from a previously studied cohort and matched for BMI (20.5 ± 0.7 vs 22 ± 1 kg/m², respectively), gender (male/female: 2/3) and age (30 ± 3 vs 37 ± 6 years). Subcutaneous adipose tissue microinusions of stepwise increasing doses of isoproterenol were performed with concomitant monitoring of blood flow, using the 133Xenon washout technique.

Results. – Although BMI was similar between responders and low responders, there were significant differences in fat mass (9.9 ± 1.6 vs 14.4 ± 1.6 kg; P < 0.05) and four-point skinfold thickness (33 ± 4 vs 52 ± 16 mm; P < 0.05). Lack of ATBF response to oral glucose was confirmed in the low responder group. In responders, ATBF was higher at baseline (5.4 ± 1 vs 3.4 ± 1 ml/min/100 g of tissue) and responded more distinctly to increasing isoproterenol doses (10⁻⁸ M: 7.6 ± 1.4 vs 4.9 ± 1; 10⁻⁶ M: 12.5 ± 1.7 vs 7.5 ± 1.6; and 10⁻⁴ M: 20 ± 1.7 vs 9 ± 0.9 ml/min/100 g of tissue).

Conclusion. – These data suggest that the lack of glucose-stimulated ATBF is associated with resistance to sympathetic activation in adipose tissue.

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Keywords: Sympathetic nervous system; Adipose tissue; Blood flow; Insulin resistance; MONW

Résumé

L’absence d’augmentation du flot sanguin dans le tissu adipeux sous-cutané en période postprandiale est associée à la résistance de ce tissu à la stimulation adrénergique.

Objectifs. – Un flot sanguin adéquat dans le tissu adipeux est indispensable pour que ce tissu puisse accomplir ses fonctions métaboliques et endocrines. Du point de vue métabolique, une hauteur suffisante de ce flot après un repas rend possible le stockage de l’excès d’énergie. Par conséquent, un bon contrôle du flot sanguin du tissu adipeux participe à l’effet protecteur du tissu adipeux vis-à-vis des effets toxiques de l’excès d’acides gras et de glucose. Nous avons montré que l’augmentation postprandiale du flot sanguin dans le tissu adipeux était très diminuée chez les sujets obèses et résistants à l’insuline et que cette réponse postprandiale résultait principalement de l’activation du système β-adrénergique. En révisant nos données, nous avons noté une grande hétérogénéité des réponses. Pour un bon nombre d’individus sains de poids normal, les non-répondeurs, le flot sanguin du tissu adipeux répondait très peu aux stimuli nutritionnels. La présente étude avait pour but de déterminer si cette absence de réponse était due à une résistance du tissu adipeux à la stimulation β-adrénergique.

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Méthodes. – Cinq répondeurs et cinq non-répondeurs ont été sélectionnés à partir des études antérieures et appariés pour l’IMC (20,5 ± 0,7 vs 22 ± 1 kg/m²), le sexe (m/f : 2/3) et l’âge (30 ± 3 vs 37 ± 6 ans). De l’isoprotéronéol à doses progressivement croissantes a été microinfusé dans le tissu adipeux sous-cutané alors qu’au même endroit le flot sanguin était mesuré en continu selon la technique appelée 133Xenon washout.

Résultats. – L’IMC était similaire dans les deux groupes, mais la masse adipeuse (9,9 ± 1,6 vs 14,4 ± 1,6 kg, P < 0,05) et le pli cutané (33 ± 4 vs 52 ± 16 mm, P < 0,05) étaient plus élevés chez les non-répondeurs. L’absence de réponse du flot sanguin du tissu adipeux à l’ingestion de glucose a été confirmée chez les non-répondeurs. Chez les répondeurs, le flot sanguin du tissu adipeux de base était plus élevé (5,4 ± 3,4 ± 1 mL/min par 100 g de tissu) et répondait à l’augmentation des doses de l’isoprotéronéol (10⁻⁸ M : 7,6 ± 1,4 vs 4,9 ± 1, 10⁻⁶ M : 12,5 ± 1,7 vs 7,5 ± 1,6 et 10⁻⁴ M : 20 ± 1,7 vs 9 ± 0,9 mL/min par 100 g de tissu).

Conclusion. – Ces données suggèrent que l’absence de réponse du flot sanguin du tissu adipeux après ingestion de glucose est associée à une résistance du tissu adipeux à l’activation sympathique.

Mots clés : Système nerveux sympathique ; Flot sanguin ; Tissu adipeux ; Résistance à l’insuline ; MONW

1. Abbreviations

ATBF Adipose tissue blood flow
BMI Body mass index
BP Blood pressure
HR Heart rate
ISO Isoproterenol/isoprenaline
MONW Metabolically obese normal weight
NEFA Non-esterified fatty acids
SFT Skinfold thickness
SNS Sympathetic nervous system
TAG Triacylglycerol

2. Introduction

Each organ and tissue of the body has a specific blood supply fitted to its needs and function, and the level of blood supply changes in response to various physiological and pathophysiological requirements and conditions. It has been shown that blood flow in adipose tissue responds primarily to nutritional and energy demands. Thus, in a fasting state, for example, increasing ATBF allows the adequate release of fatty acids into the circulation. On the other hand, in a postprandial state, a sufficient increase in ATBF enables lipid and glucose disposal into fat. This mechanism is involved in the protection of other tissues against the undesirable effects of hyperlipidaemia and hyperglycaemia. Hampered increases in ATBF after meals appear to be an important component of diabetes pathogenesis.

Fasting and postprandial rises in ATBF negatively correlate with BMI [1], while the primary determinant of responsiveness is not obesity per se, but the associated insulin resistance instead [2,3]. It was previously demonstrated that an oral glucose load results in a doubling of ATBF in healthy, lean individuals, while obese and/or insulin-resistant subjects have lower fasting ATBF and blunted postprandial responses [2]. Dimitriadis et al. [4] recently showed that postprandial ATBF responses are progressively blunted until suppression, while successive stages leading to type 2 diabetes follow one after the other. In contrast to what has been proposed for other tissue beds, insulin per se does not alter ATBF [5]. In a previous study [6], it was hypothesized that, during the postprandial period, insulin may act indirectly via sympathetic activation. Using non-selective beta blockers, the study showed that, in healthy normal weight subjects, nearly 60% of the postprandial rise in ATBF results from β-adrenergic activation in fat tissue.

Examination of the individual data for postprandial ATBF responses to glucose revealed substantial underlying heterogeneity, with several normal weight subjects failing to show the expected postprandial ATBF enhancement. For this reason, the normal weight subjects were arbitrarily divided into two groups: ‘responders’ (ATBF increased by > 50% of baseline blood flow after a 75 g glucose load); and ‘low responders’ (post-oral glucose ATBF enhancement < 50%).

It was also hypothesized that the responsiveness to β-adrenergic stimulation is altered in low responders. Given the presence of adrenergic receptors in adipose tissue [7], local agonist stimulation of vascular tone was found to be a suitable and valid method for testing tissue sympathetic reactivity in adipose tissue [5,6]. Subcutaneous infusion of isoproterenol, a β-agonist, stimulates ATBF in a manner similar to local endogenous release of norepinephrine. Isoproterenol has been used systemically [8] or via microdialysis [9] to reveal lower ATBF responses in obese compared with lean subjects.

The aim of the present study was to determine whether or not, in lean low responders to oral glucose, ATBF exhibits resistance to adrenergic stimulation at the adipose tissue level.

3. Methods

3.1. Subjects

Our previously studied subjects [2,5,6,10] showed a continuum of ATBF responses to 75 g of oral glucose (Fig. 1). Of 47 normal weight subjects, 15 (32%) were considered to be low responders, while the remaining 32 were responders, based on our threshold of 50%. Of these subjects, five lean (BMI < 25 kg/m²), non-smoking, normoglycaemic responders and five low responders agreed to participate in a further study. They were also matched for gender and age. The studies were approved by the Oxfordshire Clinical Research Ethics Committee and were in conformity with the Declaration of Helsinki, and all subjects gave their informed consent to participate.
3.2. Study design

Subjects were asked to refrain from any strenuous exercise or alcohol intake 24 h prior to the experiment and, following an overnight fast, were studied at rest in a recumbent position. Height, weight, waist and hip circumferences, body composition measured by bioelectric impedance using the Bodystat 1500 (Bodystat Ltd, Isle of Man, UK), and SFT measured by calipers (Holtain Limited, Crymych, Pembrokeshire, UK) were also recorded. SFT was measured at four sites—biceps, triceps, scapular and suprailliac—as recommended [11]. In addition, HR and BP were recorded at baseline and prior to each blood sampling thereafter. A 22 g Venflon cannula was inserted retrogradely into a distal forearm vein and kept patent by slow infusion of saline (NaCl 0.9%). The hand was heated to provide arterialized blood. Samples were drawn (for frequency, see Fig. 2) into refrigerated heparinized tubes and immediately placed on ice. Plasma was separated at +4 °C and frozen within 15 min. At 120 min, 75 g of glucose was ingested, and the experiment ended 90 min later.

Subjects completed two well-established standardized questionnaires to evaluate their level of occupational [12] and physical [13] activities. Also, their family history, taking into account first-degree relatives, was documented for obesity, diabetes (type 2), high BP, heart attack (before age 55 years in men and age 65 years in women) and stroke.

3.3. Microinfusion protocol

This technique has been described in detail elsewhere [5,6], although an outline of the protocol with the timetable is shown in Fig. 2. In the present experiments, catheters (Quick-set Infusion Set, MiniMed, Applied Medical Technology Ltd, Cambridge, UK) were inserted 8–10 cm on either side of the medial line and 8–10 cm above the umbilicus to obtain optimal responses [10]. A saline infusion was started at 2 μL/min (CMA 100 pump, CMA Microdialysis Ltd, Sunderland, UK) on both sides. 133Xenon was injected through the port of the catheter hub, and a gamma-counter probe (Oakfield Instruments, Eynsham, Oxfordshire, UK) was placed over the infusion devices.

Three solutions (10⁻⁸ M, 10⁻⁶ M and 10⁻⁴ M) of isoproterenol (Saventrine IV, 1 mg/mL, Pharmax, Bexley, Kent, UK) were prepared by dilution in saline before the experiment. The total amount of isoproterenol administered over the 3.5 h microinfusion period was 5.216 μg (0.0004 μg/min) during the 10⁻⁶ M infusion period and 0.04 μg/min during the 130-min 10⁻⁴ M infusion period. The British National Formulary recommended dosages are 0.5–10 μg/min for the therapeutic use of isoproterenol by intravenous (IV) infusion.

At time zero at one site chosen randomly, saline was switched to a 10⁻⁸ M isoproterenol concentration and maintained thereafter for 40 min at an infusion rate of 2 μL/min. The isoproterenol infusion was subsequently increased twice, to 10⁻⁶ M for another 40 min and to 10⁻⁴ M until the end of the experiment. The saline infusion was concomitantly continued on the other side.

3.4. Biochemical measurements

Plasma glucose was measured the same day from samples stored at +4 °C using an enzymatic method [14]. The remaining plasma was stored at −20 °C for measurement of NEFA, using a Wako NEFA C test kit (Alpha Laboratories, Eastleigh, Hampshire, UK), and TAG concentrations (Randox Laboratories, Crumlin, County Antrim, UK) using enzymatic methods. Plasma insulin was measured by a double-antibody radioimmunoassay (Pharmacia & Upjohn, Milton Keynes, UK); the interassay coefficients of variation were 5.8% at 12 mU/L and 6.5% at 65 mU/L.
3.5. Calculations and statistics

Skinfold thickness was calculated as the sum of the four measurements. Occupational and physical activities were scored [12,13], and the family history of diabetes and cardiovascular disease was recorded, with one point scored for each event. Blood flow was calculated over 10 min time periods, as previously described [5,6]. Effects of the various isoproterenol concentrations were estimated by calculating the mean of the last two ATBF values at each concentration after subtraction of baseline (−15 min and −5 min) values and comparison with the saline control site.

The effect of fasting on ATBF was calculated from the saline side as the difference between baseline and the average of two ATBF time points prior to glucose intake (‘end-of-fast’).

After glucose ingestion, peak values of ATBF were calculated as the mean of three selected contiguous points, including the highest value; glucose excursions and insulin increments were calculated as iAUCs, taking the average glucose reading as the 115 min time point, and time-averaged [dividing the area under the curve (AUC) value by time (min)].

Insulin sensitivity indices for glucose (ISIgly) and NEFA suppression (ISINEFA) were calculated using the method described by Belfiore et al. [15]. Higher values of ISI indicate greater insulin sensitivity. Insulin sensitivity was also analyzed by homoeostasis model assessment (HOMA) [16].

3.6. Statistical analyses

These were performed with SPSS version 19 for Windows software (SPSS Inc., Chicago, IL, USA). Analytical data were expressed as means ± standard error of mean (SEM) and as medians and interquartile range (IQR). Differences between groups were assessed by Mann-Whitney U test. The overall effects of isoproterenol compared with the control were analyzed by the Wilcoxon test and repeated measures (RM) analysis of variance (Anova). The effect of isoproterenol was evaluated with paired t tests within subjects. For biochemical data, changes in concentration over time were assessed by RM Anova.

4. Results

4.1. Characteristics of subjects

Although the two test groups were matched for BMI, fat mass was greater in the low responders (8.1 and 11.2 kg vs 14.6 and 14.2 kg for males and females, respectively; Table 1; Fig. 1). HR, physical activity and occupational activity did not differ between groups (data not shown), and HR and BP remained unchanged during the course of the study (data not shown). The total number of first-degree relatives was similar in both groups (17 vs 18), but the score for family history events was higher in low responders.

4.2. Systemic responses

From baseline to intake of oral glucose, plasma glucose, insulin and TAG concentrations remained unchanged, whereas NEFA concentrations increased significantly in responders (from 538 ± 55 to 795 ± 61 μmol/L, + 48%; P = 0.004). Following glucose intake, plasma glucose increased; the increase in insulin concentrations was lower in responders (iAUC: 1.53 ± 0.15 vs 2.70 ± 0.71 μU/mL; P = 0.047); NEFAs and TAG decreased similarly in both groups to 50 ± 8 vs 81 ± 20 μmol/L and 0.38 ± 0.05 vs 0.64 ± 0.22 mmol/L, respectively, at time + 210 min (both not significant). Neither HOMA %S or %β
Table 1
Clinical and biochemical characteristics of responders and low responders, selected according to adipose tissue blood flow (ATBF) response to 75 g of glucose (> 50% from baseline or not, respectively).

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 5)</th>
<th>Low responders (n = 5)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>2/3</td>
<td>2/3</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 ± 3.4</td>
<td>37 ± 5.8</td>
<td>ns</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 ± 0.06</td>
<td>1.71 ± 0.02</td>
<td>ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.9 ± 5.9</td>
<td>64.6 ± 3.8</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.5 ± 0.7</td>
<td>22 ± 1</td>
<td>ns</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>70 ± 4</td>
<td>76 ± 4</td>
<td>ns</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.77 ± 0.05</td>
<td>0.81 ± 0.03</td>
<td>ns</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>113 ± 6/66 ± 7</td>
<td>114 ± 6/69 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>Four skinfolds (mm)</td>
<td>33.5 ± 4.2</td>
<td>52.2 ± 16.5</td>
<td>0.021</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>16.9 ± 2.8</td>
<td>22.7 ± 2.6</td>
<td>ns</td>
</tr>
<tr>
<td>Body fat (kg)</td>
<td>9.96 ± 1.57</td>
<td>14.38 ± 5.18</td>
<td>0.047</td>
</tr>
<tr>
<td>Lean body mass (%)</td>
<td>83 ± 3</td>
<td>77 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>51 ± 6</td>
<td>50 ± 4</td>
<td>ns</td>
</tr>
<tr>
<td>Family history (score)b</td>
<td>3</td>
<td>11</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5 ± 0.1</td>
<td>4.9 ± 0.2</td>
<td>ns</td>
</tr>
<tr>
<td>Plasma insulin (mU/L)</td>
<td>6.2 ± 0.7</td>
<td>9.7 ± 4.2</td>
<td>ns</td>
</tr>
<tr>
<td>Plasma TAG (mmol/L)</td>
<td>0.468 ± 0.40</td>
<td>0.914 ± 0.210</td>
<td>0.008</td>
</tr>
<tr>
<td>Plasma NEFA (µmol/L)</td>
<td>539 ± 55</td>
<td>549 ± 43</td>
<td>ns</td>
</tr>
<tr>
<td>HOMA IS%b</td>
<td>22.7 ± 2.1</td>
<td>33 ± 6.9</td>
<td>ns</td>
</tr>
<tr>
<td>HOMA %Sc</td>
<td>885 ± 116</td>
<td>627 ± 121</td>
<td>ns</td>
</tr>
<tr>
<td>ISIgly</td>
<td>1.15 ± 0.05</td>
<td>0.98 ± 0.14</td>
<td>ns</td>
</tr>
<tr>
<td>ISI NEFA</td>
<td>1.2 ± 0.08</td>
<td>0.97 ± 0.19</td>
<td>ns</td>
</tr>
</tbody>
</table>

* P: differences between groups (independent t test) for comparison of progression of isoproterenol effect.

Data are presented as means ± SEM. ns: not significant; TAG: triacylglycerol; ISIgly: glucose area under the curve (AUC) after oral glucose [15]; ISI NEFA: non-esterified fatty acid AUC after oral glucose [15]; conversion factors: glucose: 0.055; TAG: 0.011; NEFA: 0.039.

Fig. 3. Adipose tissue blood flow (ATBF) in response to local β-stimulation with three concentrations of isoproterenol (Iso) in responders (■) and low responders (□), using microinfusion followed by 75 g of oral glucose. Glucose (arrow) was given at time + 120 min. On the control side, saline was infused in responders (●) or low responders (○). Data are presented as means ± SEM.

(+ 2.6 ± 0.6 mL/min/100 g of tissue (P = 0.11) in responders, and +0.3 ± 0.2 mL/min/100 g of tissue (P = 0.60) in low responders (Fig. 3)).

During the stepwise increase in isoproterenol, ATBF quadrupled in responders, with a statistically significant rise from baseline that was observed even with the lowest isoproterenol concentration (10⁻⁸ M; Table 2). In the low responder group, a statistically significant increase from baseline was seen only at the highest dose.

There was a distinct difference in ATBF response to oral glucose between the two groups. The responders showed a 93% increase from the end-of-fast whereas the low responders exhibited a low increase (+5.0 ± 0.5 vs 0.4 ± 0.3 mL/min/100 g of tissue, respectively; P = 0.001). This response validated the initial group allocation, and also confirms the reproducibility of this physiological trait [1,10].

There was no further increase in blood flow after oral glucose on the isoproterenol-stimulated side, with both groups instead showing a lowering of ATBF after oral glucose intake (change from peak: −4.8 ± 2.6 in responders vs −1.7 ± 1.2 mL/min/100 g of tissue in low responders; P < 0.001).

5. Discussion

The present study reveals that ATBF responses to isoproterenol are dose-dependent in subjects with inherently high responses to oral glucose. Subjects with a low ATBF response to oral glucose failed to react to isoproterenol.

An earlier report [6] had already shown that postprandial enhancement of ATBF is controlled principally by the β-adrenergic system. Taken together with the present study, the overall interpretation of the results is that failure to respond...
with increased ATBF after glucose intake is dependent on tissue resistance to β-adrenergic stimulation.

Previous studies using β-adrenergic agonists to stimulate ATBF either through IV administration [8] or microdialysis [17] showed that ATBF responses are impaired in obese subjects, although it was not possible to determine whether such impairment of β-adrenergic stimulation is neural, humoral or both. As the effect of isoproterenol on ATBF is similar using either IV administration [8] or local delivery (as in the present study), the suggestion is that the β-adrenergic stimulation of ATBF is unlikely to be of humoral origin.

It has also been previously shown that insulin has no direct effect on ATBF regulation, thereby suggesting that the sympathetic nervous system (SNS), among other mechanisms, is the probable mediator of insulin action in the regulation of ATBF [5]. In mice, insulin modulates the sympathoadrenal response to hypoglycaemia via hypothalamic action [18]. In humans, insulin increases SNS activation [19,20]. However, SNS sensitivity to insulin is difficult to assess directly in humans. Nevertheless, it has been shown that insulin permeates the blood–brain barrier [21], and that neurons located in the hypothalamus are sensitive to glucose and insulin [22] and, thus, help to determine the level of sympathetic activation (and sensitivity to isoproterenol). This hypothesis is in agreement with several animal experiments [23] and consistent with the present results in our responders.

In contrast, in low responders, the absence of a nutrient- ingestion-induced increase in ATBF may arise from failure of the insulin–sympathetic axis at two levels. First, although no direct measure of whole-body insulin sensitivity was performed nor, for obvious reasons, of insulin sensitivity in subjects with respect to SNS regulation in the brain, it may be speculated that the SNS was centrally resistant to insulin [2]. Second, the adrenergic system shows substantial regional tissue differences in activity [24], and is subject to significant changes under pathological conditions such as obesity and hypertension [25] and, third, the adrenergic system may be locally non-responsive—and in other words, there could be some level of local sympathoresistance in adipose tissue.

Several mechanisms of adipose tissue resistance to adrenergic stimulation may be hypothesized. First, β-adrenoceptors may show down-regulated surface expression in response to repeated stimuli. Second, genetic variability at the β-adrenoceptor level is a possible mechanism. Several polymorphisms have been identified and characterized in the coding region of the human α- and β-adrenoceptors. Polymorphisms have been shown to confer altered vasconstrictive or vasodilator responses [26] and variable degrees of desensitization or responsiveness to agonists [27], which may modulate cardiovascular autonomic function [28]. Nevertheless, the genetic characterization of β-adrenoceptors has yet to be done in low responders. Finally, adipose tissue per se may also bring about resistance to adrenergic stimulation as a simple result of, for example, an expanded fat mass with increased distances between nerve terminals, vessels and adipocytes or an altered spectrum of cytokines. All these factors may influence adipose tissue sensitivity to normal/increased norepinephrine from either local nerve terminals and/or the systemic circulation [29]. On the other hand, an insufficient response to catecholamines may be associated with poorer catabolic sympathetic effects on adipose tissue and a worsened lipolytic capability. Interestingly, ATBF showed a trend to increase in high responders, although there was no difference between baseline and end-of-fast in low responders. Furthermore, a linear relationship was found between the increases in NEFA and ATBF between baseline and the end-of-fast (data not shown).

Low responders appeared to behave like obese subjects in some respects, with blunted ATBF responses to glucose and isoproterenol, higher fasting TAG concentrations and greater plasma insulin responses to oral glucose, although insulin resistance was not statistically confirmed by HOMA and ISI indices. It is also worth noting that low responders exhibited a greater hereditary burden of diabetes and cardiovascular disease. Thus, ATBF low responsiveness could be another facet of the MONW phenotype [30,31], which postulates that a subset of reasonably lean people can be ‘metabolically obese’ in the absence of obesity and also at risk of cardiometabolic diseases.

The postprandial decrease in ATBF, despite sustained high-dose isoproterenol stimulation and oral glucose load, was somewhat unexpected. There are several conceivable reasons for such a decrease [32–34]. Down-regulation has already been mentioned; another reasonable hypothesis is that ATBF has an upper limit depending on vessel-wall stiffness and elastic capacity. The highest blood flows ever observed in our laboratory were 23.6 mL/min/100 g of tissue after glucose load and 23.8 mL/min/100 g of tissue during isoproterenol microinfusion, thus suggesting the possibility that another as yet unknown counterbalancing system may come into play after pharmacological provocation.

6. Conclusion

ATBF responsiveness to glucose ingestion clearly differs between obese and lean subjects, but is nevertheless highly variable within the group of lean individuals. Several lines of evidence suggest that a vast portion of ATBF variance needs to be determined at the tissue level. The present study demonstrates the presence of resistance to adrenergic activation in the adipose tissue in subjects exhibiting lower basal ATBF such that it fails to increase appropriately in response to oral glucose stimulation. In spite of their normal weight, BMI, and other anthropometric values and calculations of insulin sensitivity, this group carries more subcutaneous fat, and displays subtle changes in fat and sugar metabolism. Thus, a perturbed ATBF might parallel the very early stages of obesity/adiposity, with β-adrenergic resistance as one of the possible mechanisms.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
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