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Original article

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

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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/m^2, respectively), gender (male/female: 2/3) and age (30 ± 3 vs 37 ± 6 years). Subcutaneous adipose tissue microinfusions of stepwise increasing doses of isoproterenol were performed with concomitant monitoring of blood flow, using the ^{133}Xenon 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.

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 hausse 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 ($20,5 \pm 0,7$ vs 22 ± 1 kg/m^2), le sexe (m/f : 2/3) et l'âge (30 ± 3 vs 37 ± 6 ans). De l'isoprotérénol 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 ^{133}Xenon *washout*.

Résultats. – L'IMC était similaire dans les deux groupes, mais la masse adipeuse ($9,9 \pm 1,6$ vs $14,4 \pm 1,6$ 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 ($5,4 \pm 1$ vs $3,4 \pm 1$ mL/min par 100 g de tissu) et répondait à l'augmentation des doses de l'isoprotérénol (10^{-8} M : $7,6 \pm 1,4$ vs $4,9 \pm 1$, 10^{-6} M : $12,5 \pm 1,7$ vs $7,5 \pm 1,6$ et 10^{-4} M : $20 \pm 1,7$ vs $9 \pm 0,9$ 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/m^2), 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.