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Impaired local microvascular vasodilatory effects of insulin and reduced skin microvascular vasomotion in obese women

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Abstract

Our study aim is to investigate whether obesity is characterized by an impairment of insulin-mediated vasodilatory effects and by a modification of basal vasomotion in the skin microvasculature. Forty healthy obese and forty healthy lean women were included. Microvascular effects of insulin as compared to a control substance were measured by cathodal iontophoresis combined with laser Doppler flowmetry. Vasomotion was examined by Fourier transform analyses of skin laser Doppler flow at rest. Locally administered insulin, as compared to the control substance, induced a microvascular vasodilatory response in lean (median (interquartile range): 31.6 (17.1–43.9) vs. 22.9 (16.4–36.7) perfusion units, $P=0.04$), but not in obese women (28.1 (14.4–47.1) vs. 27.5 (17.5–48.2) perfusion units, $P=0.7$). The relative insulin-induced increase in blood flow corrected for the control substance was higher in lean than obese women (ANOVA for repeated measures $F=3.93$, $P=0.05$). The contribution of the total frequency spectrum 0.01–1.6 Hz and of the frequency intervals 0.01–0.02 Hz and 0.02–0.06 Hz (representative of endothelial and neurogenic activity, respectively) to basal microvascular vasomotion was lower in obese than in lean women ($P<0.05$ for all). These findings show that obesity is characterized by an impaired direct microvascular vasodilatory effect of insulin and by decreased skin microvascular vasomotion in a way that is suggestive for alterations of endothelial and neurogenic activity.

Keywords: Insulin; Iontophoresis; Microcirculation; Vasodilation; Vasomotion; Obesity

Introduction

Obesity is associated with increased cardiovascular risk, which may, in part, be related to obesity-associated microvascular dysfunction (Agapitov et al., 2002; Clerk et al., 2006; de Jongh et al., 2004b). On the one hand, obesity-associated microvascular dysfunction may contribute directly to the development of diseases which are at least in part determined by microangiopathy, such as nephropathy and heart failure (de Jong et al., 2002; Kenchaiah et al., 2002). On the other hand, microvascular dysfunction has been proposed to contribute to the development of hypertension by increasing peripheral vascular resistance, and to the development of insulin resistance by limiting glucose and insulin delivery to muscle cells (Clark et al., 2003; de Jongh et al., 2004b; Levy et al., 2001; Serné et al., 1999, 2002).

There is increasing evidence that insulin can redirect blood flow from non-nutritive to nutritive microvessels resulting in enhanced access of glucose and insulin to muscle cells (Clark et al., 2003; de Jongh et al., 2004a; Serné et al., 2002). Impairment of these insulin-induced microvascular effects may contribute to obesity-associated insulin resistance (Clerk et al., 2006; de Jongh et al., 2004b; Wallis et al., 2002). Indeed, in lean individuals, hyperinsulinemia induces capillary recruitment in both skin and muscle, and concomitantly increases peripheral glucose uptake in muscle (Coggins et al., 2001; Serné et al., 2002), whereas these insulin-induced responses are blunted in obesity (Clerk et al., 2006; de Jongh et al., 2004b). However, these studies have

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applied systemic hyperinsulinemia and thus (part of) the observed effects may be secondary to systemic effects of insulin. In healthy lean individuals, however, insulin has been shown to have a direct vasodilatory effect on the skin microvasculature as assessed by cutaneous delivery of insulin by cathodal iontophoresis and simultaneous laser Doppler flowmetry (Rossi et al., 2005; Serné et al., 2002). Such data are not available in obese individuals. It is of interest to study whether such direct vasodilatory effects of insulin on the skin microvasculature are impaired in obesity. Several studies have suggested that the features of the skin microvasculature mirror the microvascular state in other vascular beds (de Jongh et al., 2004a; Rossi et al., 2006a; Serné et al., 2002; Stewart et al., 2004). Thus, impairments of insulin-induced effects on the skin microvasculature may represent a generalized microvascular feature and thereby may play a role in obesity-associated insulin resistance.

The rhythmic dilatation and contraction of arterioles, so-called vasomotion, is thought to be an important factor in the regulation of microvascular blood flow distribution (Parthimos et al., 1996). An optimal microvascular blood flow distribution may reduce microvascular resistance and ensure an adequate transport of oxygen, nutrients and waste products to and from the peripheral cells (Bertuglia et al., 1991; Intaglietta, 1991; Parthimos et al., 1996; Slaaf et al., 1988; Ursino et al., 1998). Frequency analysis of the laser Doppler signal allows the non-invasive assessment of the contribution of different mechanisms, such as endothelial, neurogenic or myogenic activity, to microvascular vasomotion (Kvernmo et al., 1999; Stefanovska et al., 1999). Previous studies have shown that patients with essential hypertension are characterized by post-ischemic impairments of microvascular vasomotion (Rossi et al., 2006a). In addition, in diabetic patients, the contribution of frequencies attributed to neurogenic activity to basal microvascular vasomotion was reduced (Bernardi et al., 1997; Lefrandt et al., 2003; Stansberry et al., 1996). Also, post-ischemic impairment of microvascular vasomotion in the leg skin is observed in peripheral arterial obstructive disease (Anvar et al., 2000). Analysis of microvascular vasomotion of the skin microvasculature has never been performed in obese subjects. In the present study we hypothesized that obesity is characterized by alterations in basal microvascular vasomotion and that these alterations may play a role in obesity-associated insulin resistance, hypertension and microangiopathy.

The aim of the present study, therefore, was to examine local and direct vasodilatory effects of insulin on the skin microvasculature and to study skin microvascular vasomotion in obese as compared to lean women.

Materials and methods

Study population

Forty healthy lean women (BMI <24 kg/m^2) and forty healthy obese women (BMI >30 kg/m^2) participated in this study. Characteristics of the lean and obese participants are presented in Table 1. All participants were Caucasian, non-smokers, non-diabetic (according to the ADA 1997 criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)) and normotensive (defined as a duplicate office measurement $<140/<90$ mm Hg). Participants did not use any medication except oral contraceptives (12 lean and 6 obese women). We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Informed consent was obtained from all participants. The study protocol was approved by the local Ethics Committee and performed to conform with the principles outlined in the Declaration of Helsinki.

Table 1
Baseline characteristics of both study groups

	Lean women ($n=40$)	Obese women ($n=40$)
Age (years)	39.1±9.4	40.1±6.6
Weight (kg)	63.1±6.1	104.6±16.4***
BMI (kg/m^2)	21.5±1.8	37.0±5.4***
Waist to hip ratio	0.77±0.09	0.87±0.08***
Systolic blood pressure (mm Hg)	113±13	125±16***
Diastolic blood pressure (mm Hg)	66±10	71±11*
Fasting cholesterol (mmol/l)	4.8±0.8	4.9±0.7
Fasting triglycerides (mmol/l)	0.9±0.4	1.2±0.5**
Fasting glucose (mmol/l)	4.7±0.4	5.1±0.5**

Data are expressed as mean±SD or median (interquartile range).
*$P<0.05$, **$P<0.01$ and ***$P<0.001$ obese vs. lean women.

Laser Doppler measurements

All measurements were performed in the fasting state in the morning in a quiet room with a controlled temperature between 22 and 24 °C. All participants had abstained from caffeine- and alcohol-containing drinks overnight. Measurements were started after a 20-min period for acclimatization and rest. Blood pressure was measured twice with an automated blood pressure device (PressMate BP-8800, Colin Co, Komaki-City, Japan). Microvascular measurements were performed in a sitting position with the investigated hand at heart level. Skin temperature was registered continuously and was above 30 °C at the start of all microvascular measurements. Skin blood flow was measured in conventional perfusion units (PU) by means of a laser Doppler system (Periflux 4000, Perimed, Stockholm, Sweden). Microvascular measurements were performed in a sequential order with one thermostatic laser Doppler probe (PF 481, Perimed, Stockholm, Sweden).

Insulin iontophoresis

All participants underwent iontophoresis of insulin (0.20 ml Velosulin 100 IE/ml; Novo Nordisk, Bagsværd, Denmark) and a control substance (0.20 ml diluting medium for soluble insulin injection; Novo Nordisk, Bagsværd, Denmark) in a double-blind randomized order. The diluting medium (control substance) had exactly the same composition as Velosulin, but did not contain insulin molecules. Therefore, any difference in skin blood flow response between the Velosulin and the control substance must be ascribed to a specific action of insulin. The first iontophoresis measurement was performed on the dorsal skin of the middle phalanx of the third finger of the dominant hand and the second measurement was performed on the same spot on the non-dominant hand. Insulin and the control substance were delivered with a cathodal current with 12 doses (0.20 mA for 20 s) with a 90-s interval between each dose (Serné et al., 2002) resulting in a incremental time–response curve of skin blood flow with a plateau phase during the final two deliveries. Baseline skin blood flow was recorded for 1 min before the start of the iontophoresis protocols. Peak skin blood flow was defined as the mean skin blood flow reached during the final two iontophoresis deliveries and relative increase in skin blood flow as the percentage change from baseline to peak skin blood flow. The response to insulin iontophoresis was corrected for the response to the control substance by subtracting the latter from the former.

Skin microvascular vasomotion

In order to perform vasomotion analyses skin blood flow was measured during 15 min with the laser Doppler probe positioned at the dorsal side of the