Insulin-mediated increases in renal plasma flow are impaired in insulin-resistant normal subjects

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Abstract

Background Impaired vasodilatation in skeletal muscle is a possible mechanism linking insulin resistance to blood pressure regulation. Increased renal vascular resistance has been demonstrated in the offspring of essential hypertensives. We assessed whether insulin-mediated renal vasodilatation is impaired in insulin-resistant normal subjects.

Design In two groups of 10 insulin-resistant and 10 insulin-sensitive normal subjects, we compared the effects of sequential physiological and supraphysiological insulin dosages (50 and 150 mU kg^{-1} h^{-1}) on renal plasma flow (RPF) and leg blood flow using the euglycaemic clamp technique, ^{131}I-labelled Hippuran clearances and venous occlusion plethysmography. Time-control experiments were performed in the same subjects.

Results Whole-body glucose uptake amounted to 4·9 ± 2·1 and 11·0 ± 2·4 mg $kg^{-1}min^{-1}$ in the insulin-resistant and to 12·7 ± 2·3 and 17·4 ± 2·6 mg $kg^{-1}min^{-1}$ in the insulin-sensitive subjects during physiological and supraphysiological hyperinsulinaemia, respectively. RPF increased more in insulin-sensitive compared to insulin-resistant subjects during physiological hyperinsulinaemia (13·7 vs. 6·8%, $P < 0·05$). RPF increased to comparable levels during supraphysiological hyperinsulinaemia. Insulin-mediated changes in leg blood flow did not differ between groups. In the combined group, we found a positive correlation between insulin-mediated glucose uptake and changes in RPF during physiological hyperinsulinaemia ($r = 0·57$, $P = 0·009$), whereas insulin-mediated glucose uptake correlated with changes in leg blood flow during supraphysiological hyperinsulinaemia ($r = 0·54$. $P = 0·017$).

Conclusions Our results suggest that the sensitivities of the skeletal muscle and renal vascular bed differ for insulin's vasodilatory action. Insulin-mediated increases in RPF are impaired in insulin-resistant but otherwise normal subjects during physiological hyperinsulinaemia.

Keywords Blood pressure, glucose, insulin, insulin resistance, leg blood flow, renal plasma flow

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Introduction

Despite extensive research, the relationship between insulin resistance and blood pressure regulation is still a matter of controversy. Impaired insulin-mediated vasodilatation has been proposed as a mechanism involved in this relationship [1,2]. Consistent with this hypothesis is the finding of reduced vasodilatation in skeletal muscle in essential hypertension [3], and other insulin-resistant states [4–6]. Moreover, in normal subjects inverse relations have been found between mean arterial blood pressure and insulin-stimulated blood flow in skeletal muscle [2,7]. Besides reduced vasodilatation in skeletal muscle, impaired insulin-mediated renal vasodilatation

may play a role in linking insulin resistance to blood pressure elevation. Renal vasoconstriction is considered as a primary renal defect responsible for blood pressure elevation [8]. In subjects with essential hypertension [9,10] and their normotensive offspring [11] reduced renal blood flow and increased renal vascular resistance can be demonstrated. Both groups are also characterized by insulin resistance [12–14]. Reduced insulin-mediated vasodilatation of the renal vasculature may therefore be instrumental in increasing renal vascular resistance.

Human studies on the effects of insulin on renal blood flow are sparse and their results contradictory. Whereas insulin increased renal plasma flow (RPF) in some studies [15–17], other studies could not confirm this [18–20]. These contradictory results may be explained in part by methodological differences and limitations. For instance, all negative studies lacked appropriate time-control experiments.

In the present study, we compared the vasodilatory effects of hyperinsulinaemia on the renal and skeletal muscle vascular bed between insulin-resistant and insulin-sensitive subjects, and, in contrast to earlier reports [15–20] also performed time-control studies. We assessed the effects both of physiological and supraphysiological hyperinsulinaemia because a relationship between insulin-mediated changes in leg blood flow and glucose uptake has especially been demonstrated during supraphysiological and/or sustained physiological hyperinsulinaemia [2,6], whereas the presence of such a relationship could be more relevant during acute physiological hyperinsulinaemia.

Methods

Subjects

It has been shown that roughly 25% of the normal population are as insulin resistant as subjects with impaired glucose tolerance or type II diabetes [21,22]. We recruited 20 healthy Caucasian volunteers from a larger group of 47 volunteers who underwent assessment of their insulin sensitivity [23]. Both the 10 subjects with the highest and the lowest insulin sensitivity were requested to participate in the present study.

For data analysis, the subjects were ranked according to their previously determined rate of whole-body glucose uptake into an insulin-resistant (IR) and an insulin-sensitive (IS) group (Table 1). All subjects were healthy as judged by medical history, were normotensive (blood

Table 1 Characteristics of the insulin-resistant (IR; $n = 10$) and insulin-sensitive (IS; $n = 10$) normal subjects

	IR	IS	P*
n (male/female).	10 (2/8)	10 (5/5)	
Age (years)	30 ± 15	34 ± 14	0·5
Height (cm)	171 ± 6	179 ± 10	0·12
Weight (kg)	74 ± 12	75 ± 13	0·9
Body mass index (kg m^{-2})	25·2 ± 3·3	23·2 ± 2·6	0·11
Waist-to-hip ratio	0·83 ± 0·10	0·79 ± 0·08	0·14
Total cholesterol (mmol L^{-1})	4·9 ± 1·1	4·4 ± 0·6	0·2
HDL cholesterol (mmol L^{-1})	1·2 ± 0·3	1·3 ± 0·4	0·4
LDL cholesterol (mmol L^{-1})	3·1 ± 0·8	2·6 ± 0·6	0·2
Triglycerides (mmol L^{-1})	1·3 ± 0·8	1·0 ± 0·4	0·3
Smokers (n)	0/10	1/10	0·9
Family history of hypertension (n)	5/10	3/10	0·7
Family history of NIDDM (n)	6/10	2/10	0·2
Fasting plasma glucose (mmol L^{-1})	4·3 ± 0·2	4·4 ± 0·3	0·6
M-value (mg kg^{-1} min^{-1})			
insulin 50	4·9 ± 2·1	10·3 ± 2·0	< 0·001
insulin 150, 45–90 min	11·0 ± 2·4	16·0 ± 3·2	< 0·01
insulin 150, 135–180 min	12·7 ± 2·3	17·4 ± 2·6	< 0·01
Plasma insulin (pmol L^{-1})†			
fasting	52 ± 29	33 ± 11	0·2
insulin 50	426 ± 133	413 ± 74	0·9
insulin 150, 45–90 min	1448 ± 455	1480 ± 123	0·8
insulin 150, 135–180 min	1557 ± 505	1626 ± 329	0·8

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes (type II).

Values are means ± SD; insulin 50 and insulin 150, insulin infusions in a dose of 50 and 150 mU kg^{-1} h^{-1}, respectively.

*For the comparison of the IR and IS subgroups, unpaired t-test for continuous variables, x^2 test for proportions.

†Data available in nine IR subjects because of haemolytic sera in one.

pressure less than 140/90 mmHg) and had a normal 75-g oral glucose tolerance test. They did not use medication. Informed consent was obtained from all subjects. The protocol had been approved by the local ethics committee, and the study was carried out in accordance with the Declaration of Helsinki.

Study design

After an overnight fast, all subjects came to the clinic at 08.00 h. They were given 10 mL of sodium perchlorate 4% before each study to block the thyroid gland. Two polytetrafluoroethylene cannulae (Venflon; Viggo, Helsinborg, Sweden) were inserted in forearm veins for intermittent blood sampling and infusions. After a baseline period of 90 min, there were three study periods of 90 min for insulin infusion. Because we performed clearance studies, the subjects were given 300 mL of water orally each hour, subtracted by the volume of glucose 20% solution given during the clamp, to ensure adequate diuresis.

Whole-body glucose uptake

The hyperinsulinaemic euglycaemic clamp technique was used to assess sensitivity to insulin-mediated glucose uptake, as described previously [24,25]. Insulin (Velosulin; Novo Nordisk, Bagsvaerd, Denmark) diluted to 50 mL with 45 mL of 0·9% saline and 5 mL of 20% human albumin, was infused in a primed, continuous manner at a rate of 50 mU kg^{-1} h^{-1} for 90 min, succeeded by an infusion rate of 150 mU kg^{-1} h^{-1} for 180 min. Normoglycaemia was maintained by adjusting the rate of a 20% D-glucose infusion based on frequent plasma glucose measurements with an automated glucose oxidase method (Yellow Springs Instruments, Yellow Springs, OH). As hepatic glucose production is completely suppressed in normal subjects at the insulin concentrations employed in the present study [26], whole-body glucose uptake (M-value, mg glucose kg^{-1} min^{-1}) was calculated from the glucose infusion rate during the last 45 min of each study period [27]. Blood samples for measurement of plasma insulin were drawn four times during these study periods. Plasma insulin concentrations were measured by immunoradiometric assay (Medgenix Diagnostics, Fleurus, Belgium).

Renal plasma flow measurements

RPF was measured using ^{131}I-labelled Hippuran (^{131}I-Hippuran), as described previously [28,29]. Briefly, a continuous infusion containing 100 mCi ^{131}I-Hippuran (Amersham Life Sciences, Amersham, UK) in 100 mL of saline was administered at a rate of 12 mL h^{-1}, after a priming dose of 20 mCi ^{131}I-Hippuran had been given. After a stabilization period of 90 min, each 45 min blood samples were drawn for measurement of ^{131}I-Hippuran. The counts of ^{131}I-Hippuran in plasma and diluted infusion solution (1 : 100) were determined in duplicate using a well-type scintillation counter (1282 Compu-Gamma, LKB Wallac, Turku, Finland). RPF was calculated as the plasma clearance of ^{131}I-Hippuran by using the formula $[(I \times V)/P]$, where I is counts per minute (c.p.m.) per mL of the infusion solution, V is volume of the infusion in mL min^{-1}, and P is c.p.m. per mL of plasma. The intra-individual day-to-day coefficient of variation is 5·0% [28].

Renal vascular resistance was calculated as the ratio of mean arterial blood pressure to RPF and expressed as resistance units.

Leg blood flow and systemic haemodynamics

Skeletal muscle blood flow was measured in the calf by venous occlusion plethysmography using mercury-in-silastic strain gauges [6,30]. Each value given for measurement of leg blood flow (mL min^{-1} dL^{-1}) represents the average of seven to 10 separate recordings. The intra-individual coefficient of variation for repeated measurements of leg blood flow on the same day amounts to 14% [6]. Systolic and diastolic blood pressure and heart rate were measured using a semi-continuous blood pressure-measuring device (Nippon Colin BP 103 N Sphygmomanometer, Hayashi, Komaki-City, Japan). Five measurements were performed during each period of measurement. Leg vascular resistance was calculated as the ratio of mean arterial blood pressure to leg blood flow and expressed as resistance units.

Mean arterial blood pressure was calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure. Haemodynamic measurements were performed during the last 45 min of each study period.

Time-control studies

On separate days, approximately 4 weeks after the insulin clamp experiment had been performed, a time-control experiment was carried out in an identical fashion with infusion of the same amount of solvent, including the intravenous saline load, and with blood sampling at the same time intervals. Control experiments were performed after the insulin clamp experiments because we could not determine beforehand the amount of 20% glucose to be infused each hour to maintain euglycaemia. To adjust for any (nonspecific) change in haemodynamic variables due to volume expansion as the result of 20% glucose infusion to maintain euglycaemia during the insulin infusion experiment, a corresponding amount of water was given orally each hour. Control experiments enabled us to adjust for nonspecific changes in the variables under evaluation, unrelated to insulin infusion.

Statistical analysis

Between-group differences in mean values were analysed with the unpaired Student's t-test (for continuous variables) or x^2 test (for proportions). All variables were analysed by the method of analysis of variance (ANOVA) for repeated measurements to detect differences over time and between the studies, followed by paired t-tests. To avoid bias caused by nonspecific treatment effects on the variables under evaluation, the measurements during the control experiments were subtracted from the corresponding measurements obtained during each intervention before statistical analysis was performed [31,32]. Likewise, to aid interpretation of the relative magnitude of changes in different parameters in the figures, the percentage change from baseline during each study was calculated and the percentage change during the time-control study was subtracted from the percentage change after insulin. Correlation analysis was applied when appropriate. Partial correlation was used to adjust the correlation between insulin sensitivity and changes in renal plasma flow for body mass index, waist-to-hip ratio and changes in blood pressure. A value of $P < 0.05$ was considered to be significant. Data are expressed as means ± SD unless stated otherwise.

Results

Subject characteristics and insulin sensitivity variables

The characteristics of the IR and IS subjects are provided in Table 1. As expected, the IR group tended to have a higher body mass index and waist-to-hip ratio than the IS group. However, anthropometric data and serum lipids did not differ between the groups.

During the euglycaemic clamp, normoglycaemia ($4\cdot4 \pm 0\cdot3$ mmol L^{-1}) was maintained. The coefficients of variation of the blood glucose level during infusion of 50 mU insulin kg^{-1} h^{-1} was $7\cdot7 \pm 2\cdot7\%$ in the IR subjects and $6\cdot8 \pm 2\cdot6\%$ in the IS subjects, and during infusion of 150 mU insulin kg^{-1} h^{-1} were $8\cdot5 \pm 2\cdot8$ and $8\cdot5 \pm 3\cdot4\%$, respectively. By definition, the whole-body glucose uptake (M-value) was clearly different between the IR and IS groups at all periods of measurement. Plasma insulin levels, both fasting and during insulin infusion, did not differ between groups.

The baseline data of mean arterial blood pressure and leg blood flow were similar in the IR and IS subjects, while basal heart rate was higher ($P = 0\cdot03$) in the IR group (Table 2). Baseline data of RPF did not differ between the groups ($P = 0\cdot4$; Fig. 1).

Effects of insulin on renal plasma flow

During the time-control studies, RPF decreased slightly in both groups, but these changes reached significance only in the IS group (Fig. 1). In contrast, RPF increased significantly during physiological insulin infusion in both groups and showed a further increase during the supraphysiological insulin infusion.

The percentage changes in RPF, corrected for time-control studies, in both groups are depicted in Fig. 2. During physiological insulin infusion, the percentage increase in RPF in the IS group exceeded the percentage increase in the IR group: $13\cdot7$ and $6\cdot8\%$, respectively ($P = 0\cdot035$). This difference persisted when changes in RPF were analysed as absolute values. During supraphysiological hyperinsulinaemia, maximal increases in RPF were similar in both groups, approximately 25% above baseline values. Thus, the curve of the increase in RPF in the IR subjects was shifted to the right in comparison to the IS subjects. Renal vascular resistance decreased to a similar degree in both groups (Table 2).

Effects of insulin on leg blood flow and systemic haemodynamics

The changes in leg blood flow and systemic haemodynamics are given in Table 2.

Leg blood flow increased in both groups during insulin infusion. However, comparison of the percentage changes in leg blood flow between the groups showed a different pattern than that observed for changes in RPF (Fig. 2). Increases in leg blood flow were similar in the IR and IS group during physiological hyperinsulinaemia. However, leg blood flow tended to increase more in the IS group than the IR group during supraphysiological hyperinsulinaemia, albeit not significantly. Leg vascular resistance showed a significant decrease in the IS group only (Table 2).

Mean arterial blood pressure showed a slight decline in the IR group, but not the IS group. Heart rate and leg blood flow gradually increased in the course of the insulin infusion period in both groups.

Additional correlation analysis

Additional correlation analysis in the combined group ($n = 20$) showed a significant correlation between whole body glucose uptake and changes in RPF during physiological hyperinsulinaemia ($r = 0\cdot57$, $P = 0\cdot009$; Fig. 3) which was lost during supraphysiological hyperinsulinaemia.

To assess the role of insulin, correlation analysis was performed between plasma insulin levels and changes in RPF and leg blood flow during physiological and supraphysiological hyperinsulinaemia. These analyses did not yield any significant correlation.

To assess a potential confounding role of body composition and of blood pressure decline in the IR subjects during insulin infusion, we also performed partial correlation analyses. The relationship between whole body

Table 2 Absolute changes in systemic haemodynamics and vascular resistances during insulin infusion after adjustment for time-control studies in insulin-resistant (IR; *n* = 10) and insulin-sensitive (IS; *n* = 10) normal subjects

		Baseline	Ins 50 45–90 min	Ins 150 45–90 min	Ins 150 135–180 min
MAP (mmHg)					
IR	insulin	85 ± 11	− 7 ± 6*	− 3 ± 5	− 6 ± 6*
	control	82 ± 10			
IS	insulin	87 ± 10	0 ± 5	− 2 ± 5	− 3 ± 8
	control	86 ± 8			
HR (beats min⁻¹)					
IR	insulin	64 ± 10	+ 3 ± 6	+ 4 ± 8	+ 5 ± 5**
	control	63 ± 8			
IS	insulin	54 ± 10	+ 4 ± 6	+ 4 ± 5*	+ 6 ± 6*
	control	53 ± 9			
LBF (mL min⁻¹ dL⁻¹)					
IR	insulin	2·11 ± 0·58	+ 0·75 ± 1·03	+ 1·01 ± 1·00*	+ 0·95 ± 0·92*
	control	2·19 ± 0·92			
IS	insulin	1·75 ± 0·62	+ 0·59 ± 0·84	+ 1·08 ± 0·67***	+ 1·42 ± 0·83***
	control	2·00 ± 0·84			
LVR (units)					
IR	insulin	43·8 ± 17·0	− 14·9 ± 23·8	− 19·5 ± 18·7	− 15·9 ± 25·7
	control	43·6 ± 18·7			
IS	insulin	55·4 ± 20·7	− 9·2 ± 21·4	− 16·6 ± 17·3*	− 18·8 ± 19·7*
	control	52·8 ± 31·9			
RVR (units)					
IR	insulin	16·7 ± 2·8	− 2·2 ± 2·1**	− 3·2 ± 1·6***	− 4·6 ± 2·0***
	control	15·0 ± 2·6			
IS	insulin	16·1 ± 4·5	− 2·2 ± 2·4*	− 3·7 ± 2·4***	− 3·8 ± 2·8**
	control	15·6 ± 4·4			

Values are expressed as means ± SD. Ins 50 and Ins 150 indicate insulin infusion in a dose of dose of 50 and 150 mU kg⁻¹ h⁻¹, and the period of measurement during insulin infusion.

MAP, mean arterial blood pressure; HR, heart rate; LBF, leg blood flow; LVR, leg vascular resistance; RVR, renal vascular resistance. Significant changes during each period of measurement over baseline values are indicated by $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

glucose uptake and changes in RPF during physiological hyperinsulinaemia persisted after controlling for body mass index and waist-to-hip ratio ($r = 0.57$, $P = 0.01$ and $r = 0.62$, $P = 0.005$, respectively). Remarkably, partial correlation analysis between whole body glucose uptake and changes in RPF controlling for changes in mean arterial blood pressure was highly significant ($r = 0.70$, $P = 0.001$).

At the end of the supraphysiological insulin infusion, insulin-mediated glucose uptake showed a significant correlation with changes in leg blood flow ($r = 0.54$, $P = 0.017$; Fig. 3).
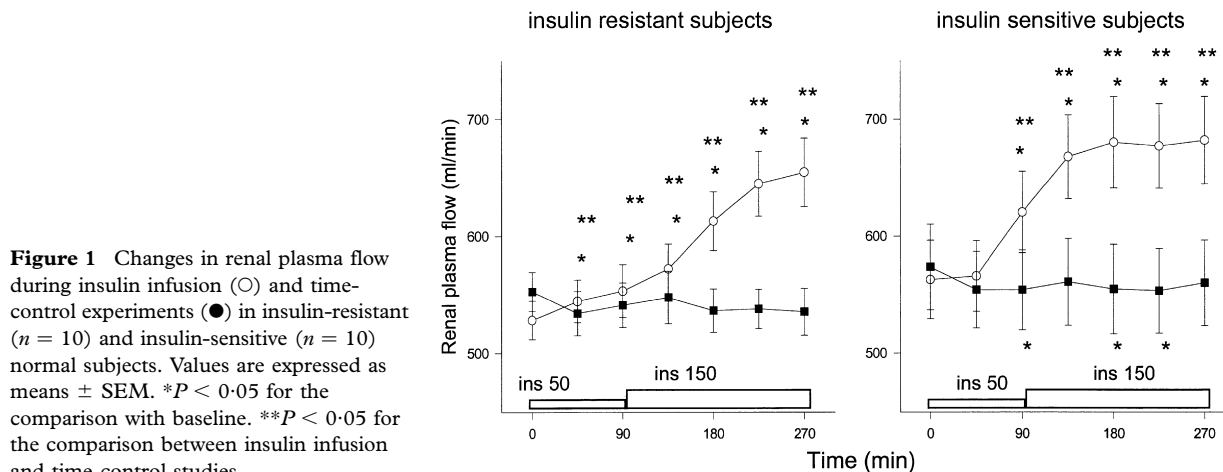

Figure 1 Changes in renal plasma flow during insulin infusion (○) and time-control experiments (●) in insulin-resistant (*n* = 10) and insulin-sensitive (*n* = 10) normal subjects. Values are expressed as means ± SEM. $*P < 0.05$ for the comparison with baseline. $**P < 0.05$ for the comparison between insulin infusion and time-control studies.
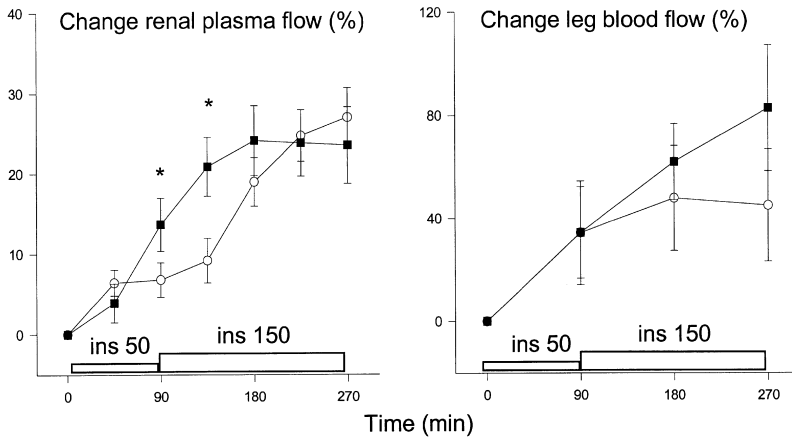
Figure 2 Percentage changes in renal plasma flow and leg blood flow during two sequential doses of insulin (50 and 150 mU kg^{-1} h^{-1}) in insulin-resistant (○, $n = 10$) and insulin-sensitive (●, $n = 10$) normal subjects. Values are expressed as means ± SEM. *$P < 0.05$ for the comparison between both groups of subjects.

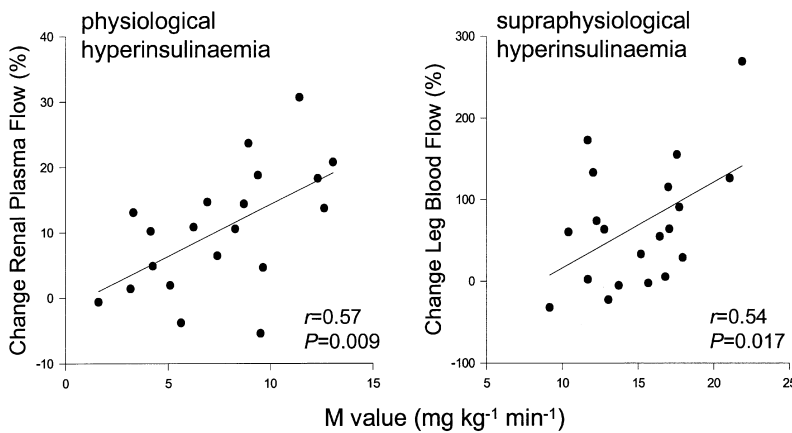**Figure 3** Scatterplots showing the relationship between the rate of insulin-mediated glucose uptake (*M*-value) and percentage changes in renal plasma flow during physiological hyperinsulinaemia, and leg blood flow during supraphysiological hyperinsulinaemia in 20 normal subjects.

Discussion

The present study clearly demonstrates that exogenously administered insulin increases RPF in normal subjects. More interestingly, during physiological hyperinsulinaemia, RPF increased more in IS than in IR but otherwise normal subjects. During supraphysiological hyperinsulinaemia, RPF showed a similar increase in both groups. In contrast, insulin-mediated increases in leg blood flow were similar in both groups during physiological hyperinsulinaemia but leg blood flow tended to increase more in the IS than the IR group during supraphysiological hyperinsulinaemia.

So far, a stimulating effect of insulin on muscle blood flow has been widely appreciated but a stimulating effect on RPF has been more controversial. Our study is the first to demonstrate in humans that acute physiological hyperinsulinaemia increases RPF in both IR and IS normal subjects. The discrepant outcome of previous human studies [15–20] assessing the effect of insulin on RPF can be explained by several factors. Most important, these studies lacked appropriate time-control experiments and administered insulin over a shorter period [15–20], whereas it has been recognized that insulin's stimulating effect on blood flow is both time- and dose-dependent [6,33]. The importance of performing time-control

experiments is illustrated by the observation that RPF decreased slightly during our time-control studies, reaching significance only in the insulin sensitive group.

Our results suggest that insulin-mediated renal vasodilatation is impaired in IR subjects during physiological hyperinsulinaemia. The curves of the insulin-mediated changes in RPF in IS and IR subjects showed a remarkable resemblance to the previously reported dose–response curves of leg blood flow by Laakso et al. [4]. They showed that leg blood flow increased in a sigmoidal fashion in both lean and obese subjects as a function of insulin concentration [4]. In addition, they observed a rightward shift of the dose–response curve in the obese, IR subjects [4]. In both their study and ours, the insulin infusion rate was increased sequentially. Therefore, it cannot be excluded that the different pattern of insulin-mediated increases in blood flow between IR and IS subjects predominantly reflects time-dependent instead of dose-dependent effects of insulin.

One could argue that the observation of a different effect of insulin on RPF between the IR and IS group refers to only a few measurements. Nevertheless, additional correlation analysis also showed a clear correlation between insulin-mediated glucose uptake and changes in RPF during physiological hyperinsulinaemia. Mean arterial blood pressure declined in the IR subjects, in analogy to

the blood pressure decline observed in type 2 diabetics during acute supraphysiological hyperinsulinaemia [32]. However, the decline in blood pressure during insulin infusion could not explain the impaired renal vasodilatation in the IR subjects either, because the correlation between insulin-mediated glucose uptake and insulin-mediated changes in RPF even gained significance after adjustment for the changes in mean arterial blood pressure.

Impaired insulin-mediated vasodilatation could link insulin resistance to blood pressure elevation in the long term if it interferes with the renal–body fluid feedback mechanism for pressure control and, thus, affects the setting of the pressure natriuresis curve [34]. The notion that impaired insulin-mediated vasodilatation may shift the setting of the pressure natriuresis curve is consistent with the concept that an increased renal vascular resistance may reset the pressure natriuresis curve to higher levels [35,36].

In addition to differences in insulin's vasodilatory effects between IR and IS subjects, the present study also suggests that insulin's action can be different in various vascular beds. Insulin increased RPF during physiological hyperinsulinaemia, but leg blood flow increased only during supraphysiological hyperinsulinaemia. Besides, differences in blood flow changes between IR and IS subjects could only be detected for RPF. We suggest that these observations reflect a different sensitivity of the renal and muscular vascular bed for insulin's vasodilatory action. By analogy, a higher sensitivity of the renal than the muscular vascular bed is a well-known characteristic of angiotensin II [37].

The similar increase in leg blood flow in the IS and IR subjects during the 1·5-h long physiological insulin infusion is consistent with most previous observations [38]. In contrast, a correlation between insulin-mediated glucose uptake and insulin-induced changes in leg blood flow has previously been demonstrated during supraphysiological, and during more prolonged physiological hyperinsulinaemia [2,6]. In the present study, we have also observed such a correlation in the course of the insulin infusion ($r = 0·54$, $P = 0·017$). Therefore, the lack of difference in leg blood flow changes during supraphysiological hyperinsulinaemia between the IR and IS groups most likely reflects a type II error.

It is interesting to speculate on the mechanisms underlying the relationship between insulin-mediated glucose uptake and insulin-mediated increases in leg blood flow and RPF. The design of the study does not allow attribution of causality to the associations reported. Therefore, it is unclear whether the relationship between insulin's effects on glucose uptake and blood flow is causal, consequential, or merely coincidental. Local metabolism has been recognized as an important determinant of blood flow in skeletal muscle [39]. The importance of renal glucose metabolism has been emphasized more recently [40]. In the postabsorptive state, the human kidney accounts for, respectively, 20 and 27% of whole body glucose uptake and production [41]. Moreover,

physiological hyperinsulinaemia in dogs stimulates renal glucose metabolism by approximately 75% [42]. The relatively small increase in RPF in the present study can hardly account for such insulin-induced changes in renal glucose uptake. In contrast, it is tempting to speculate that renal glucose metabolism affects RPF.

Alternatively, insulin-induced increases in RPF could also be due to direct vasodilatory properties of insulin. It has been shown that insulin-mediated vasodilatation in renal vessels is nitric oxide dependent [43,44]. A common factor by which insulin could affect both glucose uptake and renal blood flow could be the stimulating of glucose transport mechanisms. The expression of insulin-sensitive glucose transporters in renal preglomerular vessels suggests that they could regulate renal vascular function in addition to glucose uptake [45].

Finally, other neurohumoral systems may be involved in mediating insulin's effects, such as the sympathetic nervous system and the renin–angiotensin–aldosterone system. Involvement of renal nerves in mediating insulin's effect on blood pressure regulation has been suggested by the prevention of hyperinsulinaemia-induced hypertension during renal denervation [46]. In analogy, involvement of the renin–angiotensin–aldosterone system has been suggested by the prevention of hyperinsulinaemia-induced hypertension during angiotensin-converting enzyme inhibition and angiotensin II receptor antagonism [47,48].

To conclude, insulin's stimulatory effect on blood flow differs between the skeletal muscle and renal vascular bed and between IR and IS normal subjects. Most importantly, increases in RPF were impaired in IR compared to IS normal subjects during exogenous hyperinsulinaemia. The potential role and relevance of impaired insulin-mediated renal vasodilatation as a link between insulin resistance and blood pressure regulation remains to be established.

Acknowledgements

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