Adapting to insulin resistance in obesity: role of insulin secretion and clearance

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Abstract

Aims/hypothesis The aim of this study was to quantify the relative contributions of increased insulin secretion rate (ISR) and decreased insulin clearance rate (ICR) in the compensatory hyperinsulinaemia characteristic of insulin-resistant individuals without diabetes.

Methods Obese (BMI ≥ 30 kg/m²) individuals without diabetes ($n = 91$) were identified from a registry of volunteers. Volunteers underwent the following measurements: oral glucose tolerance; insulin resistance (steady-state plasma glucose [SSPG] concentration during the insulin suppression test [IST]); ISR (using the graded glucose infusion test [GGIT]); and ICR (using the IST and GGIT). Participants were stratified into tertiles based on SSPG concentration: SSPG-1 (insulin-sensitive); SSPG-2 (intermediate); and SSPG-3 (insulin-resistant).

Results There were no differences in BMI and waist circumference among the SSPG tertiles. Serum alanine aminotransferase concentrations were higher in the SSPG-2 and SSPG-3 groups compared with the SSPG-1 group ($p = 0.02$). Following an oral glucose challenge, there was a progressive increase in the total integrated insulin response from the most insulin-sensitive to the most insulin-resistant tertiles ($p < 0.001$). Following intravenous glucose, the SSPG-3 group had significantly greater integrated glucose (median [interquartile range], 32.9 [30.8–36.3] mmol/l $\times$ h) and insulin responses (1711 [1476–2223] mmol/l $\times$ h) compared with the SSPG-1 group (30.3 [28.8–32.9] mmol/l $\times$ h, $p = 0.04$, and 851 [600–1057] pmol/l $\times$ h, $p < 0.001$, respectively). Furthermore, only the SSPG-3 group had significant changes in both ISR and ICR ($p < 0.001$). In the SSPG-2 group, only the ICR was significantly decreased compared with the SSPG-1 group. Therefore, ICR progressively declined during the IST with increasing insulin resistance (SSPG-1, 0.48 [0.41–0.59]; SSPG-2, 0.43 [0.39–0.50]; SSPG-3, 0.34 [0.31–0.40]).

Conclusions/interpretation While both increases in ISR and decreases in ICR compensate for insulin resistance, decreases in ICR may provide the first adaptation to decreased insulin sensitivity.

Keywords Hyperinsulinaemia · Insulin clearance rate · Insulin resistance · Insulin secretion rate · Obesity

Abbreviations

ALT Alanine aminotransferase
G-AUC Area under the curve for glucose

GGIT Graded glucose infusion test
I-AUC Area under the curve for insulin
ICR Insulin clearance rate
ICR_{en} Endogenous insulin clearance rate
ICR_{ex} Exogenous insulin clearance rate
ISR Insulin secretion rate
IST Insulin suppression test
SSPG Steady-state plasma glucose
SSPI Steady-state plasma insulin

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Introduction

Currently, the pathogenesis of type 2 diabetes is thought to involve the failure of pancreatic beta cells to secrete sufficient insulin to satisfy demand in the context of obesity and/or

increased insulin resistance [1]. While this hypothesis is widely accepted, an increase in the insulin secretion rate (ISR) is not the only adaptation to insulin resistance. Decreases in the insulin clearance rate (ICR) also help to maintain hyperinsulinaemia in insulin-resistant states [2]. However, the relative roles of increases in ISR vs decreases in ICR in maintaining hyperinsulinaemia and glucose tolerance in insulin resistance are unclear.

The aim of this study was to better understand the physiological adaptations to insulin resistance prior to the development of type 2 diabetes in a sample of 91 obese individuals who have had direct measurements of insulin resistance using the insulin suppression test (IST). We compared glucose tolerance, ISR and ICR in equally obese individuals with varying degrees of insulin sensitivity.

Methods

The study population consisted of 91 individuals who had previously responded to an advertisement seeking volunteers for research studies on the role of insulin resistance in human disease. All individuals were apparently healthy without coronary, kidney or liver disease. The Stanford Institutional Review Board approved all studies and all participants provided informed consent.

We identified 152 individuals in our ongoing registry of participants who had undergone an OGTT, IST and graded glucose infusion test (GGIT). For the current study, we included individuals with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$, $n = 96$). Five additional individuals were excluded for having 2 h glucose $\geq 11 \text{ mmol/l}$ [3]. Therefore, 91 participants were included in the final sample.

The study population was stratified into tertiles based on their degree of insulin resistance as defined by their steady-state plasma glucose (SSPG) concentration during the IST as described below.

IST Peripheral insulin resistance was directly measured with the modified version of the IST [4]. Measures of insulin action with the IST are highly correlated ($r \geq 0.87$) with those obtained with the hyperinsulinaemic–euglycaemic clamp [5, 6]. In brief, after an overnight fast, an intravenous catheter was placed in each of the participants' arms. One arm was used for the administration of a 180 min infusion of octreotide ($0.27 \text{ mg m}^{-2} \text{ min}^{-1}$), insulin ($32 \text{ mU m}^{-2} \text{ min}^{-1}$) and glucose ($267 \text{ mg m}^{-2} \text{ min}^{-1}$); the other arm was used for collecting blood samples. Blood was drawn at 10 min intervals from 150 min to 180 min of the infusion to determine the SSPG and steady-state plasma insulin (SSPI) concentrations. Under these conditions SSPI concentration was comparable for all participants and the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; the higher the SSPG concentration, the greater the degree of insulin

resistance. Based on the SSPG concentrations, the population was divided into tertiles: insulin-sensitive (SSPG-1); intermediate (SSPG-2); and insulin-resistant (SSPG-3).

OGTT All participants underwent a 75 g OGTT in which plasma glucose and insulin concentrations were measured before and 30, 60, 120 and 180 min after the glucose challenge. The AUCs for glucose (G-AUC) and insulin (I-AUC) were calculated using the trapezoidal method.

GGIT All participants received graded intravenous infusions of glucose at progressively increasing rates (1, 2, 3, 4, 6 and $8 \text{ mg kg}^{-1} \text{ min}^{-1}$) as previously described [2, 7–9]. Each glucose infusion rate was administered for a total of 40 min. Glucose, insulin and C-peptide concentrations were measured at 0, 30, 40, 70, 80, 110, 120, 150, 160, 190, 200, 230 and 240 min. The last two glucose and insulin values at the end of each 40 min infusion period (e.g. 30 and 40 min values) were averaged and used as the mean for that infusion.

Measurement of ISR ISRs were derived by deconvolution covering 240 min and 13 sampling time points for peripheral plasma C-peptide concentrations, using a two-compartment model of C-peptide kinetics and standard variables for C-peptide clearance estimated for each participant based on body surface area and age [9]. Previously, we have also used 25 sampling time points [2, 7, 8]. In a subset of 14 individuals, we found no significant differences in ISR using 13 vs 25 sampling time points (S. H. Kim, unpublished data). For each participant, the mean ISR before and during the six glucose infusion periods was plotted against the corresponding mean glucose to construct a dose–response relationship. The beta cell sensitivity represented the slope of the line relating glucose and ISR.

Measurement of ICR ICR was calculated during the IST and GGIT. During the IST, ICR was calculated by dividing the insulin infusion rate by the SSPI concentration [10, 11]. As octreotide is infused to inhibit endogenous insulin secretion, ICR during the IST represents exogenous ICR (ICR_{ex}). During the GGIT, ICR was calculated by using the following formula:

$$\frac{\text{ISR-AUC}}{\text{I-AUC}} - \left(\frac{V \times I(t240) - I(t0)}{\text{I-AUC}} \right).$$

The AUCs for ISR and insulin were calculated using the trapezoidal method. V refers to volume of distribution of insulin, which was estimated as 0.14 l/kg [12]. I refers to insulin concentration at time (t) 0 min and 240 min.

Metabolic measurements Glucose was determined by the oxidase method (Analyzer 2; Beckman, Brea, CA, USA). Insulin and C-peptide concentrations were measured at Washington University (St Louis, MO, USA) using radioimmunoassay (Millipore, St Charles, MO, USA). The inter- and intra-assay coefficient of variation ranged between 4.7% and 9.7% for insulin, and 5.2% and 10.9% for C-peptide. Creatinine and alanine aminotransferase (ALT) were measured in the clinical laboratory at Stanford Health Care (Stanford, CA, USA).

Statistical analysis Statistical analysis was performed using SPSS (version 23 for Windows; SPSS, Armonk, NY, USA). Data are reported as mean $\pm$ SD or median (interquartile range). Non-parametric variables were log-transformed prior to analyses. Comparisons among groups were made using one-way ANOVA. A probability value of <0.05 was considered to be statistically significant in all analyses.

Results

Table 1 presents the demographic and clinical characteristics of the study population stratified into tertiles based on degree of insulin resistance (SSPG concentration). By selection, magnitude of insulin resistance increased progressively from the least (SSPG-1) to the most insulin-resistant tertile (SSPG-3). Despite the dramatic differences in SSPG concentration, the three groups were otherwise well matched and did not differ in age, sex distribution, race/ethnicity, BMI, waist circumference or fasting plasma glucose concentration. However, ALT concentrations were significantly higher and creatinine concentration was lower in the two most insulin-resistant groups (SSPG-2 and SSPG-3).

Plasma glucose and insulin concentrations following the oral glucose challenge are shown in Fig. 1. The total area under the glucose response curves (G-AUC) of the three groups are illustrated in Fig. 1a. The three groups were significantly different ($p = 0.001$), with the G-AUC of the most insulin-resistant tertile (SSPG-3) being significantly higher than the other two groups ($p < 0.05$). The insulin responses (I-AUC) of the three SSPG groups to oral glucose (Fig. 1b) separated more dramatically ($p < 0.001$) and I-AUC increased progressively from the most insulin-sensitive to the most insulin-resistant tertile.

Figure 2 presents the changes in plasma glucose and insulin concentrations and ISR in response to the graded glucose infusion in the three SSPG groups. The quantitative comparisons between the three groups are shown in Table 2. Plasma glucose concentrations increased modestly in all three groups (Fig. 2a), with the G-AUC being significant higher in the most insulin-resistant group (SSPG-3) compared with the most insulin-sensitive group (SSPG-1). The changes in insulin concentration and ISR (Fig. 2b, c) in response to the intravenous glucose infusion were more pronounced in the most insulin-resistant tertile (SSPG-3), and the AUCs were significantly greater in this group than in the other two groups.

The changes in ICR, as measured during the GGIT and IST, are illustrated in Fig. 3. During the GGIT, endogenous ICR (ICR_{en}) differed among the three groups ($p < 0.001$). In contrast to insulin concentration and ISR, ICR_{en} progressively decreased from the most insulin-sensitive to the most insulin-resistant tertiles (Fig. 3a). That is, ICR_{en} was significantly lower in SSPG-2 vs SSPG-1 ($p = 0.03$) and SSPG-3 vs SSPG-2 ($p = 0.003$). The results were similar when ICR_{ex} was calculated during the IST (Fig. 3b). Thus, ICR_{ex} was highest in the SSPG-1 group, intermediate in the SSPG-2 group and

Table 1 Characteristics of obese individuals (BMI ≥ 30 kg/m²) by SSPG tertile

	SSPG-1 (<9.7 mmol/l)	SSPG-2 (9.7 – 12.7 mmol/l)	SSPG-3 (≥ 12.8 mmol/l)	<i>p</i> value
<i>n</i>	30	31	30	
SSPG, mmol/l	7.2 ± 2.0	$11.3 \pm 0.9^{a,b}$	$14.3 \pm 1.2^{b,c}$	<0.001
Age, years	54.3 ± 9.2	54.1 ± 10.5	52.8 ± 9.7	0.82
Female sex, <i>n</i> (%)	21 (70)	20 (65)	18 (60)	0.71
Non-Hispanic white, <i>n</i> (%)	24 (80)	20 (65)	18 (60)	0.21
BMI, kg/m ²	33.7 ± 2.3	33.7 ± 2.4	33.8 ± 2.2	0.99
Waist circumference, cm	110.7 ± 7.5	110.3 ± 8.8	110.6 ± 9.0	0.98
Fasting glucose, mmol/l	5.8 ± 0.5	5.8 ± 0.5	6.0 ± 0.4	0.11
ALT, U/l	36 ± 14	45 ± 14^a	48 ± 26^c	0.02
Creatinine, μ mol/l	88.4 ± 17.7	79.6 ± 17.7^a	79.6 ± 17.7	0.04

Data are presented as mean $\pm$ SD or *n* (%)

^a Significant difference between tertile 1 and 2

^b Significant difference between tertile 2 and 3

^c Significant difference between tertile 1 and 3

Fig. 1 (a) Glucose and (b) insulin concentrations during the OGTT are shown for the SSPG-1 (white circles), SSPG-2 (black triangles) and SSPG-3 (black squares) groups. G-AUC and I-AUC significantly differed among the three SSPG groups ($p \leq 0.001$). The most insulin-resistant group (SSPG-3) had the highest G-AUC and I-AUC. Data are means $\pm$ SEM

lowest in the SSPG-3 group (all pairwise comparisons were significant, $p < 0.05$).

Finally, the relationship between the plasma glucose concentration and ISR were compared among the three SSPG groups. As shown in Fig. 4, the curve in the most insulin-resistant group (SSPG-3) shifted upward and to the left. Thus, the individuals in the SSPG-3 group had significantly higher beta cell sensitivity to glucose (Table 2) and secreted more insulin at any given plasma glucose concentration compared with the other more insulin-sensitive groups.

Discussion

The aim of the current analysis was to understand how obese individuals adapt to the demands of insulin resistance prior to the development of type 2 diabetes. By evaluating equally obese individuals with varying degrees of insulin sensitivity, we were able to define the relative contributions of ISR and ICR in maintaining hyperinsulinaemia as the magnitude of

insulin resistance increased. The most novel finding was seen in the group with intermediate insulin resistance (SSPG-2), who had a significant decrease in ICR but no change in ISR compared with the insulin-sensitive group (SSPG-1). The most insulin-resistant group (SSPG-3) had a significant decrease in ICR and an increase in ISR compared with the insulin-sensitive group. This suggests that the first compensation for insulin resistance is a decrease in ICR, which occurs prior to any significant increase in ISR.

Prior studies have shown significant differences in ISR and ICR in insulin-resistant vs insulin-sensitive groups [2, 13–15]. In the majority of these studies [13–15], degree of obesity and not direct measurement of insulin resistance was used to identify individuals as insulin-resistant vs insulin-sensitive. This is problematic as we have recently shown that obesity itself can increase ISR [16]. Furthermore, we have previously used the IST to identify non-obese insulin-sensitive and insulin-resistant individuals [2]. Similar to the comparisons between the SSPG-3 and SSPG-1 groups in the present study, we found significant increases in ISR and decreases in ICR in insulin-

Fig. 2 (a) Glucose, (b) insulin and (c) ISR during the GGIT are shown for the SSPG-1 (white circles), SSPG-2 (black triangles) and SSPG-3 (black squares) groups. The G-AUC ($p = 0.04$), I-AUC ($p < 0.001$) and ISR-AUC ($p < 0.001$) differed among the groups, using ANOVA. The most insulin-resistant group (SSPG-3) had the highest G-AUC, I-AUC and ISR-AUC. In post hoc analysis, there were no significant differences between the SSPG-1 and SSPG-2 groups. Data are means $\pm$ SEM

Table 2 Quantitative results of the GGIT by SSPG tertile

	SSPG-1 (<9.7 mmol/l)	SSPG-2 (9.7–12.7 mmol/l)	SSPG-3 (≥12.8 mmol/l)	<i>p</i> value
<i>n</i>	30	31	30	
G-AUC _(0–4h) (mmol/l×h)	30.3 (28.8–32.9)	32.8 (29.0–33.8)	32.9 (30.8–36.3) ^c	0.04
I-AUC _(0–4h) (pmol/l×h)	851 (600–1057)	945 (689–1277) ^b	1711 (1476–2223) ^{b,c}	<0.001
ISR-AUC _(0–4h) (pmol/min×h)	1929 (1625–2365)	1912 (1471–2489) ^b	2744 (2426–3681) ^{b,c}	<0.001
Beta cell sensitivity (pmol/min×mmol/l)	124 (87–187)	115 (59–173) ^b	171 (118–242) ^b	0.01

Data are presented as median (interquartile range)

^a Significant difference between tertile 1 and 2

^b Significant difference between tertile 2 and 3

^c Significant difference between tertile 1 and 3

resistant individuals compared with insulin-sensitive individuals. However, since these comparisons were performed in dichotomous groups, insulin-resistant vs insulin-sensitive, the results did not permit an evaluation of the potential importance of differences in magnitude of insulin resistance.

By comparing the three SSPG groups, our study demonstrates the importance of ICR in adapting to the demands of insulin resistance, as it appears to occur prior to a significant increase in ISR. While we are unaware of other human studies demonstrating the early role of ICR in insulin resistance, a

longitudinal study in dogs demonstrated the relevance of ICR in maintaining hyperinsulinaemia in insulin resistance [17]. The dogs were fat-fed for 12 weeks and had a significant increase in fasting hyperinsulinaemia and insulin resistance. ISR transiently increased at 6 weeks but returned to baseline at 12 weeks. At the end of the study, hyperinsulinaemia was maintained due to a significant decrease in ICR. The authors speculated that a decrease in insulin catabolism may help ‘rest’ the beta cells in the face of chronic insulin resistance. As our study was cross-sectional, we cannot comment on the dynamic changes in ISR and ICR as insulin resistance develops. However, it is clear that ICR plays an important and early role in maintaining hyperinsulinaemia in insulin resistance.

The mechanism for the decrease in ICR in insulin resistance remains unclear but could relate to an increase in hepatic lipid associated with insulin resistance [18]. The liver is the major site for insulin degradation [19] and hepatic steatosis has been shown to correlate negatively with ICR [20]. Consistent with this possibility are the findings of similarly elevated ALT concentrations in the SSPG-2 and SSPG-3 groups compared with the most insulin-sensitive group (SSPG-1).

Although ICR is important in maintaining hyperinsulinaemia in insulin resistance, the decrease in ICR is apparently not sufficient compensation in the most insulin-resistant tertile (SSPG-3), whose SSPG concentration was double that of the most insulin-sensitive tertile (SSPG-1). In these people, the hyperinsulinaemia is the result of both a decrease in ICR and an increase in ISR. Interestingly, the glucose concentration was also significantly, albeit modestly, increased in the SSPG-3 group compared with the SSPG-1 group. The modest increase in blood glucose is likely to have a direct effect on pancreatic beta cell insulin synthesis and secretion [21]. In support, beta cell sensitivity to glucose was significantly increased in the SSPG-3 group, as demonstrated by the upward shift in the ISR curve in Fig. 4.

Based upon our findings, we propose the following overall hypothesis to describe the adaptation to insulin resistance in obesity prior to the development of type 2 diabetes. A relative modest degree of insulin resistance is associated with an

Fig. 3 ICR_{en} and ICR_{ex} are shown for the SSPG-1, SSPG-2 and SSPG-3 groups during the (a) GGIT and (b) IST. Both measures of ICR progressively declined from SSPG-1 to SSPG-3. All pairwise comparisons were significantly different (*p* < 0.05). Data are means ± SEM

Fig. 4 The relationship between glucose and ISR is shown for the SSPG-1 (white circles), SSPG-2 (black triangles) and SSPG-3 (black squares) groups. The curve, representing beta cell sensitivity to glucose, was shifted up and to the left in the most insulin-resistant group (SSPG-3) compared with the other two groups ($p = 0.01$). Data are means $\pm$ SEM

increase in hepatic fat content, leading to a decrease in ICR and, based on the findings shown in Fig. 1, an increase in plasma insulin concentrations sufficient to maintain euglycaemia. However, the decrease in ICR is not sufficient compensation in the most insulin-resistant tertile (SSPG-3); in these people, hyperinsulinaemia is the result of both a decrease in ICR and an increase in ISR.

There are limitations to our study. First, the data were cross-sectional, derived from prior experimental studies, and selected to include only obese individuals. Furthermore, despite the fact that overall (BMI) and abdominal (waist circumference) obesity of the three groups were essentially identical (Table 1), the analysis lacks direct measurements of regional fat distribution. Thus, the conclusion that the relationships among insulin resistance, plasma insulin concentration, ISR and ICR discerned in the analysis are independent of differences in adiposity should be tempered. Furthermore, we used a modified protocol for sampling blood (13 vs 25), which may have affected calculation of ISR and ICR. Nevertheless, the qualitative results for ICR were similar to calculations based on the IST. Finally, we did not measure hormones, in particular incretin hormones, which also play significant roles in postprandial glucose and insulin modulation [22]. Differences in incretin hormones may also explain the differences in plasma insulin concentration during the OGTT among the three groups compared with during the GGIT. Despite these shortcomings, we are unaware of published specific quantitative measurements of insulin resistance, ISR and ICR in obese, apparently healthy individuals over a wide range of insulin resistance. As such, our findings provide a coherent view demonstrating the relative changes in ICR and ISR with increases in insulin resistance. While changes in both ISR and ICR occur, decreases in ICR may provide the first adaptation to decreased insulin sensitivity.

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Data availability The datasets analysed during the current study are not publicly available for reasons of privacy. Anonymous data is available from the corresponding author on reasonable request.

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