Possible role of alpha cell insulin resistance in exaggerated glucagon responses to arginine in type 2 diabetes

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Running Title: α-cell insulin resistance in type 2 diabetes

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Abstract

OBJECTIVE—Inappropriate excessive secretion of glucagon, which contributes to postprandial hyperglycemia, is a novel target for the treatment of diabetes. In this study, we sought to determine the factors associated with exaggerated glucagon secretion in response to an arginine challenge in patients with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS—Changes in circulating C-peptide immunoreactivity (CPR) and immunoreactive glucagon (IRG) after an arginine challenge were investigated in 35 patients with type 1 diabetes, 130 patients with type 2 diabetes, and 35 non-diabetic control subjects.

RESULTS—No significant differences were found in the basal level and the area under the concentration–time curve (AUC) of IRG (AUCIRG) among type 1 and type 2 diabetic patients and non-diabetic subjects. However, the correlation between the AUCIRG and the AUC of CPR (AUCCPR) was inverse between type 1 (r = –0.388, P = 0.023) and type 2 diabetic patients (r = 0.396, P < 0.0001), whereas AUCIRG was not correlated with AUCCPR in non-diabetic subjects (r = -0.079, P = 0.655). In type 1 diabetic patients, the AUCCPR decreased and the AUCIRG increased with increasing disease duration. In type 2 diabetic patients, both AUCIRG and AUCCPR increased with increasing BMI, basal CPR level, and homeostatic model assessment of insulin resistance (HOMA-IR) value.

CONCLUSIONS—Our findings suggest that the pathophysiology of the exaggerated glucagon response differs between the types of diabetes. Intra-islet insulin deficiency and alpha cell insulin resistance may be the primary contributors to this condition in type 1 and type 2 diabetes, respectively.
Diabetes is associated with increased hepatic glucose production, which is linked to fasting and postprandial hyperglycemia (1). This is caused by the reduced suppression of glucagon (2) along with the impairment of insulin secretion and insulin action. Arginine-stimulated hyperglucagonemia in patients with various forms of diabetes was first discovered by Unger et al. (3; 4). Their results demonstrated that excess glucagon or an elevated ratio of glucagon to insulin is etiologically important in the development of endogenous hyperglycemia in diabetes mellitus, through the mediation of glucose overproduction from the liver (2; 5-7). Thus, glucagon and its receptor have been examined extensively in recent years as being potential targets for the treatment of diabetes (8; 9). In fact, glucagon-like peptide-1 (GLP-1) analogs, which are forthcoming antidiabetic agents, lower postprandial hyperglycemia partly by inhibiting excessive secretion of glucagon in not only type 2 but also type 1 diabetes (10). An absolute deficiency in insulin secretion has been suggested to cause an exaggerated response of glucagon to arginine in patients with diabetes (11; 12). Insulin replacement therapy can correct this deficiency in patients with type 1 diabetes (11; 12) but not in those with type 2 diabetes (11). The pathophysiology associated with an exaggerated glucagon response to arginine remains unclear, particularly in patients with type 2 diabetes.

Here, we comprehensively analyzed factors associated with the exaggerated glucagon secretion response to an arginine challenge in patients with diabetes and showed that the glucagon response to arginine reflects distinctly different pathophysiology in type 1 versus type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

Subjects
The subjects were 223 Japanese patients with diabetes mellitus hospitalized in the Division of Endocrinology and Metabolism, Kanazawa University Hospital (Ishikawa, Japan) for the management of diabetes and patient education. The study was conducted from April 2003 to May 2006. Patients were diagnosed according to the criteria established by an expert committee on the diagnosis and classification of diabetes mellitus (13). Type 1 diabetes was determined based on the presence of islet autoantibodies (anti-GAD antibody). In addition, all type 2 diabetic patients met the requirements for insulin therapy as defined by the American Diabetes Association (ADA). Among the 36 patients with type 1 diabetes, we excluded one patient with Wilson’s disease (Supplemental Fig. 1 available at http://care.diabetesjournals.org). Among the 187 patients with type 2 diabetes, we excluded 57 patients with secondary diabetes related to conditions including liver disease, pancreatic disease, and hormonal disorders (Supplemental Fig. 1). Thus, 35 patients with type 1 diabetes and 130 with type 2 diabetes were enrolled in this study. Additionally, 35 non-diabetic healthy volunteers were enrolled as control subjects. The characteristics of the study subjects are shown in Table 1. Of those with type 1 diabetes, 26 patients were diagnosed with an acute onset form, and nine were diagnosed with slowly progressive insulin-dependent diabetes mellitus (SPIDDM) (14). Informed consent was obtained from all patients prior to study initiation. The study was approved by the relevant ethics committee and was conducted in accordance with the Declaration of Helsinki.

On admission, the patients received a standard diet of 30 kcal/kg. All patients with type 1 diabetes were treated with intensive insulin therapy. Among the patients with type 2 diabetes, 78 were treated with insulin (57 with pre-meal dosing of a rapid-acting insulin analog alone), 32 were treated with oral
antidiabetic agents (14 with glucosidase inhibitors, 16 with nateglinide, 4 with metformin, and 5 with sulfonylureas), and 20 received diet therapy alone.

Arginine stimulation test
After an overnight fast, patients were kept at rest for ≥30 min, and endogenous insulin and glucagon levels, as measured by C-peptide immunoreactivity (CPR) in serum and immunoreactive glucagon (IRG) in plasma, respectively, were assessed at preloading baseline (0 min). Arginine (30 g) was administered by intravenous infusion of an L-arginine hydrochloride 10% solution over 30 min. Blood was collected at seven time points: preloading (0 min), and 15, 30, 45, 60, 90, and 120 min after arginine loading. Circulating IRG and CPR were measured at each time point and were used to construct the arginine-stimulated time–response curves. The values of the area under the concentration–time curve for IRG (AUC IRG) and CPR (AUC CPR) between time 0 and 120 min were calculated by means of the trapezoidal and indicate the insulin- and glucagon-secreting responses to arginine. The homeostasis model assessment (HOMA-IR) method (15) and quantitative insulin sensitivity index (QUICKI) (16) were used as conventional indices for insulin resistance. The values for HOMA-IR and QUICKI were calculated using the following formulas: HOMA-IR = [(fasting insulin (µU/ml) × fasting plasma glucose (mmol/l))/22.5; and QUICKI = 1/[log(fasting plasma glucose (µU/ml)) + log(fasting insulin (mmol/l))]
The immunoenzymometric assays used for quantifying C-peptide and insulin were performed using kits purchased from Tosoh Corp. (Shunan, Japan). Plasma glucagon levels were measured using a radioimmunoassay kit (Daiichi, Daiichi Radioisotope Labs., Tokyo, Japan). The lower limits of quantification for CPR and IRG were 0.2 ng/ml and 15.6 pg/ml, respectively. The intra- and inter-assay coefficients of variation were all <6%. Glucose and HbA1c (A1C) were measured by standard methods.

Statistical analysis
The data are expressed as means ± SD. Statistical analyses were performed with StatView software (SAS Institute, Cary, NC). Differences among groups were tested by analysis of variance with a post hoc test of Fisher’s protected least significant differences. Pearson’s product moment correlation coefficients were obtained to estimate linear correlation among the variables. A P < 0.05 was considered statistically significant.

RESULTS
Responses of insulin and glucagon to arginine challenge in patients with type 1 and type 2 diabetes and non-diabetic subjects
Responses of CPR and glucagon to arginine are shown in Fig. 1. Type 2 diabetic patients and non-diabetic subjects had relatively high levels of basal CPR and AUC CPR, compared with type 1 diabetic patients (Fig. 1). Interestingly, the mean glucagon response did not differ among the three treatment groups (i.e., type 1, type 2, and control). However, some type 1 or type 2 diabetic patients exhibited an exaggerated glucagon response to arginine.

Distinct relationship between AUC IRG and AUC CPR in patients with type 1 versus type 2 diabetes
To address the pathophysiology underlying the exaggerated glucagon response to an arginine challenge, we examined the relationship between AUC IRG and AUC CPR in type 1 and type 2 diabetic patients and in non-diabetic control subjects (Fig. 2). In patients with type 1 diabetes, AUC IRG was negatively correlated with AUC CPR (Fig. 2A; AUC IRG = 32.462 – 17.8 AUC CPR, r = -0.388, P = 0.023). In contrast, AUC IRG was positively correlated with AUC CPR in type 2
$\alpha$-cell insulin resistance in type 2 diabetes

Diabetic patients (Fig. 2B; $\text{AUC}_{\text{IRG}} = 19,419 + 18.8 \text{ AUC}_{\text{CPR}}$, $r = 0.396$, $P < 0.0001$). No correlation was found between $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ in non-diabetic subjects (Fig. 2C; $\text{AUC}_{\text{IRG}} = 30,803 - 4.7 \text{ AUC}_{\text{CPR}}$, $r = -0.079$, $P = 0.655$). These results suggest that the mechanisms involved in the glucagon response to arginine challenge are distinctly different between type 1 and type 2 diabetic patients.

The relationship between $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ stratified by the class of diabetic duration in patients with type 1 diabetes Intra-islet insulin deficiency may determine the exaggerated glucagon response to arginine challenge (17). To test our hypothesis that type 1 diabetic patients with a longer history after the onset of diabetes are deficient in insulin secretory capacity, we analyzed the relationship between the $\text{AUC}_{\text{IRG}}$ or $\text{AUC}_{\text{CPR}}$ and diabetic duration in type 1 diabetic patients (Table 2 and Supplemental Fig. 2A) and further investigated the correlation between $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ stratified by the class of diabetic duration, i.e., 0–72 months and 96–348 months (Supplemental Fig. 2B). The patients with SPIDDM were excluded from this analysis because the onset of diabetes seemed to be unclear. As the diabetic duration increased, $\text{AUC}_{\text{CPR}}$ decreased and $\text{AUC}_{\text{IRG}}$ increased in type 1 diabetic patients (Table 2 and Supplemental Fig. 2). This relationship was not evident in patients with type 2 diabetes (data not shown). These findings suggest that intra-islet insulin deficiency with long disease duration determine the exaggerated glucagon response to arginine challenge in patients with type 1 diabetes.

To rule out possible influences of insulin treatment on the glucagon response to arginine in type 1 diabetic patients, we analyzed the relationship of the $\text{AUC}_{\text{IRG}}$ or $\text{AUC}_{\text{CPR}}$ to insulin dose (Supplemental Fig. 3) and glycemic control indices such as A1C and fasting plasma glucose (Table 2 and Supplemental Fig. 4). We found that neither the $\text{AUC}_{\text{IRG}}$ nor $\text{AUC}_{\text{CPR}}$ was correlated with either insulin dose or glycemic control status, and thus exogenous insulin replacement therapy and glycemic control status were unlikely to affect our results and conclusions in patients with type 1 diabetes.

The relationship between $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ stratified by the class of BMI and insulin resistance indices in patients with type 2 diabetes

Previous studies have suggested that the glucagon response to arginine is inversely related to insulin sensitivity (18–21). To test the hypothesis that obese type 2 diabetic patients have impaired insulin sensitivity, hyperinsulinemia, and hyperglucagonemia, we analyzed the relationship between the $\text{AUC}_{\text{IRG}}$ or $\text{AUC}_{\text{CPR}}$ and insulin resistance indices such as BMI, basal CPR level, HOMA-IR, and QUICKI in patients with type 2 diabetes (Table 2 and Supplemental Fig 5A). Both the $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ were positively correlated with BMI, basal CPR level, and HOMA-IR, and both were negatively correlated with QUICKI. No significant correlation was found between the $\text{AUC}_{\text{IRG}}$ and any of the insulin resistance indices in either patients with type 1 diabetes (Table 2 and Supplemental Fig. 6) or non-diabetic subjects (Table 2 and Supplemental Fig. 7). We further analyzed the relationship between the $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ stratified by BMI class, basal CPR level, HOMA-IR, and QUICKI (Supplemental Fig. 5B). Both the $\text{AUC}_{\text{IRG}}$ and $\text{AUC}_{\text{CPR}}$ significantly increased in relation to increases in BMI, basal CPR level, and HOMA-IR in patients with type 2 diabetes, whereas both significantly decreased with increases in QUICKI. In contrast, neither glycemic control status (Table 2 and Supplemental Fig. 8) nor treatment (Supplemental Fig. 9) affected the $\text{AUC}_{\text{IRG}}$ in type 2 diabetic patients. These
results suggest that insulin resistance contributes to the exaggerated glucagon response to arginine in patients with type 2 diabetes but not in those with type 1 diabetes or in non-diabetic subjects.

CONCLUSIONS

The arginine stimulation test has been demonstrated to be a valid method for evaluating residual beta cell function even during periods of hyperglycemia (3; 4; 22-24). However, the relevance of the glucagon response to arginine remains uncertain and has not yet been comprehensively analyzed in patients with type 1 and type 2 diabetes. In the present study, we revealed the pathophysiology of the glucagon secretion response to an arginine challenge in patients with diabetes. Although no difference was observed in the glucagon response between patients with type 1 and type 2 diabetes, the glucagon response reflected a distinct pathophysiology in each type of diabetes. In patients with type 1 diabetes, AUCIRG was inversely correlated with AUCCPR in the arginine challenge test, and the insulin response to arginine was inversely correlated with diabetic duration, suggesting that intra-islet insulin deficiency determines the exaggerated glucagon response to arginine. Autoimmune type 1 diabetes is caused by a beta cell-targeted immune reaction and destruction with relatively conserved alpha cell mass (25). Therefore, the glucagon response to arginine cannot be suppressed by intrinsic insulin in hypoinsulinemic diabetic patients (12). Conversely, in patients with type 2 diabetes, the AUCCPR, but not the AUCIRG, was negatively correlated with diabetic duration (data not shown). In addition, patients with insulinopenic type 2 diabetes did not exhibit an exaggerated glucagon response to arginine (Fig. 2B). Based on these findings, we hypothesize that only absolute insulin deficiency, as observed in type 1 diabetes, is associated with an exaggerated glucagon response. These results are in agreement with a previous study that suggested absolute deficiencies in insulin secretion as the cause of an exaggerated glucagon response to arginine in patients with diabetes (11; 12). In addition, insulin replacement therapy can correct these deficiencies in patients with type 1 diabetes (11; 12). The molecular mechanism underlying this observation may involve the suppression of glucagon release by intra-islet insulin via the GABA-GABA<sub>A</sub> receptor system (26). Given that some patients displayed no C-peptide response and a relatively conserved glucagon response to arginine in the present study, it is possible that other currently unknown factors may also regulate glucagon and CPR responses to arginine.

In hyperinsulinemic patients with impaired glucose tolerance or type 2 diabetes, the glucagon response to arginine was reported to be inversely related to insulin sensitivity (19-21). In these studies, however, it remained unclear whether the exaggerated glucagon response to arginine was caused by intra-islet insulin deficiency or alpha cell insulin resistance. In the present study, we demonstrated a positive correlation between AUCCPR and AUCCPR in type 2 diabetes, which was opposite the relationship in type 1 diabetes. The exaggerated glucagon response to arginine was also related to insulin resistance. The mean AUCCPR values increased with increases in BMI and insulin resistance indices, suggesting that beta cell hypertrophy associated with obesity might determine the exaggerated glucagon secretion in response to arginine in patients with type 2 diabetes. This pathology was not evident in patients with type 1 diabetes. Thus, we speculate that alpha cell insulin resistance may be a key pathology causing the exaggerated glucagon response to arginine in patients with type 2 diabetes. In this regard, Hamaguchi et al. (18) previously reported that
an exaggerated alpha cell response to arginine infusion in obese hyperinsulinemic patients with glucose intolerance was secondary to a reduction in insulin action on the pancreatic alpha cell. In addition, they observed that exogenous insulin replacement normalized these abnormalities (18), suggesting that compensatory hyperinsulinemia can overcome alpha cell insulin resistance. However, we did not observe such compensation in type 2 diabetic patients with severe hyperinsulinemia (Fig. 2B). Our results are in agreement with a previous report that insulin replacement cannot correct an exaggerated glucagon response in patients with type 2 diabetes (11). These findings further support the hypothesis that alpha cell insulin resistance occurs with increasing systemic insulin resistance in patients with type 2 diabetes.

In summary, intra-islet insulin deficiency and alpha cell insulin resistance may cause exaggerated glucagon secretion in response to arginine, which might in turn contribute to impaired suppression of hepatic glucose output in both type 1 and type 2 diabetes. Collectively, our data support the idea that exaggerated secretion of glucagon may be a therapeutic target in both insulinopenic diabetes and type 2 diabetes with insulin resistance. Therefore, the arginine challenge test could be useful for assessing the heterogenous nature of diabetes and may be a valid method for identifying responders to therapy targeted at glucagon and its receptor, such as GLP-1 analogs. Large-scale clinical studies are needed to test this hypothesis.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, see: http://www.textcheck.com/cgi-bin/certificate.cgi?id=6uXXML
References

1. Consoli A: Role of liver in pathophysiology of NIDDM. *Diabetes Care* 15:430-441, 1992
Table 1. Characteristics of the study subjects with type 1 and type 2 diabetes and non-diabetic subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1 Diabetic Patients</th>
<th>Type 2 Diabetic Patients</th>
<th>Non-diabetic Subjects</th>
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<tr>
<td>n</td>
<td>35</td>
<td>130</td>
<td>35</td>
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<tr>
<td>Acute/SPIDDM</td>
<td>26/9</td>
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<td>Sex (men/women)</td>
<td>14/21</td>
<td>81/49</td>
<td>15/20</td>
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<tr>
<td>Age (years)</td>
<td>49 ± 15</td>
<td>57 ± 13 *</td>
<td>33 ± 6 **</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.4 ± 4.3</td>
<td>23.8 ± 3.6</td>
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<td>Diabetes duration (months)</td>
<td>99.4 ± 92.5</td>
<td>123.9 ± 142.8</td>
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<td>A1C (%)</td>
<td>9.7 ± 2.8</td>
<td>8.9 ± 2.6</td>
<td>5.0 ± 0.4 ***</td>
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<td>Urinary C-peptide (mg/day)</td>
<td>9.9 ± 13.0</td>
<td>43.4 ± 42.1 *</td>
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<td>Therapy (Insulin/ODA/Diet therapy alone)</td>
<td>35/0/0</td>
<td>78/34/20</td>
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</table>

SPIDDM, slowly progressive insulin-dependent diabetes mellitus; ODA, oral antidiabetic agent. Data are shown as number (n) or means ± SD. *P < 0.01 vs. type 1 diabetic patients, **P < 0.01 vs. type 2 diabetic patients.
Table 2. The relationship between AUCIRG or AUCCPR and clinical parameters in type 1 and type 2 diabetic patients and non-diabetic control subjects

<table>
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<tr>
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<th>Diabetic duration</th>
<th>BMI</th>
<th>Basal CPR</th>
<th>HOMA-IR</th>
<th>QUICKI</th>
<th>A1C</th>
<th>FPG</th>
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<tr>
<td>AUC&lt;sub&gt;IRD&lt;/sub&gt;</td>
<td>r 0.445</td>
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<td></td>
<td>P 0.033</td>
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<td>0.024</td>
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<td><strong>Type 2 Diabetic Patients</strong></td>
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<tr>
<td>AUC&lt;sub&gt;CPR&lt;/sub&gt;</td>
<td>r -0.174</td>
<td>0.467</td>
<td>0.269</td>
<td>0.361</td>
<td>-0.319</td>
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<td></td>
<td>P 0.057</td>
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<td>0.851</td>
<td>0.502</td>
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|                      | r -0.477         | 0.359 | 0.938     | ND      | ND     | -0.194 | -0.137|
|                      | P 0.021          | 0.047 | <0.001    | ND      | ND     | 0.323  | 0.447|

|                      | r -0.260         | 0.455 | 0.844     | 0.343   | -0.385 | -0.204 | -0.155|
|                      | P 0.005          | <0.001 | 0.002    | 0.001   | 0.089  | 0.173 |

HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity index; FPG, fasting plasma glucose; ND, not determined.
Figure Legends

**Figure 1.** The IRG and CPR response curve to arginine. The glucagon responses were similar among type 1 and type 2 diabetic patients and non-diabetic control subjects, whereas the CPR responses of type 2 diabetic patients and control subjects were greater than that of type 1 diabetic patients. Data are shown as mean values; error bars denote SD. NS, not significant.

**Figure 2.** The relationship between AUC\textsubscript{IRG} and AUC\textsubscript{CPR} in patients with type 1 diabetes (A), type 2 diabetes (B), and non-diabetic control subjects (C). AUC\textsubscript{IRG} was negatively correlated with AUC\textsubscript{CPR} in type 1 diabetic patients ($r = -0.388$, $P = 0.023$), whereas AUC\textsubscript{IRG} was positively correlated with AUC\textsubscript{CPR} in type 2 diabetic patients ($r = 0.396$, $P < 0.0001$). In the control group, AUC\textsubscript{IRG} was not correlated with AUC\textsubscript{CPR} ($r = -0.079$, $P = 0.655$).
Fig. 1

α-cell insulin resistance in type 2 diabetes
Fig. 2

AUC_{IRG} = 32,462 - 17.8 \ AUC_{CPR} \\
\ r = -0.388 \\
\ P = 0.023

AUC_{IRG} = 19,418 + 18.8 \ AUC_{CPR} \\
\ r = 0.396 \\
\ P < 0.0001

AUC_{IRG} = 30,803 - 4.7 \ AUC_{CPR} \\
\ r = -0.079 \\
\ P = 0.655