Acute effects of hydrocortisone on the metabolic response to a glucose load: 

increase in first-phase insulin secretion

Running title: Acute metabolic effects of hydrocortisone

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ABSTRACT

Background and aim: Several basic science studies support the existence of non-genomic glucocorticoid signaling in pancreas, liver and adipocytes, but their clinical relevance has not yet been elucidated. This study aimed at investigating the rapid effects of hydrocortisone on the human metabolic response to glucose.

Subjects and methods: Ten healthy men received in a randomized placebo-controlled crossover study once an intravenous bolus of 0.6 mg/kg hydrocortisone and once placebo four minutes before the administration of 330 mg/kg glucose. Cortisol, glucose, insulin, C-peptide, ghrelin and peptide YY (PYY) were measured during the following 3 hours. Minimal model analysis was performed for evaluating the metabolic response.

Results: Hydrocortisone attenuated the rise in plasma glucose during the initial 15 minutes following glucose administration (P=0.039) and led to lower glucose levels during the first 2 hours (P=0.017). This was accompanied by enhanced circulating insulin (P=0.02) and C-peptide levels (P=0.03) during the initial 15 minutes, and a 35% increase in the first-phase beta cell function (P=0.003). Hydrocortisone decreased PYY concentrations during the initial 30 minutes (P=0.014), but did not affect the ghrelin response to glucose.

Conclusion: One intravenous bolus of hydrocortisone induces rapid effects on carbohydrate metabolism increasing first-phase beta cell function. The modulation of PYY plasma levels suggests possible non-genomic effects of glucocorticoids on appetite regulatory hormones.

Key words:

glucocorticoids, hydrocortisone, beta cell function, first-phase insulin secretion, gut hormones, minimal model analysis

Abbreviations:

AUC, areas under the concentration curves; IVGTT, intravenous glucose tolerance test; PYY, peptide YY; S_I, insulin sensitivity index; S_G, glucose effectiveness
Introduction

Glucocorticoids are widely-used therapeutics with diabetogenic side effects (1, 2). Chronic glucocorticoid therapy and syndromes of cortisol excess are associated with increased glucose concentrations, glucose intolerance and diabetes (3). The underlying mechanisms are: suppression of insulin secretion from the pancreas, promotion of gluconeogenesis in the liver and inhibition of glucose uptake in peripheral tissues (3).

Classical glucocorticoid actions are mediated via the genomic pathway that involves ligand binding to the intracellular glucocorticoid receptor (4) and clinical effects are anticipated to occur after several hours. Nonetheless, the rapid secretion of cortisol in response to any type of stressor is not in line with the late effects mediated via the genomic signaling pathway (1, 5). Several clinical effects of glucocorticoids occur within a few minutes (5) and these observations have led to an increasing number of studies that elucidate rapid glucocorticoid signaling mediated by non-genomic mechanisms (6, 7). Non-genomic steroid effects occur within a few minutes and may be mediated by specific receptors, transporters, other known (nonsteroid) membrane receptors, or classical steroid receptor isoforms in non-nuclear locations (8). Non-genomic glucocorticoid effects may be different to the known genomic actions, for example hydrocortisone rapidly excites and later on inhibits neural cell activity (9).

Several basic and clinical studies have investigated the rapid effects of glucocorticoids on glucose metabolism. In vitro experiments and rodent studies have identified non-genomic glucocorticoid signaling in pancreas, liver and adipose tissue (10, 11, 12). In humans, oral administration of hydrocortisone was found to decrease insulin secretion within 30 minutes (13). A single oral dose of dexamethasone 150 minutes before an oral glucose tolerance test impairs glucose tolerance without changing insulin sensitivity (14). Although non-genomic effects occur within minutes, there are no clinical data on changes in glucose metabolism and beta cell function during the initial minutes following a single glucocorticoid bolus in healthy
men. We addressed this question using the intravenous glucose tolerance test (IVGTT), which provides a reliable measurement of first-phase insulin secretion and allows an accurate calculation of the first-phase beta cell function (15-17). The precise timing and the known amount of glucose directly administered into the circulation, as well as the bypass of gastrointestinal effects that accompany a meal or an oral glucose load, make IVGTT the test of choice for studying rapid changes in the beta cell response to glucose (18).

We present here the results of a randomized, placebo-controlled crossover trial where a bolus of hydrocortisone (or placebo) was administered only 4 minutes before the start of an IVGTT in healthy volunteers.

**Methods**

*Study participants*

The clinical study was approved by the Ethics Committee of the Medical University of Vienna and performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines (Clinical trial reg. no. NCT00709839, [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Ten healthy volunteers were enrolled after signed informed consent. All participants (Table 1) presented no history of acute or chronic disease, were taking no medication, had normal BMI, normal clinical examination and normal biochemical tests (full blood count, fasting plasma glucose, fasting insulin, electrolytes, cholesterol, triglycerides, cortisol and renal, hepatic, and thyroid function).

*Study protocol*

The study was planned as a prospective, randomized, single-blinded, placebo-controlled crossover trial. Each participant was scheduled to two study sessions, performed at least three weeks apart, for administering in a randomised design once hydrocortisone and once placebo. The randomization was performed using the randomization plan generator ([www.randomization.com](http://www.randomization.com)). Based on our own in vitro experiments in isolated rat pancreatic
islets, we expected an increase in insulin secretion during the first 10 minutes following a single glucocorticoid bolus. The sample size calculation revealed that a hydrocortisone-induced 30% decrease in first-phase beta cell function can be detected with 80% power in a group of 10 volunteers (based on α=0.05 and β=0.2). Volunteers entered the Clinical Research Unit of the Division of Endocrinology and Metabolism between 8:00 and 8:30 AM after overnight fasting. Two indwelling catheters were positioned: one in the right antecubital vein for drug administration and one in the left antecubital vein for blood sampling. Then the subjects rested for approximately 15 min. Basal blood samples were collected at time-points –10 and –5 min.

The intravenous bolus of 0.6 mg/kg hydrocortisone 21-sodium succinate (Hydrocortison-100, Rotexmedica, Trittau, Germany) or placebo (0.9% NaCl, identical colour and volume as hydrocortisone) was administered within 30 sec at time-point –4 min. 330 mg/kg glucose (33% glucose) was intravenously injected between 0 and 0.5 min. Blood samples were obtained at 3, 4, 5, 6, 8, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150 and 180 min for the measurement of glucose, insulin and C-peptide. Additional blood was collected at –10, 0, 30, 60, 90, 120 and 180 min for the measurement of cortisol, ghrelin and PYY.

Assays

Samples obtained from a single subject (in both study days) were analyzed in one assay and in duplicates. Cortisol levels were determined using an in-house RIA with an intra-assay coefficient of variation of 5% and inter-assay variation of 5.4%. Glucose was measured in fluoride/heparin plasma using the hexokinase method, with an inter- and intra-assay coefficient of variation of 1.3%. Plasma insulin, C-peptide and peptide YY (PYY) levels were determined using commercially available RIAs from Linco (St. Charles, MO). The inter- and intra-assay variations were respectively: 2.5% and 3% for insulin, both 4.4% for C-peptide and 8.2% and 9% for PYY. Total plasma ghrelin concentrations were determined using a RIA from Peninsula Laboratories (Bachem, Bubendorf, Switzerland) with inter- and intra-assay
variations <10.9%. Plasma PYY concentrations were measured using a RIA kit (Linco Research, St.Charles, MO) with inter- and intra-assay variations of 8.2 and 9%, respectively.

**Mathematical modeling and statistical analysis**

The areas under the concentration curves (AUC) of glucose, insulin, C-peptide, ghrelin and PYY were calculated using the trapezoidal rule for two time intervals: 0-15 min for measuring acute effects and 120-180 min for measuring the later response. Acute insulin (dAIRg) and C-peptide (dACPRg) responses were calculated as the mean suprabasal concentration during the time interval 3-10 min. Early and late beta cell function or insulin delivery were calculated as the ratio of C-peptide or insulin AUC to glucose AUC in the intervals 0-10 min and 30-180 min, respectively. Hepatic extraction was calculated using the insulin AUC and C-peptide AUC as previously described (19). The tolerance index $K_G$ (% min$^{-1}$) was calculated as the slope of the log transformed glucose vs. time in the time interval 10-40 min and describes the glucose disappearance rate in that interval. The original minimal model, used for IVGTT data analysis (20), provides the insulin sensitivity index ($S_I$) that describes the insulin action on glucose disappearance following the glucose load and the glucose effectiveness ($S_G$) that reflects glucose action on its own disappearance without changes in insulin (15, 18). The glucose distribution volume (Vd, liters) is calculated as the glucose dose divided by the theoretical zero intercept of the glucose concentration, which is a parameter estimated by the minimal model. The adaptation index ($S_I \times dACPRg$), including insulin sensitivity and C-peptide, reflects the ability of the beta cell to adapt its secretion in relation to the prevailing insulin resistance (16). The disposition index ($S_I \times dAIRg$), including insulin sensitivity and post-hepatic insulin concentration, reflects the modulating effect that peripheral insulin exerts to allow glucose disposal with regard to the prevailing insulin resistance (17).

Differences between AUCs and metabolic parameters obtained in hydrocortisone and placebo days were tested by paired t-test after checking for normality. Differences in plasma cortisol concentrations were tested by repeated measurements ANOVA, following by post hoc
Achieved circulating cortisol concentrations

Administration of 0.6 mg/kg hydrocortisone as bolus led to significantly elevated plasma cortisol levels throughout the study period (P < 0.001) (Fig. 1). The hydrocortisone bolus induced a rapid increase in plasma cortisol levels: 428 ± 21 µg/dl in hydrocortisone sessions, as compared to 17 ± 3.7 µg/dl in placebo sessions (P < 0.001) at time point 0. Then cortisol concentrations continuously decreased reaching 26.2 ± 1.4 µg/dl in hydrocortisone sessions as compared to 7.7 ± 0.9 µg/dl in placebo sessions at time point 3 hours (Fig. 1).

Glucose, insulin, and C-peptide responses to IVGTT

Basal levels of glucose, insulin and C-peptide were similar in both study days (Table 1). Hydrocortisone reduced the glucose peak, plasma glucose concentrations during the initial 15 minutes and during the initial 2 hours, but led to higher glucose concentrations during the third hour of the study when compared to placebo sessions (Fig. 2, Table 2). Regarding insulin, hydrocortisone increased the first-phase response to the glucose bolus, despite lower glucose (Fig. 2, Table 2). This was accompanied by a significant increase in the first-phase C-peptide concentrations, which was followed by a decrease in C-peptide concentrations during the third study hour (Fig. 2, Table 2).

Minimal model analysis

Hydrocortisone significantly increased the acute insulin and C-peptide responses to glucose (Table 3), reflected by an augmented first-phase beta cell function. This was accompanied by a reduction in the hepatic insulin clearance and increased post-hepatic insulin delivery (Table 3). The late phase beta cell function was decreased. Hydrocortisone tended to increase the rate of glucose disappearance, but this effect was not statistically significant as regards insulin
sensitivity ($S_I$), glucose effectiveness ($S_G$) and the tolerance index ($K_G$) (Table 3). However, when $S_I$ and the insulin response were combined, the disposition and adaptation indices significantly increased in the presence of hydrocortisone. No changes were observed in the glucose distribution volume (Table 3).

**Changes in ghrelin and PYY**

Hydrocortisone had no impact on the glucose-induced changes in ghrelin plasma levels (Fig. 3). PYY concentrations significantly decreased during the initial 30 min, as demonstrated by changes in the respective $\Delta AUC$ ($25 \pm 30.5$ pg/ml per 30 min with placebo vs. $-216.6 \pm 47.2$ pg/ml per 30 min with hydrocortisone; $P = 0.014$, Fig. 3).

**Discussion**

Despite recent findings on non-genomic glucocorticoid signaling in metabolic organs, there exist no data on changes in glucose metabolism during the early minutes following a glucocorticoid bolus. The results presented here bring the first clinical evidence for three novel rapid functions of hydrocortisone in men: the acute increase in beta cell function and the decrease in plasma glucose levels in response to an IVGTT, accompanied by a reduction in circulating PYY concentrations. The decrease in hepatic insulin clearance suggests a rapid glucocorticoid action on liver function. These effects occur within a few minutes and must be non-genomic in nature.

The initial response to hydrocortisone is an enhancement of glucose-induced insulin secretion despite lower circulating glucose concentrations, revealing a markedly (over 35%) increased first-phase beta cell function, calculated as C-peptide secretion in relation to the glucose stimulus. Thus, hydrocortisone makes the beta cell more sensitive to changes in glucose during the initial 10 min and this is accompanied by an increase in the first-phase insulin delivery. These non-genomic effects of hydrocortisone are fully different from the known genomic actions that lead to a decrease in insulin secretion and increase in circulating glucose.
concentrations. Similar differences between genomic and non-genomic glucocorticoid effects were recently observed also in other contexts. The corticosterone-induced promotion of the excitability of hippocampal neurons in response to stress precedes the classic negative effects exerted via the genomic signaling pathway (9). The biphasic glucocorticoid effects on neural functions are accompanied by a similar profile of mitochondrial activity in cortical neurons (21). The hydrocortisone bolus leads to lower plasma glucose concentrations not only during the initial 15 minutes, but during the initial two hours following the IVGTT. The pattern of changes is inverted later on, as hydrocortisone diminishes late-phase beta cell function with increased glucose concentrations during the last hour of the test. The unchanged glucose distribution volume with and without hydrocortisone indicates that the different glucose patterns do not depend upon this kinetic variable. The interpretation of second-phase effects is complicated, as they might be influenced by differences in the first-phase effects. Nevertheless, these changes are important in the clinical practice and support previous observations that hydrocortisone bolus therapy in septic shock patients leads to a marked undulation in blood glucose levels (22). Although the hydrocortisone bolus administered in this study aimed to reach supra-physiological hormone levels, the results presented here may also reflect pathophysiological effects of increased glucocorticoid secretion during the circadian rhythm or in response to stressors. The early insulin response to a meal is higher in the morning than in the afternoon, and this fact can only partially be explained by a moderately increased secretion of incretins (23). Rapid non-genomic effects of higher cortisol levels in the morning might be, at least in part, responsible for this finding.

Only a few studies have addressed the rapid metabolic effects of glucocorticoids in humans, revealing reduction in insulin secretion and in glucose tolerance already within 0.5 to 2.5 hours following oral administration (13, 14). The apparent contrast between the findings of these studies and the data presented here can be explained with the methodological differences. In the current study both hydrocortisone and glucose were administered
intravenously (allowing immediate delivery of exact amounts and bypassing gastro-intestinal effects) and hydrocortisone was administered only 4 minutes before the glucose challenge. This protocol ensures the measurement of the effects on glucose, insulin and C-peptide at minute intervals, allowing an accurate calculation of the beta cell function using minimal model analysis. Our finding that hydrocortisone diminishes late-phase beta cell function is in line with previous evidence on diminished glucose tolerance 2.5 hours after glucocorticoid administration (14).

The site of action of hydrocortisone is at this point speculative, as glucocorticoids may directly act on beta cells and metabolic organs, but may also modulate the neuroendocrine counterregulatory mechanisms activated by hyperglycemia. Rapid glucocorticoid inhibition of insulin secretion from pancreatic islets was already demonstrated decades ago (10). Our experiments in rat beta cell lines reveal that glucocorticoids rapidly exert both stimulatory and inhibitory transitory effects on insulin secretion, depending on the amount of glucose and nutrients in the culture medium (unpublished data). In parallel, glucocorticoids rapidly modify neural functions (6, 9) and we cannot exclude a possible neural mediation of metabolic effects. Glucose sensing in the hepatoporal system activates vagal afferents that project to the hypothalamic nuclei and coordinate complex adaptive responses (24). This is a potential rapid target site for glucocorticoids, which bind to receptors located in the hypothalamus and were shown to inhibit endocannabinoid release in the paraventricular nucleus via non-genomic mechanisms (3, 25).

Several rodent studies have supported a positive role of glucocorticoids in increasing appetite (26). The mechanisms mediating these effects in humans are still unclear. The role of ghrelin is excluded, as both endogenous hypercortisolism and exogenous administration of glucocorticoids were found to reduce plasma ghrelin levels in men, and this is expected to lead to reduced appetite (27). Here we show that hydrocortisone induces a rapid and transitory decrease in the plasma concentrations of PYY, a gut-derived anorexigenic peptide (28).
Although the response to an intravenous glucose challenge is far from physiological in regards of studies on appetite regulating hormones, this is the first study to link glucocorticoids to changes in PYY concentrations.

It is important to emphasize that the hydrocortisone-induced increase in beta cell function is found in response to acute hyperglycaemia, a test that exposes men to a new challenge of homeostasis. Glucocorticoids are known for their rapid alleviative role in the stress response and the concomitant prevention of over-shooting mechanisms (1). If we consider high glucose as a stressor, it seems plausible that hydrocortisone aims to primarily counteract this stressor via increasing insulin secretion and thereby decreasing circulating glucose. To our knowledge, clinical studies on rapid effects of glucocorticoids on insulin secretion in response to hypoglycaemia have not been performed.

In summary, the data presented here reveal a novel pattern of glucocorticoid actions on carbohydrate metabolism that might be important in the pathophysiology of stress responses and in acute glucocorticoid therapy. Hydrocortisone increases first-phase beta cell function, enhances early-phase post-hepatic insulin delivery and initially lowers plasma glucose levels in response to intravenous glucose administration. A rapid decrease in PYY concentrations might suggest glucocorticoid effects on appetite-regulatory hormones. Taken together, these data reveal that the biology of metabolic effects of glucocorticoids is complex and the mechanisms underlying the dynamics of these changes require future investigation.

**Disclosure**

This study was supported by research grants from the Austrian National Bank (Grant 13018 to AL) and from the Austrian Diabetes Association (to CM), which are gratefully acknowledged. The authors of this paper declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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**Figure legends**

**Figure 1**

*Plasma cortisol concentrations*

Either placebo (open circles) or 0.6 mg/kg hydrocortisone (filled circles) was administered as a bolus at time point –4 minutes, 330 mg/kg glucose was given within 30 seconds at time point 0 minutes.

**Figure 2**

*Plasma concentrations of glucose, insulin and C-peptide during the IVGTT.*

Either placebo (open circles) or 0.6 mg/kg hydrocortisone (filled circles) was administered as a bolus at time point –4 minutes, 330 mg/kg glucose was given within 30 seconds at time point 0 minutes. To convert glucose values in mmol/l: mg/dl × 0.0555 = mmol/l.

**Figure 3**

*Ghrelin and PYY concentrations*

Either placebo (open circles) or 0.6 mg/kg hydrocortisone (filled circles) was administered as a bolus at time point –4 minutes, 330 mg/kg glucose was given within 30 seconds at time point 0 minutes.
Figure 1

![Graph showing cortisol levels over time for Placebo and Hydrocortisone bolus.](image)
Figure 2.
Figure 3
Table 1. Clinical and biochemical characteristics of the study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.9 (21 – 43)*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.6 ± 1.8</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>82.9 ± 1.5</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.9 ± 0.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>85.2 ± 1.5</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>10.8 ± 1.5</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/ml)</td>
<td>1.51 ± 0.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.04 ± 0.004 †</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.92 ± 0.29 †</td>
</tr>
</tbody>
</table>

Basal values of glucose, insulin and C-peptide are shown once for placebo study days and once for hydrocortisone study days. BMI body mass index; HbA1c glycated hemoglobin; CRP C-reactive protein; TSH, thyroid stimulating hormone. Data are presented as mean ± SE.

* age range; † normal ranges: TSH (0.44–3.77 µU/ml), CRP (< 0.1 mg/dl). To convert glucose values in mmol/l: mg/dl × 0.0555 = mmol/l.
Table 2. Hydrocortisone effects on the areas under the concentration curves of glucose, insulin and C-peptide

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Hydrocortisone</th>
<th>Units</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose_{AUC(0-15)}</td>
<td>3453 ± 76</td>
<td>3215 ± 116</td>
<td>mg/dl per 15 min</td>
<td>0.039</td>
</tr>
<tr>
<td>Glucose_{AUC(0-60)}</td>
<td>10471 ± 76</td>
<td>9344 ± 328</td>
<td>mg/dl per 60 min</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose_{AUC(120-180)}</td>
<td>5067 ± 126</td>
<td>5436 ± 120</td>
<td>mg/dl per 60 min</td>
<td>0.004</td>
</tr>
<tr>
<td>Insulin_{AUC(0-15)}</td>
<td>629.7 ± 119</td>
<td>766.3 ± 125</td>
<td>µU/ml per 15 min</td>
<td>0.020</td>
</tr>
<tr>
<td>Insulin_{AUC(120-180)}</td>
<td>546.7 ± 65.8</td>
<td>537.3 ± 57.2</td>
<td>µU/ml per 60 min</td>
<td>0.732</td>
</tr>
<tr>
<td>C-peptide_{AUC(0-15)}</td>
<td>54.85 ± 6</td>
<td>63.03 ± 7.7</td>
<td>ng/ml per 15 min</td>
<td>0.030</td>
</tr>
<tr>
<td>C-peptide_{AUC(120-180)}</td>
<td>97.29 ± 12.9</td>
<td>77.76 ± 10</td>
<td>ng/ml per 60 min</td>
<td>0.006</td>
</tr>
</tbody>
</table>

AUC area under the concentration curve; in parentheses the time interval during which AUC is computed. Data are presented as mean ± SE.
Table 3. Metabolic parameters obtained from IVGTT data analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Hydrocortisone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>dAIRg&lt;sub&gt;(3-10)&lt;/sub&gt; [µU/ml]</td>
<td>42.9 ± 10.6</td>
<td>54.9 ± 11.7</td>
<td>0.036</td>
</tr>
<tr>
<td>dACPRg&lt;sub&gt;(3-10)&lt;/sub&gt; [ng/ml]</td>
<td>2.51 ± 0.4</td>
<td>3.19 ± 0.5</td>
<td>0.032</td>
</tr>
<tr>
<td>SI [10^4 min&lt;sup&gt;-1&lt;/sup&gt;/(µU/ml)]</td>
<td>6.84 ± 1.1</td>
<td>9.06 ± 1.7</td>
<td>0.061</td>
</tr>
<tr>
<td>SG [min&lt;sup&gt;-1&lt;/sup&gt;]</td>
<td>0.021 ± 0.004</td>
<td>0.026 ± 0.002</td>
<td>0.268</td>
</tr>
<tr>
<td>Disposition Index [min&lt;sup&gt;-1&lt;/sup&gt;]</td>
<td>0.026 ± 0.007</td>
<td>0.045 ± 0.011</td>
<td>0.033</td>
</tr>
<tr>
<td>Adaptation Index [min&lt;sup&gt;-1&lt;/sup&gt;]</td>
<td>0.087 ± 0.018</td>
<td>0.153 ± 0.035</td>
<td>0.042</td>
</tr>
<tr>
<td>Tolerance index K&lt;sub&gt;G&lt;/sub&gt; (%min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.74±0.26</td>
<td>2.09±0.29</td>
<td>0.052</td>
</tr>
<tr>
<td>Glucose distribution volume Vd (liters)</td>
<td>9.0±0.3</td>
<td>9.3±0.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Early phase insulin delivery function* [µU/mg]</td>
<td>0.188 ± 0.046</td>
<td>0.251 ± 0.049</td>
<td>0.005</td>
</tr>
<tr>
<td>Early phase beta cell function [ng/mg]</td>
<td>0.011 ± 0.002</td>
<td>0.015 ± 0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Late phase insulin delivery function* [µU/mg]</td>
<td>0.084 ± 0.010</td>
<td>0.075 ± 0.007</td>
<td>0.186</td>
</tr>
<tr>
<td>Late phase beta cell function [ng/mg]</td>
<td>0.016 ± 0.002</td>
<td>0.013 ± 0.001</td>
<td>0.037</td>
</tr>
<tr>
<td>Hepatic extraction [%]</td>
<td>62.7 ± 3.1</td>
<td>58.4 ± 3.4</td>
<td>0.009</td>
</tr>
</tbody>
</table>

dAIRg, suprabasal acute insulin response to glucose; dACPRg, suprabasal acute C-peptide response to glucose; S<sub>i</sub>, insulin sensitivity index; S<sub>G</sub>, glucose effectiveness. * post-hepatic.

Data are presented as mean ± SE.