

## CLINICAL STUDY

# Acute effects of hydrocortisone on the metabolic response to a glucose load: increase in the first-phase insulin secretion

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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 its 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:** In a randomized placebo-controlled crossover study, ten healthy men received an i.v. bolus of 0.6 mg/kg hydrocortisone once and placebo once 4 min before the administration of 330 mg/kg glucose. Cortisol, glucose, insulin, C-peptide, ghrelin, and peptide YY (PYY) levels were measured during the following 3 h. Minimal model analysis was performed for evaluating the metabolic response.

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

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

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## Introduction

Glucocorticoids are widely used drugs 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 (non-steroid) membrane receptors, or classical steroid receptor isoforms in non-nuclear locations (8). Non-genomic glucocorticoid effects may be different from 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 (10–12). In humans, oral administration of hydrocortisone was found to decrease insulin secretion within 30 min (13). A single oral dose of dexamethasone 150 min before an oral glucose tolerance test impairs glucose tolerance without changing insulin sensitivity (14). Although non-genomic effects occur within minutes, there is no clinical data available on the changes in glucose metabolism and  $\beta$ -cell function during the initial few

minutes following the administration of a single glucocorticoid bolus in healthy men. We addressed this question using the intravenous glucose tolerance test (IVGTT), which provides a reliable measurement of the 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 the rapid changes in the  $\beta$ -cell response to glucose (18).

Here, we present the results of a randomized, placebo-controlled crossover trial where a bolus of hydrocortisone (or placebo) was administered only 4 min 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 was 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 obtaining signed informed consent. All the participants (Table 1) presented no history of acute or chronic disease, were not taking any medication, and had normal body mass index, 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).

**Table 1** Clinical and biochemical characteristics of the study subjects. Data are presented as mean  $\pm$  S.E.M. Basal values of glucose, insulin, and C-peptide are given for the study days when placebo was administered and the values within parentheses are for those when hydrocortisone was administered.

Parameter	Value
Age (years)	27.9 (21–43) <sup>a</sup>
Weight (kg)	77.6 $\pm$ 1.8
Waist (cm)	82.9 $\pm$ 1.5
BMI (kg/m <sup>2</sup> )	23.9 $\pm$ 0.5
Fasting glucose (mg/dl)	85.2 $\pm$ 1.5 (84.6 $\pm$ 1.9)
Fasting insulin ( $\mu$ U/ml)	10.8 $\pm$ 1.5 (10.2 $\pm$ 1.3)
Fasting C-peptide (ng/ml)	1.51 $\pm$ 0.2 (1.55 $\pm$ 0.2)
HbA1c (%)	4.9 $\pm$ 0.1
CRP (mg/dl)	0.04 $\pm$ 0.004 <sup>b</sup>
TSH ( $\mu$ U/ml)	1.92 $\pm$ 0.29 <sup>b</sup>

BMI, body mass index; CRP, C-reactive protein.

<sup>a</sup>Age range.

<sup>b</sup>Normal ranges: TSH, 0.44–3.77  $\mu$ U/ml; CRP, <0.1 mg/dl. To convert glucose values into mmol/l: mg/dl  $\times$  0.0555 = mmol/l.

### Study protocol

The study was planned as a prospective, randomized, single-blind, placebo-controlled crossover trial. Each participant was scheduled to two study sessions, performed at least 3 weeks apart, for administering in a randomized manner hydrocortisone once and placebo once. 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 min following the administration of a single glucocorticoid bolus. The sample size calculation revealed that a hydrocortisone-induced 30% decrease in the first-phase  $\beta$ -cell function can be detected with 80% power in a group of ten volunteers (based on  $\alpha=0.05$  and  $\beta=0.2$ ). Volunteers entered the Clinical Research Unit of the Division of Endocrinology and Metabolism between 0800 and 0830 h after an overnight fast. Two indwelling catheters were positioned: one in the right antecubital vein for drug administration, and the other in the left antecubital vein for blood sampling. Then, the subjects rested for  $\sim$ 15 min. Basal blood samples were collected at time points  $-10$  and  $-5$  min.

The i.v. bolus of 0.6 mg/kg hydrocortisone 21-sodium succinate (Hydrocortisone 100, Rotexmedica, Trittau, Germany) or placebo (0.9% NaCl, identical color and volume as hydrocortisone) was administered within 30 s at time point  $-4$  min. Between 0 and 0.5 min, 330 mg/kg glucose (33% glucose) was i.v. injected. 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 that were obtained from a single subject (on 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 (CV) of 5% and an inter-assay CV of 5.4%. Glucose was measured in fluoride/heparin plasma using the hexokinase method, with an inter- and intra-assay CV of 1.3%. Plasma insulin, C-peptide, and peptide YY (PYY) levels were determined using commercially available RIA kit obtained from Linco (St Charles, MO, USA). The inter- and intra-assay CV 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 an RIA kit obtained from Peninsula Laboratories (Bachem, Bubendorf, Switzerland), with inter- and intra-assay CV <10.9%. Plasma PYY concentrations were measured using a RIA kit (Linco Research), with inter- and intra-assay CV of 8.2 and 9% respectively.

## Mathematical modeling and statistical analysis

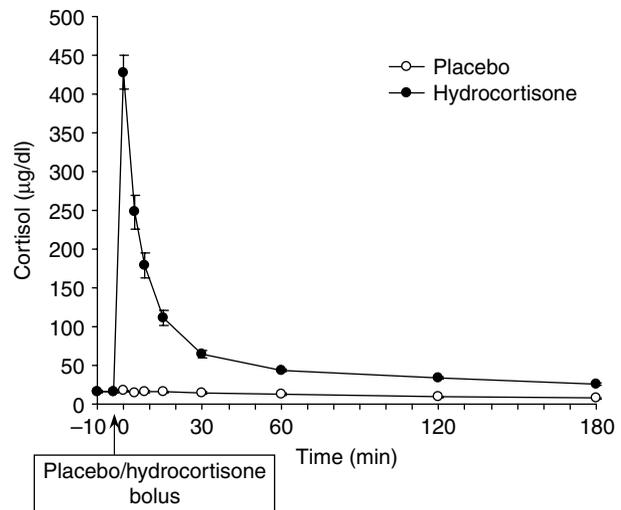
The areas under the concentration curves (AUCs) of glucose, insulin, C-peptide, ghrelin, and PYY were calculated using the trapezoidal rule for two time intervals: 0–15 min for measuring the acute effects and 120–180 min for measuring the later response. Acute insulin (dAIRg) and C-peptide (dACPRg) responses were calculated as the mean suprabasal concentrations during the time interval 3–10 min. Early- and late-phase  $\beta$ -cell function or insulin delivery was calculated as the ratio of C-peptide or insulin AUC to glucose AUC during the time intervals 0–10 and 30–180 min respectively. Hepatic extraction was calculated using the insulin AUC and C-peptide AUC as described previously (19). The tolerance index  $K_G$  (%/min) was calculated as the slope of the log-transformed glucose versus time during the time interval 10–40 min, and it 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 administration of a 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 ( $V_d$ , l) 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 during the days hydrocortisone and placebo were administered were tested by paired *t*-test after checking for normality. Differences in plasma cortisol concentrations were tested by repeated-measures ANOVA, followed by *post hoc* statistics for specific time points. SPSS (Chicago, IL, USA) was used as the statistical software. Data and results are presented as means  $\pm$  S.E.M., unless otherwise indicated.

## Results

### Achieved circulating cortisol concentrations

The administration of 0.6 mg/kg hydrocortisone as a 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 the plasma cortisol levels:  $428 \pm 21$   $\mu$ g/dl in the hydrocortisone



**Figure 1** Plasma cortisol concentrations. Either placebo (open circle) or 0.6 mg/kg hydrocortisone (solid circle) was administered as a bolus at time point  $-4$  min, and 330 mg/kg glucose was administered within 30 s at time point 0 min.

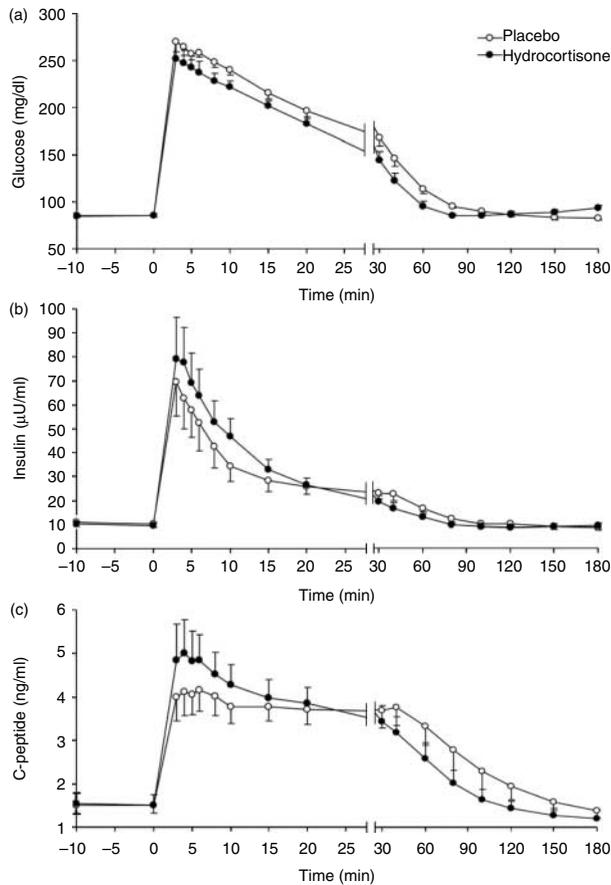
sessions compared with  $17 \pm 3.7$   $\mu$ g/dl in the placebo sessions ( $P < 0.001$ ) at time point 0 min. Then, the cortisol concentrations continuously decreased reaching  $26.2 \pm 1.4$   $\mu$ g/dl in the hydrocortisone sessions compared with  $7.7 \pm 0.9$   $\mu$ g/dl in the placebo sessions at time point 3 h (Fig. 1).

### Glucose, insulin, and C-peptide responses to IVGTT

Basal levels of glucose, insulin, and C-peptide were similar on both study days (Table 1). Hydrocortisone reduced the glucose peak and plasma glucose concentrations during the initial 15 min and during the initial 2 h, but led to higher glucose concentrations during the third hour of the study when compared with the placebo sessions (Fig. 2 and Table 2). Regarding insulin, hydrocortisone increased the first-phase response to the glucose bolus, despite lower glucose concentrations (Fig. 2 and 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 and 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 an increased post-hepatic insulin delivery (Table 3). The late-phase  $\beta$ -cell function was decreased. Hydrocortisone tended to increase the rate of glucose



**Figure 2** Plasma concentrations of glucose, insulin, and C-peptide during the IVGTT. Either placebo (open circle) or 0.6 mg/kg hydrocortisone (solid circle) was administered as a bolus at time point  $-4$  min, and 330 mg/kg glucose was administered within 30 s at time point 0 min. To convert glucose values into mmol/l:  $\text{mg/dl} \times 0.0555 = \text{mmol/l}$ .

disappearance, but this effect was not statistically significant with regard to  $S_I$ ,  $S_G$ , and  $K_G$  (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 levels

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  $\Delta\text{AUC}$  ( $25 \pm 30.5$  pg/ml per 30 min with placebo versus  $-216.6 \pm 47.2$  pg/ml per 30 min with hydrocortisone;  $P=0.014$ , Fig. 3).

### Discussion

Despite the recent findings on non-genomic glucocorticoid signaling in metabolic organs, there exists no data on changes in glucose metabolism during the initial few minutes following the administration of a glucocorticoid bolus. The results presented here reveal the first clinical evidence for three novel rapid functions of hydrocortisone in men: the acute increase in  $\beta$ -cell function, the decrease in plasma glucose levels in response to an IVGTT, and the 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 the lower circulating glucose concentrations, revealing a markedly (over 35%) increased the 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 an increase in circulating glucose concentrations. Similar differences between genomic and non-genomic glucocorticoid effects were also observed recently 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

**Table 2** Hydrocortisone effects on the areas under the concentration curves of glucose, insulin, and C-peptide. Data are presented as mean  $\pm$  S.E.M.

	Placebo	Hydrocortisone	Units	P
Glucose <sub>AUC(0–15)</sub>	3453 $\pm$ 76	3215 $\pm$ 116	mg/dl per 15 min	0.039
Glucose <sub>AUC(0–60)</sub>	10 471 $\pm$ 76	9344 $\pm$ 328	mg/dl per 60 min	0.006
Glucose <sub>AUC(120–180)</sub>	5067 $\pm$ 126	5436 $\pm$ 120	mg/dl per 60 min	0.004
Insulin <sub>AUC(0–15)</sub>	629.7 $\pm$ 119	766.3 $\pm$ 125	$\mu$ U/ml per 15 min	0.020
Insulin <sub>AUC(120–180)</sub>	546.7 $\pm$ 65.8	537.3 $\pm$ 57.2	$\mu$ U/ml per 60 min	0.732
C-peptide <sub>AUC(0–15)</sub>	54.85 $\pm$ 6	63.03 $\pm$ 7.7	ng/ml per 15 min	0.030
C-peptide <sub>AUC(120–180)</sub>	97.29 $\pm$ 12.9	77.76 $\pm$ 10	ng/ml per 60 min	0.006

AUC, area under the concentration curve; the time interval during which AUC was computed is given in the parentheses.

**Table 3** Metabolic parameters obtained from intravenous glucose tolerance test data analysis. Data are presented as mean  $\pm$  S.E.M.

	Placebo	Hydrocortisone	P
dAIRg <sub>(3-10)</sub> ( $\mu$ U/ml)	42.9 $\pm$ 10.6	54.9 $\pm$ 11.7	0.036
dACPRg <sub>(3-10)</sub> (ng/ml)	2.51 $\pm$ 0.4	3.19 $\pm$ 0.5	0.032
S <sub>i</sub> ( $10^4$ /min per $\mu$ U/ml)	6.84 $\pm$ 1.1	9.06 $\pm$ 1.7	0.061
S <sub>G</sub> (per minute)	0.021 $\pm$ 0.004	0.026 $\pm$ 0.002	0.268
Disposition index (per minute)	0.026 $\pm$ 0.007	0.045 $\pm$ 0.011	0.033
Adaptation index (per minute)	0.087 $\pm$ 0.018	0.153 $\pm$ 0.035	0.042
Tolerance index K <sub>G</sub> (%/min)	1.74 $\pm$ 0.26	2.09 $\pm$ 0.29	0.052
Glucose distribution volume V <sub>d</sub> (l)	9.0 $\pm$ 0.3	9.3 $\pm$ 0.4	0.13
Early-phase insulin delivery function <sup>a</sup> ( $\mu$ U/mg)	0.188 $\pm$ 0.046	0.251 $\pm$ 0.049	0.005
Early-phase $\beta$ -cell function (ng/mg)	0.011 $\pm$ 0.002	0.015 $\pm$ 0.002	0.003
Late-phase insulin delivery function <sup>a</sup> ( $\mu$ U/mg)	0.084 $\pm$ 0.010	0.075 $\pm$ 0.007	0.186
Late-phase $\beta$ -cell function (ng/mg)	0.016 $\pm$ 0.002	0.013 $\pm$ 0.001	0.037
Hepatic extraction (%)	62.7 $\pm$ 3.1	58.4 $\pm$ 3.4	0.009

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.

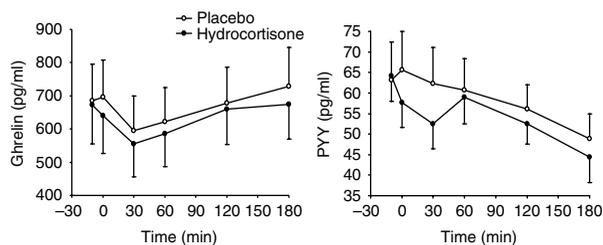
<sup>a</sup>Post-hepatic.

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 min, but also during the initial 2 h following the IVGTT. The pattern of changes is inverted later on, as hydrocortisone diminishes the late-phase  $\beta$ -cell function with increased glucose concentrations during the final 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 the 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 was aimed at attaining supraphysiological 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 the reduction in insulin secretion and in glucose tolerance already within 0.5–2.5 h following oral administration (13, 14). The apparent contrast between the findings of these studies and the data presented here can be explained by methodological differences. In this study, both hydrocortisone and glucose were administered i.v. (allowing immediate delivery of exact amounts and bypassing gastrointestinal effects), and hydrocortisone was administered only 4 min 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 the late-phase  $\beta$ -cell function is in line with previous evidence on diminished glucose tolerance 2.5 h after glucocorticoid administration (14).

At this point, the site of action of hydrocortisone is 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 has been 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 hepatoportal 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



**Figure 3** Ghrelin and PYY concentrations. Either placebo (open circle) or 0.6 mg/kg hydrocortisone was administered as a bolus at time point  $-4$  min, and 330 mg/kg glucose was administered within 30 s at time point 0 min.

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 have shown that hydrocortisone induces a rapid and transitory decrease in the plasma concentrations of PYY, which is a gut-derived anorexigenic peptide (28). Although the response to an i.v. glucose challenge is far from physiological with regard to 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 hyperglycemia, which is 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 overshooting 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 hypoglycemia 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 the first-phase  $\beta$ -cell function, enhances the early-phase post-hepatic insulin delivery, and lowers the plasma glucose levels in response to i.v. glucose administration initially. 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 in future, the mechanisms underlying the dynamics of these changes require investigation.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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