β-Cell Activity and Hepatic Insulin Extraction Following Dexamethasone Administration in Healthy Subjects

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Glucocorticoids induce an increase of hepatic glucose production and peripheral resistance to insulin action. It is further assumed that dexamethasone administration in humans causes insulin hypersecretion, although inferences on β-cell activity have been made in absolute terms and mostly from observations of systemic insulin concentration. In fact, the role of hepatic insulin extraction in humans treated long-term with glucocorticoids has not been investigated. The aim of the present study was to factor out quantitatively the main components of the insulin pathway that are responsible for the peripheral hypersecretion observed after steroids. Frequently sampled intravenous (FSIGT) and oral (OGTT) glucose tolerance tests were performed in healthy subjects before and after 5 days of oral dexamethasone administration (4 mg/d). Insulin sensitivity, β-cell secretion, and hepatic insulin extraction were estimated by means of mathematical modeling. After steroids, insulin sensitivity decreased from 6.00 ± 1.29 to 4.23 ± 1.04 $min^{-1}/(\mu U/mL)$ ($P < .04$). Basal β-cell secretion increased from 45 ± 7 to 104 ± 26 $pmol/L \cdot min^{-1}$ ($P < .004$) during the FSIGT and from 40 ± 6 to 88 ± 21 ($P < .05$) during the OGTT; total insulin release increased from 19 ± 5 to 36 ± 7 nmol/L in 180 minutes ($P < .005$) and from 33 ± 5 to 50 ± 10 ($P < .02$), respectively. FSIGT data also showed that first-phase β-cell sensitivity increased from 236 ± 39 to 309 ± 33 $pmol/L \cdot min^{-1}/(mg/dL)$ ($P < .04$), and second-phase from 631 ± 154 to 1,103 ± 196 10^4 $pmol/L \cdot min^{-2}/(mg/dL)$ ($P < .03$). Posthepatic insulin delivery increased only insignificantly during the FSIGT (from 3.4 ± 0.6 to 4.5 ± 0.5 nmol/L, $P = .073$) due to an augmented hepatic insulin extraction from 73.0% ± 7.2% to 83.0% ± 3.5% ($P < .05$). During the OGTT, posthepatic insulin delivery increased after treatment from 6.6 ± 1.2 to 11.4 ± 2.5 nmol/L ($P < .035$) due to an increase, although slight, of hepatic insulin extraction from 77.4% ± 1.9% to 79.3% ± 3.3% ($P = .319$). The increased overall β-cell activity during both tests was observed also by analyzing OGTT profiles of islet amyloid polypeptide (IAPP), the secretion of which was higher after steroids (basal, 0.081 ± 0.012 *v* 0.272 ± 0.082 pmol/L/min, $P < .02$; total, 35 ± 8 *v* 116 ± 48 pmol/L in 3 hours, $P < .05$). In conclusion, after dexamethasone administration, peripheral hyperinsulinemia due to marked prehepatic β-cell insulin hypersecretion is partially ameliorated by a concomitant increase of hepatic insulin clearance, which is more evident during a FSIGT. Model-derived secretion parameters from the OGTT and FSIGT produced comparable results, indicating that both tests, when properly analyzed, are feasible tools to evaluate insulin secretion.

THE GLUCOCORTICOID hormones play an important role in many fundamental steps in glucose metabolism. Glucose intolerance or even the development of frank diabetes are well-known complications in patients treated with glucocorticoids for inflammatory processes or for immunosuppression.[1-3] Glucocorticoids are known to be involved in the regulation of hepatic glucose metabolism, peripheral sensitivity to insulin, and β-cell secretion. It is well established that administration of glucocorticoids leads to increased hepatic glucose production, to peripheral insulin resistance,[4] and to enhanced insulin release. However, different interpretations have been reported of in vivo and in vitro effects of glucocorticoids on β cells.[5-9] For instance, in vitro studies have shown inhibition of insulin release and cell replication[5-7]; in contrast, a stimulatory effect on pancreatic β cells has been observed in vivo.[8] We have previously shown that dexamethasone treatment worsens glucose tolerance.[10] In particular, steroid-treated subjects were characterized by a reduced insulin sensitivity and a sustained hyperinsulinemia. To the best of our knowledge, the processes responsible for elevated peripheral insulin levels, ie, prehepatic β-cell release and hepatic insulin extraction, have not been thoroughly investigated in subjects treated with glucocorticoids. Thus, we studied β-cell and liver behavior in response to glucose challenges before and after dexamethasone treatment to evaluate possible relationships between glucocorticoids and the two processes. We exploited a recently introduced mathematical model that allows reconstruction of the prehepatic β-cell secretion time course of C-peptide, insulin, and islet amyloid polypeptide (IAPP) during the oral glucose tolerance test (OGTT).[11] In addition, the widely used minimal model of C-peptide dynamics[12] was used to assess β-cell secretion during the intravenous test.

SUBJECTS AND METHODS

Subjects

Nine healthy young control subjects (five men and four women; age, 27 ± 1 years; body mass index [BMI], 22 ± 1 $kg \cdot m^{-2}$; hemoglobin A_{1c}, 5.1%) underwent the study approved by the Ethics Committee of the University of Vienna after provision of informed consent. We performed, in random order, an OGTT and a frequently sampled intravenous glucose tolerance test (FSIGT) on different days after an overnight fast. After the tests, the volunteers received 4 mg dexamethasone orally every morning for 5 days. The OGTT and FSIGT were repeated in random order on days 4 and 5 after administration of the dexamethasone dose in the morning.

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Glucose Tests

FSIGT. At 8 AM after an overnight fast, a catheter was inserted into an antecubital vein for blood sampling and into a contralateral antecubital vein for glucose injection. Basal samples were drawn at −20, −10, and −1 minute. At time 0, glucose (300 mg · kg^{-1}) was injected in 1 minute. Additional samples were collected at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes. No pharmacologic agent (tolbutamide) or exogenous insulin was used to avoid confounding effects on β-cell secretory profiles.

OGTT. After collection of a basal blood sample, a glucose load of 75 g was administered and blood was drawn at 10, 20, 30, 60, 90, 120, 150, and 180 minutes for measurement of glucose, insulin, C-peptide, and IAPP levels.

Assays

Blood was rapidly centrifuged and glucose level immediately measured by the glucose oxidase method with an automated glucose analyzer (Beckman Instruments, Fullerton, CA). The remaining plasma was stored at −20°C for later insulin (Pharmacia, Uppsala, Sweden) and C-peptide (Byk Sangtec, Dietzenbach, Germany) determination by commercially available radioimmunoassays. IAPP was determined according to a radioimmunoassay developed in our laboratory as previously described.[10,13]

Data Analysis

The characteristic parameters of β-cell secretion were calculated by submitting FSIGT data to computer programs that fit insulin and C-peptide concentration time courses under glucose stimulation.[12,14] The models describe both the ability of β cells to secrete C-peptide in response to the glycemic stimulus, and the linear kinetics of C-peptide and insulin after entry into the peripheral circulation.[12] These models provide the time courses of C-peptide secretion per unit volume, $CPS_{IV}(t)$ (pmol/L · min^{-1}), and of posthepatic insulin delivery, $IDR_{IV}(t)$, in addition to the following parameters: k_{01}, C-peptide fractional clearance rate (min^{-1}); and Φ_1 (pmol/L · min^{-1}/(mg/dL) and Φ_2 (pmol/L · min^{-2}/(mg/dL), dynamic (suprabasal) first- and second-phase β-cell (prehepatic) sensitivity to glucose, respectively.

OGTT concentration data of C-peptide, insulin, and IAPP have been described by means of a mathematical model with three compartments each representing their respective kinetics. The model assumes linear kinetics for the three compounds, equimolar release between insulin and C-peptide, and a proportional release between C-peptide and IAPP. The physiologic assumptions and mathematical descriptions have been detailed elsewhere.[11,15] The model, by simultaneous analysis of the three time courses, provides the fractional clearance of IAPP (min^{-1}) and reconstructs the patterns per unit volume of C-peptide secretion, $CPS_{OG}(t)$, which equals insulin prehepatic release, of the posthepatic insulin appearance into peripheral circulation and of IAPP secretion (all pmol/L · min^{-1}).[11] By fitting the FSIGT glucose concentration time course under insulin control, the minimal model provides two indexes of glucose disposal: one for insulin-mediated glucose uptake (insulin sensitivity, min^{-1}/(μU/mL)), and the other for glucose-mediated glucose disappearance (glucose effectiveness, min^{-1}).[14]

Calculations

FSIGT parameters were estimated according to a previously reported method.[16] The OGTT model[15] was implemented using PANSYM[17] and was resolved with a nonlinear weighted least-squares estimation technique. For all data sets, a uniform variance structure was assumed for the measurement error: the coefficient of variation assessed by our laboratory procedures for a single determination was ±1.5% for glucose, ±7% for insulin, ±12% for C-peptide, and ±10% for IAPP. Because insulin and C-peptide are equimolarly secreted, $CPS_{IV}(t)$ and $CPS_{OG}(t)$ also represent the time courses of β-cell (prehepatic) insulin secretion. For the FSIGT, the amount of insulin secreted by the β-cell (TIS_{IV}) and that of insulin delivered to the periphery (TID_{IV}) per unit volume, ie, per liter of distribution space, were computed by the integral of $CPS_{IV}(t)$ and $IDR_{IV}(t)$, respectively, between zero and 180 minutes for the total release and from zero to 60 minutes for the highly dynamic part of the test. For the OGTT, the total amount of insulin released by the β cell per unit volume during the 3-hour test (TIS_{OG}) was computed by the integral, between zero and 180 minutes, of $CPS_{OG}(t)$, and the total amount of secreted IAPP (TIR) was the integral of IAPP secretion. The OGTT model also computes basal IAPP secretion rate (BIR). For the FSIGT, the time course of hepatic insulin extraction, $HE_{IV}(t)$, as a percent of secreted hormone, was computed as the difference between $CPS_{IV}(t)$ and $IDR_{IV}(t)$, normalized to $CPS_{IV}(t)$[12,16]; mean degradation H_{IV} was computed as the integral of $HE_{IV}(t)$ between zero and 180 minutes, divided by the length of the observation period. For the OGTT, hepatic insulin degradation, H_{OG}, was calculated by an estimated model parameter.[15] The difference between $CPS_{OG}(t)$ and hepatic insulin extraction gives the value for the appearance of insulin into the periphery (TID_{OG}). For both tests, basal prehepatic insulin secretion rate per unit volume, BSR, is the product between k_{01} and the measured basal C-peptide concentration. Basal insulin delivery rate into the periphery (posthepatic) per unit volume, BDR, is calculated from BSR and basal hepatic extraction. All data are reported as the mean ± SE, unless otherwise designated; statistical comparisons were made by a one-tailed paired Student's *t* test. Conversions are as follows: 1 nmol/L = 0.331 ng/mL for C-peptide; 1 pmol/L = 6 μU/mL for insulin; and 1 pmol/L = 0.26 pg/mL for IAPP.

RESULTS

FSIGT

The mean concentration curves before and after dexamethasone treatment are shown in Fig 1. After glucocorticoid administration, basal insulin levels increased from 59.4 ± 15.6 to 91.8 ± 19.8 pmol/L ($P < .01$) and basal C-peptide levels increased from 0.87 ± 0.12 to 1.69 ± 0.51 nmol/L ($P < .005$), while basal glucose levels did not change significantly (from 4.7 ± 0.3 to 5.4 ± 0.3 mmol/L). Peak insulin concentration immediately after the intravenous glucose bolus increased from 509 ± 33 to 869 ± 153 pmol/L, ($P < .05$), and C-peptide level increased from 3.20 ± 0.33 to 5.67 ± 0.89 nmol/L ($P < .02$). The total area under the curve of insulin concentration during the 180 minutes of the test increased from 21.6 ± 4.2 to 30.0 ± 6.0 min · nmol/L ($P < .001$) and the same value for C-peptide increased from 341 ± 77 to 550 ± 135 min · nmol/L ($P < .01$).

Parameters related to β-cell secretion are summarized in Table 1. Both the dynamic first-phase β-cell sensitivity to glucose, Φ_1, and the second phase, Φ_2, increased after dexamethasone treatment, as well as basal and total prehepatic β-cell insulin secretion (BSR_{IV} and TIS_{IV}). The increase in basal and total posthepatic insulin delivery per unit volume in 3 hours did not reach statistical significance

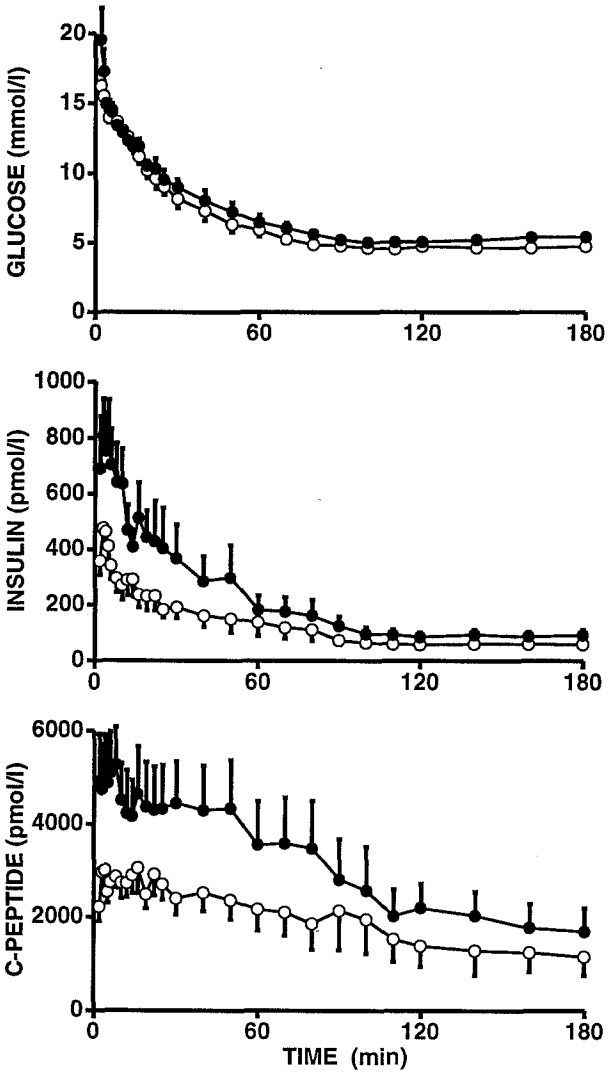

Fig 1. Mean time courses of glucose, insulin, and C-peptide concentrations ± SE during the FSIGT before (○) and after (●) dexamethasone administration.

(BDR_{IV}, 9.3 ± 2.2 *v* 11.3 ± 2.1 pmol/L/min, $P = 0.260$; TID_{IV}, 3.4 ± 0.6 *v* 4.5 ± 0.5 nmol/L, $P = .073$). However, when posthepatic insulin delivery rate was computed from the beginning of the test to 60 minutes, TID_{IV} was statistically augmented (from 2.2 ± 0.3 to 3.1 ± 0.3, $P < .05$); also, TIS_{IV} computed in the same 1-hour interval confirmed the increased total secretion (1.2 ± 0.3 *v* 2.3 ± 0.4, $P < .01$).

The fractional clearance rate of C-peptide did not change after glucocorticoid ($k_{01} = 0.053 \pm 0.008$ *v* 0.064 ± 0.005 min^{-1}), whereas the average hepatic insulin clearance increased (H_{IV}, 73.0% ± 7.2% *v* 83.0% ± 3.5%, $P < .050$). The insulin sensitivity index decreased significantly (4.23 ± 1.04 *v* 6.00 ± 1.29 $min^{-1}/(\mu U/mL)$, $P < .04$) while glucose effectiveness remained unchanged (0.022 ± 0.002 *v* 0.026 ± 0.004 min^{-1}).

OGTT

Concentrations of the measured compounds are shown in Fig 2. After treatment, basal insulin levels increased from 54.8 ± 15.0 to 85.9 ± 28.3 pmol/L ($P < .05$), basal C-peptide from 0.76 ± 0.15 to 1.11 ± 0.20 nmol/L ($P < .05$), and basal IAPP from 2.8 ± 0.4 to 4.9 ± 0.6 pmol/L ($P < .005$), while basal glucose concentrations remained unchanged (4.8 ± 0.3 *v* 4.7 ± 0.3 mmol/L). There was no difference between the corresponding basal values before the FSIGT and OGTT. At variance with the FSIGT results, during the OGTT the stimulated glucose concentration increased following dexamethasone treatment, but glucose tolerance was normal according to the criteria of the National Diabetes Data Group.

An overall increased activity of the β cell after treatment was demonstrated by the elevated areas under the curve of C-peptide during the 3-hour test, which increased from 521 ± 85 to 796 ± 160 min · nmol/L ($P < .012$), and of IAPP (from 1,081 ± 197 to 2,004 ± 434 min · pmol/L, $P < .008$). Also, the total area under insulin concentration increased from 49 ± 9 to 78 ± 14 min · nmol/L ($P < .03$). The modeling analysis showed that all the components of C-peptide secretion and those of IAPP release increased (Table 1). Posthepatic insulin delivery increased after treatment (BDR_{OG}, 7.7 ± 2.1 *v* 12.0 ± 4.0 pmol/L/min, $P < .05$; TID_{OG}, 6.6 ± 1.2 *v* 11.4 ± 2.5 nmol/L, $P < .035$), as did hepatic insulin extraction (H_{OG}, 77.4% ± 1.9% *v* 79.3% ± 3.3%), the latter without reaching statistical significance ($P = .319$). IAPP clearance did not change significantly (0.034 ± 0.004 *v* 0.050 ± 0.010 min^{-1}, $P = .08$).

DISCUSSION

Steroid administration is commonly associated with insulin resistance, diminished carbohydrate tolerance,[10,18-20] and hyperinsulinemia. Regarding a direct effect of glucocorticoids on the β cell, in vitro investigations[6,7] have shown an inhibition of insulin secretion. Studies in vivo reported a decreased insulin response to glucose load after acute glucocorticoid exposure (single infusion or oral dexamethasone treatment for 24 hours)[21-23] and an increased insulin secretion following more extended (2 to 3 days)[18,24] as well as long-term (>1 week)[25,26] glucocorticoid treatment. It is

Table 1. β-Cell Parameters (mean ± SE) From the FSIGT (subscript IV) and OGTT (subscript OG) Before and After Dexamethasone Administration

	Before	After	*P*
Φ_1	236 ± 39	309 ± 33	.041
Φ_2	631 ± 154	1103 ± 196	.030
BSR_{IV}	45 ± 7	104 ± 26	.004
BSR_{OG}	40 ± 6	88 ± 21	.050
TIS_{IV}	19 ± 5	36 ± 7	.005
TIS_{OG}	33 ± 5	50 ± 10	.020
BIR	0.081 ± 0.012	0.272 ± 0.082	.020
TIR	35 ± 8	116 ± 48	.050

Abbreviations: Φ_1, dynamic first-phase β-cell sensitivity to glucose, pmol/L · min^{-1}/(mg/dL); Φ_2, dynamic second-phase β-cell sensitivity to glucose, 10^4 pmol/L · min^{-2}/(mg/dL); BSR, basal insulin secretion rate per liter of distribution volume, pmol · min^{-1}; TIS, total amount of secreted insulin per liter of distribution volume in 3 hours, nmol; BIR, basal secretion rate of IAPP per liter of distribution volume, pmol/min; and TIR, total amount of secreted IAPP per liter of distribution volume in 3 hours, pmol.

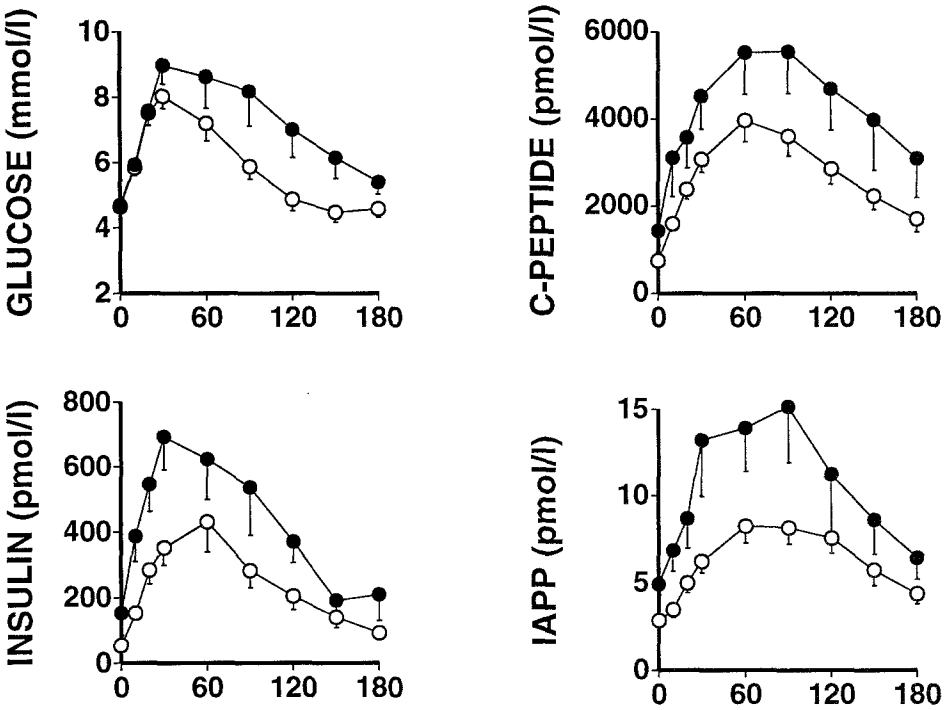

Fig 2. Mean ± SE time courses of glucose, insulin, C-peptide, and IAPP concentrations during the OGTT before (○) and after (●) dexamethasone administration.

worth noting that the above in vivo investigations are based on the observation of peripheral posthepatic insulin concentration. However, in the present study, by using C-peptide data and mathematical models, we were able to reconstruct the prehepatic profile of β-cell release after both an oral and an intravenous glucose load, and confirmed the marked increase in overall β-cell secretory activity.

One of the novelties of the present study is that we quantified β-cell insulin secretion, hepatic insulin extraction, and delivery of insulin into the systemic circulation before and after dexamethasone administration. The noninvasive method we have applied was already used in a large variety of pathophysiologic conditions (eg, the review[27]). Recently, it has been suggested that the minimal model technique should be used with a modified intravenous glucose protocol that aims to increase the dynamics of insulin concentration. This allows a better estimation of insulin sensitivity overall in those cases characterized by a low insulin response. A more dynamic insulin pattern can be obtained either by directly infusing exogenous insulin[28] or by stimulating endogenous release with tolbutamide.[29] We have avoided these modified protocols because insulin sensitivity has already been widely investigated under steroid treatment,[4,10] whereas the main purpose and novelty of this study was the assessment of β-cell and liver behavior, which would have been impossible using either exogenous insulin or a pharmacologic agent acting on the β cell. Besides, both insulin and C-peptide profiles of our subjects were expected to contain enough dynamics to render unnecessary the use of stimulating agents. Moreover, if an error exists, it would be systematic and would affect pretreatment and posttreatment in the same way. Modeling analysis of glucose-test data are based on a series of assumptions. The underlying hypotheses, pitfalls, and advantages of the approach used in this study have been extensively detailed in previous publications (for FSIGT[12,16,27] and for OGTT[11,15] modeling). The minimal model technique allowed estimation of factors involved in the insulin secretory and degrading mechanisms, which are not directly measurable. Basal secretion (BSR) almost doubled after treatment, as did the second-phase dynamic β-cell sensitivity to glucose (Φ_2) and the total amount of C-peptide secreted by the cells (TIS), which equals that of insulin because of the equimolar release. First-phase dynamic sensitivity to glucose (Φ_1) increased, on average, by 24%. This means that under dexamethasone treatment, both the dynamic capacity of promptly releasing insulin and synthesizing newly releasable hormone are enhanced. Also during the OGTT, the modeling analysis allowed segregation of the relative contributions of clearance and secretion to C-peptide and IAPP dynamics. Again, the elevated peripheral concentration of the two peptides observed after treatment was mainly due to an increased β-cell production.

It is now widely assumed that despite a direct inhibitory effect of the steroid on β cells, the indirect stimulatory effect is predominant in humans in vivo.[18,30] Hyperinsulinemia is thought to be an adaptive response to insulin resistance, mediated by mild hyperglycemia and maybe also by an increased β-cell responsiveness to glucose. Glucose intolerance was confirmed by the lower insulin sensitivity, whereas glucose effectiveness did not change after treatment, indicating that glucose-dependent glucose utilization was not affected by glucocorticoid treatment. It is accepted that any intervention that decreases insulin sensitivity will cause a secondary increase in β-cell activity in healthy subjects. Unfortunately, this modeling technique cannot elucidate whether hypersecretion was caused by a primary

increase in β-cell activity due to the direct effect of the steroids or whether it is simply a compensatory mechanism to overcome the decrease of insulin sensitivity. While no differences were detected between glucose patterns during the FSIGT (Fig 1), our subjects were hyperglycemic after steroid treatment during the OGTT (Fig 2), which may be due to the different route of administration of glucose, ie, slower appearance in the periphery due to glucose gut absorption. Basal levels, in fact, remained almost unchanged, but stimulated glucose levels increased; nevertheless, the criteria of normal glucose tolerance were maintained.

Peripheral above-basal insulin concentrations increased during both tests. In the FSIGT, this finding was reflected by an overall moderate increase of posthepatic insulin delivery (BDR_{IV} and TID_{IV}). However, when considering the total appearance of insulin in the periphery during the first 60 minutes, the period of maximum dynamics, the magnitude of the increment was evident. In the OGTT, posthepatic delivery of the hormone (TID_{OG}) was augmented during the whole test. β-cell insulin secretion after dexamethasone increased almost twofold in the FSIGT, but posthepatic insulin release only by 1.4-fold. This fact was explained by an increase of hepatic extraction of insulin during the FSIGT. In the OGTT, we only saw a slight increase of hepatic extraction. The fact that β-cell hypersecretion was accompanied by an increase of hepatic extraction in both tests but the increase only reached statistical significance following the intravenous glucose challenge might be due to the less dynamic and smoother time course of insulin and C-peptide after oral glucose ingestion. Hepatic insulin extraction, in fact, is regarded to be adequately estimated from the more dynamic FSIGT.[12] The possible implications of the qualitative and quantitative behavior of the insulin and C-peptide concentration patterns on the modeling formulation and consequently on the estimation of hepatic insulin extraction have been discussed in detail in a previous report[12] and review.[27] Waldhäusl et al,[31] using the hepatic vein catheter technique, found that fractional extraction of insulin slightly increased in the basal state and decreased postprandially after acute glucocorticoid infusion. The present study instead investigated the role of hepatic insulin extraction in humans after chronic glucocorticoid exposure, which is a novelty of this investigation. Chap et al[32] studied hepatic glucose and insulin metabolism after oral glucose in conscious dogs, and reported a significantly reduced basal fractional hepatic extraction of insulin, which increased after oral glucose administration in the steroid-treated animals. Caro and Amatruda[25] found an increased insulin degradation in freshly isolated rat hepatocytes after 1 week of in vivo dexamethasone exposure. It was suggested that degradation could be regulated by a postbinding mechanism. Although the mechanism leading to a faster rate of insulin degradation is unknown, one possibility is the stimulation of either the quantity or the activity of degrading enzymes. For example, steroids are known to increase hepatic extraction of glucose precursors and to induce key enzymes required for gluconeogenesis.[33] It could also be hypothesized that there exist autoregulatory mechanisms for the control of insulin degradation, which are governed at least partially by the level of insulin in the plasma.[34] Previous studies in patients with primary hyperparathyroidism[35] and in patients with essential hypertension,[36] both insulin-resistant states associated with hyperinsulinemia, also revealed elevation of hepatic extraction of insulin during a FSIGT. This might lead to the hypothesis that increased hepatic insulin extraction prevents exaggerated peripheral hyperinsulinism following β-cell hypersecretion in response to insulin resistance.

Another novelty of this report is the quantification of the overproduction of IAPP. In a previous report simply speculating on insulin to IAPP ratios, we could not detect any significant changes in the molar insulin to IAPP ratio after cortisone treatment.[10] However, in a later study, we have shown that during an OGTT, endogenous IAPP and insulin have markedly different kinetics and therefore we raised some doubts about validity of the IAPP to insulin molar ratio in the non–steady state.[11] Possible pitfalls of the molar ratio are also evinced by the model analysis of FSIGT data that revealed a discrepancy between β-cell secretion and peripheral insulinemia due to a significant change in hepatic insulin extraction following cortisone treatment. Following these observations, we introduced a new method based on a simple ("minimal") mathematical description of insulin, C-peptide, and IAPP behavior during the OGTT to obtain IAPP production and clearance in relationship to those of insulin and C-peptide by analyzing peripheral concentration data.[11,15] To the best of our knowledge, this is the first study that directly quantified β-cell IAPP release in dexamethasone-treated humans, but it has already been successfully used to infer whole β-cell activity during the OGTT in obese and hypertensive subjects.[11] We applied this new method to our subjects and showed that IAPP release was threefold higher after dexamethasone treatment, as compared with the 1.9-fold increase of C-peptide. Our findings are in accordance with two recent in vitro investigations in rats that found a more pronounced increase of IAPP secretion relative to that of insulin[37,38] following glucocorticoid treatment, and concluded that this relative IAPP hypersecretion could facilitate islet amyloid formation and thus play an essential role in the development of glucose intolerance.

In summary, the marked increase of β-cell insulin secretion after glucocorticoid administration is associated with a significantly augmented hepatic extraction of insulin, preventing excessive peripheral hyperinsulinemia. The concomitant and even more pronounced overproduction of IAPP, with the potential induction of amyloid fiber formation, could be another factor provoking the well-known glucose intolerance observed in subjects under steroid treatment. Finally, the good agreement between results on β-cell activity obtained by the well-accepted modeling analysis of FSIGT data and the corresponding parameters evaluated by a recently introduced technique for OGTT data analysis demonstrates that it is possible to quantify β-cell insulin secretion with the latter test, which can be easily performed and causes lower discomfort to the patients.

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