Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans

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Schneiter, P., and L. Tappy. Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E806–E813, 1998.—Six healthy human subjects were studied during three 75-g oral, [13C]glucose tolerance tests to assess the kinetics of dexamethasone-induced impairment of glucose tolerance. On one occasion, they received dexamethasone (4 × 0.5 mg/day) during the previous 2 days. On another occasion, they received a single dose (0.5 mg) of dexamethasone 150 min before ingestion of the glucose load. On the third occasion, they received a placebo. Postload plasma glucose was significantly increased after both 2 days dexamethasone and single dose dexamethasone compared with control (P < 0.05). This corresponded to a 20–23% decrease in the metabolic clearance rate of glucose, whereas total glucose turnover ([6,6-2H]glucose), total (indirect calorimetry) and exogenous glucose oxidation (13CO2 production), and suppression of endogenous glucose production were unaffected by dexamethasone. Plasma insulin concentrations were increased after 2 days of dexamethasone but not after a single dose of dexamethasone. In a second set of experiments, the effect of a single dose of dexamethasone on insulin sensitivity was assessed in six healthy humans during a 2-h euglycemic hyperinsulinemic clamp. Dexamethasone did not significantly alter insulin sensitivity. It is concluded that acute administration of dexamethasone impairs oral glucose tolerance without significantly decreasing insulin sensitivity.

Glucose production; glucose clearance; insulin resistance; glucocorticoids

INCREASED CONCENTRATIONS of glucocorticoid hormones are recognized to impair glucose metabolism at multiple sites (3). Glucocorticoids, at high physiological doses, inhibit insulin-stimulated glucose transport on various isolated cells (6, 14) and decrease whole body insulin-mediated glucose uptake, oxidation, and storage (25, 31). This effect appears to be essentially due to a deficit of cellular glucose transport since dexamethasone decreases glucose transport in response to both insulin and non-insulin-related stimuli such as hypoxia (35). Glucocorticoids also interfere with insulin-induced stimulation of muscle blood flow (26). This may impair glucose utilization by decreasing the delivery of both glucose and insulin itself to insulin-sensitive tissue (1). In addition, supraphysiologial doses of glucocorticoids increase endogenous glucose production (EGP) and gluconeogenesis (34). As a consequence of these effects, various degrees of impairment of glucose tolerance are generally observed in patients with excessive production of endogenous glucocorticoids or with long-term glucocorticoid hormone treatment.

It is generally admitted that the effects of glucocorticoids on glucose metabolism lead to the development of insulin resistance after a significant time delay (1–2 days). Alterations of glucose tolerance have however been reported in healthy volunteers within 12 h of intravenous administration of relatively large doses of glucocorticoids (4). Little is known about the kinetics with which glucocorticoids interfere with the various pathways of glucose metabolism. It has been demonstrated that glucocorticoid analogs decrease insulin secretion of cultured β-cells within hours of their administration (22). Similarly, stimulation of glycogen synthase activity and increased hepatic and skeletal muscle glycogen concentrations have been observed in animals treated with glucocorticoids for a few hours (29). Such a stimulation of glycogen synthesis may secondarily lead to the development of insulin resistance due to the inhibitory effect of increased glycogen concentrations on glycogen synthase activity (7, 28). Stimulation of lipolysis and lipid oxidation has also been shown to be involved in the metabolic alterations induced by glucocorticoids (12, 31). An early stimulation of lipid oxidation may therefore possibly impair endogenous glycogen utilization and contribute to increased muscle glycogen concentrations. This may in turn lead to the development of insulin resistance.

To gain further insights on the kinetics with which high physiological concentrations of glucocorticoids affect glucose metabolism, we assessed the effects of a single administration of dexamethasone 150 min before or of administration of dexamethasone over 2 days on the metabolism of an oral glucose load. Exogenous glucose oxidation, hepatic glucose uptake, and peripheral glucose storage were measured by means of a dual isotope technique. In addition, the effect of a single dose of dexamethasone on insulin sensitivity was also measured in another group of healthy volunteers.

METHODS

Subjects. Twelve healthy volunteers were selected to take part in one of two protocols. They were in good health and had no personal or family history of obesity or diabetes. The experimental protocols were approved by the ethical committee of Lausanne University School of Medicine, and every subject provided an informed written consent.

General procedure. Experiments began between 7:00 and 8:00 AM after a 10- to 12-h fast. After having voided, subjects laid quietly supine in a bed. One indwelling venous cannula was inserted into an antecubital vein for infusion of tracers and/or 20% glucose. Another cannula was inserted into a wrist vein of the contralateral hand and served for the periodical collection of blood samples. This hand was placed in a thermostabilized box heated at 55°C to achieve partial...
arterialization of venous blood. Throughout the experiments, respiratory gas exchanges were monitored by open circuit indirect calorimetry using a ventilated hood (18).

Protocol 1. Six volunteers (4 males, 2 females, age 24.8 ± 2.7 yr, weight 71.6 ± 2.8 kg, height 174.3 ± 4.1 cm, body mass index 23.7 ± 1.1 kg/m², means ± SE) participated in this protocol in which the effects of dexamethasone on the metabolism of an oral glucose load were studied. Each subject took part in three experiments, separated by at least 14 days. On one occasion, 2 mg/day dexamethasone had been administered as four doses of 0.5 mg at 7:00 AM, 12:00 AM, 6:00 PM, and 10:00 PM during the previous 2 days, and one dose of 1 mg was administered at their arrival the morning of the test (2 days dexamethasone). On another occasion, a placebo was administered four times a day during the previous 2 days, and one dose of 1 mg dexamethasone was administered at their arrival (single dose dexamethasone). On the third occasion, placebo was administered during the previous 2 days and in the morning of the test (control). Subjects were blinded to their treatment they received.

During each test, an infusion of [6,6-2H]glucose (4-mg/kg bolus, 40 µg·kg⁻¹·min⁻¹; Mass Trace, Woburn, MA) was started immediately after the insertion of the venous cannulas and was continued throughout the 390 min of the experiment. After 2 h of tracer equilibration, two blood samples were taken 30 min apart for the determination of basal EGP, followed by an ingestion of 75 g glucose labeled with 0.066% [U-13C]glucose (Cambridge Isotope Laboratories, Andover, MA) and dissolved in 300 ml lemon-flavored water over 5 min (time 150). Blood samples, for determination of tracers, hormones, and substrates and breath samples for determination of 13CO₂, were subsequently collected every 30 min.

Protocol 2. Six subjects took part in this protocol aimed at determining the effects of a single administration of 1 mg dexamethasone on insulin sensitivity. Each subject took part in two experiments. On one occasion, 1 mg dexamethasone was administered at their arrival the morning of the test. On another occasion, a placebo was administered. Subjects were blinded to their treatment. Immediately after the insertion of the cannulas, a primed-continuous infusion of [U-13C]glucose was started. After 3 h equilibration of the tracer, two blood samples were obtained 30 min apart to determine basal EGP. Thereafter, a 2-h euglycemic hyperinsulinemic clamp was performed. Exogenous glucose was labeled with 0.04% [U-13C]glucose (Hot infusate technique; see Ref. 10). Blood samples for determination of [13C]glucose, hormones, and substrate concentrations and breath samples for determination of 13CO₂ were collected every 30 min.

Analytic procedures. Plasma glucose isotopic enrichments were determined on deproteinized samples partially purified over sequential cation-anion exchange resins (AG 1-X8 and AG 50W-X8; Bio-Rad, Richmond, CA). For [6,6-2H]glucose measurements, penta-acetyl [13C]glucose was analyzed with gas chromatography-mass spectrometry (Hewlett Packard, Palo Alto, CA) in electron impact mode with selective monitoring of mass-to-charge ratios 200 and 202. For [13C]glucose, samples were purified with HPLC on an Aminex HPX-87C column, as described (11), evaporated to dryness, and analyzed with continuous-flow isotope ratio mass spectrometry (Roboprep CN/Tracermass; Europa Scientific, Crewe, UK). Breath [13C]O₂ was analyzed with continuous-flow isotope ratio mass spectrometry (Roboprep G/Tracermass, Europa Scientific).

Plasma insulin (kit from Biodata SpA, Guidonia Montecelio, Italy) and plasma and urine glucose concentrations were measured with a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA). Urine nitrogen concentrations were measured with the method of Kjeldahl (15).

Calculations. In protocol 1, glucose rates of appearance (Rd) and disappearance (Rd) were calculated from plasma [6,6-2H]glucose using Steele’s equations for nonsteady state (8) using a pool fraction of 0.75 and distribution volume of 0.2. In protocol 2, Rd and Rd were calculated from plasma [13C]glucose using the labeled infusate technique (10).

Metabolic clearance rate of glucose was calculated as Rd divided by plasma glucose concentration.

Glucose uptake was calculated as oral glucose ingestion − Δglucose concentration (240 min × body weight × 0.2), where 0.2 is the volume of distribution of extracellular glucose in liters per kilogram. This calculation assumes that glucose absorption was completed after 4 h.

First-pass hepatic glucose uptake was calculated as the difference between the amount of glucose ingested (75 g) and the systemic appearance of exogenous glucose cumulated over 4 h. Exogenous glucose storage was calculated as the difference between glucose ingested and exogenous glucose oxidation cumulated over 4 h.

Systemic appearance of exogenous glucose was calculated from Rd and plasma [13C]glucose using the equations of Pietro et al. (23).

EGP was calculated as Rd − the systemic appearance of exogenous glucose.

Exogenous glucose oxidation was calculated from the 13C enrichment of ingested glucose and 13C CO₂ production as follows:

\[
\text{exogenous glucose oxidation (µmol/min)} = \frac{13\text{CO}_2}{13\text{C} \text{glucose}} \times V_{\text{CO}_2} \times \frac{1}{0.54} \times \frac{1}{0.134}
\]

where 0.54 is the recovery in breath of 13C CO₂ produced during oxidation of [U-13C]glucose (27). VCO₂ is in milliliters per minute and 13C O₂ and [13C]glucose in atom percent excess. This factor was determined as the recovery in breath of 13C CO₂ as an equimolar mixture of [13C]bicarbonate and [1,2-13C]acetate in healthy volunteers during an infusion of glucose in resting conditions. This factor differs from that obtained with bicarbonate alone because recovery in breath of the two carbons of acetyl-CoA is substantially lower than that of bicarbonate (36, 37). The factor 0.134 is the CO₂ production in milliliters during oxidation of 1 µmol glucose.

Exogenous glucose storage was calculated as glucose uptake − exogenous glucose oxidation.

Net substrate oxidation rates and energy expenditure were calculated from respiratory gas exchanges and urinary nitrogen excretion using the equations of Livesey and Elia (19).

Data analysis. The various components of glucose metabolism are expressed in micromoles per kilogram per minute. The changes in hormone and substrate concentrations over time were analyzed by multiple-way ANOVA, ANOVA for repeated measurements, and paired t-tests. Cumulated values (in grams) over the 4 h after ingestion of the glucose load are also presented. Comparisons of means were performed with ANOVA and paired t-test. All data are expressed as means ± SE.

RESULTS

Protocol 1. In placebo-treated subjects, plasma glucose increased to a peak of 8.3 ± 0.4 mmol/l 45 min after ingestion of 75 g glucose and returned to basal values after 180 min. Plasma insulin increased to a maximum
of 410 ± 134.4 pmol/l after 90 min and returned to basal values after 180 min (Fig. 1). Net carbohydrate oxidation increased significantly after 60 min, whereas lipid oxidation showed a mirror decrease (Fig. 2). Evolution of labeled plasma glucose and breath 13CO2 are shown in Fig. 3. Ra increased to a peak of 31.1 ± 4.3 µmol·kg-1·min-1 after 30 min and decreased progressively thereafter to return to values (10.3 ± 1.5 µmol·kg-1·min-1) close to basal values after 4 h. Exogenous glucose appearance represented on average 69% of total Ra over the 4 h after ingestion of the load. EGP was decreased by 50% after 120 min and increased progressively thereafter (Fig. 4).

Average glucose uptake was 77.0 ± 0.6 g/4 h. Ra totaled 62.2 ± 3.7 g glucose over the 4 h after ingestion of the glucose load. Of this, 69% corresponded to exogenous glucose metabolism, whereas EGP contributed only 31%. Forty-three percent of the oral load was taken up by the splanchnic bed, and 57% was disposed of nonoxidatively (Table 1).

Administration of dexamethasone as a single dose or as a 2-day treatment increased the peak glucose concentration after glucose ingestion by 14–19% and glucose concentration after 4 h by 46%. The plasma glucose curves were similar after a single dose and after 2 days of dexamethasone. Plasma insulin was increased by 74% in the basal state, by 124% at 120 min, and by 375% after 4 h after a 2-day treatment but was not affected by administration of a single dose (Fig. 1). Glucose uptake was slightly decreased to 73.9 ± 0.7 g/4 h (P < 0.05) and 73.9 ± 1.5 (not significant) after a single dose and 2 days of dexamethasone, respectively.

Carbohydrate and lipid oxidation, Ra, and EGP were not affected by dexamethasone, but the metabolic clearance of glucose was decreased on average by 23% after a single dose of dexamethasone and by 27% after a 2-day treatment (Figs. 2 and 4 and Table 1). Exogenous glucose appearance, splanchnic glucose uptake, exogenous glucose oxidation, and nonoxidative exogenous glucose disposal were all unaffected by dexamethasone (Fig. 4).

Protocol 2. In this protocol, plasma glucose was clamped at 5.53 ± 0.03 mmol/l in subjects having received a single dose of placebo and at 5.60 ± 0.06 mmol/l after a single dose of dexamethasone. Steady-state plasma insulin was identical under both conditions (511.2 ± 4.8 vs. 507.6 ± 3.6 pmol/l). The glucose infusion rate required to maintain euglycemia was not significantly altered by dexamethasone (Table 2). Evolution over time of plasma [13C]glucose and breath...
administered 2.5 h before ingestion of a glucose load significantly increased postprandial glycemia, indicating an early effect of glucocorticoid on glucose metabolism.

The increase in postprandial glycemia observed after a single dose of dexamethasone does not appear to be related to an inhibition of insulin actions because insulin-stimulated glucose disposal and oxidation, assessed at a constant plasma insulin concentration that produces a submaximal stimulation of glucose disposal.

DISCUSSION

Glucocorticoids are generally held to interfere with glucose tolerance after a significant time delay. In contrast with this concept, we observed in the present experiments that a single dose of 1 mg dexamethasone

13CO2 and of exogenous [13C]glucose infusion are shown in Fig. 5. Net carbohydrate oxidation, lipid oxidation, and [13C]glucose oxidation were also not altered by dexamethasone (Fig. 6). EGP was similarly suppressed by hyperinsulinemia under both conditions (Table 2).

Fig. 3. Breath 13CO2 (A), plasma [13C]glucose (B), and plasma [6,6-2H]glucose (C) during an oral glucose tolerance test performed after a single dose (●) or after a 2-day treatment with dexamethasone (○) or in control experiments (□) during protocol 1.

Fig. 4. Glucose appearance rate (A), endogenous glucose production (B), and exogenous glucose appearance rate (C) during an oral glucose tolerance test performed after a single dose (●) or after a 2-day treatment with dexamethasone (○) or in control experiments (□) during protocol 1.
were not significantly affected by a dexamethasone administration of such a short duration. The suppression of EGP was also not affected. This contrasts with the effects of a 2-day treatment with dexamethasone, which has been shown to produce a 40% decrease in insulin-mediated glucose disposal and of glucose oxidation in healthy subjects (21, 31).

The mechanisms responsible for this early impairment of oral glucose tolerance after acute dexamethasone administration remain unknown. Whole body glucose metabolism and EGP were identical with those observed in control experiments over the 4 h after ingestion of the glucose meal. The metabolic clearance rate of glucose was however decreased by 23% on average after acute dexamethasone administration. This occurred in the absence of demonstrable alterations of carbohydrate or lipid oxidation. This observation, linked to the documentation that insulin sensitivity at euglycemia was not significantly altered, may have suggested an impaired non-insulin-mediated glucose disposal. Other investigators however have clearly established that this portion of glucose metabolism is unaffected by glucocorticoids (2). Two possible mechanisms may be postulated. First, dexamethasone has been shown to inhibit insulin secretion both on \( \beta \)-cells in vitro (22) and in transgenic mice with increased \( \beta \)-cell glucocorticoid sensitivity (9). Such an effect of dexamethasone may be responsible for a shift to the right of the glucose-insulin secretion curve; as a consequence, plasma glucose may increase until normal postprandial insulin concentrations are attained. With this scheme, a normal stimulation by insulin of glucose utilization and oxidation would be attained at the expense of an increase in glycemia. Due to the relatively slight increase in glycemia, glucose-mediated glucose disposal is however not expected to increase to any great extent. This scheme may explain the apparent paradox of an increased glycemia and decreased

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**Table 1. Parameters of glucose metabolism after oral glucose (cumulated over 4 h)**

<table>
<thead>
<tr>
<th></th>
<th>Glucose Appearance Rate, g/4 h</th>
<th>Exogenous Glucose Appearance Rate, g/4 h</th>
<th>Exogenous Glucose Oxidation, g/4 h</th>
<th>Endogenous Glucose Production, g/4 h</th>
<th>Exogenous Glucose Storage, g/4 h</th>
<th>Glucose Clearance, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>62.2 ± 3.7</td>
<td>43.0 ± 2.4</td>
<td>31.9 ± 2.1</td>
<td>19.2 ± 2.4</td>
<td>45.1 ± 2.1</td>
<td>0.26 ± 0.02</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>61.0 ± 2.3</td>
<td>40.9 ± 2.2</td>
<td>30.6 ± 1.9</td>
<td>20.1 ± 2.0</td>
<td>43.3 ± 2.2</td>
<td>0.20 ± 0.03*</td>
</tr>
<tr>
<td>2 day</td>
<td>59.7 ± 2.8</td>
<td>38.8 ± 2.9</td>
<td>29.5 ± 1.4</td>
<td>20.9 ± 2.6</td>
<td>44.5 ± 1.3</td>
<td>0.19 ± 0.02†</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 and †P < 0.02 vs. controls.

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**Table 2. Parameters of glucose metabolism during euglycemic hyperinsulinemic clamp**

<table>
<thead>
<tr>
<th></th>
<th>Glucose Infusion, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
<th>Endogenous Glucose Production, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
<th>Exogenous Glucose Oxidation, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>12.5 ± 0.4</td>
<td>5.1 ± 1.0</td>
<td>17.9 ± 0.9</td>
</tr>
<tr>
<td>Clamp</td>
<td>47.2 ± 5.2</td>
<td>12.8 ± 0.4</td>
<td>15.9 ± 1.7</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>37.7 ± 8.0</td>
<td>12.8 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Clamp</td>
<td>37.7 ± 8.0</td>
<td>15.9 ± 1.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.002 vs. basal.

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Fig. 5. Breath \(^{13}\text{CO}_2\) (A), plasma \(^{13}\text{C}\)glucose (B), and \(^{13}\text{C}\)glucose (C) infusion rate during a euglycemic hyperinsulinemic clamp performed after a single dose of dexamethasone (●) or in control experiments (□).
glucose clearance in the presence of unchanged glucose fluxes and insulin sensitivity. Second, plasma glucose concentration per se is recognized to be a major factor for the regulation of EGP (30). It is therefore possible that dexamethasone acutely decreased the inhibitory effect of glucose on its production at the level of liver cells. The observation that, after acute dexamethasone administration, EGP remained similar even though plasma glucose had increased, would be consistent with such a “desensitization” of liver cells to glucose. In regard of these two possible mechanisms, it is of interest to note that patients with Maturity Onset Diabetes of the Young secondary to a mutation of the glucokinase gene display similar alterations. These patients have both an impaired insulin secretion and a decreased postprandial inhibition of glucose production. Their mild hyperglycemia however restores basal and postprandial plasma insulin concentrations comparable to those observed in healthy subjects and hence normal glucose utilization. As a result, their glucose clearance decreases even though insulin sensitivity is not grossly altered (5, 30).

The metabolic response to an oral glucose load was identical in most aspects when the volunteers received dexamethasone as an acute single dose or during 2 days. Plasma glucose increments, whole body glucose utilization, first-pass splanchnic glucose uptake, exogenous glucose oxidation, and nonoxidative glucose disposal were all comparable. The only significant difference between these two conditions was a marked increase in basal and postprandial insulin concentrations. This increase in insulin secretion is likely to be related to the important decrease in insulin sensitivity known to occur after 2 days of dexamethasone treatment (30, 31). Interestingly, stimulation of insulin secretion under these conditions was able to completely overcome insulin resistance, resulting in normal whole body glucose uptake, oxidation, storage, and EGP.

The estimation of first-pass splanchnic glucose uptake in this study was substantially higher than values reported elsewhere in the literature (20, 24). Methodological aspects may explain these differences. Glucose absorption may not have been completed after 4 h, leading to underestimation of exogenous Ra. In addition, the accuracy with which Ra was calculated may have been low because relatively few determinations were performed over the 4-h postprandial period, especially during the first 2 h during which both glucose concentrations and glucose enrichment changed rapidly. In this regard, markedly lower rates of first-pass splanchnic uptake (about 10%) were observed in healthy volunteers receiving a continuous intragastric infusion of glucose and amino acids (17). It is interesting to note that in the same study administration of high doses of prednisone, during 10 days, did not alter splanchnic glucose extraction and endogenous glucose production (17).

The kinetics with which [13C]glucose appeared in the plasma was very similar with or without dexamethasone, indicating that glucocorticoid-induced alterations of glucose absorption or of first-pass glucose uptake were unlikely. The rate of exogenous [13C]glucose appearance was calculated from plasma [13C]glucose enrichment measured with isotope ratio mass spectrometry. This method does not differentiate between uniformly labeled glucose having escaped splanchnic uptake and partially labeled glucose issued from splanchnic degradation of oral glucose to three carbon compounds and subsequent reconversion into glucose. It is therefore possible that the latter pathway was increased after dexamethasone due to stimulation of gluconeogenesis, whereas the systemic absorption of unchanged exogenous glucose was decreased. Results obtained by Horber et al. (17), showing that the systemic absorption of enteral [6,6-2H]glucose was not altered by high-dose glucocorticoids, suggest however that this was not the case. Finally, the model used for calculation of glucose kinetics (monocompartmental) may account for part of the differences observed.

The mechanisms responsible for the development of insulin resistance over time cannot be determined from the present experiments. Several reports in humans and in rats indicate that dexamethasone is likely to interfere with glucose transport (31, 33, 35). Because GLUT-4 protein appears unaltered in muscle cells of
rats treated with dexamethasone, it has been suggested that GLUT-4 specific activity may be decreased (13). Increased hepatic and muscle glycogen concentrations have also been substantiated after glucocorticoid treatment (29). If present, an increase in muscle glycogen may possibly participate in insulin resistance by exerting a feedback inhibition on glycogen synthase activity (7).

The mechanisms by which insulin secretion is increased after a 2-day treatment with dexamethasone also remain a mystery. Increased glucose concentrations cannot be incriminated since the plasma glucose curves were strictly identical after acute or 2 days of dexamethasone treatment, whereas insulin concentrations were increased only in the latter condition. It was recently reported during hyperglycemic clamp studies that infusion of a lipid emulsion that induces acute insulin secretion during such lipid infusions, or induced insulin secretion during such lipid infusions, or exerting a feedback inhibition on glycogen synthase (7).

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