Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 6035–6039, July 1992
Medical Sciences

The diabetogenic effects of glucocorticoids are more pronounced in low- than in high-insulin responders

(prediabetes/increased risk of developing non-insulin-dependent diabetes mellitus)

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Communicated by Rolf Luft, January 6, 1992 (received for review July 3, 1991)

ABSTRACT **We investigated in six low- and six high-insulin responders (LIR and HIR) the effect of dexamethasone (Dex, 15 mg orally during 48 hr) on oral glucose tolerance (OGTT), glucose turnover under basal conditions and during glucose infusion of 2 mg·kg^{-1}·min^{-1}, and insulin response during hyperglycemic clamp. Dex increased fasting glucose more in LIR ($P < 0.05$). During OGTT, Dex caused a more prominent increment in glucose in LIR, whereas the increment in insulin was less in LIR ($P < 0.05$). After Dex, in three LIR but in no HIR, a diabetic OGTT was observed. Dex significantly increased basal hepatic glucose production (turnover measured with [6-^{3}H]glucose), hepatic total glucose output (turnover measured with [2-^{3}H]glucose), and glucose cycling (hepatic total glucose output − hepatic glucose production) only in LIR. Dex decreased basal glucose metabolic clearance to the same extent in LIR and HIR. Hyperglycemic clamp revealed that Dex induced a significant increase ($P < 0.05$) in insulin response only in HIR. Dex effects on insulin release during hyperglycemic clamp were negatively correlated with the glucose area during Dex OGTT ($P < 0.01$). Thus, the double tracer method provided a new insight into the pathogenesis of the steroid effect on carbohydrate tolerance. Dex increased basal glycemia more in LIR because only in LIR was glucose production increased. During OGTT, the LIR who were not able to counteract the effects of Dex by an appropriate enhancement in insulin secretion developed a decreased OGTT. The evaluation of insulin response after Dex may thus allow differentiation of the subset of LIR that run an increased risk of non-insulin-dependent diabetes mellitus.**

The dynamics of insulin response can be studied after a standardized glucose infusion test (GIT), which induces a biphasic insulin release (1). In humans, the magnitude of this response is to a large extent genetically determined (2). Cerasi and Luft (1) proposed that around 20% of healthy subjects have a low initial insulin response and may be considered as prediabetics for non-insulin-dependent diabetes mellitus (NIDDM). This hypothesis is supported by prospective studies that demonstrate that subjects with low insulin response appear to run an increased risk of developing NIDDM (3, 4). A relationship between diminished insulin response and NIDDM was also suggested by the studies of Rull *et al.* (5), which demonstrate that an acute administration of cortisone decreased oral glucose tolerance (OGTT) mainly in subjects with low insulin response.

We have compared the effects of steroid-induced resistance on β-cell secretory capacity in low- and high-insulin responders (LIR and HIR) (6). There was significant positive correlation between pre-dexamethasone (pre-Dex) insulin response and the enhancement of insulin secretion in response to a glucose challenge during Dex treatment. Therefore, we assumed that LIR would not appropriately compensate for steroid-induced insulin resistance by an adequate enhancement of insulin secretion. The present study aims (*i*) to investigate the action of Dex on OGTT and glucose turnover in LIR and HIR and (*ii*) to relate these effects to the β-cell secretory capacity. We measured hepatic glucose production (HGP; turnover measured with [6-^{3}H]glucose), hepatic total glucose output (HTGO; turnover measured with [2-^{3}H]glucose), and glucose cycling (GC; HTGO − HGP). This study therefore contributes to the exploration of the pathogenetic mechanisms for the difference in Dex effects on glucose tolerance in LIR and HIR by the use of the hyperglycemic clamp (HC) technique and isotopic studies with the double tracer technique.

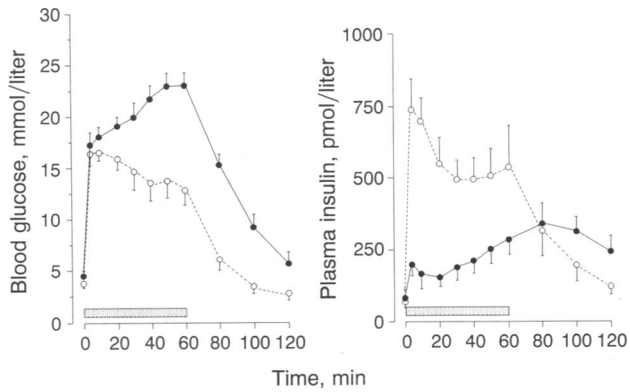

FIG. 1. Effect of a GIT on glucose and insulin levels (mean ± SEM) in six LIR (●) and six HIR (○).

MATERIALS AND METHODS

Subjects and Protocols. Six LIR (five males, one female) and six HIR (all males) participated. The mean age of LIR was 41.3 years (range, 28–58 years) and of HIR was 43.7 years (range, 40–52 years). The mean (and range) of body mass index was 23.2 (20.8–26.2 kg/m^2) in LIR and 23.4 (21.2–26.7 kg/m^2) in HIR. In LIR insulin response to a GIT was blunted (Fig. 1). Insulin secretion during a GIT was analyzed by a mathematical model that assumes that glucose initiates insulin release by an immediate action (parameter KI) (1). This parameter was previously used in designating subjects as LIR (KI < 0.30) or HIR (KI > 0.30) (7). To obtain clear separation of groups, criteria were arbitrarily set for

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Abbreviations: Dex, dexamethasone; OGTT, oral glucose tolerance; LIR, low-insulin responders; HIR, high-insulin responders; NIDDM, non-insulin-dependent diabetes mellitus; HGP, hepatic glucose production; HTGO, hepatic total glucose output; GC, glucose cycling; HC, hyperglycemic clamp; GIT, glucose infusion test; MCR, metabolic clearance rate; M/I ratio, insulin sensitivity index.

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Table 1. Effects of Dex on fasting blood glucose and plasma insulin concentrations in LIR and HIR

	Glucose, mmol/liter		Insulin, pmol/liter	
Subjects	Control	Dex	Control	Dex
LIR	4.55 ± 0.16	5.84 ± 0.22**†	69.6 ± 7.9	142.8 ± 26.6*
HIR	4.51 ± 0.17	5.18 ± 0.17**†	81.1 ± 8.6	135.6 ± 11.5**

Values are the mean ± SEM of three experiments: OGTT, HC, and glucose turnover. *, $P < 0.02$, and **, $P < 0.005$, Dex vs. control experiments. †, $P < 0.05$, LIR vs. HIR; P not significant for other LIR vs. HIR.

LIR at KI < 0.3 and for HIR at KI > 0.6. All subjects had normal fasting blood glucose (<6 mmol/liter).

The protocols used were approved by the Ethical and Radioisotope Committees. Studies were performed after an overnight fast and in randomized order with a lapse of at least 7 days between two studies. Each subject was studied on seven occasions during a period of under a year. In all protocols, except one, 15 mg of Dex was taken orally over 48 hr, 3 mg in the morning and evening for 2 days and a last dose of 3 mg of Dex in the morning of the experimental day.

Three sets of experiments were performed. (*i*) OGTT was performed according to World Health Organization criteria (8). (*ii*) In isotope studies a primed constant infusion of [2-^{3}H]glucose and [6-^{3}H]glucose (New England Nuclear) was started at 08:00 and continued for 240 min. The priming dose was 24–30 μCi and the rate of infusion was 0.20–0.25 μCi/min (1 Ci = 37 GBq). Following a 120-min equilibration, unlabeled glucose was infused at 2 mg·kg^{-1}·min^{-1}. (*iii*) In HC studies glucose concentrations were kept at 11.0 mmol/liter (9). By dividing the amount of glucose infused (M) with the mean insulin level (I), a measure of insulin sensitivity was obtained (M/I index) (10).

Tracer Methods and Calculations. The radioactivity of [6-^{3}H]glucose was determined by the dimedone procedure (11). The radioactivity of [2-^{3}H]glucose was calculated as the difference between total radioactivity and that of [6-^{3}H]glucose.

At the end of the equilibration period, HGP and HTGO (R_a, rates of appearance of [6-^{3}H]glucose and [2-^{3}H]glucose, respectively) were calculated as the rate of tracer infusion (R_{a*}) divided by the specific activity of [6-^{3}H]glucose or [2-^{3}H]glucose. During the glucose infusion, R_a and rate of disappearance of glucose (R_d) were determined by a modified single-compartment analysis of glucose turnover (12–14).

GC was determined as the difference between HTGO and HGP (14). GC values were considered as zero if the numerical values were negative. Metabolic clearance rate (MCR) was calculated as R_d, divided by the glucose concentration. Glucose was determined with a glucose oxidase method, and insulin and glucagon were determined by RIA.

Results are expressed as mean ± SEM. Student's *t* test was performed for nonpaired and paired data and Pearson's coefficient for correlation.

RESULTS

Basal Levels of Glucose and Insulin. Basal blood glucose and plasma insulin concentrations were the same in LIR and HIR and increased significantly in both groups after Dex treatment (Table 1). In Dex experiments glucose concentrations were significantly higher in LIR than in HIR ($P < 0.05$). Insulin levels were not different between groups after Dex, despite higher plasma glucose in LIR.

OGTT With and Without Pretreatment with 7.5 or 15 mg of Dex. LIR and HIR displayed normal OGTT. The rise in blood glucose during control OGTT was similar in LIR and HIR (Table 2). Dex treatment increased glucose and insulin areas during OGTT in HIR and LIR. However, in Dex experiments the glucose area was greater in LIR, whereas the insulin area was greater in HIR.

When individual responses to Dex were analyzed it appeared that Dex had a more pronounced diabetogenic effect in LIR. Thus, with low and high Dex doses, one and three LIR, respectively, developed diabetic OGTT. Among HIR, none developed a diabetic OGTT.

Plasma Glucose and Hormone Concentrations During Tracer Studies. At the end of the equilibration period, plasma glucose values were 4.9 ± 0.3 mmol/liter in LIR vs. 5.2 ± 0.2 mmol/liter in HIR (no significant difference). When treated with 15 mg of Dex, basal glucose increased to higher levels in LIR (6.5 ± 0.2 mmol/liter) than in HIR (5.6 ± 0.2 mmol/liter) ($P < 0.02$).

The basal insulin values in LIR and HIR were 58.8 ± 1.4 vs. 75.3 ± 7.9 pmol/liter (no significant difference). During treatment with Dex, insulin increased to similar levels in both groups (114.8 ± 13.6 and 114.8 ± 9.3 pmol/liter, respectively).

During glucose infusion, the plasma glucose pattern was similar in LIR and HIR and plateaued at 6.1 ± 0.2 and 6.2 ± 0.1 mmol/liter. Insulin levels also were similar. However, in Dex experiments, higher plasma glucose values were attained in LIR than HIR (8.4 ± 0.2 vs. 7.0 ± 0.3 mmol/liter, $P < 0.005$), whereas insulin levels were insignificantly lower (172 ± 17 vs. 245 ± 51 pmol/liter). Glucagon levels were similar in LIR and HIR under basal conditions and during glucose infusion.

Total Glucose Output, Production, Cycling, and MCR. In each experiment, an isotopic plateau was reached during the last 30 min of the equilibration period. The mean coefficient of variation (CV) was <4% for both isotopes in LIR and HIR. Plasma glucose was also stable, with an average CV of <1.6%.

Basal HTGO was the same in LIR (10.60 ± 0.39 μmol·kg^{-1}·min^{-1}) and in HIR (10.38 ± 0.28 μmol·kg^{-1}·min^{-1})

Table 2. Effects of Dex on incremental glucose (mmol/liter per 2 hr) and insulin (pmol/liter per 2 hr) areas during OGTT in LIR and HIR

	LIR		HIR	
Exp.	Incremental glucose area	Incremental insulin area	Incremental glucose area	Incremental insulin area
Control	21.5 ± 3.2	1377 ± 237	18.9 ± 2.0	2375 ± 388
Dex, mg				
7.5	41.7 ± 3.8**†	2533 ± 488*†	26.8 ± 5.3†	4750 ± 703*†
15	39.7 ± 3.8**††	2310 ± 330*	23.6 ± 2.9††	4571 ± 983

Values are the mean ± SEM. *, $P < 0.05$, and **, $P < 0.001$, Dex vs. control experiments. †, $P < 0.05$, and ††, $P < 0.01$, LIR vs. HIR.

Table 3. Effects of Dex on basal HGP and HTGO

	HGP, μmol·kg^{-1}·min^{-1}		HTGO, μmol·kg^{-1}·min^{-1}	
Subjects	Control	Dex	Control	Dex
LIR	9.55 ± 0.28	10.88 ± 0.44*†	10.60 ± 0.39	13.26 ± 0.61*†
HIR	10.10 ± 0.56	9.27 ± 0.33†	10.38 ± 0.28	10.88 ± 0.61†

Values are the mean ± SEM. *, $P < 0.01$, Dex vs. control experiments. †, $P < 0.02$, LIR vs. HIR; P not significant for other LIR vs. HIR.

(Table 3). However, when Dex was administered, HTGO increased significantly in LIR but not in HIR. Basal HGP was comparable in LIR (9.55 ± 0.28 μmol·kg^{-1}·min^{-1}) and HIR (10.10 ± 0.56 μmol·kg^{-1}·min^{-1}). Again, Dex significantly increased HGP in LIR but not in HIR. At the end of the glucose infusion, suppression of HGP and HTGO was of the same magnitude in LIR and HIR in control and Dex experiments (Fig. 2).

Under basal conditions, a significant GC was operative in LIR and HIR (Table 4). After Dex treatment, GC increased in LIR and HIR, but this increase was only significant in LIR. Basal MCR was comparable in LIR and HIR in control experiments (Table 5). Dex treatment suppressed basal MCR significantly and to the same extent in both groups.

During glucose infusion, in Dex experiments there was a significant but transient decline in MCR in HIR ($P < 0.05$). This suppression was more pronounced in LIR ($P < 0.001$) (Fig. 2). There was no significant correlation between fasting plasma glucose and HTGO, HGP, GC, and MCR in control experiments. In Dex experiments, fasting plasma glucose was positively correlated with HGP ($P < 0.01$) and HTGO ($P < 0.05$) but was not correlated with GC or MCR.

Notably, when the glucose increments during OGTT in control experiments were compared to turnover parameters (Fig. 2), a significant positive correlation with GC ($r = 0.67$, $P < 0.05$) but not with HTGO, HGP, or MCR was found.

HC. During HC, levels of blood glucose were close to 11.0 mmol/liter in both groups. The amounts of glucose that had to be infused during the period 20–120 min to maintain the HC were much higher in HIR (101.1 ± 20.5 μmol·kg^{-1}·min^{-1}) than in LIR (42.0 ± 5.0 μmol·kg^{-1}·min^{-1}), ($P < 0.02$). In the Dex experiments, the amount of glucose required to maintain

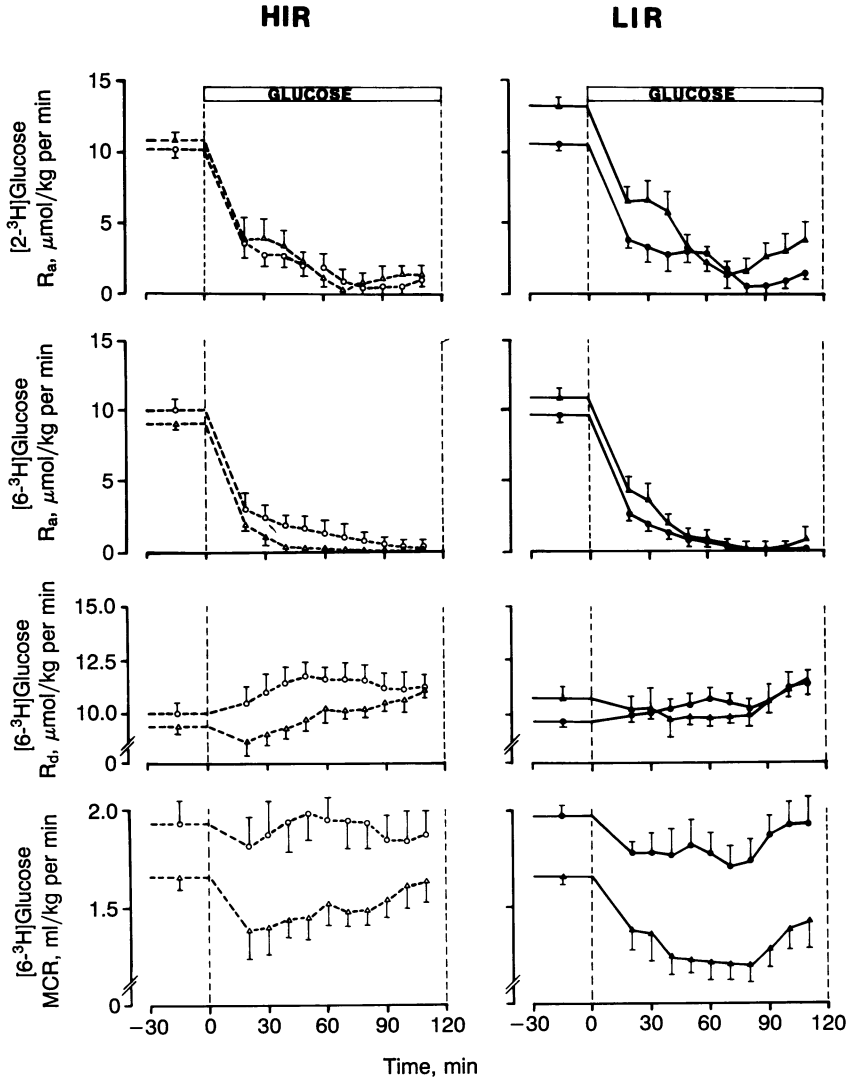

FIG. 2. Effect of glucose infusion (2 mg·kg^{-1}·min^{-1}; mean ± SEM) on rate of appearance of glucose (R_a), rate of disappearance of glucose (R_d), and MCR of glucose without Dex (LIR, ●; HIR, ○) and after administration of 15 mg of Dex (LIR, ▲; HIR, △).

Table 4. Effect of Dex on GC in basal state in control and Dex experiments in LIR and HIR

Subjects	Basal GC, μmol·kg^{-1}·min^{-1}	
	Control	Dex
LIR	1.05 ± 0.28	2.38 ± 0.33*
HIR	0.47 ± 0.17	1.61 ± 0.39

Values are the mean ± SEM. *, $P < 0.05$, Dex vs. control experiments. P not significant for LIR vs. HIR.

Table 5. Effect of Dex on MCR in basal state in control and Dex experiments in LIR and HIR

Subjects	Basal MCR, ml·kg^{-1}·min^{-1}	
	Control	Dex
LIR	1.97 ± 0.05	1.66 ± 0.02*
HIR	1.94 ± 0.11	1.66 ± 0.07*

Values are the mean ± SEM. *, $P < 0.005$, Dex vs. control experiments. P not significant for LIR vs. HIR.

constant hyperglycemia decreased by about 50% in both groups (44.6 ± 8.2 μmol·kg^{-1}·min^{-1} in HIR vs. 24.3 ± 3.3 μmol·kg^{-1}·min^{-1} in LIR) ($P < 0.05$).

During HC, the release of insulin was biphasic (Fig. 3), in control and Dex experiments, but in HIR the biphasic pattern was more pronounced. The mean level of insulin during the entire 120-min period was significantly higher in HIR than in LIR in control ($P < 0.05$) and Dex experiments ($P < 0.01$). Notably, Dex treatment increased insulin response in HIR but not in LIR. Insulin sensitivity index (M/I ratio), an indicator of insulin sensitivity, was comparable in LIR and HIR in control (22.2 ± 3.2 vs. 19.2 ± 4.2) and Dex experiments (8.2 ± 1.1 vs. 5.6 ± 0.7). Thus, the Dex-induced decrease of insulin sensitivity was similar in both groups.

In Dex experiments, the glucose area during OGTT was inversely correlated with insulin secretory capacity measured as the mean insulin level during the 120-min glucose clamp period (Fig. 4). In contrast, there was no correlation between basal plasma glucose and insulin concentrations in either control or Dex experiments.

DISCUSSION

The diabetogenic effects of chronic treatment with glucocorticoids have been well documented (15). The acute hepatic effects of corticosteroids are less well characterized. In our recent study in healthy humans, Dex increased HTGO and decreased MCR but did not increase HGP (14). In addition, Dex increased GC, which is one of the three substrate cycles operating in the liver. GC comprises glucose phosphorylation to glucose 6-phosphate and its dephosphorylation back to glucose, resulting in the consumption of one ATP.

In subjects between the ages of 20 and 39 years, the acute administration of a moderate dose of cortisone decreased glucose tolerance in 3% of control subjects and in 28% of first-degree relatives of NIDDM patients (16). Furthermore, long-term follow-up studies revealed that 26% of individuals with decreased cortisone OGTT progressed to clinical diabetes compared with 3.6% in subjects with normal cortisone OGTT (16). Hypothetically, the propensity of the diabetogenic effect of steroids on insulin sensitivity may vary in the liver or extrahepatic tissues or both. Alternatively, the β-cell secretory response to cortisone-induced insulin resistance may vary in different subjects; this would result in decreased OGTT in subjects whose enhancement of β-cell secretory capacity is not adequate. The latter possibility is supported by studies of Rull *et al.* (5), who studied nondiabetic first-degree relatives of patients with NIDDM and showed that subjects with diminished insulin response developed a decreased oral glucose tolerance if acutely treated with cortisone acetate (5). The present investigation strongly supports

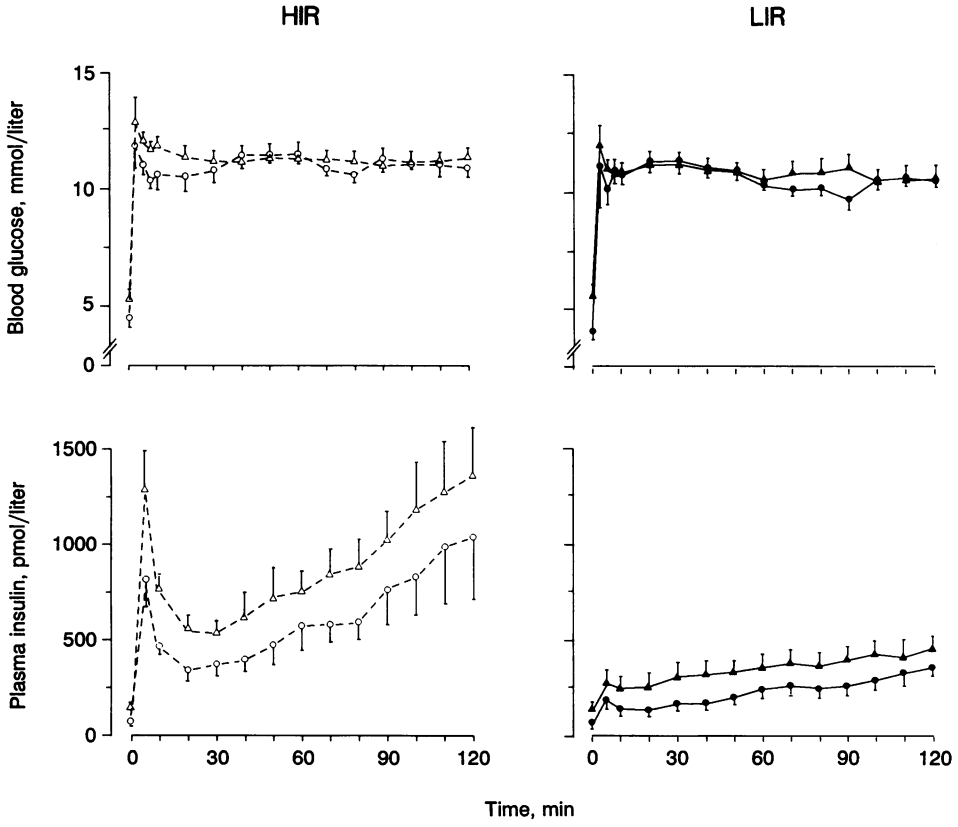

FIG. 3. Glucose (*Upper*) and insulin (*Lower*) levels during HC without Dex (LIR, ●; HIR, ○) and after administration of 15 mg of Dex (LIR, ▲; HIR, △).

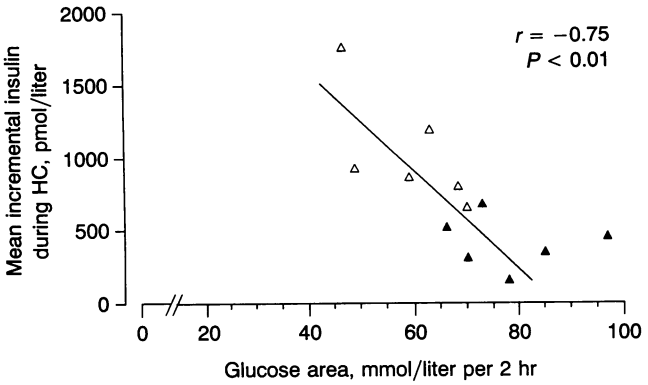

FIG. 4. Correlation between glucose area (mmol/liter per 2 hr) during OGTT after administration of 15 mg of Dex and mean incremental insulin level during HC after administration of 15 mg of Dex (LIR, ▲; HIR, △).

the notion that in healthy humans the main determinant of the variations of the steroid effect on glucose response during OGTT is the β-cell capacity to increase insulin release. Thus, in Dex experiments the area under the glucose curve during OGTT was negatively correlated with Dex-mediated insulin response during the HC. In addition, it was not correlated with the effect of steroids on insulin sensitivity (MCR or M/I ratio) or basal glucose production (HGP, HTGO).

In line with the above observations, three of six LIR and none of HIR developed diabetic OGTT after Dex treatment. The impaired β-cell response to Dex could be a more sensitive probe for prediabetes than determination of insulin responsiveness to GIT in basal conditions. In fact, in some subjects, the reduction in β-cell response under basal conditions may be secondary to high insulin sensitivity. However, in our LIR there was no indication of increased sensitivity vs. HIR as assessed by basal MCR and by M/I ratios.

In the present study, LIR and HIR had similar postabsorptive glucose and insulin concentrations as in the previous investigations (6, 7, 17). After Dex treatment, blood glucose values increased more in LIR than in HIR. Notably, Dex only increased HGP in LIR, whereas it decreased basal MCR to the same extent in both groups. This implies that postabsorptively, the propensity for a more marked diabetogenic effect of Dex in LIR results from a differential liver response and not from a differential impairment of glucose clearance. The Dex-induced decrease in peripheral insulin sensitivity was similar in HIR and LIR not only postabsorptively, as seen by basal MCR, but also during HC, as seen by the M/I ratio.

HTGO was significantly increased in LIR and not in HIR after Dex treatment. This reflects an augmented activity of glucose-6-phosphatase in the liver in LIR. Our experiments do not answer the question of whether the Dex-mediated increase in glucose-6-phosphatase is solely a consequence of increased concentration of glucose 6-phosphate due to hyperglycemia or is also mediated by a direct effect of steroids on enzyme activity. The latter notion is supported by *in vitro* experiments in isolated hepatocytes demonstrating a direct augmenting effect of cortisol on the activity of this enzyme (18). Hence, an increased activity of glucose-6-phosphatase could reflect a primary acute hepatic effect of Dex, which then may lead to increased HGP. The mechanism behind an increased hepatic susceptibility to Dex in LIR is not clear. It could be due to a diminished integrated daily insulin secretion. Insulin is known to inhibit glucose-6-phosphatase as well as the gluconeogenic enzymes (19). However, it cannot be excluded that at least some LIR have a primary hepatic defect, perhaps at the level of glucose-6-phosphatase.

In the postabsorptive state, when liver produces glucose, GC is regulated by glucokinase, which operates in the opposite direction to the net glucose flux. Accordingly, an increase in postabsorptive glucose cycling in LIR after Dex treatment reflects an increased activity of glucokinase and is probably a consequence of the integrated steroid-mediated hyperglycemia. Indeed, during basal conditions, GC was related to the area under the glucose curve during OGTT.

In summary, the diabetogenic effect of Dex was more pronounced in LIR than in HIR. Under postabsorptive conditions the degree of the diabetogenic effect of Dex was determined by differential liver responses, whereas during OGTT the effect of Dex on glucose response was mainly determined by the degree of augmentation of the secretory capacity of the β-cell.

This work was supported by the Swedish Medical Research Council, Nordisk Insulin Foundation, Swedish Hoechst AG, Swedish Diabetes Association, Magnus Bergvalls Foundation, and Medical Research Council of Canada.

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