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Dexamethasone treatment in vivo counteracts the functional pancreatic islet alterations caused by malnourishment in rats

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Abstract

The effects of dexamethasone (Dex) on the metabolic parameters, peripheral insulin, and glucose sensitivity in vivo as well as on islet function ex vivo of rats submitted to low-protein diet were analyzed. Dexamethasone (1.0 mg/kg body weight) was administered intraperitoneally daily to adult Wistar rats fed on a normal-protein diet or low-protein diet (LPD) for 5 days, whereas control rats fed on a normal-protein diet or low-protein diet (LP) received saline alone. At the end of the experimental period, LP rats showed a significant reduction in serum insulin, total serum protein, and serum albumin levels compared with rats fed on a normal-protein diet ($P < .05$). All these parameters tended to be normalized in LPD rats ($P < .05$); furthermore, these rats exhibited increased serum glucose and nonesterified fatty acid levels compared with LP rats ($P < .05$). Rats submitted to the low-protein diet demonstrated normal peripheral glucose sensitivity and improved peripheral insulin sensitivity, which was reversed by Dex treatment. A reduced area of islets from LP rats was partially recovered in LPD rats ($P < .05$). At 16.7 mmol/L glucose, insulin secretion from LPD islets was also partially recovered and was significantly higher than that from LP islets ($P < .05$). In conclusion, induction of insulin resistance by Dex treatment reverses most of the metabolic alterations in rats submitted to a low-protein diet. In addition, several islet functions were also improved by Dex, confirming the plasticity of pancreatic islets in adverse conditions.

1. Introduction

The impairment of pancreatic β-cell function is the main event that leads to the development of type 2 diabetes mellitus [1]. However, before the onset of diabetes, several morphologic and physiological adaptations of the endocrine pancreas take place to maintain glucose homeostasis. These adaptations are also observed in some specific periods of life such as pregnancy, obesity, aging, and malnutrition [2-6].

Rats submitted to low-protein diet (LP) exhibit reduced body weight, higher hepatic glycogen content, normoglycemia, hypoalbuminemia, and lower plasma insulin levels [7]. The LP rat islets show impaired glucose-stimulated insulin secretion, lack of the typical secretory biphasic pattern in response to a glucose challenge, and reduction in glucose sensitivity [5,6]. Morphologic alterations such as a reduction in total pancreatic islet number are also present in this experimental model [8]. However, to compensate for the failure of pancreatic islet function, the peripheral sensitivity to insulin is increased in LP rats [9].

The endocrine adaptations to malnourishment seem to be the opposite of those observed in animals where the insulin resistance is induced by treatment with glucocorticoids. It is well known that dexamethasone (Dex) treatment impairs insulin action in peripheral tissues (ie, muscles, fat, and liver), leading to insulin resistance. Rats submitted to Dex treatment in vivo exhibit increased plasma insulin levels and marginal hyperglycemia [4,10]. In contrast to observations in islets from malnourished rats, islets from insulin-resistant rats show increased total insulin content, increased glucose-stimulated insulin secretion, and higher sensitivity to glucose based on reduced EC_{50} values. Hypertrophy of pancreatic islets is the main morphologic adaptation provoked by insulin resistance [11].

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Table 1
Composition of control (17% protein) and low-protein (6% protein) diets (Reeves et al 1993)

Ingredient	Control (17% protein)	Low protein (6% protein)
	g/kg	
Casein (84% protein)	202.0	71.5
Cornstarch	397.0	480.0
Dextrinized cornstarch	130.5	159.0
Sucrose	100.0	121.0
Soybean oil	70.0	70.0
Fiber	50.0	50.0
Mineral mix (AIN-93G)	35.0	35.0
Vitamin mix (AIN-93G)	10.0	10.0
L-Cystine	3.0	1.0
Choline chlorhydrate	2.5	2.5

The pancreatic islets exhibit morphofunctional plasticity, depending on the environment in which they evolve. However, there are no studies concerning the effects of induced insulin resistance (eg, by Dex) in an animal model that exhibits increased insulin sensitivity, such as LP rats. Here, we studied the effects of Dex treatment on metabolic adaptation of LP rats, as well as the morphophysiological alterations in their islets.

2. Materials and methods

2.1. Materials

Dexamethasone phosphate (Decadron) was from Aché (Campinas, SP, Brazil). Sodium pentobarbital (3% Hypnol) was from Cristália (Itapira, SP, Brazil). Human recombinant insulin (Biohulin N) was from Biobrás (Montes Claros, MG, Brazil). Enzymatic colorimetric assay for the quantification of nonesterified fatty acids (NEFAs) was from Wako Chemicals (Richmond, VA). Total serum protein and serum albumin detection kits were from In Vitro Diagnostica (DI, MG, Brazil). Dextrose, NaCl, KCl, $CaCl_2$, $MgCl_2$, $NaHCO_3$, KOH, and Na_2SO_4 were from Mallinckrodt Baker (Paris, France). Collagenase, HEPES, albumin, activated charcoal, and dextran were from Sigma (St Louis, MO). Ethanol, methanol, chloroform, and phenol were from Synth (Diadema, SP, Brazil).

2.2. Animals and diet

Male Wistar rats (21 days old) from the University of Campinas Animal Breeding Center were kept at 24°C on a 12-hour light/dark cycle. The rats were randomly assigned into 2 groups and fed an isocaloric diet containing 6% (LP) or 17% (control diet, NP) protein for 8 weeks. The composition and difference between the 2 isocaloric diets are described in Table 1. During the experimental period, rats had access to food and water ad lib. The institutional São Paulo State University Committee for Ethics in Animal Experimentation approved the experiments with rats.

2.3. Dexamethasone treatment

After 8 weeks of treatment, malnourished and control rats were distributed into 4 groups with 40 animals each (NP, normal-protein diet with Dex [NPD], LP, and low-protein diet with Dex [LPD]). Rats from these groups received daily intraperitoneal (IP) injections of Dex (1 mg/kg body weight, dissolved in saline) between 7:30 AM and 8:30 AM for 5 consecutive days (NPD and LPD) or saline alone (NP and LP).

2.4. Metabolic, hormonal, and biochemical measurements

On the day after the last Dex administration, fasted (12-14 hours) rats were weighed; and glucose levels were measured with a glucometer ("one touch" Johnson & Johnson, Milpitas, CA) in samples collected from the tail. The rats were then killed (by exposure to CO_2 followed by decapitation), and the blood was collected. Serum insulin levels were measured by radioimmunoassay (RIA) using rabbit anti–rat insulin antibody and rat insulin as standard. The NEFA was determined by enzyme-linked immmunosorbent assay according to the manufacturer's instructions. Total serum protein and serum albumin were quantified by spectrophotometer according to the manufacturer's instructions.

2.5. Liver glycogen measurements

Hepatic glycogen content was measured as previously described [12], but with some modifications. Briefly, the liver samples (300 to 500 mg) were transferred to test tubes containing 30% KOH (wt/vol) and boiled for 1 hour until complete homogenization. The Na_2SO_4 was then added, and the glycogen was precipitated with ethanol. The samples were centrifuged at 800*g* for 10 minutes, the supernatants were discarded, and the glycogen was dissolved in hot distilled water. Ethanol was added; and the pellets, obtained after a second centrifugation, were dissolved in distilled water in a final volume of 25 mL. Glycogen content was measured by treating a fixed volume of sample with phenol reagent and H_2SO_4. Absorbance was

Table 2
Body weight, serum protein, albumin, glucose, insulin, NEFA, and liver glycogen of NP, NPD, LP, and LPD rats

Parameters	NP	NPD	LP	LPD
Body weight (g)	409 ± 13	360 ± 12 [a]	282 ± 4 [a]	254 ± 10 [b,c]
Protein (g/dL)	6.3 ± 0.15	9.1 ± 0.14 [a]	4.9 ± 0.16 [a]	7.8 ± 0.09 [b, c]
Albumin (g/dL)	3.5 ± 0.02	4.0 ± 0.09 [a]	3.2 ± 0.09 [a]	4.3 ± 0.09 [b]
Glucose (mg/dL)	67.3 ± 4.5	135.3 ± 10.0 [a]	67.6 ± 5.9	131.3 ± 18.3 [b]
Insulin (ng/mL)	0.45 ± 0.02	1.76 ± 0.06 [a]	0.23 ± 0.02 [a]	1.70 ± 0.03 [b,c]
NEFA (mmol/L)	1.05 ± 0.15	2.04 ± 0.13 [a]	0.73 ± 0.03	1.60 ± 0.37 [b]
Liver glycogen (mg/100 mg tissue)	4.26 ± 0.3	6.68 ± 0.4 [a]	8.79 ± 0.6 [a]	9.65 ± 0.6 [c]

Values are the means ± SEM. n = 10, $P < .05$.
[a] Significantly different vs NP.
[b] Significantly different vs LP.
[c] Significantly different vs NPD.

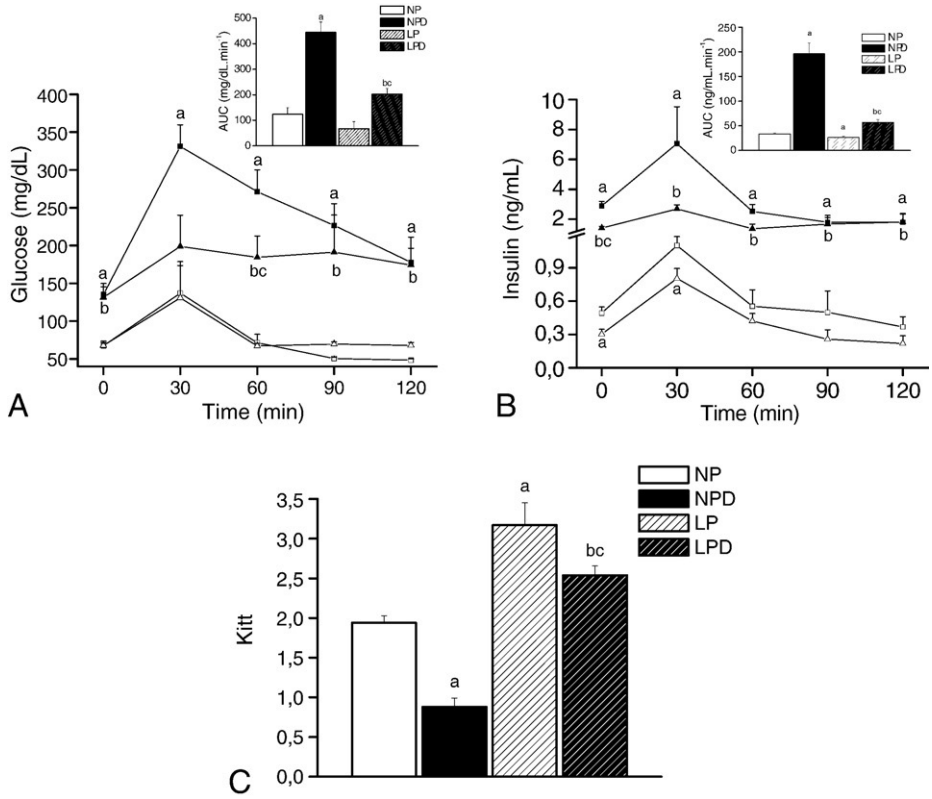

Fig. 1. Glucose intolerance in LPD rats. A, Glycemic profile obtained by ipGTT experiments in NP (o), NPD (n), LP (r), and LPD (p). Even after 120 minutes of glucose load, LPD rats showed elevation of blood glucose levels compared with LP. Note increment of area under the curve (AUC) data from LPD group compared with LP group (inset). B, Insulinemia obtained during ipGTT experiments. Blood insulin levels from LPD rats continue to be higher than those of LP rats. C, Glucose disappearance rate, measured through the blood glucose levels during the IP insulin tolerance test in NP, NPD, LP, and LPD rats. The inset depicts the increment in AUC data for LPD rats compared with LP rats. Data are means ± SEM. Significantly different [a]vs NP, [b]vs LP, and [c]vs NPD. $P < .05$, n = 10. Analysis of variance with Tukey post test.

then read at 490 nm with a spectrophotometer (Spectronic 20, Genesis, Rochester, NY).

2.6. IP glucose tolerance test

On the day after the last Dex administration, fasted (12-14 hours) rats were anaesthetized with sodium pentobarbital (3% Hypnol, 1 mL/kg body weight). After verifying the absence of corneal and pedal reflexes, unchallenged samples (time 0) were obtained from the rats' tails. Immediately, 50% glucose (2 g/kg body weight, IP) was administered; and blood samples were collected at 30, 60, 90, and 120 minutes from the tail tip for determination of glucose and insulin concentrations.

2.7. IP insulin tolerance test

Fed rats were anaesthetized as described above. A sample of blood was collected from the tail tip for glucose measurement at time 0. Human recombinant insulin, equivalent to 2 U/kg body weight, was then injected IP. Further samples were collected at 5, 10, 15, 20, 25, and 30 minutes for blood glucose measurement. The constant rate for glucose disappearance (Kitt) was calculated from the slope of the regression line obtained with log-transformed glucose values between 0 and 30 minutes after insulin administration.

2.8. Isolation of islets and static and dynamic secretion protocols

Islets were handpicked after collagenase digestion of the pancreas, following the technique previously described [13]. For static incubation, groups of 5 islets were first incubated for 1 hour at 37°C in 1 mL of Krebs-bicarbonate buffer solution of the following composition (in millimoles per liter): 115, NaCl; 5, KCl; 2.56, $CaCl_2$; 1, $MgCl_2$; 24, $NaHCO_3$; 15, HEPES; and 5.6, glucose, supplemented with 0.5% bovine serum albumin and equilibrated with a mixture of 95% O_2 and 5% CO_2 (pH 7.4). The medium was then replaced by another 1 mL of fresh buffer containing different glucose concentrations, as indicated in the respective figure, and further incubated for 1 hour. At the end of the incubation, the samples were stored at –20°C for subsequent measurement of insulin content by RIA. For analysis of dynamic insulin secretion, 20 freshly isolated islets were transferred to perfusion chambers and perifused with Krebs-bicarbonate

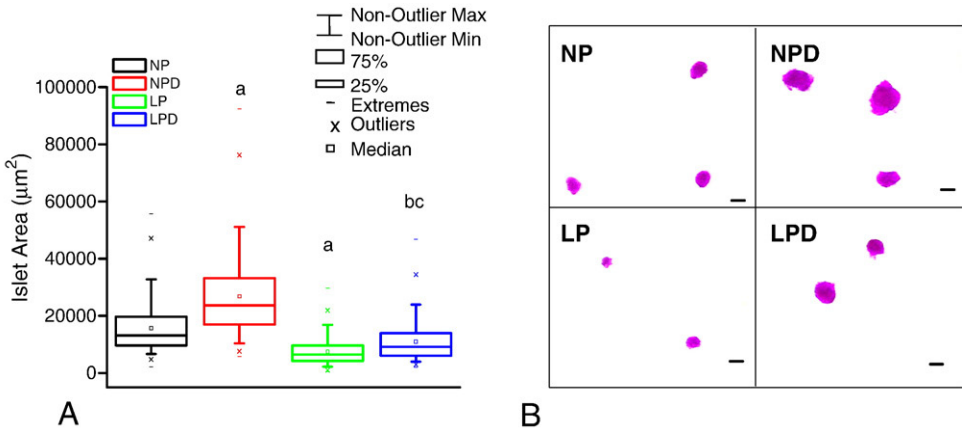

Fig. 2. Adaptive hypotrophy and hypertrophy of pancreatic islet. A, Box plot graphic representation of islet area values. Each plot is the mean of at least 700 islets per group. B, Representative images obtained from a charge-coupled device camera. Significantly different [a]vs NP, [b]vs LP, and [c]vs NPD. $P < .001$. Analysis of variance with Tukey post test; ×100 magnification. The bar corresponds to 100 μm.

buffer solution at a flow rate of 1 mL/min for 100 minutes. The effluent was collected every 2 minutes into tubes that were stored at –20°C for insulin RIA. Perifusion consisted of 3 consecutive periods: 50 minutes with 2.8 mmol/L glucose, 30 minutes with 16.7 mmol/L glucose, and finally 20 minutes with 2.8 mmol/L glucose. Collection of the samples started from 30 minutes of perifusion.

2.9. Histomorphometric analysis

To determine the area, pools of 700 islets from each group were submitted to Feulgen DNA method "en bloc." The islet images were then registered by a charge-coupled device camera, and area (in square micrometers) values were automatically obtained by the Image-Pro-Plus Media, Cybernetics program (Bethesda, MD), coupled to a BX-60 Olympus photomicroscope (Tokyo, Japan).

2.10. Statistical analysis

All numerical results are expressed as the means ± SEM of the indicated number of experiments. Analysis of variance (1-way) for unpaired groups, followed by Tukey post test, was used for multiple comparisons of parametric data. The significance level adopted was $P < .05$.

3. Results

3.1. Characteristics of the rats

The LP rats showed a significant reduction in body weight, total serum protein, albumin, and insulin serum levels compared with NP rats (n = 10, $P < .05$). The liver glycogen content of LP rats increased significantly, and serum glucose levels were similar to those of NP rats (n = 10, $P < .05$) (Table 2). After Dex treatment, however, total serum protein, serum albumin, and NEFA levels of LPD rats increased significantly compared with LP rats (n = 10, $P < .05$). Blood glucose and insulin in LPD rats were significantly higher compared with LP rats (n = 10, $P < .05$). The liver glycogen content was similar between LPD and LP rats (Table 2). The data for NPD rats were similar to those previously reported by others [14-16].

3.2. LPD rats exhibit decreased glucose and insulin sensitivity

The mean glucose blood levels during the intraperitoneal glucose tolerance test (ipGTT), except for 30 minutes, in LPD rats were significantly higher than those in LP rats (n =10, $P < .05$), but similar to those found in NPD rats. No differences were observed between LP and NP rats (Fig. 1A). Blood insulin levels were significantly increased at all times in LPD rats compared with LP rats, suggesting glucose intolerance in this group (n = 10, $P < .05$) (Fig. 1). During the IP insulin tolerance test, LP rats were more sensitive to insulin than NP rats, as judged by the Kitt values (Fig. 1C, $P < .05$). Although LPD rats showed a higher sensitivity to insulin than NP and NPD groups, this sensitivity was significantly lower than that of LP rats ($P < .05$). The Kitt values were 0.45-fold, 1.67-fold, and 1.31-fold altered compared with the NP value for the NPD, LP, and LPD groups, respectively (Fig. 1C; n = 10; $P < .05$ for LP vs NP, NPD vs NP, and LPD vs LP groups).

3.3. Morphologic islet adaptation in LP and LPD rats

The LP islets showed a marked hypotrophy compared with NP islets. However, Dex treatment caused a significant increase in islet area in NPD and LPD rats compared with NP and LP rats, respectively (Fig. 2). The islet area values were 15 700 ± 320, 26 800 ± 530, 7500 ± 180, and 10 900 ± 250 μm^2 for the NP, NPD, LP, and LPD groups, respectively (n = 700 islets, $P < .001$). This may reflect an adaptation imposed by the increased sensitivity and decreased sensitivity to insulin action at the periphery in LP and LPD animals, respectively.

3.4. Glucose-stimulated insulin secretion is increased in LPD rats

As depicted in Fig. 3, after normalization by the total islet insulin content, at a subthreshold glucose concentration (2.8 mmol/L), insulin secretion was significantly decreased in LP and LPD (0.57-fold and 0.5-fold compared with NP and LP, respectively). At 16.7 mmol/L glucose, the insulin secretion was significantly decreased in LP islets (0.17-fold compared with NP islets, n = 12, $P < .05$), whereas the insulin secretion was significantly increased in NPD and LPD islets (2.4-fold and 1.7-fold higher compared with NP and LP islets, respectively; n = 12; $P < .05$) (Fig. 3A). The dose-response curve to glucose (2.8-22 mmol/L) was significantly shifted to the right in LP compared with NP islets. Nevertheless, the dose-response curve to glucose was shifted to the left in islets derived from the NPD and LPD groups compared with their respective controls (Fig. 3B). The EC_{50} values were 9.08 ± 0.10, 6.84 ± 0.32, 9.78 ± 0.19, and 7.11 ± 0.46 mmol/L for NP, NPD, LP, and LPD, respectively ($P < .05$ for LP vs NP, NPD vs NP, and LPD vs LP).

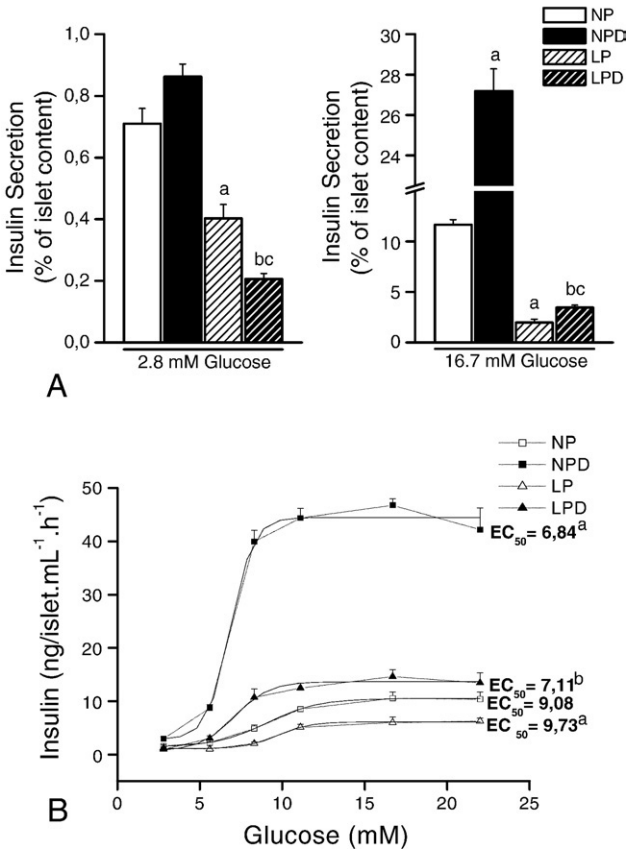

Fig. 3. The LPD islets show increased glucose-induced insulin release. Insulin release from islets isolated from NP, NPD, LP, and LPD rats. A, At a concentration of 2.8 mmol/L, glucose insulin secretion was not different between NP vs LP and LP vs LPD. At a stimulatory glucose concentration (16.7 mmol/L), the insulin secretion in LP islets was diminished compared with NP islets; however, in LPD islets, the insulin secretion was 150% higher than that of LP islets. The absolute values for insulin secretion at 2.8 mmol/L glucose were 0.5 ± 0.04, 0.9 ± 0.04, 0.2 ± 0.02, and 0.2 ± 0.01 ng per islet per milliliter per hour for NP, NPD, LP, and LPD, respectively ($P < .05$ for LP vs NP and NPD vs NP). At 16.7 mmol/L glucose, insulin secretion was 8.4 ± 0.3, 29.3 ± 1.2, 1.2 ± 0.2, and 2.9 ± 0.6 ng per islet per milliliter per hour for NP, NPD, LP, and LPD, respectively ($P < .05$ for LP vs NP and NPD vs NP). B, Dose-response curve to glucose (2.8-22 mmol/L) obtained from insulin release by static incubation of the islets. The EC_{50} value was significantly shifted to the right in LP islets compared with NP islets and significantly shifted to the left in LPD islets compared with LP islets. Data are means ± SEM. Significantly different [a]vs NP, [b]vs LP, and [c]vs NPD. $P < .05$, n = 12. Analysis of variance with Tukey post test.

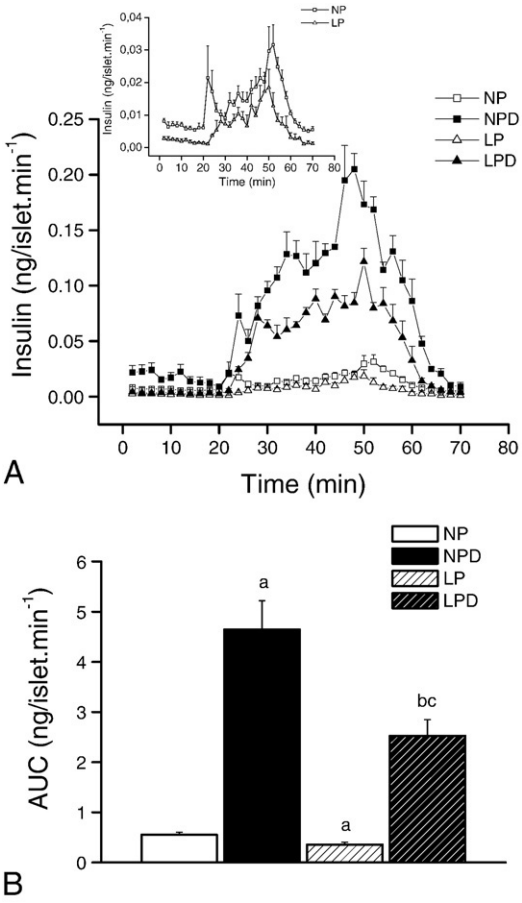

Fig. 4. Perifused LPD islets show altered insulin-output pattern. Glucose-stimulated insulin secretion in isolated perfused islets of NP, NPD, LP, and LPD rats. The typical biphasic insulin pattern was observed in NP islets (inset). The LP islets showed no characteristic first phase and a second phase of insulin release that was lower than that in NP islets. The LPD islets showed both phases of insulin release with a marked and sustained second phase compared with LP islets. The inset shows the insulin secretion from NP and LP islets. B, The AUC data revealed an increased insulin response to glucose in NPD and LPD. A, Each point represents the mean ± SEM of 4 different experiments. B, Data are means ± SEM. Significantly different [a]vs NP, [b]vs LP, and [c]vs NPD. $P < .05$, n = 12. Analysis of variance with Tukey post test.

3.5. Kinetics of glucose-induced insulin secretion in LPD islets

In the presence of nonstimulatory glucose concentrations (minutes 0-20), the islets from the NPD and LPD groups released more insulin than their respective controls (Fig. 4).

A typical biphasic pattern of insulin secretion was observed in NP islets after the introduction of 16.7 mmol/L glucose (minutes 20-50) (inset). The insulin secretion in LP islets did not show a characteristic first-phase release; but despite a lower release than NP islets, the second phase exhibited a sustained increase in insulin release. The LPD islets showed a biphasic response to glucose, with a first peak followed by a sustained and progressive increased second phase. Insulin secretion in both phases was significantly higher in LPD than LP islets. As expected, NPD islets secreted significantly more insulin during stimulation with 16.7 mmol/L glucose than NP islets. Finally, the insulin secretion in all groups of islets returned to basal values when the glucose concentration was reduced to 2.8 mmol/L glucose (minutes 50-70).

4. Discussion

In this study, several physiological parameters were assessed in adult Wistar rats submitted to a low-protein diet (28 to 90 days of life) and turned resistant to insulin by the administration of Dex. Morphometric adaptations, provoked by these treatments, were also investigated as well as alterations in insulin secretion in isolated pancreatic islets.

Rats fed on a low-protein diet (LP) had similar characteristics to those observed in experimental malnourishment models, such as a reduction in body weight and serum protein levels and an increase in hepatic glycogen content [5,7]. These biochemical parameters were modified by the treatment of NP and LP rats with Dex and are in agreement with data reported in the literature concerning glucocorticoid-induced insulin resistance, that is, body weight reduction [17-19] and increase in plasma protein levels [10,15,16], NEFAs [14,20,21], and hepatic glucose output [10,22]. The body weight reduction is usually accompanied by muscle atrophy [16,17,19], probably due to an increase in cathepsin L expression, one of the main mediators of muscle proteolysis [17]. The proteolysis caused by glucocorticoid treatment [23] might justify the elevated serum protein in our NPD and LPD rats. Glucocorticoids also stimulate lipolysis and potentiate the lipolytic effect of other hormones, leading to an increase in serum NEFA concentrations [24], in accordance with the increased serum NEFA concentration in LPD rats. Higher NEFA plasma levels could increase hepatic glycogen synthesis because the increase in NEFA may suppress hepatic glycolysis and favor hepatic glycogen synthesis [25].

The data regarding islet area reported herein are also in agreement with previous data, suggesting a reduction in islet area in malnourished animal models [8] and an increase in islet area in glucocorticoid-treated animals [10,11,26,27]. The islet hypotrophy is probably an adaptation in the protein-restricted rats to a lower body weight associated with an increased sensitivity to insulin in periphery tissues. The effects on islet morphology imposed by malnutrition in LPD rats were counteracted by an adaptive response to the development of peripheral insulin resistance induced by the Dex treatment. This increase in islet size seems to be a result of increased β-cell number and/or size [28].

The postabsorptive insulin levels are another interesting finding of our study. The LP rats showed a significant reduction in insulin serum levels; and according to previous results, this may be explained by a decreased β-cell mass associated with functional alterations such as impairment of nutrient metabolism and calcium uptake [5,6,8]. Moreover, these reduced insulin levels could reflect a response to the increased sensitivity to glucose peripherally, which, in turn, would demand less insulin to maintain glucose homeostasis. Despite low insulin levels, LP rats showed normal blood glucose and normal glucose tolerance together with an improvement in the peripheral insulin sensitivity as judged by the Kitt, in agreement with a previous study [29]. The improvement in insulin sensitivity might be a consequence of an increase in the phosphorylation of insulin receptor (IR) and IR substrate 1, favoring a greater association of IR substrate 1 with phosphatidylinositol-3-kinase [9]. In contrast, LPD rats exhibited increased blood glucose and insulin levels associated with decreased peripheral insulin and glucose sensitivity. Increased insulin secretion is an adaptive response of β-cells, imposed by the Dex-induced peripheral insulin resistance [27] and mediated by concomitant elevation of blood glucose levels [30]. The hyperglycemic effect of glucocorticoids is explained, at least in part, by their gluconeogenic action on hepatic tissue. In addition, glucocorticoids induce muscle and fat tissue insulin resistance, which contributes to the aggravation of hyperglycemia [31,32].

We also demonstrated alterations in lipid metabolism, particularly increases in NEFA levels in NPD and LPD groups. Evidence exists to suggest that glucocorticoids may increase serum NEFA levels by the activation of hormone-sensitive lipase [33]. The increases in serum insulin concentrations observed in NPD and LPD rats, however, were not sufficient to avoid hypertriglyceridemia and increased NEFA concentrations in this group. It has been proposed [34] that the increase in plasma NEFA concentrations, while contributing to the induction or aggravation of peripheral insulin resistance, could, in parallel, mediate insulin hypersecretion either directly [35,36] or by favoring triglyceride synthesis in β-cells and subsequent generation of lipid signaling molecules through lipolysis [37]. Elevated serum NEFA levels have been implicated in the pathogenesis of glucocorticoid-induced peripheral insulin resistance [14,20,21].

We also studied insulin release in isolated islets ex vivo in these rats. In agreement with a previous study [5], LP islets showed an impairment of glucose-induced insulin release, probably as a consequence of a reduction in islet number per pancreas, as well as a reduction in the quantity, size, and volume of β-cells [8]. In addition, the lower ability of glucose to induce Ca^{2+} uptake and/or to reduce Ca^{2+} efflux from β-cells could play an important role in this process [5].

However, LPD islets showed augmented glucose-induced insulin secretion in stimulatory (16.7 mmol/L) glucose concentrations associated with lower EC_{50} values for glucose. Thus, β-cells from LPD rats are more responsive to glucose. Controversies exist concerning the secretion of insulin from perfused pancreas and isolated islets of rodents after in vivo glucocorticoid treatment. Enhanced [38,39] or unaltered [40] insulin secretion has been described in both preparations. These heterogeneous results are linked to the countless protocols used (strain, dose, time, glucose concentration, etc). Our results suggest that the increase in insulin secretion observed in the LPD group, in response to suprathreshold glucose concentrations, implies some degree of islet adaptation (ie, decrease in EC_{50} values for glucose), which could be a reflection of the impairment of insulin action at the periphery.

Finally, we demonstrated that LP rats exhibit an improvement in insulin sensitivity, a normal glucose tolerance, a diminished islet area, and an impairment of islet function, reflecting an adaptation imposed by the protein deficiency in the diet. However, when insulin resistance is induced by Dex treatment in LP rats, several adaptations occur at the periphery as well as in the islets to counteract these common features induced by the malnourishment. The classic metabolic and islet alterations observed in rodents submitted to Dex-induced insulin resistance include the decrease of insulin and glucose sensitivity, islet hypertrophy, and enhanced glucose-stimulated insulin secretion. All of these parameters are also observed in LPD rats even after well-established alterations imposed by the protein restriction in the diet. Thus, Dex reverts the main features related to metabolism and islet function caused by protein restriction in the diet. These observations may exemplify and reinforce the wide plasticity of pancreatic β-cells in adverse conditions. Understanding these adaptations is of relevance because they may lead us to classify the degrees of these pathophysiological conditions, providing directions for future studies.

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