Effect of Lipectomy and Long-Term Dexamethasone on Visceral Fat and Metabolic Variables in Rats

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Intraperitoneal (IP) fat accumulation in humans is a risk factor for a number of diseases. We tried to increase this particular adipose mass in rats by long-term administration of low-dose dexamethasone (Dex) and/or elimination of other fat depots. Male adult Wistar rats were lipectomized (Lip) or sham-operated (Sh). Bilateral lipectomy of retroperitoneal and inguinal fat pads was performed under anesthesia with Na pentobarbital 40 mg/kg supplemented with ether. After 8 days, half the animals of each group received Dex in their drinking water (0.1 μg/mL) while the other half received water (W), for a total of four groups: Sh-W, Lip-W, Sh-Dex, and Lip-Dex. Body weight (BW) and food and water intake were measured throughout the treatment period. A glucose tolerance test was performed 34 days after starting Dex treatment, and then rats were killed, fat depots were weighed, and plasma and liver were obtained for metabolic determinations. Dex rats ate the same amount of food as W controls, but gained significantly less weight (2.02 ± 0.18 *v* 3.82 ± 0.10 g/d, $P < .01$). Mean daily W intake was approximately 40 mL/d in all groups, which means that Dex rats ingested approximately 4 μg/d Dex. Average glycemic values during the 180-minute glucose tolerance test were as follows: Sh-W, 162 ± 13; Lip-W, 166 ± 7; Sh-Dex, 118 ± 6; and Lip-Dex, 229 ± 27 mg/dL. These values show that glucose tolerance was improved by Dex treatment alone, but was impaired in Lip-Dex animals. The same trend was evident for the relative weights (percent of BW) of two intact adipose depots: IP and epididymal (EPI) (Sh-W, 2.08 ± 0.13 and 1.35 ± 0.11, respectively; Lip-W, 1.67 ± 0.15 and 1.17 ± 0.11; Sh-Dex, 1.66 ± 0.10 and 1.28 ± 0.07; Lip-Dex, 2.41 ± 0.11 and 1.53 ± 0.09). Average glycemia for all rats was significantly correlated with IP ($r = .55$, $P < .01$) but not with EPI; moreover, it was also correlated in the Sh-W control group ($r = .81$, $P < .05$), suggesting a normal relation between these variables. Liver triglycerides (LTG), which were elevated in Dex rats, were also correlated with IP ($r = .51$, $P < .02$ for all rats and $r = .82$, $P < .05$ for Sh-W rats). The results show that long-term administration of low-dose Dex has some different effects in normal versus Lip rats concerning mainly the IP fat depot, the relative mass of which seems to significantly affect glucose tolerance.

VAGUE[1] SUGGESTED that abdominal obesity constitutes a risk factor for a number of diseases, mainly diabetes mellitus and atherosclerosis, about 40 years ago. More recent studies confirmed this relation,[2,3] showing that intraabdominal fat stores are specifically linked to metabolic alterations.[4] In humans, upper-body obesity induces decreased glucose tolerance, hyperinsulinemia, hypertriglyceridemia, and decreased levels of high-density lipoprotein cholesterol.[5,6] In comparison to subcutaneous fat, human visceral fat is reported to have a higher density of glucocorticoid receptors,[7,8] an enhanced sensitivity to catecholamines,[9,10] and a decreased sensitivity to the antilipolytic action of insulin.[11] Cushing's syndrome patients, who produce large amounts of glucocorticoids, have an android pattern of fat deposition,[12] and elevated glucocorticoid levels are associated with a specific increase in mesenteric fat tissue in rats.[13]

On the other hand, some investigators suggested that removal of a given portion of adipose tissue brings about deposition of fat in other intact fat stores.[14] Faust et al[15] reported a compensatory deposition of fat in nonexcised adipose tissues after removal of epididymal (EPI) and inguinal fat pads in rats. More recently, it was shown that extensive surgical reduction of subcutaneous adipose tissue induces an increase in intraabdominal fat in rats.[16] However, some other studies noted a complete lack of fat restoration in lipectomized (Lip) rats.[17]

The general purpose of the present study was to examine individual and combined effects of lipectomy and long-term dexamethasone (Dex) administration on several fat depots and on some related liver and serum variables in rats.

MATERIALS AND METHODS

Animals

Twenty-four adult male Wistar rats (3 to 4 months old) were housed in individual cages in a temperature-controlled room (23° ± 1°C) with a 12-hour light/dark cycle. Powdered rodent chow and tap water were available ad libitum.

Surgery

Before surgery, rats weighed 261.6 ± 3.6 g (mean ± SE). Twelve rats underwent bilateral retroperitoneal and inguinal lipectomy under Na pentobarbital anesthesia (40 mg/kg), supplemented when necessary with ethyl ether. Retroperitoneal fat pads along the posterior wall, including perirenal depots, were dissected after dorsal bilateral incisions. Care was taken not to cut the peritoneum. Inguinal fat pads were excised from the subcutaneous region

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of the inner thighs after an incision on each leg. Muscles were sewn with surgical thread, and the skin was closed with clips. Sham surgery (n = 12) consisted of the same incisions and manipulation of the region of the fat pads. Antibiotics were injected daily for the next 3 days.

Treatment

After 8 days of recovery, all rats had gained approximately the same weight: sham-operated (Sh) rats weighed 292.6 ± 6.0 g, versus 260.0 ± 5.5 g before the operation, and Lip rats weighed 285.9 ± 6.1, versus 263.3 ± 4.7 g. Then half the animals of each group matched by body weight (BW) started to receive Dex (Decadron; Laboratorio Prosalud, México, D.F., Mexico) 0.1 μg/mL in their drinking water, while the other half received tap water. In this way, four experimental groups were formed: Lip rats received either (1) water (Lip-W) or (2) Dex (Lip-Dex), and Sh rats received (3) water (Sh-W) or (4) Dex (Sh-Dex). During Dex treatment, one operated and Dex-treated (group Lip-Dex) animal died, and the group was left with five rats.

Measurements

Throughout the treatment, BW and food and water intake were measured twice weekly. BW gain and food and water ingestion were calculated per day for each rat.

After 34 treatment days, glucose tolerance was determined in the overnight-fasted rats. Blood was obtained from the tail tip, and whole-blood glucose concentration was measured (Enzymatic-colorimetric kit; Farmacéuticos Lakeside, México, D.F., Mexico) before and 30, 60, 120, and 180 minutes after an intraperitoneal (IP) glucose injection of 3.6 g/10 mL · kg.

Three days later, the animals were killed by decapitation after an overnight fast; blood was collected and immediately centrifuged, and plasma samples were frozen at −20°C for further analysis. Then liver and EPI, inguinal, IP (mesenteric and omental), and retroperitoneal adipose depots were removed and weighed.

Liver (LTG) and plasma triglycerides (TG) and total cholesterol concentrations were measured by commercial enzymatic-colorimetric kits from Merck (Merck, México, D.F., Mexico) and CHOD-PAP Lakeside (Boehringer, Mannheim, Germany), respectively. Plasma β-hydroxybutyrate was also determined by an enzymatic assay (Sigma Chemical, St Louis, MO).

Statistics

Values are expressed as the mean ± SE. For comparisons between groups, the data were subjected to two-way ANOVA (Dex × Lip). The Neuman-Keuls test was used for post hoc comparisons between means. Glucose tolerance results are reported as the total area of increase in glucose concentration over 180 minutes (average glycemia). Correlation analyses were performed between some variables.

RESULTS

Long-term Dex administration significantly affected BW gain during the treatment period (Table 1). Group Sh-Dex gained even less weight than group Lip-Dex. Mean daily water and food intakes were not significantly different between the four groups. Accordingly, food efficiency showed the same trend as weight gain (Table 1).

Figure 1 shows two intact fat depot (IP and EPI) weights expressed as a percent of BW; this unit was used because significant correlations were found between these weights and BW. Lipectomy or Dex treatment alone decreased the relative weight of the intact IP fat depot by 20% (Lip-W or Sh-Dex *v* Sh-W, $P < .05$). In contrast, as indicated by a significant interaction, when these manipulations were combined the opposite effect was found, ie, an increase in IP fat weight of 41% (Lip-Dex *v* Lip-W or Sh-Dex, $P < .05$). The increment of 16% versus the absolute control group, Sh-W, was not significant by the parametric test, but P was less than .05 when the nonparametric Mann-Whitney test was used (see Fig 5 for individual values). A similar trend of the combined Lip and Dex effect appears, albeit less markedly, for the intact EPI fat depot; indeed, weights of EPI and IP fat were significantly correlated ($r = .64$, $P < .01$).

As expected, excised retroperitoneal and inguinal depots weighed less 5 weeks after surgery in Lip than in Sh animals (1.91 ± 0.31 *v* 3.9 ± 0.47 for retroperitoneal fat and 0.9 ± 0.33 *v* 1.9 ± 0.35 g for inguinal fat). We cannot ascertain what proportion of adipose tissue still present in Lip rats was due to regeneration or to remnant nonexcised fat.

Dex treatment alone (Sh-Dex) improved the glucose tolerance curve, but this effect was reversed by lipectomy, as indicated by the poor tolerance presented by the Lip-Dex group, especially toward the end of the test period (Fig 2A). The calculated average glycemia illustrates the relationship

Table 1. BW, Intakes, and Food Efficiency

Group	BW		Intake (g/d)		Food Efficiency (%)
	Total (g)	Gain (g/d)	Food	Water	
Sh-W	372 ± 7[a]	3.7 ± 0.1[a]	25.9 ± 0.5	41.1 ± 1.4	14.3 ± 0.6[a]
Lip-W	371 ± 12[a]	3.9 ± 0.1[a]	26.7 ± 1.4	44.2 ± 1.6	14.7 ± 0.7[a]
Sh-Dex	315 ± 14[b]	1.7 ± 0.2[b]	24.1 ± 1.0	42.3 ± 2.2	6.9 ± 0.6[b]
Lip-Dex	326 ± 6[b]	2.4 ± 0.2[c]	24.7 ± 0.6	39.4 ± 2.0	9.8 ± 0.8[c]
ANOVA (F)					
Sh/Lip	0.6	6.6*	0.4	0	6.0*
W/Dex	23.2†	100.8†	3.4	0.9	87.3†
Interaction	0.6	2.2	0	2.7	2.4

NOTE. Values are the mean ± SE. Means sharing the same superscript in a column are not significantly different at $P < .05$ by Neuman-Keuls post hoc analysis. Food efficiency = 100 · BW gain (g)/ingested food (g).

*$P < .05$.

†$P < .01$.

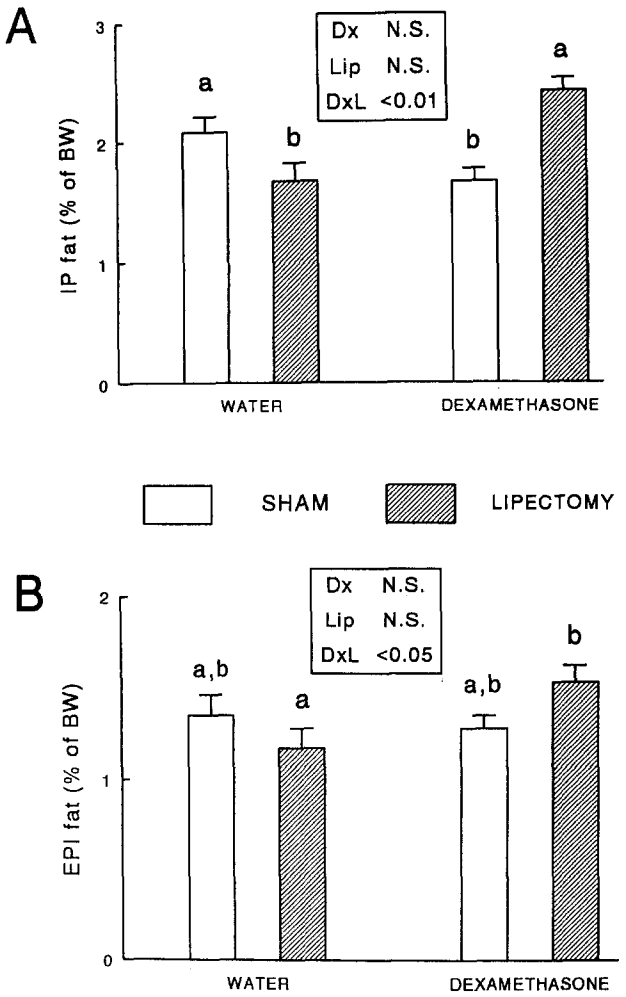

Fig 1. Relative weight of IP (A) and EPI (B) fat, expressed as a percent of total BW. Two-way ANOVA (Dx × Lip) results are inserted. NS, nonsignificant. Bars not sharing the same superscript are significantly different at $P < .05$ by Neuman-Keuls post hoc analysis.

between groups: as shown by the significant interaction, Dex effects on glucose tolerance depended on lipectomy (Fig 2B).

LTG (but not cholesterol) levels were elevated in Dex groups, and to a greater extent in Lip-Dex than in Sh-Dex rats (Fig 3). Plasma TG and cholesterol also showed higher values in Dex rats (Fig 4), whereas β-hydroxybutyrate levels, although increased in the same rats, showed nonsignificant differences with levels in W groups (not shown). Plasma TG and cholesterol showed significant correlations with LTG ($r = .53$, $P < .01$ and $r = .47$, $P < .01$, respectively).

We considered it of interest to analyze more thoroughly the relations between LTG and average glycemia in the glucose tolerance test with the relative IP and EPI fat weights, since the last two variables presented similar tendencies in response to the treatments applied. Individual data and group means of LTG (Fig 5) or average glycemia (Fig 6) were plotted against IP fat weight. In both cases, a significant correlation was found when considering all rats or only Sh-W rats (see figure legends), but not for any other individual group, suggesting that each one of the applied treatments had specific influences on the relation between the variables considered. In this context, Sh-Dex rats had low IP fat but high LTG (Fig 5), and the correlation is higher if this group is excluded ($r = .73$, $P < .001$). In contrast, Lip-W animals also had low IP fat but elevated average glycemia (Fig 6), and again the correlation is higher if this group is excluded ($r = .73$, $P < .001$). These differences are illustrated by the means plotted in both figures and strongly suggest that average glycemia does not depend on LTG levels—actually, they are not significantly correlated.

As reported earlier, IP and EPI fat are significantly correlated when all rats are considered; however, no correlation was found for individual groups. Besides, LTG and average glycemia of control Sh-W rats did not significantly correlate with EPI fat, suggesting that in normal animals these variables were related more to IP than to EPI fat.

DISCUSSION

To organize the discussion, we will first examine the global effects of the two procedures used separately.

Lipectomy

Lip rats (Lip-W and Lip-Dex) differed from Sh rats (Sh-W and Sh-Dex) in BW gain and glucose tolerance (Table 1 and Fig 1). However, in both cases, this was due to differences between Sh-Dex and Lip-Dex subgroups and will be discussed later.

Our experimental model, although in agreement with some studies,[17] could not reproduce earlier reports showing that removal of some fat depots promotes fat deposition in other adipose stores.[14,15] However, it is possible that an increase in fat deposition could only be found when certain conditions were met, such as the type of diet and/or a certain minimum time elapsed after the operation. In this way, subcutaneous lipectomy followed by a 6-month high-fat diet induced a slight increase in internal fat depots.[18] On the other hand, there are other factors that can affect fat deposition. Some hormones such as testosterone inhibit abdominal fat deposition in male rats, and accumulation of fat in this depot after lipectomy has been reported only if castrated rats are used.[19,20]

An unexpected result is that IP fat was significantly reduced in Lip-W rats as compared with Sh-W controls. Since BW gain was not different in the two groups, other (subcutaneous?) fat depots were perhaps increased, but we have no data on total body fat.

Dex Treatment

Long-term Dex administration of approximately 4 μg/d per rat reduced food efficiency: Dex-treated rats, although eating on average the same amount of food, gained significantly less weight than controls. Dex is a relatively pure type

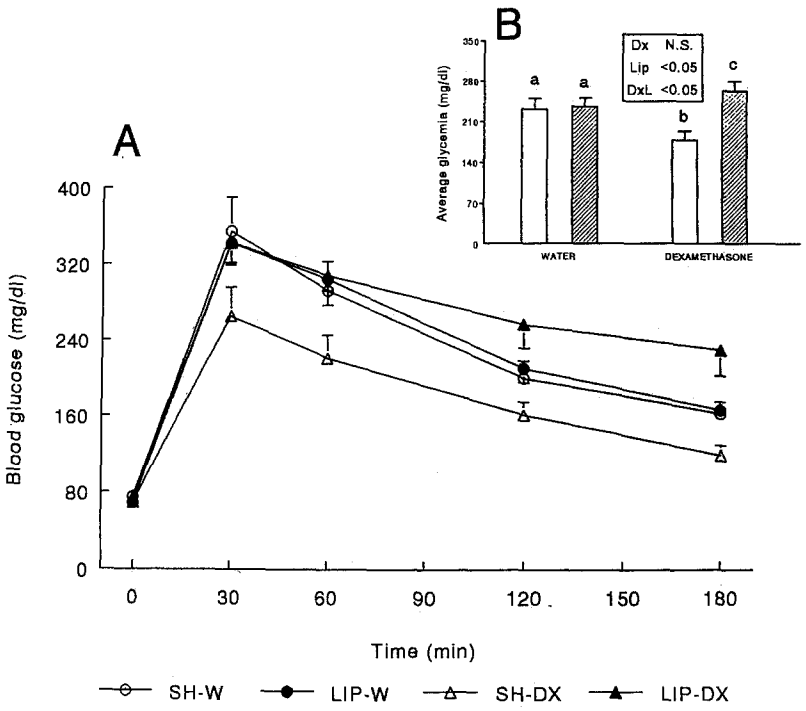

Fig 2. (A) Evolution of blood glucose levels after IP administration of 3.6 g/10 mL · kg dextrose. (B) Integrated average glycemia during 180 minutes. Two-way ANOVA (Dx × Lip) results are inserted. NS, nonsignificant. (□) Sh rats; (▨) Lip rats. Bars not sharing the same superscript are significantly different at $P < .05$ by Neuman-Keuls post hoc analysis.

II glucocorticoid agonist and its overall effects are mainly catabolic,[21] which would explain the reduced food efficiency in these animals. Other have reported that long-term Dex treatment decreases both food intake and BW, but much higher doses were used in their experiments.[22,23]

Dex treatment increased LTG and plasma TG, confirming other reports in rats.[24,25] Dex has been shown to exert a permissive action on catecholamine-induced lipolysis in vitro[26] and to reverse the reduced lipolysis in fat cells obtained from adrenalectomized rats.[27] We did not measure plasma free fatty acid (FFA) or glycerol levels, but the fact that plasma TG were elevated in Dex rats suggests that this was caused by the known glucocorticoid-induced increase in FFA. It has been reported that FFA originated extrahepatically are the preferred substrate for both intrahepatic oxidation and esterification.[28] Ketonemia was not significantly enhanced by Dex treatment in our experiment; this may be due to the fact that glucocorticoids preferentially channel acetyl coenzyme A, the product of β-oxidation, through the lipogenetic pathway,[29] or that in rats incomplete β-oxidation is not significant.[30]

Dex treatment alone significantly improved recovery of normal glucose levels after a glucose challenge. Improved glucose tolerance could be due to the fact that glucocorticoids increase insulin response to glucose both in vitro[31] and in vivo.[32] However, glucocorticoids induce peripheral insulin resistance,[33] which has been reported to be mainly hepatic in short-term glucocorticoid administration.[7,33] Treatment of rats with corticosterone impaired insulin-stimulated glucose utilization in muscle (but not in white adipose tissue) and also insulin inhibition of hepatic glucose production.[34] However, contradictory results were reported according to the type and dose of glucocorticoid used.[35] Since Devenport et al[21,36] described two types of receptors for glucocorticoids, with different effects and dose-dependent affinities, it has been proposed that glucocorticoids that bind to type I receptors are responsible for development of obesity,[21,36-38] whereas Dex, which binds specifically to type II receptors, has catabolic effects. In this way, long-term exposure to cortisol, such as in Cushing's syndrome, increases lipoprotein lipase (LPL) activity and reduces lipolytic activity in abdominal adipocytes in women,[39] whereas treatment with low-dose Dex increases lipolysis, especially in the abdominal depot, and decreases LPL activity in adipose tissue in rats.[24,40,41] Nevertheless, when using only Dex, there have been conflicting effects that seem to be time-dependent: ie, long-term administration of low-dose Dex produces different effects[7,42-44] and can even increase glucose disappearance during a glucose tolerance test.[33] In rats treated for 21 days with higher doses than in the present study, the reduced binding of insulin returned to normal in adipocytes and was partially normalized in hepatocytes.[7] In addition, it has been reported that Dex increases glucose transporter (GLUT4) content in rat muscle.[34,45]

It is possible that with long-term Dex treatment, abdominal fat would be reduced due to increased lipolysis and decreased LPL activity.[40] Abdominal fat reduction would improve insulin sensitivity in this depot. This, in turn, would decrease FFA delivered to the liver, and hepatic insulin resistance would be decreased, which would result in increased glucose tolerance.

Combined Treatments

Lip-Dex rats, as compared with Sh-Dex rats, showed better food efficiency, greater weight gain, and increased IP

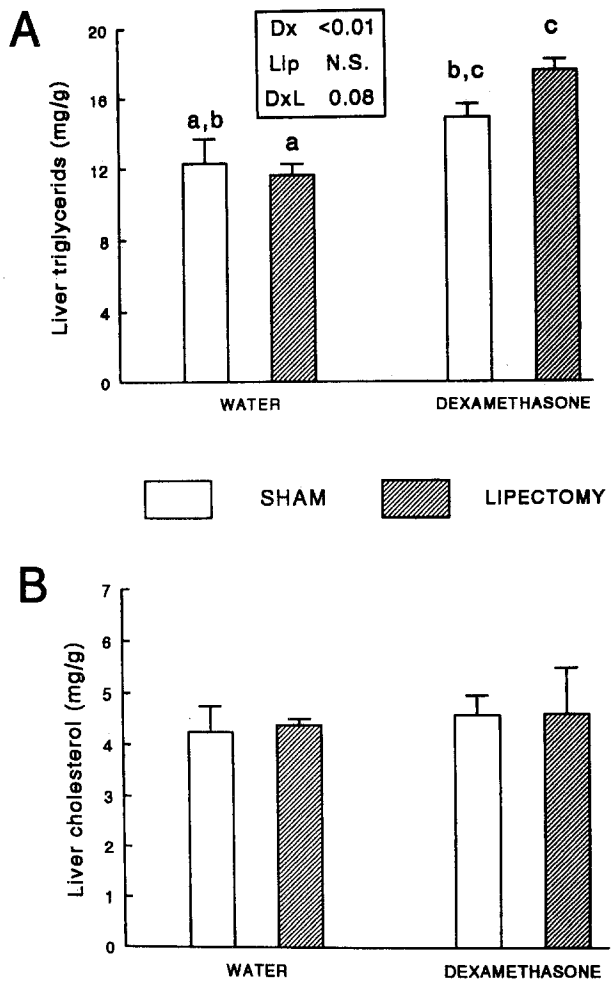

Fig 3. LTG (A) and liver cholesterol (B). Two-way ANOVA (Dx × Lip) results are inserted. NS, nonsignificant. Bars not sharing the same superscript are significantly different at $P < .05$ by Neuman-Keuls post hoc analysis.

and EPI fat. The significantly higher weight gain in Lip-Dex rats was possibly caused by increased fat storage in these rats, judging by the fact that IP and EPI fat depots weighed more in this group. In other words, the Dex hypertrophic and/or hyperplastic effect on IP and EPI fat was significant only when other lipid stores were reduced, ie, both lipectomy and Dex administration were necessary to produce this increase.

Our present results suggest that LTG and average glycemia are in some way positively related to IP fat (LTG and average glycemia are not significantly correlated); control rats showed significant correlations in both cases, suggesting a normal connection between these variables. As a matter of fact, liver fat in humans was found to correlate significantly with the waist to hip ratio.[46] It must be emphasized that in both cases correlation coefficients were higher for the six control rats than for all 23 animals. This indicates that the different treatments applied to each of the three groups affected in a distinct manner the two "dependent" variables.

Sh-Dex rats presented better glucose tolerance, whereas Lip-Dex rats showed high glycemic values. The rapid recovery of normal glycemia in the Sh-Dex group is probably due to Dex activation of insulin secretion[29,31,32] and/or to decreased insulin resistance in adipose tissue and liver, as mentioned earlier.

Average glycemia in the glucose tolerance test correlates with IP fat in Dex-treated groups. The slope of linear regression, if the Lip-W group is excluded, is similar to the slope in the Sh-W control group, strongly suggesting that the level of hyperglycemia depended on the different effects of Dex treatment on IP fat mass, which effects in turn depended on lipectomy (Fig 6).

A correlation between induced hyperglycemia and IP fat was recently reported in humans as a function of age.[47] The question arises as to what this correlation means. Although some investigators reported that IP fat is less responsive to insulin than other fat pads,[10,11,48] Blackard et al[49] found that

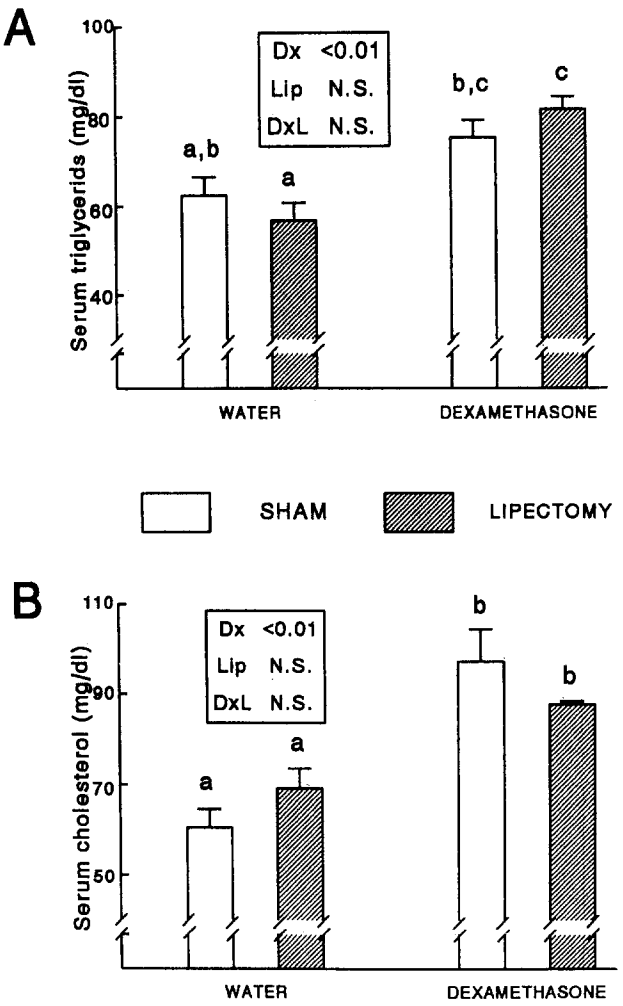

Fig 4. Serum TG (A) and cholesterol (B). Two-way ANOVA (Dx × Lip) results are inserted. NS, nonsignificant. Bars not sharing the same superscript are significantly different at $P < .05$ by Neuman-Keuls post hoc analysis.

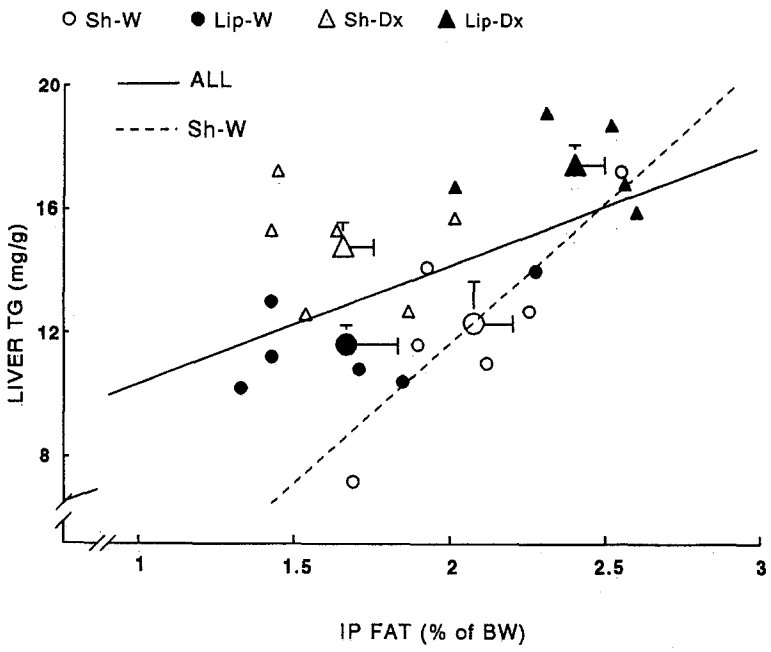

Fig 5. Individual and mean ± SE correlation values (large symbols) for LTG and IP fat per BW (IP FAT) for the 4 groups. (—) Linear regression for all 23 rats ($r = .51$, $P < .02$); (---) linear regression for 6 control (Sh-W) rats ($r = .82$, $P < .05$).

IP fat has greater insulin sensitivity than peripheral adipose tissue in obese humans. This suggests that hypertrophy of this particular fat store is an effect of hyperinsulinemia, which in turn is induced by insulin resistance due to obesity. Although Dex stimulates glucose-induced insulin secretion,[31,32] it did not cause IP hypertrophy in our experimental conditions when lipectomy was not performed. So the causal relation of hyperinsulinemia inducing IP fat accumulation does not appear to be valid in normal rats as it was claimed to be in obese humans.[49]

On the other hand, Dex treatment increased LTG and plasma TG in both Lip and Sh rats. These results suggest a preponderance of Dex action on lipolysis and LTG accumulation, confirming other data.[25,29] The increment of LTG may also have resulted from the lipogenetic action of both insulin and Dex.[50]

It is tempting to suggest that a relative increase in IP fat (and probably adipose tissue insulin resistance), with its enhanced sensitivity to lipolytic agents,[9,10] would chronically elevate FFA portal flux through the liver. A higher flux of FFA should stimulate gluconeogenesis,[51] which would not be impaired by the glucocorticoid-induced hyperinsulinemia because of hepatic insulin resistance elicited by both high portal FFA levels[52,53] and Dex.[54]

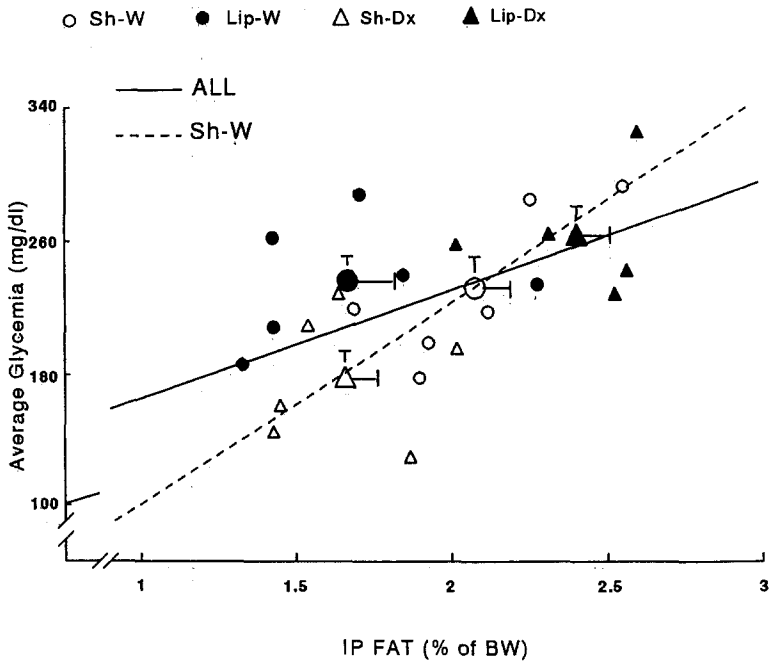

Fig 6. Individual and mean ± SE correlation values (large symbols) for average glycemia during the glucose tolerance test and IP fat per BW (IP FAT) for the 4 groups. (—) Linear regression for all 23 rats ($r = .55$, $P < .01$); (---) linear regression for 6 control (Sh-W) rats ($r = .81$, $P < .05$).

In conclusion, the present results show that long-term low-dose Dex treatment in male rats induces an increment in LTG and serum TG but improves glucose tolerance. However, the same treatment in rats subjected to excision of some extraperitoneal fat depots enhances IP fat deposition and induces impaired glucose tolerance, probably due to elevated IP lipolysis, high levels of portal FFA, and hepatic insulin resistance.

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