Modulation of triglyceride metabolism by glucocorticoids in diet-induced obesity

LINE MANTHA, ELENA PALACIOS, AND YVES DESHAIES
Center for Research on Energy Metabolism and Department of Physiology,
School of Medicine, Laval University, Quebec, Canada G1K 7P4

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fatty acid uptake by tissues, namely postheparin plasma, adipose, and muscle LPL activity. Glycemia and insulinemia were monitored because of the central role played by insulin in both the production/secretion of endogenous TG and their intravascular hydrolysis by LPL and because GC modulate insulin secretion and efficiency of action.

**MATERIALS AND METHODS**

Animals and treatments. A first cohort of animals was used to determine the postprandial response of plasma glucose, insulin, and triglycerides to the diets. Twenty-four male Sprague-Dawley rats (Charles River, St. Constant, Quebec, Canada) initially weighing 225–250 g were housed individually in stainless steel cages in a room maintained at 24 ± 1°C, with a 12:12-h light-dark cycle (lights on at 2000). The animals were cared for and handled in compliance with the Canadian Guide for the Care and Use of Laboratory Animals, and the experimental procedures were approved by our institutional animal care committee. Rats were divided into two dietary groups of 12 animals each and for 2 wk had ad libitum access to water and either one of two diets. The first diet was a commercial, nonpurified diet (Charles River rodent chow #5075, Charles River, St. Constant, Quebec, Canada) with a gross energy content of 14.4 kJ/g, which maintains low levels of plasma lipids in the rat. The second diet consisted of a purified diet that leads to obesity, hyperlipidemia, and insulin resistance (22). The composition of the diet was the following: 41% of energy as carbohydrate (sucrose), 39% as lipid (corn oil:lard, 1:1), 20% as protein (casein), DL-methionine (0.3% wt/wt), vitamins (1.2%, vitamin mix no. 40060, Teklad Test Diets, Madison, WI), minerals (5.5%, AIN-76 mineral mix, ICN Biochemicals, Montreal, Quebec, Canada), and fiber (5.5%, Alphacel, ICN Biochemicals), with a gross energy content of 19.4 kJ/g. The purified diet, termed the high-sucrose, -fat (HSF) diet herein, was in the form of a paste and was provided to the animals in stainless steel, wire mesh-covered feeders attached to the inside of the cages. The nonpurified, pelletized diet was ground to a powder and provided in a similar manner. During the experimental period body weight and food intake were recorded every other day. To accurately monitor postprandial changes in the variables of interest, rats were subjected to the following meal intake protocol during the third week of treatment. At the beginning of the third week, access to food was restricted to the dark period. The animals were adapted during a total of 5 days to eat a meal within a period of 30 min 1 h after the onset of the dark period. The amount of food was not restricted during meal intake, and the animals typically ingested 5–8 g of food during the 30-min period. Free access to food was restored 90 min after the beginning of the meal, except on the day of the experiment. The meal intake protocol did not alter cumulative daily energy intake compared with ad libitum feeding. Two days into the meal adaptation period, the animals were fitted under isoflurane anesthesia with a permanent intrajugular cannula to allow harvesting of multiple blood samples in the postprandial state under unanesthetized, unrestrained conditions. After 3 days of continuation of the meal-intake protocol after the 12-h fasting period, a first blood sample (0.15 ml) was taken under dim lighting from the jugular catheter at the onset of the dark period (fasting sample). The animals were then given their 30-min meal beginning 1 h after the first blood sampling. Additional blood samples were taken through the catheter 30, 60, 120, 240, and 360 min after the onset of the meal. Plasma was stored at −70°C until later biochemical measurements. Two additional cohorts of rats were used to investigate how GC modulate TG-rich lipoprotein metabolism in diet-induced obesity. Each cohort was composed of 56 male Sprague-Dawley rats, which were cared for as described above. In each of the cohorts, the animals were randomly assigned to six groups according to a 2 × 3 factorial design. The factors were the diet, with two levels (nonpurified diet and HSF diet), and the Cort status, with three levels (Intact, adrenalectomy (ADX), and ADX plus corticosterone (ADX+Cort) replacement). The bilateral removal of the adrenals was achieved through two small lateral skin incisions performed under isoflurane anesthesia. The adrenals were pulled out through the incision by holding the periadrenal fat and severed with scissors. After each excision surgery, incisions were appropriately sutured. The animals of the ADX+Cort groups were subcutaneously implanted in the interscapular region with cholesterol pellets containing 40 mg of Cort, whereas the ADX group received pellets containing cholesterol alone. Intact, sham-operated animals were handled in the same way as ADX animals except that the adrenals were not excised. All rats were given 0.15 M NaCl in lieu of water to drink throughout the experiment and were fed the nonpurified diet or the HSF diet. Seven days after the ADX, the animals were fitted with a permanent polyethylene cannula in the right jugular vein under isoflurane anesthesia. On the same day, the animals were subcutaneously implanted with a second slow-release pellet, with or without Cort, to maintain relatively constant levels of Cort in the blood throughout the experiment. Rats were treated for a total of 12 days. Food intake and body weight were measured every other day throughout the experimental period. The first cohort of animals was used to determine in vivo the rate of hepatic very low density lipoprotein-TG (VLDL-TG) secretion. Postheparin plasma and tissue LPL activities as well as plasma variables were determined in the second cohort. The postheparin plasma LPL procedure and tissue harvesting were separated by a 4-day period. The animals were fasted for 12 h during the lighted period before the procedures described below were performed so as to avoid the strong acute effects on lipid metabolism of the nutritional status, which was expected to differ between intact and ADX animals fed ad libitum.

**VLDL-TG secretion rate**. An initial blood sample (0.15 ml) was withdrawn through the venous catheter, and rats were injected through the catheter with 300 mg/kg body wt of Triton WR-1339 (Sigma, St. Louis, MO), a detergent that prevents intravascular TG catabolism (35). Blood samples (0.15 ml) were then taken 20, 40, and 60 min after the Triton injection. The rate of VLDL-TG secretion into the circulation was determined from regression analysis of TG accumulation in plasma versus time. Secretion rate was calculated by multiplying the slope of the regression line by plasma volume estimated from body weight and was expressed as micromoles per minute.

Postheparin plasma LPL. Approximately 0.5 ml of blood was drawn from the jugular catheter 10 min before and 10 min after the rapid intrajugular administration of 200 IU/kg body wt of sodium heparin (porcine intestinal mucosa, 1,000 USP/ml, Sigma) to release LPL from the vascular endothelium (33). Blood was centrifuged at 1,500 g, 4°C, for 15 min, and plasma was stored at −70°C for later measurement of postheparin plasma LPL activity.

Blood and tissue harvesting. Rats were killed by decapitation in the fasted state. Blood collected from the neck wound was centrifuged at 1,500 g, 4°C, for 15 min. Plasma was stored at −70°C for later biochemical measurements. A sample of liver was immediately frozen and stored at −70°C until later determination of TG content. Epididymal white
adipose tissue (WAT) and red vastus lateralis muscle (VLM) were excised. Tissues were weighed, ~50 mg were taken from WAT and the red portion of VLM, and tissue samples were homogenized using all-glass tissue grinders (Kontes, Vineland, NJ). The WAT samples were homogenized in 1 ml of a solution containing 0.25 M sucrose, 1 mM EDTA, 10 mM Tris-HCl, and 12 mM deoxycholate, pH 7.4. The VLM samples were homogenized in 1 ml of a solution containing 1 M methylene glycol, 50 mM Tris-HCl, 3 mM deoxycholate, 10 IU/ml heparin, and 5% (vol/vol) aprotinin (Trasylol, Miles Pharmaceuticals, Rexdale, Ontario, Canada), pH 7.4. These homogenizing media were found to yield optimal LPL activity. Only total LPL activity is presented below. Statistical analysis. Data are expressed as means ± SE. Factorial analysis of variance with repeated measures was performed to compare the acute postprandial response of glucose, insulin, and triglycerides to the two diets (cohort 1), the between-group factor being diet with two levels (nonpurified diet and HSF diet), and time after meal intake being the factor with repeated measures. A two-tailed Student's t-test was used to compare means of the two dietary groups at the 0 (fasting) time point. Main treatment effects of diet and Cort status and treatment interactions were analyzed using factorial analysis of variance (cohorts 2 and 3), the factors being diet with two levels (nonpurified diet and HSF diet) and Cort status with three levels (intact, ADX, and ADX+Cort). In some instances, the intact and ADX groups were compared using a 2 × 2 factorial design to reveal treatment interactions without diluting the effect of the Cort status by the ADX+Cort group, which was expected to be comparable to the intact group. Individual between-group comparisons were performed using Fisher’s protected least squares difference post hoc test. Data were log transformed before analysis when group variances were not homogeneous (O’Brien’s test), but untransformed values are presented below. Pearson’s linear correlation coefficients were calculated to determine statistical associations between variables. Differences were considered statistically significant at P < 0.05.

RESULTS

The postprandial response of plasma glucose, insulin, and TG to the intake of a meal consisting of the habitual diet is shown in Fig. 1. Fasting plasma glucose was slightly (6%) but significantly (P < 0.04) higher in the HSF than in the nonpurified group (Fig. 1A). Both diets elicited the same postprandial rise in plasma glucose (main effect of time, P < 0.0001), and the incremental area under the glucose curve (not shown) did not differ among groups. The animals fed the HSF diet displayed fasting hyperinsulinemia (+284%, P < 0.02) compared with rats fed the nonpurified chow diet. Peak postprandial insulinemia was reached 30 min after the onset of the meal in both dietary groups, at which time it reached 0.50 and 1.84 nmol/l in the chow-fed and HSF-fed groups, respectively (Fig. 1B). Insulinemia remained higher in the HSF than in the chow group throughout the 6-h postprandial period, as witnessed by a significant treatment interaction [diet (D) × time (T) interaction, P < 0.04]. The incremental area under the insulin curve (not shown) was fourfold larger in the HSF than in the chow group. The slight difference between fasting plasma TG did not reach statistical significance (Fig. 1C). However, the postprandial rise in triglyceridemia, which peaked at 1–2 h after the onset of the meal, was significantly larger in the HSF than in the chow group throughout the period studied (D × T, P < 0.0008). The incremental area under the triglyceride curve (not shown) was 3.4-fold larger in the HSF than in the chow group.

ADX animals subcutaneously implanted with cholesterol pellets containing no Cort had undetectable levels...
of Cort in their blood (Fig. 2A). The implantation of Cort-containing pellets in ADX rats increased plasma Cort levels up to 0.1 µmol/l in both dietary cohorts, which were lower than in intact animals. Cort concentrations were significantly higher in intact rats fed the HSF diet than those fed chow [D × Cort status (C) interaction, P < 0.004], but they were unaffected by diet in ADX + Cort animals.

Diet and Cort status interacted on daily energy intake (D × C, P < 0.05), as depicted in Fig. 2B. The interaction was due to the fact that intact animals fed the HSF diet ingested 17% more energy than their counterparts fed the nonpurified diet, whereas both ADX and Cort replacement in ADX animals brought about similar energy intakes in the two dietary cohorts. ADX significantly reduced daily caloric intake in both dietary cohorts, but more so in HSF-fed (30% or 110 kJ/day) than in chow-fed rats (21% or 65 kJ/day), to levels that were identical in the two dietary cohorts. Cort replacement in ADX animals prevented the effects of ADX on energy intake in a diet-dependent fashion (D × C, P < 0.05), inasmuch as prevention was total in chow-fed rats but only partial in HSF-fed rats. Cort replacement maintained energy intake at identical levels in the two dietary groups. As expected, final body weight correlated with energy intake (r = 0.68, P < 0.0001). The treatments also interacted significantly...
(D × C, P < 0.05) on final body weight (Fig. 2C). The interaction stemmed from the following factors. Body weight was higher in intact (P < 0.03), but not in ADX or ADX + Cort rats fed the HSF diet compared with those fed chow; Cort replacement prevented the ADX-induced weight loss in chow-fed animals, but failed to do so in rats fed the HSF diet. ADX lowered body weight (main effect of C, P < 0.0004) in both chow-fed (−24 g) and HSF-fed (−48 g) animals. The treatment effects on energy intake and body weight described above were confirmed in the two consecutive studies.

Hepatic TG content was quantitated as an index of long-term liver triglyceride synthetic activity. The HSF diet increased liver TG content almost threefold (Fig. 3A) compared with the nonpurified diet. Diet strongly interacted with the Cort status on liver TG content (D × C, P = 0.0006). In the chow-fed cohort, although ADX tended to reduce liver TG (−0.036 mmol/g) and this was reversed by Cort replacement, post hoc analysis revealed that these effects were not significant. In contrast, the Cort status strongly influenced liver TG content in the HSF-fed cohort. ADX abolished the increase in hepatic TG associated with the intake of the HSF diet (−0.158 mmol/g, a reduction of 61%), and Cort replacement restored TG content to that of the intact group. Figure 3B shows that the HSF diet resulted in mild fasting hypertriglyceridemia compared with chow. Treatments interacted on triglyceridemia (D × C, P < 0.04), inasmuch as the Cort status had no impact in chow-fed animals but did interact in HSF-fed rats. In the latter, ADX tended to lower plasma triglyceride levels, which were returned to intact levels with Cort replacement. Figure 3C shows that TG secretion rate was altered according to the Cort status (main effect of C, P < 0.002), whereas diet had no overall effect. ADX decreased TG secretion rate slightly in chow-fed rats and by 32% in HSF-fed animals, whereas ADX + Cort groups had secretion rates comparable to those of intact animals. Whereas hepatic TG secretion rate and triglyceridemia evaluated in the same animals were modestly associated with each other (r = 0.43, P < 0.004) when all groups were considered together, correlation analysis according to diet revealed that the two variables were not related in chow-fed rats (r = 0.02) but were significantly related in HSF-fed animals (r = 0.58, P < 0.002).

Plasma levels of insulin were determined at the end of the experimental period, because the hormone is affected by the Cort status and obesity and because it constitutes an important comodulator of lipid metabolism. Figure 4A shows that the HSF diet caused hyperinsulinemia (main effect of D, P < 0.0001). ADX greatly lowered insulin concentrations in both chow (−73%) and HSF-fed (−81%) groups, but the absolute decrease was almost twofold larger in the HSF-fed animals (−0.186 nmol/l) than in those fed chow (−0.106 nmol/l), as witnessed by the significant treatment interaction (P < 0.003). In fact, removal of Cort through ADX in HSF-fed animals brought their insulin levels to those of ADX animals fed chow and therefore prevented diet-induced hyperinsulinemia. Cort replacement restored insulinaemia to the intact range in both dietary cohorts, without any diet-related difference in the levels attained. Glycemia (Fig. 4B) was slightly but significantly affected by the Cort status (main effect of C, P < 0.0001). Plasma glucose levels were reduced in the ADX animals compared with intact and ADX + Cort groups. Post hoc analysis revealed that intact rats fed the HSF diet were hyperglycemic relative to their chow-fed counterparts, but that ADX + Cort groups fed either diet were identical to each other and to the intact chow-fed group. Plasma concentrations of NEFA, which
partly determine rates of hepatic TG synthesis and secretion, were found to remain unaltered by diet or the Cort status (data not shown). Figure 5 indicates that fasting postheparin plasma LPL, another major determinant of triglyceridemia, also remained unaffected by treatments. Both diet and the Cort status exerted strong actions on adipose tissue weight, and despite the lack of change in the global availability of LPL in the intravascular compartment, the treatments exerted major, tissue-specific actions on LPL activity (Fig. 5). Diet and the Cort status exerted significant main effects (P < 0.0001 and 0.0003, respectively) on retroperitoneal adipose weight without interacting with each other. Intact animals fed the HSF diet had 80% more retroperitoneal fat mass than their counterparts fed the nonpurified diet (Fig. 5A). ADX decreased adipose weight by 60% in both chow-fed and HSF-fed rats, which represented an absolute reduction of 0.63 and 1.10 g of fat, respectively. Cort replacement in ADX animals restored retroperitoneal weight toward intact values, but somewhat dampened the diet-related difference in tissue weight. Similar treatment effects were noted in the epididymal and inguinal adipose depots, as well as in the sum of the three depots (data not shown). As to retroperitoneal adipose LPL activity (Fig. 5B), diet and the Cort status also exerted significant main effects (P < 0.0003 and 0.001), and the Cort status tended to have stronger effects in HSF-fed than in chow-fed rats, as indicated by a nearly significant treatment interaction (P = 0.07). Indeed, post hoc analysis revealed that ADX resulted in a small (−4.6 µU/tissue) but nonsignificant reduction in adipose LPL in chow-fed rats, whereas the reduction reached 68% (−17.6 µU/tissue) in the HSF cohort. As in the case of adipose weight, Cort replacement restored LPL activity to levels that were not significantly different from those of intact animals, as well as the diet-related difference observed in intact animals. Adipose weight and LPL activity were significantly associated with each other (r = 0.65, P < 0.0001). There was no significant main effect of the diet on muscle weight. Cort replacement restored muscle weight toward that of intact rats, although in the HSF-fed cohort muscle weight remained significantly below intact values despite Cort treatment. The HSF diet reduced muscle LPL activity by an average of 42% (P < 0.003) relative to the chow cohort (Fig. 5D), whereas the Cort status did not alter enzyme activity in this skeletal muscle.

There were significant statistical associations between energy intake and most variables of TG metabolism that were evaluated in the same animals, including hepatic TG content (r = 0.70, P < 0.0001), triglyceridemia (r = 0.50, P < 0.0005), adipose tissue mass (r = 0.85, P < 0.0001), and LPL activity (r = 0.62, P < 0.0001). Insulinemia was in turn correlated with energy intake (r = 0.66, P < 0.0001) as well as with most variables of TG metabolism mentioned above (0.51 < r < 0.55, P < 0.0004).

**DISCUSSION**

This study aimed to assess the contribution of Cort to the adaptations of TG-rich lipoprotein metabolism and lipid deposition associated with diet-induced obesity. The findings demonstrate that GC modulated fasting TG metabolism only minimally in rats fed chow, a diet that maintains a low lipid flux. In contrast, GC were necessary for the stimulation of hepatic TG production and hypertriglyceridemia and for the adipose-specific increase in LPL in response to the HSF diet. Removal of GLUCOCORTICOIDS AND TRIGLYCERIDE METABOLISM

![Image](image-url)
Cort abolished the diet-related differences in most determinants of TG metabolism and deposition, whereas these differences tended to be reestablished by Cort replacement. These findings indicate that Cort is among the necessary factors that facilitate lipid production and deposition in response to an obesity-promoting diet.

The HSF diet was particularly efficient in increasing lipid flux, confirming earlier studies (22, 30), because of both an increase in energy intake and the composition of the diet. After feeding the diet for 12 days, hepatic TG content, which reflects long-term endogenous TG production, was tripled in the HSF-fed intact animals, mainly because of the highly lipogenic potential of dietary sucrose (19). Fasting triglyceridemia was also slightly increased by the HSF diet, an effect that was dependent on the carbohydrate, rather than the fat content of the diet, as shown earlier (8). The rate of hepatic TG secretion measured after a 12-h fast was not affected by diet to a large extent. As shown by us and others (5, 19, 31), sucrose increases fasting hepatic TG secretion compared with a starch-based diet, but the presence of a high amount of fat in the diet tends to counteract this increase (8). The full impact of the HSF diet on triglyceridemia was also slightly increased by the HSF diet, an effect that was dependent on the carbohydrate, rather than the fat content of the diet, as shown earlier (8). The rate of hepatic TG secretion measured after a 12-h fast was not affected by diet to a large extent. As shown by us and others (5, 19, 31), sucrose increases fasting hepatic TG secretion compared with a starch-based diet, but the presence of a high amount of fat in the diet tends to counteract this increase (8). The full impact of the HSF diet on triglyceridemia was also slightly increased by the HSF diet, an effect that was dependent on the carbohydrate, rather than the fat content of the diet, as shown earlier (8). The rate of hepatic TG secretion measured after a 12-h fast was not affected by diet to a large extent. As shown by us and others (5, 19, 31), sucrose increases fasting hepatic TG secretion compared with a starch-based diet, but the presence of a high amount of fat in the diet tends to counteract this increase (8). The full impact of the HSF diet on triglyceridemia was also slightly increased by the HSF diet, an effect that was dependent on the carbohydrate, rather than the fat content of the diet, as shown earlier (8). The rate of hepatic TG secretion measured after a 12-h fast was not affected by diet to a large extent. As shown by us and others (5, 19, 31), sucrose increases fasting hepatic TG secretion compared with a starch-based diet, but the presence of a high amount of fat in the diet tends to counteract this increase (8).

Diet-induced alterations in insulin levels were likely involved in the tissue-specific adaptations of LPL activity (9, 42). Finally, the HSF diet elicited insulin resistance, as reflected by fasting and postprandial hyperinsulinemia in the presence of normal glycemia compared with the chow-fed animals. As in the case of triglyceridemia, HSF-induced hyperinsulinemia was particularly evident in the postprandial state. The fat component of the diet was mainly involved in the development of insulin resistance (32), with some contribution from sucrose (40). Therefore, the HSF-fed rat can be considered as a model of diet-induced metabolic perturbations that are quite similar to those that define the plurimetabolic syndrome, which is frequently associated with human obesity (44).

Removal of the adrenals decreased circulating Cort to undetectable levels, whereas the implantation of pellets containing 40 mg of Cort in ADX animals increased plasma Cort levels up to 0.1 µmol/l, which were below those of intact rats. Cort levels in intact animals were obtained at 0800 (beginning of dark period) and correspond to peak values of the circadian rhythm of Cort (16). Therefore, the difference between Cort levels of intact and ADX+Cort groups was smaller.
at other times of the day than at the time of sampling. On the other hand, diet affected plasma levels of Cort, inasmuch as intact rats fed the HSF diet had higher fasting plasma Cort concentrations than those fed chow, in agreement with a previous study by Tannenbaum et al. (49) with high fat-fed rats.

The ADX-induced reduction in food intake, body weight, and fat mass confirms the well-established involvement of GC in energy balance (10, 17, 48, 52). Treatment of ADX animals with Cort restored most of the metabolic alterations brought by ADX, indicating that removal of Cort was the principal causative factor in the effects of ADX. However, the degree of restoration of energy intake was diet dependent, confirming earlier findings (2). Indeed, whereas Cort treatment restored food intake to intact levels in chow-fed animals, the anorectic action of ADX was partially maintained in HSF-fed animals implanted with Cort. Body and tissue weights reflected these diet-related differences in the effects of Cort replacement on energy intake. The findings are in agreement with the previously reported dependence on diet composition of the magnitude of effect of GC receptor blockade on adipose mass (38). The reasons for the lack of full reversal of the effects of ADX on energy intake by Cort in HSF-fed animals are unknown. Indexes of insulin action were also affected by the Cort status in a diet-dependent manner. The influence of the Cort status was clearly more robust in the HSF-fed than in the chow-fed cohort, as indicated by the treatment interaction on insulinemia. Improvement of insulin sensitivity by ADX has been reported in other models of obesity (7, 26). Cort replacement prevented the effects of ADX on glycemia and insulinemia in proportion to its action on energy intake, that is, a full and partial reversal in chow- and HSF-fed animals, respectively.

Removal of GC through ADX had a major impact on all determinants of TG metabolism that was strongly diet dependent. Indeed, although weak, nonsignificant trends were noted in the chow-fed cohort, variables of TG metabolism remained essentially unaffected by the Cort status, including liver TG content, hepatic TG secretion rate, triglyceridemia, and adipose tissue LPL activity. This lack of effect of the Cort status on fasting TG metabolism in chow-fed rats occurred despite fluctuations of as much as 20% in energy intake. Therefore, Cort does not appear to modulate TG metabolism to any significant extent when lipid flux tends to be low, such as when a nonpurified, low-fat diet high in complex carbohydrates is fed. In sharp contrast, Cort proved to be essential in the establishment of diet-related differences in indexes of lipid metabolism, and all were greatly reduced by ADX in animals fed the HSF diet. In fact, in HSF-fed ADX animals, liver TG content, hepatic TG secretion rate, triglyceridemia, and adipose tissue LPL activity became indistinguishable from those of their chow-fed counterparts, despite the high lipogenic potential of the constituent macronutrients of the HSF diet. The one exception to this was muscle LPL, which remained lower in HSF-fed than in chow-fed animals regardless of the Cort status. Muscle LPL may be particularly sensitive to lipid flux and oxidation (23), and the absence of effect of the Cort status on muscle LPL confirms earlier findings (18).

As was the case for ADX itself, Cort replacement did not significantly affect determinants of TG metabolism in the chow-fed cohort. In contrast, liver TG content, triglyceridemia, hepatic TG secretion, and adipose tissue LPL of HSF-fed rats, which were all decreased by ADX, were fully restored to intact levels by Cort treatment of ADX animals. Moreover, most of the diet-related differences that were observed in intact animals were reestablished in Cort-implanted animals, despite the absence of hyperphagia in HSF-fed rats relative to their chow-fed counterparts. These findings indicate that determinants of TG metabolism are particularly sensitive to diet composition, because they were modulated by the nature of the diet even in the presence of equal caloric intake and similar plasma Cort concentration. However, Cort had to be present for such diet-related differences to be expressed, because they were no longer seen in ADX animals without Cort replacement. This may be related to the fact that pair feeding among the two dietary cohorts was achieved at lower intake levels in ADX rats compared with ADX+Cort animals.

The modes of action of GC on lipid metabolism are manifold. First, the centrally mediated anorectic and thermogenic effects of GC removal evidently decrease TG synthesis in the liver, their secretion and transport into the circulation, as well as their deposition into lipid stores. Second, GC exert several direct peripheral actions that sustain lipid production, transport, and storage, which would be liable to be downregulated after ADX. In vitro studies have shown that GC directly stimulate hepatic fatty acid and TG synthesis (11, 21) and increase apolipoprotein B secretion in hepatocytes (51), thereby favoring VLDL secretion into the circulation (4, 43). Although without much effect by themselves (1, 15), GC potentiate the positive modulation of adipose tissue LPL by insulin (3, 27, 39). Third, GC tend to stimulate insulin secretion through several mechanisms (7, 50). Insulin shares with Cort most of its actions on lipid production and storage, including the stimulation of hepatic lipogenesis and adipose LPL activity, with the exception of VLDL secretion by the insulin-sensitive liver (34). The respective contribution of central and peripheral actions of GC on overall lipid metabolism remains to be determined. In the present studies, there was a strong association between energy intake and most of the determinants of lipid production, transport, and deposition. In addition, basal, or threshold, levels of these determinants (e.g., hepatic TG production and secretion, adipose LPL activity) were maintained in total absence of Cort. These findings suggest that the peripheral actions of GC may serve as supportive adaptations to accommodate the central action of GC on ingestive behavior.

Perspectives

Sustained consumption of diets high in insulinogenic/ lipogenic carbohydrates and in fat promotes obesity
and its metabolic complications. The deleterious effects of diet-induced obesity include alterations in the metabolism of lipid substrates. These are partly caused by complex endocrine adaptations that occur to adjust the organism to an elevated energy flux. The present studies underline the role of GC in these processes. As stated by Tannenbaum et al. (49), high-energy (particular high fat) diets act as a background form of chronic stress that elevates basal GC levels. A vicious cycle is established, as high GC levels are liable to favor increased food intake through their action on the central regulatory pathways of energy balance. At the periphery, GC have the potential to directly facilitate lipid production from carbohydrates as well as deposition of triglycerides from endogenous and exogenous sources. In addition, high GC levels favor an increased insulin secretion. They also contribute to the development of insulin resistance of metabolic pathways that tend to decrease lipid flux (anorectic action, glucose use, inhibition of lipolysis, VLDL secretion), whereas pathways that increase lipid flux remain responsive to insulin (liver lipid production, deposition-promoting adipose lipoprotein lipase). GC themselves potentiate the action of insulin on several of these pathways. Comitantly, endocrine factors that promote triglyceride mobilization and utilization, such as the sympathetic nervous system, are dissociated. The sum of these adaptations constitutes an exquisitely integrated response of the organism to increased energy availability, which has evolved when the latter was sporadic, to promote energy storage in the form of triglycerides in preparation for leaner times. With virtually unlimited accessibility and overconsumption of energy, there is a continuous maintenance of an integrated set of adaptations that originally developed for short-term operation. As is often the case, this proves to be deleterious. The authors are indebted to José Lalonde for invaluable professional assistance. This work was supported by a grant from the Natural Sciences and Engineering Research Council of Canada.

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