Responses of Adipose and Muscle Lipoprotein Lipase to Chronic Infection and Subsequent Acute Lipopolysaccharide Challenge

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Infection of male Swiss Webster mice with Toxoplasma gondii or Neospora caninum leads to long-term alterations in energy balance. Following an initial 20 to 30% weight loss in all T. gondii-infected mice, half of the animals regain most of the lost weight (gainers), whereas the others maintain their low body weight (nongainers). Infection with N. caninum does not elicit weight loss. Lipoprotein lipase (LPL), the enzyme responsible for plasma triglyceride (TG) clearance and partitioning among tissues, is under tissue-specific modulation associated with energy balance. It is also a major determinant of infection-induced hypertriglyceridemia. This study aimed to assess the long-term modulation of adipose and muscle LPL activity in mice infected with T. gondii or N. caninum, to evaluate the effects of subsequent acute lipopolysaccharide (LPS) administration, and to relate LPL modulation in these conditions with infection-related changes in body weight gain. Twenty-eight days after infection, LPL activity in muscle of both gainer and nongainer T. gondii-infected mice was reduced by 40 to 50% compared with the levels in controls and N. caninum-infected mice, whereas LPL activity in adipose depots remained unchanged in all infected groups compared to the level in controls. LPS (from Escherichia coli, 100 ng/kg) injection induced a global reduction in adipose LPL in all groups, as assessed 90 min later. In both T. gondii-infected subgroups, muscle LPL was not further reduced by LPS treatment, whereas it was decreased by 40 to 50% in muscles of control and N. caninum-infected mice. Pre-LPS TG levels in plasma were similar in all groups. LPS greatly increased TG levels in plasma in both control and N. caninum-infected animals, whereas it did not alter those of T. gondii-infected gainer or nongainer animals. These results show that (i) independently of the extent of postinfection weight gain, long-term infection with T. gondii chronically reduces muscle LPL, which becomes unresponsive to acute endotoxemia; (ii) modulation of tissue LPL activity during chronic T. gondii infection favors TG partitioning towards adipose tissue; and (iii) skeletal muscle LPL is a key determinant of the acute response of triglyceridemia to LPS.

Infection with parasites results in profound alterations in host energy metabolism that lead to cachexia. One of the major and early responses of host metabolism to infection is an increase in the circulating triglyceride (TG) concentration (21). Hypertriglyceridemia is due to both an increase in hepatic secretion of very-low-density lipoproteins (29, 31) and alterations in the rate of clearance of TG (4, 30), which is brought about by a cytokine-mediated reduction in lipoprotein lipase (LPL; EC 3.1.1.34) activity in nearly all tissues (14), thereby decreasing overall TG clearance in the vascular compartment (40). Recently, two studies reported the beneficial effects of synthetic LPL activators on cachexia and triglyceridemia (27, 41), suggesting that modulation of the activity of the enzyme during infection may also affect energy partitioning among tissues.

LPL is the rate-limiting enzyme for the hydrolysis of TG within circulating lipoproteins (12). The enzyme is also implicated in TG partitioning, as it is usually modulated in a reciprocal fashion in storage and oxidative tissues (50). The tissue-specific modulation of LPL is intimately associated with whole-body energy balance, as high adipose and low muscle LPL are associated with obesity and the opposite pattern is associated with leanness (50). One rare exception to the tissue-specific, reciprocal modulation of LPL is sepsis (which is mimicked by infection and endotoxemia). The acute decrease in LPL activity in adipose tissue and skeletal muscle in these conditions is caused by the action of several cytokines and is dependent on posttranslational mechanisms (20). Whereas interleukin-1 (IL-1) and gamma interferon (IFN-γ) have been shown to affect muscle LPL activity in vivo (14, 19), tumor necrosis factor alpha (TNF-α) appears to be an important mediator of the effects of endotoxemia on adipose tissue LPL in vivo (14, 33) as well as in cultured adipocytes (47, 48).

Besides their role in host defense, cytokines interact with factors implicated in body weight regulation and energy metabolism (23, 24). Arsenijevic et al. have described a model (2, 3) in which mice infected with Toxoplasma gondii lose weight (20 to 30%) during the first 14 days of infection; of those surviving (>75%), some regain weight (gainers) whereas other infected mice remain at their reduced body weight indefinitely (nongainers). On the other hand, infection with Neospora caninum blunts weight gain without eliciting an initial weight loss (8, 11).

Since the tissue-specific modulation of LPL activity in adipose and muscle tissues is likely to affect lipid partitioning as...
TABLE 1. Body and tissue weights recorded in infected mice 28 days after i.p. injection of 10 cysts of either *T. gondii* or *N. caninum*.

| Group       | Body weight (g) | Epididymal WAT* (mg) | Inginal WAT (mg) | Gastrocnemius (mg) | VLM (mg) |
|-------------|----------------|----------------------|-----------------|-------------------|---------|
| Control     | 39.3 ± 1.2 A    | 894 ± 68 A           | 275 ± 44 A      | 167 ± 13 A        | 182 ± 8 A |
| *T. gondii* gainers | 34.8 ± 1.1 B    | 514 ± 59 B           | 187 ± 24 B      | 155 ± 10 A        | 186 ± 20 A |
| *T. gondii* nongainers | 27.5 ± 0.8 C    | 176 ± 46 C           | 118 ± 12 C      | 114 ± 10 B        | 120 ± 7 B  |
| *N. caninum* | 33.3 ± 0.9 B    | 314 ± 36 D           | 195 ± 9 B       | 148 ± 9 A         | 175 ± 5 A  |

*Means are values ± SEM for six animals. Values not sharing the same letter next to them are different from each other (P < 0.05).*

well as triglyceridemia during infection-induced cachexia in a way that can relate to energy balance, the aim of the present study was to evaluate the effects of *T. gondii* and *N. caninum* infection on lipid metabolism, specifically on variables influencing triglyceridemia, i.e., TG content in the liver and peripheral TG clearance through adipose and muscle LPL activity. Infection profoundly alters the activity of the hypothalamic-pituitary-adrenal axis (22, 39) as well as insulin homeostasis (9, 49). The levels of corticosterone and insulin in plasma were therefore assessed because of their involvement in energy balance (46) and because they constitute important modulators of tissue LPL activity (12). A subsequent challenge with lipopolysaccharide (LPS) was performed to determine the acute responsiveness of lipid metabolism in mice previously infected with either *T. gondii* or *N. caninum*.

**MATERIALS AND METHODS**

**Mice and diet.** Specific-pathogen-free female Swiss Webster mice (BRL, Füllinsdorf, Switzerland) of approximately 1 month of age were housed individually in plastic cages with wood shavings under controlled temperature (25 ± 1°C) and lighting (lights on between 0700 and 1900 h) and had ad libitum access to food (4.5% fat, 14.4 kJ/g, pelleted stock diet, Charles River Rodent Animal Diet;Ralston Products, Woodstock, Ontario, Canada) and tap water. All mice were cared for and handled in conformance with the Canadian Guide for the Care and Use of Laboratory Animals, and the protocol was approved by our institutional animal care committee. One week after their arrival, mice were injected intraperitoneally (i.p.) with either 10 cysts of the Me49 strain of *T. gondii* (kindly provided by L. L. Johnson, Saranac Lake, N.Y.) or 10 cysts of *N. caninum* (kindly provided by J. D. Bartu, University of Guelph, Guelph, Ontario, Canada). Cysts were obtained from isolated brain homogenates of infected mice, purified by Percoll centrifugation (25), and diluted in phosphate-buffered saline. Control mice were injected with 0.5 ml of phosphate-buffered saline. Twenty-eight days after cyst administration, mice were injected with either saline or LPS (100 µl of thawed tissue homogenates was incubated under gentle agitation for 1 h at 28°C with 100 µl of a substrate mixture consisting of 0.2 mol of Tris-HCl buffer/liter (pH 8.6), which contained 10 MBq of [carboxyl-14C]tri olein (Amersham, Oakville, Canada)/liter and 2.52 mmol of cold tri olein/liter emulsified in 50 g of gum arabic/liter, as well as 20 g of fatty-acid-free bovine serum albumin/liter, 10% human serum as a source of apolipoprotein C-II, and either 0.2 or 2 mol of NaCl. Free oleate released by LPS was then separated from intact tri olein in a liquid partitioning system and mixed with Universol (NEN, Montréal, Canada), and sample radioactivity was determined in a scintillation counter. LPL activity was calculated by subtracting lipolytic activity determined in a final NaCl concentration of 1 mol/liter (non-LPL activity) from total lipolytic activity measured in a final NaCl concentration of 0.1 mol/liter. LPL activity was expressed as microns (1 µU = 1 µmol of nonesterified fatty acids released per h of incubation at 28°C). The interassay coefficient of variation was 4.6% and was determined by using bovine skim milk as a standard source of LPL. The protein content of the tissue extracts was measured by the method of Lowry et al. (34). Data are expressed as the specific activity of LPL (microns per gram of tissue protein).

**Statistical analysis.** Data are presented as means ± standard errors of the mean (SEM). Group means were compared by using a 4-by-2 factorial analysis of variance to determine the main effects of chronic infection with four levels (control, *T. gondii* gainers, *T. gondii* nongainers, and *N. caninum*), acute LPS with two levels (saline and LPS), and their interactions. Differences between individual group means were analyzed by Fisher’s protected least squares difference test to evaluate the effects of LPS on *T. gondii* - and *N. caninum*-infected mice separately. Pearson’s correlation coefficients were calculated to determine statistical significance between variables. Differences were considered statistically significant at *P < 0.05.*

**RESULTS**

Twenty-eight days after cyst administration, mice infected with *T. gondii* had lower body weights than did control animals (*P < 0.002*) (Table 1). After having lost 28% of their body weight during the first 14 days of infection (data not shown), *T. gondii*-infected mice showed a bimodal pattern of body weight regulation, as approximately half of the animals regained an average of 62% of the lost weight (gainers) whereas the other half did not (nongainers; *P < 0.05* between gainers and nongainers). Mice infected with *N. caninum* did not lose weight but displayed a blunted weight gain (Table 1). At the end of the experiment, *N. caninum*-treated mice had body weights similar to those of *T. gondii*-infected -gainer animals. Changes in body weight were more closely related to fat than to lean mass accretion (Table 1) and were in the same proportion as the effects of infection on body weight. It is noteworthy that de-
Values are means ± SEM of results for three animals.

Despite the similar body weights of *T. gondii*-infected gainer mice and *N. caninum*-infected animals, mice that previously lost weight had heavier epididymal fat pads than did infected mice that did not lose weight (514 versus 314 mg, respectively; *P* < 0.05). This association was not found in the subcutaneous inguinal adipose depot.

TG content in the liver was strongly affected by infection (Table 2). *T. gondii*-infected gainers had decreased levels of TG per gram of liver tissue but had more than their nongainer counterparts compared to uninfected controls (−45%, *P* < 0.02; and −71%, *P* < 0.001, respectively). The TG content in liver of *N. caninum*-infected mice was similar to that of control animals. The strongest correlate of final body weight was TG content in the liver (*r* = 0.719; *P* = 0.008). Acute LPS injection resulted in an elevation in TG content in the liver (Table 2), which was similar in absolute terms in all groups (12 to 17 μmol/g of liver; *P* < 0.0002).

Glucose levels in plasma were similar between groups as measured 90 min after the injection of saline (Table 2). LPS treatment resulted in an increase in glycemia in noninfected controls and *N. caninum*-infected mice (*P* < 0.05) and in a decrease in the glucose levels in plasma in *T. gondii*-infected nongainer animals (*P* < 0.03). LPS did not affect glycemia in *T. gondii*-infected gainer mice. Long-term infection or acute LPS injection had no effect on insulinemia, except in *N. caninum*-infected animals, in which LPS strongly increased insulin levels in plasma (*P* < 0.05). LPS also increased the corticosterone concentration in plasma (*P* < 0.05) independently of the infection status.

Comparing the data to control animals, the gastrocnemius LPL activity of *T. gondii*-infected animals, whether gainers or nongainers, was reduced by at least 50% (*P* < 0.03) (Fig. 1A). In contrast, no difference in muscle LPL activity was observed between *N. caninum*-treated mice and controls. Acute LPS administration resulted in a 48% reduction in gastrocnemius muscle LPL activity in control mice (*P* < 0.05) and a 51% decrease in *N. caninum*-infected animals (*P* < 0.04). LPS did not further reduce the already low gastrocnemius LPL levels in either group of *T. gondii*-infected mice as measured 90 min after the injection (chronic infection-LPS interaction; *P* < 0.01). Modulation of LPL in VLM displayed a pattern of response to long-term infection and acute LPS similar to that of the gastrocnemius (Fig. 1B). Infection with *T. gondii* decreased VLM LPL by 36% (*P* < 0.05), whereas infection with *N. caninum* did not alter VLM LPL activity. In both control and *N. caninum*-infected mice, LPS injection reduced LPL activity in VLM by 40% (*P* < 0.0052). In contrast, LPS failed to significantly alter VLM LPL activity in either group of *T. gondii*-infected mice.

Long-term infection (with either *T. gondii* or *N. caninum*) did not significantly alter the activity of LPL in either the epididymal (Fig. 2A) or inguinal (Fig. 2B) white adipose depots, although in the latter depot, LPL activity tended to be decreased by infection with *N. caninum*. Ninety minutes after LPS injection, adipose LPL activity in the epididymal depot was decreased in all groups (LPS main effect; *P* < 0.005, no interaction with chronic infection status). In the subcutaneous

**TABLE 2.** TG content in the liver and glucose, insulin, and corticosterone levels in plasma

| Group            | Liver TG (μmol/g) | Glucose (mmol/liter) | Insulin (pmol/liter) | Corticosterone (nmol/liter) |
|------------------|------------------|----------------------|----------------------|-----------------------------|
|                  | Saline | LPS               | Saline | LPS               | Saline | LPS               | Saline | LPS               |
| Control          | 58 ± 10 | 72 ± 2b           | 11.5 ± 2.5 | 16.5 ± 1.7b         | 124 ± 55 | 99 ± 29           | 105 ± 63 | 497 ± 39b         |
| *T. gondii* gainers | 32 ± 3 | 49 ± 10b          | 9.3 ± 1.0 | 7.1 ± 1.2          | 100 ± 62 | 144 ± 19          | 126 ± 76 | 417 ± 122b        |
| *T. gondii* nongainers | 17 ± 3 | 29 ± 1b            | 8.0 ± 1.0 | 4.6 ± 0.3b         | 88 ± 22 | 92 ± 2            | 255 ± 88 | 542 ± 90b         |
| *N. caninum*     | 52 ± 2  | 67 ± 2b           | 11.1 ± 0.5 | 13.1 ± 0.5b        | 57 ± 18 | 162 ± 31b         | 46 ± 2   | 500 ± 27b         |

*Levels measured 90 min after saline or LPS (from *E. coli*, 100 ng/kg) i.p. injection into mice infected for 28 days with either *T. gondii* or *N. caninum*. Values are means ± SEM of results for three animals.

*Significantly different from values for saline-injected mice (*P* < 0.05).

![FIG. 1. LPL specific activity in gastrocnemius (A) and VLM (B) muscles 90 min after saline or LPS (from *E. coli*, 100 ng/kg) i.p. injection into mice infected for 28 days with either *T. gondii* (*ToxG*) or *N. caninum* (*NeoC*). Bars are means ± SEM of the results for three animals. *+, significantly different from results for saline-injected mice with the same infection status (*P* < 0.05); †, significantly different from results for noninfected, saline-injected mice (*P* < 0.05).
FIG. 2. LPL specific activity in epididymal (A) and inguinal (B) white adipose depots 90 min after saline or LPS (from E. coli, 100 ng/kg) i.p. injection into mice infected for 28 days with either T. gondii (ToxG) or N. caninum (NeoC). Bars are means ± SEM of the results for three animals. *, significantly different from results for saline-injected mice (P < 0.05).

chronic phase of infection with T. gondii the modulation of adipose and muscle LPL favors TG partitioning towards lipid storage; and that skeletal muscle LPL is a key determinant of the acute response of triglyceridemia to endotoxemia.

The weight loss that occurs in all animals during the first 14 days of infection with T. gondii is associated with cachexia (3) and decreased fat mass accretion, as confirmed in the present study. Of the mice surviving this acute phase (over 75%), approximately half show a partial weight regain (gainers), whereas the other half remain at a stable, reduced body weight (nongainers), which is caused by persistent cachexia and hypermetabolism (3). In all likelihood, the divergence in weight gain in response to T. gondii infection is related to different expression profiles of cytokines between gainers and nongainers once weight stabilization has occurred (1–3). Recently, it was shown that after 30 days of T. gondii infection—as in the present study—the levels of IL-1β and TNF-α in serum and tissue were very low to undetectable in both gainer and nongainer mice but that IFN-γ levels in serum (undetectable in uninfected mice) remained high, and much more so in nongainers than in gainers (67 and 6 pg/ml, respectively) (1). Accordingly, IFN-γ knockout mice were shown not to develop the hypermetabolic phase characteristic of T. gondii infection (1). It should also be noted that LPS administration to both gainer and nongainer T. gondii-infected mice results in a greater acute elevation in TNF-α, IL-10, and IFN-γ levels in serum than occurs in noninfected mice (2). Regarding the metabolic response to N. caninum infection, its features remain incompletely established (5, 32) but it is considered less severe (blunted weight gain rather than weight loss) than T. gondii infection (8, 11). The present findings therefore confirm the respective effects of T. gondii and N. caninum on body weight regulation.

TG content in the liver was altered by chronic infection in parallel with body weight. This underlines the close association between liver lipid production and food intake (36). In the short term, LPS induced a generalized increase in TG content in the liver, in accordance with the potent stimulatory effect of cytokines, particularly TNF-α, IL-1, and IFN-γ, on hepatic TG synthesis (15, 28, 38). The increase in TG in the liver was of similar magnitude in all groups, but LPS administration did not

DISCUSSION

The present study aimed to assess the effects of chronic infection and acute endotoxemia on lipid metabolism, with special emphasis on determinants of TG production and clearance, in mice with various stable states of energy balance after infection with the parasites T. gondii and N. caninum. The findings show that, independently of changes in weight gain, long-term infection with T. gondii reduces muscle LPL activity, which becomes unresponsive to acute endotoxemia; that in the

FIG. 3. TG concentration in plasma 90 min after saline or LPS (from E. coli, 100 ng/kg) i.p. injection into mice infected for 28 days with either T. gondii (ToxG) or N. caninum (NeoC). Bars are means ± SEM of the results for three animals. *, significantly different from results for saline-injected mice (P < 0.05).
result in hypertriglyceridemia in T. gondii-infected nongainer mice, in which LPL activity remained unaltered. These observations suggest that the group-specific changes in triglyceridemia that occurred after LPS injection at the dose used were the consequence of differences in the reduction in LPL activity (TG clearance) rather than in TG secretion, in accordance with the results of previous studies (4, 16, 43). In addition, the ability of LPS to bring about hypercorticosteronemia remained intact in all infected mice, ruling out a contribution of corticosterone to the variable changes in triglyceridemia in response to endotoxemia.

Of note is the fact that acute glucose responses to LPS administration were proportionally associated with fat mass. It is well known that besides its impact on lipid metabolism, LPS also affects glucose uptake, which becomes resistant to the action of insulin during endotoxemia (6, 26). Whether this process is related to infection and to the magnitude of weight loss remains to be fully characterized.

Both gainer and nongainer T. gondii-infected groups displayed low muscle LPL activity in the chronic infection phase, whereas muscle LPL in N. caninum-infected animals was similar to that of uninfected mice. Chronic conditions associated with low skeletal muscle LPL activity include obesity and a state of resistance of glucose metabolism to the action of insulin (insulin resistance). The T. gondii-infected animals were obviously not obese, and plasma glucose and insulin levels were not indicative of insulin resistance, pointing to other factors as the cause of the chronic reduction in muscle LPL. Some cytokines, such as IL-1β and IFN-γ, strongly reduce LPL activity in muscle (14). Since both gainer and nongainer T. gondii-infected animals display chronically higher serum levels of IFN-γ than do noninfected mice (1), this is likely to have contributed at least partly to the low muscle LPL activity observed for both T. gondii-infected groups. Although infection with N. caninum acutely induces the production of large amounts of IFN-γ (35, 37), the long-term cytokine profile of N. caninum-infected mice is not well established. It can be suggested that the diverging effects of T. gondii and N. caninum on muscle LPL may be due to differences in the cytokine profiles present after long-term infection. This hypothesis remains to be determined experimentally. It is also possible that muscle sympathetic tone is reduced in T. gondii-infected mice, as it is in tumor-bearing animals (10), which could in turn affect muscle LPL, since the adrenergic system is a potent activator of LPL activity in tumor-bearing rats (10), which could in turn affect muscle LPL, since the adrenergic system is a potent activator of LPL activity in tumor-bearing rats (10). This study was supported by grants from the Canadian Institutes of Health Research. F. Picard was the recipient of a studentship from the Canadian Institutes of Health Research.

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The present results support the notion that skeletal muscle is a key factor in the determination of triglyceridemia after acute LPS administration. Indeed, in both control and N. caninum-infected animals, LPS increased TG levels in plasma and decreased adipose and muscle LPL activity. However, in the presence of a similar increase in hepatic TG content and an impaired inhibition of muscle LPL, LPS injection failed to induce hypertriglyceridemia in T. gondii-infected gainer mice even if adipose LPL activity was decreased to an extent similar to that of control animals. Therefore, in the present study, a reduction in muscle LPL brought about by LPS appeared to be a necessary condition to induce hypertriglyceridemia. This notion is further supported by recent findings involving uninfected rats and mice acutely given LPS at high doses (43).

In conclusion, the present findings show that independently of the extent of postinfection weight gain, chronic infection with T. gondii reduces muscle LPL activity, which becomes unresponsive to a subsequent acute LPS administration. The results also suggest that in the chronic state of infection with T. gondii, adipose and muscle tissue LPL modulation favors TG partitioning toward storage tissues. Finally, the present findings strongly suggest that skeletal muscle LPL is a major determinant of acute LPS-induced hypertriglyceridemia.

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