Search for Mediators of the Lipogenic Effects of Tumor Necrosis Factor: Potential Role for Interleukin 6

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ABSTRACT

The significance of potential second messengers as mediators of the metabolic effects of tumor necrosis factor (TNF) was explored by studying their role in stimulating hepatic lipogenesis. Platelet-activating factor and prostaglandins have previously been suggested to mediate some of the toxic effects of TNF. An inhibitor of platelet-activating factor (WEB 2086) and two inhibitors of the synthesis of prostaglandins (ibuprofen and aspirin) had no effect on the ability of TNF to increase hepatic lipogenesis or serum triglyceride levels in the rat. Another inhibitor of the toxic effects of TNF, pentoxifylline, also had no effect on lipid metabolism in the rat. Catecholamines are increased after TNF administration, but α- and β-adrenergic blockade did not prevent the lipogenic effects of TNF. However, interleukin 6, a cytokine whose synthesis and secretion are induced by TNF, is able to acutely stimulate hepatic lipogenesis in mice. Interleukin 6 stimulates hepatic lipogenesis by increasing hepatic citrate concentrations, the same mechanism by which TNF stimulates hepatic lipogenesis. These data suggest that interleukin 6, but not platelet-activating factor, prostaglandins, or catecholamines, could potentially mediate the lipogenic effects of TNF.

INTRODUCTION

The host response to infection is accompanied by disturbances in intermediary metabolism including hypertriglyceridemia (1). These metabolic disturbances are now thought to be caused by cytokines, in particular TNF. Administration of TNF mimics the changes in lipid metabolism that occur during infection. TNF induces a rapid and sustained increase in serum triglyceride levels (2), increases hepatic lipogenesis (2, 3), and decreases LPL activity (4–8).

It is now recognized that stimulation of hepatic lipogenesis is the major mechanism by which TNF increases serum triglycerides in vivo. (a) The time course of TNF stimulation of de novo hepatic lipogenesis parallels the increases in serum triglycerides (2). (b) While TNF decreases LPL in the epididymal fat pad, this effect takes several hours and begins after the increase in serum triglycerides (7–9). (c) Little or no decrease is seen in LPL activity in multiple other sites of adipose tissue or muscle, while hepatic and postheparin lipase are increased (7–9). (d) TNF is able to increase serum triglycerides in diabetic rats where there is very little adipose tissue LPL activity and where no further decrease in hepatic tissue LPL activity occurs with TNF treatment; yet TNF still stimulates hepatic lipogenesis in diabetic animals (10). (e) The clearance of triglyceriderich lipoproteins is not altered by TNF treatment (9, 10).

Total hepatic triglyceride production is increased in TNF-treated animals (11). (f) Finally, the increase in hepatic lipogenesis results in an increase in hepatic very low density lipoprotein production as measured by the Triton WR1339 technique (Ref. 11; Footnote 4).

TNF has complex effects on tissues, including the generation of other cytokines and small molecular weight secondary messengers. Certain activities of TNF in vivo do not appear to be direct actions of TNF, but are now thought to be mediated by these cytokines or small molecule mediators. For example, PAF induces hemorrhagic necrosis of the bowel and shock (12–15) that are similar to the hemorrhagic necrosis and shock seen with TNF (16, 17). TNF is known to induce PAF production by the small intestine (18) and vascular endothelial cells (19). Most important, PAF antagonists block TNF-induced bowel necrosis (18). Therefore it is likely that induction of PAF by TNF is responsible for at least part of the toxicity of TNF (and endotoxin).

TNF (and PAF) also induces prostaglandin synthesis in a variety of tissues including hypothalamus (20), bone cells (21–23), and vascular endothelial cells (24, 25). Inhibitors of prostaglandin synthesis block TNF-induced fever (20) and the bone-resorbing effects of TNF (21, 22). Prostaglandin synthetase inhibitors also block the induction of hypotension and shock, which may be secondary to production of prostaglandins by vascular cells (25–29).

Pentoxifylline can protect against TNF-induced lung injury, perhaps by inhibiting the effects of TNF on neutrophil function or on endothelial cells (30). TNF increases serum catecholamine levels (29, 31, 32), and catecholamines are thought to play a role in some of the metabolic disturbances of infection (32–34).

Finally, a single cytokine may induce the synthesis of other cytokines (20, 35–40). In particular, TNF has been shown to induce the synthesis of IL-6 in a variety of tissues (36–40). The characteristics of TNF induction of IL-6 and the properties of IL-6 make it a candidate for a mediator of multiple actions of TNF (41–43). For example, IL-6 is thought to mediate another hepatic effect of TNF, the induction of proteins involved in the acute-phase response with concomitant suppression of other hepatic secretory proteins (42, 43).

In this paper we examine an early metabolic response to TNF, stimulation of hepatic lipogenesis, to determine whether any of the known mediators of the actions of TNF could be responsible for lipogenic effects. We show that a PAF antagonist, prostaglandin synthetase inhibitors, pentoxifylline, and complete α- and β-adrenergic blockade have no effects on TNF stimulation of hepatic lipogenesis. However, IL-6 administration mimics the lipogenic actions of TNF, raising the possibility...
that IL-6 may be responsible for some of the metabolic effects of TNF.

MATERIALS AND METHODS

Materials. Trinitiated water (1 Ci/g) was purchased from ICN Radiochemicals (Irvine, CA). [1-14C]Cholesterol and [1-14C]oleic acid were purchased from Du Pont-New England Nuclear (Boston, MA). Ready-Safe scintillation fluid was purchased from Beckman. The thin-layer chromatographic polygram Silica G plates were purchased from Brinkmann Instruments, Inc. (Westbury, NY). Human TNF-α with a specific activity of 5 × 10^8 units/mg produced by recombinant DNA technology was provided by Genentech, Inc. (South San Francisco, CA). Propranolol and phenoxybenzamine were purchased from ICN Biochemical. Pentoxifylline and aspirin were purchased from Sigma Chemical Co. Ibuprofen in saline was kindly provided by The Upjohn Co. (Kalamazoo, MI). WEB 2086 was kindly provided by Dr. Jennenein, Dr. Heuer, and Dr. Letts of Boehringer Ingelheim (Ingelheim Mannheim, Federal Republic of Germany). IL-6 (44) with a specific activity of 1.7 × 10^8 units/mg was purified from the medium of transformed yeast cells.7

Animal Procedures. Male Sprague-Dawley rats (approximately 200 g) were purchased from Simonsen or Bantin Kingman animal vendors. The animals were maintained on a reversed 12-h light cycle (3 a.m. to 3 p.m. dark, 3 p.m. to 3 a.m. light) and were fed Simonsen rat Chow and water ad libitum. The animals were given injections via the tail vein with 25 µg of TNF in 0.5 ml of 0.9% saline solution or saline solution alone. This dose is approximately one-fourth that shown to produce tumor necrosis in vivo and, based on our previous studies, is the optimal dose for increasing hepatic lipid synthesis.

WEB 2086 was administered i.p. at a dose of 1.5 mg/kg in a 0.2-ml saline solution 10 min prior to TNF treatment. When administered under these conditions, WEB 2086 has been shown to produce prolonged blockade of PAF-induced shock (45–47). Ibuprofen was administered i.v. at a dose of 10 mg/kg in a 0.2-m saline solution simultaneously with TNF treatment. Aspirin was administered i.v. at a dose of 25 mg/kg in a 0.2-ml saline solution simultaneously with TNF. Ibuprofen and aspirin administered under these conditions have been shown to block the toxic effects of cytokines (27–29, 48). Pentoxifylline was administered under these conditions, WEB 2086 has been shown to produce pro

RESULTS

Effect of Inhibitors on TNF-induced Changes in Lipid Metabolism. As discussed in the "Introduction," PAF has been shown to mimic several of the actions of TNF in vivo, and some of the biological effects of TNF are blocked by PAF inhibitors (12–15, 18). In Table 1, the effect of a PAF antagonist, WEB 2086, on the TNF-induced increase in serum triglyceride levels and hepatic fatty acid synthesis is shown. As in our previous studies, TNF administration acutely increases both hepatic fatty acid synthesis and serum triglyceride levels in rats. WEB 2086

Table 1 Effect of a PAF antagonist (WEB 2086) on TNF-induced lipid changes

<table>
<thead>
<tr>
<th></th>
<th>Serum triglyceride levels (mg/dl)</th>
<th>Hepatic fatty acid synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 5)</td>
<td>35 ± 3 ± 6</td>
<td>6.07 ± 0.5</td>
</tr>
<tr>
<td>2. TNF (n = 5)</td>
<td>69 ± 6.2</td>
<td>9.17 ± 0.4</td>
</tr>
<tr>
<td>3. TNF + WEB 2086 (n = 5)</td>
<td>73 ± 4.3</td>
<td>8.70 ± 0.3</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>1 vs. 3</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>2 vs. 3</td>
<td>NS4</td>
<td>NS4</td>
</tr>
</tbody>
</table>

* Mean ± SE.

† NS, not significant.
administration did not prevent the TNF-induced increase in erum triglyceride levels or hepatic fatty acid synthesis.

Prostaglandins have been shown to mediate some of the actions of TNF (20-22, 25-28). In Table 2, the effect of two prostaglandin synthetase inhibitors on the ability of TNF to alter lipid metabolism is shown. Neither ibuprofen nor aspirin treatment inhibited the TNF-induced increase in serum triglyceride levels or hepatic fatty acid synthesis. In fact, there is a consistent trend for serum triglyceride levels to be increased in the animals treated with the prostaglandin inhibitors and TNF compared with TNF alone, but this did not achieve statistical significance.

Pentoxifylline administration has been shown to prevent the lung abnormalities that occur following TNF treatment (30). As shown in Table 3, pentoxifylline had no effect on the increases in serum triglyceride levels or hepatic fatty acid synthesis induced by TNF.

It has been postulated that the increased catecholamine levels found in infection and following TNF administration might be responsible for some of the observed metabolic effects (29-34). To determine if the lipid changes induced by TNF are mediated by catecholamines, animals were pretreated with α- and β-adrenergic inhibitors at concentrations known to block the effects of catecholamines (52). The increase in serum triglyceride levels and hepatic fatty acid synthesis following TNF administration is not affected by complete adrenergic blockade (Table 4).

Table 2 Effect of inhibitors of prostaglandin synthesis on TNF-induced lipid changes

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Serum triglyceride levels (mg/dl)</th>
<th>Hepatic fatty acid synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (n = 5)</td>
<td>61 ± 5.9*</td>
<td>3.68 ± 0.14</td>
</tr>
<tr>
<td>2. TNF (n = 5)</td>
<td>99 ± 9.7</td>
<td>4.62 ± 0.26</td>
</tr>
<tr>
<td>3. TNF + ibuprofen (n = 5)</td>
<td>136 ± 15</td>
<td>6.47 ± 0.57</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>P &lt; 0.02</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>1 vs. 3</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>2 vs. 3</td>
<td>NS</td>
<td>P &lt; 0.02</td>
</tr>
</tbody>
</table>

* Mean ± SE.

Table 3 Effect of pentoxifylline on TNF-induced lipid changes

Saline solution or pentoxifylline (15 mg/kg) in a volume of 0.3 ml was administered i.p. as indicated. Thirty min later animals received TNF or saline solution (25 µg/200 g rat) i.v. An h later all animals received 50 mCi of 3H2O i.p. One h after the 3H2O, blood was drawn for measuring the serum triglyceride levels, the animals were killed, and hepatic fatty acid synthesis was measured as described in "Materials and Methods."

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Serum triglyceride levels (mg/dl)</th>
<th>Hepatic fatty acid synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (n = 5)</td>
<td>35 ± 4.6*</td>
<td>2.14 ± 0.17</td>
</tr>
<tr>
<td>2. TNF (n = 5)</td>
<td>52 ± 3.9</td>
<td>3.23 ± 0.23</td>
</tr>
<tr>
<td>3. TNF + pentoxifylline (n = 5)</td>
<td>72 ± 8.8</td>
<td>3.81 ± 0.37</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>1 vs. 3</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>2 vs. 3</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Mean ± SE.

Table 4 Effect of adrenergic blockade on TNF-induced lipid changes

SALINE solution or propranolol (5 mg/kg) and phenoxybenzamine (5 mg/kg) in a volume of 0.5 ml were administered i.m. as indicated. Fifteen min later, animals received saline solution or TNF (25 µg/200 g) i.v. as indicated. One h later, all animals received 50 mCi of 3H2O i.p. One h after the 3H2O was administered, blood was drawn for measuring the serum triglyceride levels, the animals were killed, and hepatic fatty acid synthesis was measured as described in "Materials and Methods."

<table>
<thead>
<tr>
<th>Effect</th>
<th>Serum triglyceride levels (mg/dl)</th>
<th>Hepatic fatty acid synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (n = 5)</td>
<td>34 ± 1.3*</td>
<td>3.00 ± 0.27</td>
</tr>
<tr>
<td>2. TNF (n = 5)</td>
<td>75 ± 10.7</td>
<td>4.53 ± 0.41</td>
</tr>
<tr>
<td>3. TNF + adrenergic blockade (n = 5)</td>
<td>83 ± 7.8</td>
<td>4.77 ± 0.39</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>1 vs. 3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2 vs. 3</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Mean ± SE.

Table 5 Effect of IL-6 on hepatic lipid synthesis

Saline solution or IL-6 at the indicated dose in a volume of 0.2 ml was administered i.m. as indicated. Twenty mCi of 3H2O were administered i.p. at either 0 or 1 h after the IL-6 or saline solution injection. One h later, animals were killed, and fatty acid and cholesterol syntheses were measured as described in "Materials and Methods."

<table>
<thead>
<tr>
<th>Effect</th>
<th>Fatty acid synthesis (µmol incorporated/g/h)</th>
<th>Cholesterol synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (n = 5)</td>
<td>1.25 ± 0.17*</td>
<td>1.17 ± 0.16</td>
</tr>
<tr>
<td>2. IL-6 (n = 5)</td>
<td>2.47 ± 0.04</td>
<td>0.95 ± 0.19</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (1 µg of IL-6)</td>
<td>Control (n = 5)</td>
<td>1.01 ± 0.09</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (3 µg of IL-6)</td>
<td>Control (n = 5)</td>
<td>1.21 ± 0.20</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (3 µg of IL-6)</td>
<td>IL-6 (n = 5)</td>
<td>1.27 ± 0.10</td>
</tr>
</tbody>
</table>

* Mean ± SE.

Table 5 Effect of IL-6 on hepatic lipid synthesis

Saline solution or IL-6 at the indicated dose in a volume of 0.2 ml was administered i.m. as indicated. Twenty mCi of 3H2O were administered i.p. at either 0 or 1 h after the IL-6 or saline solution injection. One h later, animals were killed, and fatty acid and cholesterol syntheses were measured as described in "Materials and Methods."

* Mean ± SE.

NS, not significant.

Table 6 Effect of IL-6 on hepatic lipid synthesis

Saline solution or IL-6 at the indicated dose in a volume of 0.2 ml was administered i.m. as indicated. Twenty mCi of 3H2O were administered i.p. at either 0 or 1 h after the IL-6 or saline solution injection. One h later, animals were killed, and fatty acid and cholesterol syntheses were measured as described in "Materials and Methods."

<table>
<thead>
<tr>
<th>Effect</th>
<th>Fatty acid synthesis (µmol incorporated/g/h)</th>
<th>Cholesterol synthesis (µmol incorporated/g/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (n = 5)</td>
<td>1.25 ± 0.17*</td>
<td>1.17 ± 0.16</td>
</tr>
<tr>
<td>2. IL-6 (n = 5)</td>
<td>2.47 ± 0.04</td>
<td>0.95 ± 0.19</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (1 µg of IL-6)</td>
<td>Control (n = 5)</td>
<td>1.01 ± 0.09</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (3 µg of IL-6)</td>
<td>Control (n = 5)</td>
<td>1.21 ± 0.20</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1–2 h (3 µg of IL-6)</td>
<td>IL-6 (n = 5)</td>
<td>1.27 ± 0.10</td>
</tr>
</tbody>
</table>

* Mean ± SE.

NS, not significant.

Table 7 Effect of IL-6 on hepatic lipid synthesis

Saline solution or IL-6 at the indicated dose in a volume of 0.2 ml was administered i.m. as indicated. Twenty mCi of 3H2O were administered i.p. at either 0 or 1 h after the IL-6 or saline solution injection. One h later, animals were killed, and fatty acid and cholesterol syntheses were measured as described in "Materials and Methods."

* Mean ± SE.

NS, not significant.
concentration indicated on the x axis immediately followed by 20 mCi i.p. of \( \text{H}_2\text{O} \). One h later, hepatic fatty acid synthesis was measured as described in "Materials and Methods." Points, mean; bars, SE. Asterisks, \(<0.05\) vs. control.

DISCUSSION

In this paper we have searched for possible mediators of a metabolic effect of TNF, acute stimulation of hepatic lipogenesis. TNF is known to induce the synthesis of a variety of small molecules and cytokines, and previous studies have demonstrated that certain actions of TNF, in particular, several of its known toxicities, are mediated by these small molecules or cytokines. For many of the potential small molecular weight mediators, antagonists or inhibitors of their synthesis exist to test their role in TNF action.

PAP antagonists have been used to demonstrate a role for TNF-generated PAF in the hemorrhagic necrosis and shock that occur with administration of high doses of TNF (18). However, a highly efficacious PAF antagonist that produces prolonged blockade of the effects of PAF \textit{in vivo}, including induction of shock, was shown to have no effect on TNF stimulation of hepatic lipogenesis (Table 1). A role has been suggested for increased prostaglandin generation in producing the hemorrhagic necrosis of the bowel and shock seen with both TNF and PAF (25–29). While inhibition of prostaglandin synthesis can block toxicity after TNF administration, we found no effect of these inhibitors on the ability of TNF to stimulate hepatic lipogenesis and increase serum triglycerides in the rat. Recently, data have been presented that, under similar conditions in dogs, ibuprofen was also unable to block the TNF-induced increase in serum triglycerides (29). Indeed in both the work by Evans \textit{et al.} (29) and in this paper (Table 2), there is a trend for serum triglycerides to increase when TNF was administered with prostaglandin synthetase inhibitors compared with TNF alone, although this did not reach statistical significance in either case. TNF has profound effects on the vasculature of the lung, inducing inflammatory infiltrates and edema; these effects are blocked by pentoxifylline (30). The mechanism by which pentoxifylline (a methylxanthine with a broad spectrum of activity) works is unknown, although it is thought to prevent the action of TNF on both neutrophils and vascular cells (30). Pentoxifylline also blocks the production of TNF by endotoxin-stimulated macrophages (57), suggesting that in inhibiting TNF action pentoxifylline may block production of TNF that occurs on an autocrine basis. However, we found no effect of pentoxifylline on the lipogenic effects of TNF (Table 3).

TNF induces increases in circulating levels of stress hormones such as the catecholamines (29, 31, 32). Other evidence has been presented that catecholamines play a role in the metabolic disturbances that occur in sepsis (32–34). However, we have now shown that complete adrenergic blockade (under conditions which block other metabolic effects of catecholamines) does not inhibit the effect of TNF on hepatic lipogenesis. In addition, it should be noted that the TNF-induced rise in catecholamines may require higher doses (31) or a longer time (29) than is required for the lipogenic effects of TNF which occur early and in the absence of major systemic toxicity (2, 3, 9, 10).

In rats and mice, TNF-induced increases in hepatic lipogenesis are seen within 1 h, peak by 2 h, and are sustained for many hours (2, 3, 9, 10). In contrast, the clearance of parentally administered cytokines is very rapid, with the half-life for TNF being between 5 and 20 min (58–61). Thus, the sustained effects of TNF seen \textit{in vivo} must be because of sustained action of TNF at target cells and/or prolonged production of secondary messengers that more directly mediate the distal actions. TNF stimulates production of a variety of cytokines, including IL-6 (20, 35–40). IL-6 is a candidate for such a secondary mediator based on previous data for the time course and specificity of TNF action. For example, administration of murine TNF to mice produces rapid but sustained (up to 9 h) rises in serum IL-6 levels (41).6 In parallel, murine TNF produces rapid and sustained stimulation of hepatic lipogenesis in mice (3). In contrast, while human TNF acutely increases serum IL-6 levels, this effect disappears by 8 h after TNF (41).6 In parallel, stimulation of hepatic lipogenesis by TNF is much shorter lived in mice (3).

In this paper we have shown that IL-6 is also capable of stimulating hepatic lipogenesis in mice. Small doses of IL-6 (0.2 \( \mu \)g) stimulate hepatic lipogenesis within 1 h of administration. The time course of IL-6 action is consistent with the previously described properties; IL-6 is also rapidly cleared, with dominant localization to the liver (41, 62)4 and in our hands, IL-6 produces an increase in hepatic lipogenesis that is very brief, found only in the first hour. Even extremely high doses of IL-6 (3 \( \mu \)g) could not sustain IL-6 stimulation of hepatic lipogenesis for 2 h. Thus, if IL-6 were to mediate the effects of TNF on hepatic lipogenesis, the ability of TNF to sustain lipogenesis should be proportional to its ability to sustain IL-6 production; the species specificity of murine and human TNF for these two actions suggests that this is true.

Finally, if IL-6 is to play a role in mediating the effects of TNF on hepatic lipogenesis, then it should increase hepatic fatty acid synthesis by the same mechanism as that found with TNF. Previous data indicate that TNF acutely increases hepatic fatty acid synthesis by increasing the hepatic levels of citrate, an allosteric activator of acetyl-CoA carboxylase, a major rate-limiting enzyme in fatty acid synthesis (56). Increases in hepatic citrate are not a universal mechanism for regulation of hepatic fatty acid synthesis. In fact, another cytokine capable of increasing hepatic lipogenesis, TNF, Previous data indicate that TNF acutely increases hepatic lipogenesis, then it should increase hepatic fatty acid synthesis. In fact, another cytokine capable of increasing hepatic lipogenesis, α-interferon, does not work by increasing hepatic citrate levels (63). However, here we have shown that IL-6 produces a rapid increase in hepatic citrate concentrations, indicating that it does indeed share the same mechanism as TNF.

In summary, we have found no evidence for a role for PAF, prostaglandins, or catecholamines in mediating lipogenic activities of TNF. On the other hand, we have now demonstrated that IL-6 is capable of acutely stimulating hepatic lipogenesis. The data presented here and previously (3, 41) suggest that the species specificity, time course, and mechanism of action of TNF are consistent with a possible role for IL-6 as a mediator of the lipogenic effects of TNF. Definitive proof of the role of IL-6 in mediating this metabolic effect of TNF awaits development of blocking antibodies that are potent enough for use in vivo or a specific inhibitor of TNF induction of IL-6 synthesis.

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REFERENCES

27. May, L. T., Helgoff, D. C., and Sehgal, P. B. Anti-beta-interferon antibodies

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