Biological Evaluation of a Lipid-mobilizing Factor Isolated from the Urine of Cancer Patients

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ABSTRACT

We have previously shown human lipid-mobilizing factor (LMF) to be homologous with the plasma protein Zn-α2-glycoprotein in amino acid sequence, electrophoretic mobility, and immunoreactivity. In this study, both LMF and Zn-α2-glycoprotein have been shown to stimulate glycerol release from isolated murine epididymal adipocytes with a comparable dose-response profile. Both LMF and Zn-α2-glycoprotein caused a stimulation of adenylyl cyclase in murine adipocyte plasma membranes in a GDP-dependent process, with maximum stimulation at 0.1 μM GDP and with saturation at protein concentrations of >5 μg/assay. Administration of LMF to athymic male mice over a 89-h period produced a decrease in body weight without a change in food and water intake. Body composition analysis showed a 42% reduction in carcass lipid when compared with controls. Treatment of ob/ob mice with human LMF over a 160-h period also produced a decrease in body weight, with a 19% reduction in carcass fat, without a change in body water or nonfat mass. Serum levels of glycerol and 3-hydroxybutyrate were significantly increased, as was oxygen uptake by interscapular brown adipose tissue, providing evidence of increased lipid mobilization and utilization. Human white adipocytes responded to both LMF and isoprenaline to the same extent, although the maximal response was lower than that for murine white adipocytes. These results suggest that LMF not only has the capacity to induce lipid mobilization and catabolism in mice, but it also has the potential to exert similar effects in cachectic cancer patients.

INTRODUCTION

Loss of body fat is a major component of the weight loss that occurs in cancer patients (1). Mobilization of triglycerides from adipose tissue may provide essential fatty acids required for tumor growth (2, 3), and in addition, it provides a high-energy fuel for normal tissues, to accommodate the extra metabolic demands of the tumor-bearing state (4). Cachexia-inducing murine tumors produce a LMF, which stimulates lipolysis by activation of HSL through an elevation of cyclic AMP (5). A similar LMF has been shown to be excreted in the urine of cachectic cancer patients (6). Evidence that this may be important in lipid catabolism in vivo has been provided by the finding of a 2-fold increase in the relative level of mRNA for HSL in the adipose tissue of cancer patients when compared with controls (7).

We have purified to homogeneity the LMF from the urine of cachectic cancer patients and shown it to be homologous with the plasma protein Zn-α2-glycoprotein in amino acid sequence, electrophoretic mobility, and immunoreactivity (8). Furthermore, expression of Zn-α2-glycoprotein in mouse tumors was found to correlate with the depletion of carcass lipids when these tumors were transplanted into mice. There was no evidence that the Zn-α2-glycoprotein was binding catecholamines, which could give the same biological effects.

Here, the ability of authentic Zn-α2-glycoprotein to stimulate lipolysis and cyclic AMP formation has been examined and compared with the effect of LMF isolated from cancer patient urine. In addition, the ability of LMF to initiate lipid catabolism in vivo has been studied using exbredder and ob/ob mice.

MATERIALS AND METHODS

Animals. Pure-bred NMRI and ob/ob mice were bred in our own colony, whereas male BKW mice (40–50 g) were purchased from Banting and Kingman (Gristonette, Hull, United Kingdom).

Serum Metabolite Determinations. NEFA was determined using a Wako-ASC-ACOD kit (Wako Chemical GmbH, Neuss, Germany). Triglycerides were determined using a triglyceride kit (Sigma Chemical Co., Poole, United Kingdom) and 3-hydroxybutyrate by a quantitative enzymatic determination kit (Sigma). Glucose was measured using a glucose analyzer (Beckman, Irvine, CA), and glycerol was determined enzymatically using the method of Wieland (9).

Lipolytic Assay. Single-cell suspensions of white adipocytes were prepared from finely minced epididymal fat pads of male BKW mice using collagenase digestion (10). Samples to be assayed were incubated with 105–2 × 106 adipocytes (determined by means of hemocytometer measurements) for 2 h at 37°C in 1 ml of Krebs-Ringer bicarbonate buffer (pH 7.2). The concentration of glycerol released was determined enzymatically by the method of Wieland (9). Control samples containing adipocytes alone were analyzed to determine the spontaneous glycerol release. Lipid-mobilizing activity was expressed as μmol glycerol released/105 adipocytes/2 h.

Isolation of Human Omental Adipocytes. Human omental adipose tissue was removed under general anesthesia and transported immediately to the laboratory. Fragments of tissue (roughly equivalent in size to a pair of murine epididymal fat pads) were digested to produce a single-cell suspension of adipocytes by incubation at 37°C for 30 min in a shaking water bath in 1 ml of Krebs-Ringer bicarbonate buffer supplemented with 4% BSA, 1 g/liter glucose, and 1.5 mg/ml collagenase.

Purification of LMF. Material capable of inducing lipolysis in isolated murine epididymal adipocytes was purified from the urine of cancer patients using a combination of ion exchange, exclusion, and hydrophobic chromatography on Resource-Iso (8). To evaluate biological activity, salt was removed from the sample through an Amicon filtration cell containing a membrane filter with a molecular weight cutoff of 10,000 against PBS. Zn-α2-glycoprotein was purified from human plasma as described previously (8).

Isolation of Adipocyte Plasma Membranes. The protocol was based on that previously published by Belsham et al. (11). White adipocytes were isolated from mouse epididymal fat pads as above, except that cells were washed in 250 mM sucrose, 2 mM EGTA, and 10 mM Tris-HCl (pH 7.4). Adipocytes were resuspended in 20 ml of the above buffer and homogenized by aspirating through a Swinnny filter at least 10 times. The cell homogenate was then centrifuged at 300 × g for 5 min, the fat cake was removed from the surface, and the remaining pellet and infranatant were transferred to clean tubes. These were centrifuged at 30,000 × g for 1 h at 4°C, and the membrane pellet formed was resuspended in the sucrose buffer (200–400 μl). Plasma membranes were separated from other organelle membranes on a self-forming Percoll gradient. The constituents were mixed in the ratio 32 parts of 250 mM sucrose, 2 mM EGTA, and 10 mM Tris-HCl (pH 7.4); 7 parts of Percoll; and 1 part of 2 M sucrose, 8 mM EGTA, and 80 mM Tris-HCl (pH 7.4), together with the membrane suspension (in a total volume of 8 ml), and the mixture was centrifuged at 10,000 × g for 30 min at 4°C. The gradient was fractionated into 0.75-ml portions, and each was assayed for the presence of succinate dehy-
drogenase (12), NADH-cytochrome c reductase (13), lactate dehydrogenase (14), and 5'-nucleotidase (15) to locate the plasma membrane fraction. The membrane fractions were resuspended in 150 mM NaCl, 1 mM EGTA, and 10 mM Tris-HCl (pH 7.4) and centrifuged at 10,000 × g at 4°C for 2 min. The process was repeated twice. The washed plasma membranes were diluted in 10 mM Tris-HCl (pH 7.4), 250 mM sucrose, 2 mM EGTA, and 4 μM phenylmethylsulfonyl fluoride at 1–2 mg/ml, snap-frozen in liquid nitrogen, and stored at −70°C until use.

Adenylate Cyclase Assay. The assay was based on that developed by Salomon et al. (16). Briefly, Briefly, water (negative control), isoprenaline (positive control), or LMF was added to an assay mix (final volume = 100 μl) containing (final concentration) 25 mM Tris-HCl (pH 7.5), 5 mM MgCl₂, GTP (at concentrations depicted in the figure legends), 8 mM creatine phosphate, 16 units/ml creatine phosphokinase, 1 mM 3-isobutyl-1-methylxanthine, and 1 mM [α-32P]ATP (specific activity = 20 M Ci/mmol). Preincubation was at 30°C for 5 min, and the reaction was initiated by the addition of plasma membrane (typically 50 μg of protein). After 10 min at 30°C, the reaction was terminated by the addition of 100 μl of a solution containing 2% SDS, 40 mM ATP, and 1.4 mM cyclic AMP. To determine recovery of cyclic AMP, [8-3H]adenosine 3',5'-cyclic phosphate (1 μCi in 50 μl of water) was added to each tube. Background binding was determined by running samples without [α-32P]ATP, and sample controls without plasma membranes were set up.

Samples containing labeled nucleotides were diluted to 1 ml with water and loaded onto Dowex 50WX-400 columns primed with 10 ml of water. After washing twice with 1 ml of water, the cyclic AMP was eluted with 3 ml of water into polypropylene tubes containing 200 μl of 1.5 M imidazole (pH 7.2). The samples were then applied to Alumina WN-3 columns (previously washed with 8 ml of 0.1 M imidazole (pH 7.5)), and the eluate was collected directly into scintillation vials containing Optiphase HiSafe 3 scintillation fluid. A further 1 ml of 0.1 M imidazole was added to the columns, and the eluate was combined with the run-through. The radioactivity was determined using a Tri-carb 2000A scintillation analyzer.

RESULTS

Both human urine LMF and human plasma Zn-α₂-glycoprotein stimulated glycerol release from isolated murine epididymal adipocytes in a dose-related manner (Fig. 1). Induction of lipolysis in adipocytes is thought to be mediated by an elevation of the intracellular mediator cyclic AMP. Incubation of murine adipocyte plasma membranes with the human LMF caused a stimulation of adenylate cyclase activity in a GTP-dependent process, with maximal stimulation occurring at 0.1 μM GTP (Fig. 2A). Activation of adenylate cyclase was saturatable, with concentrations of LMF of >5 μg/assay (Fig. 3A). Human plasma Zn-α₂-glycoprotein also stimulated murine adipocyte plasma membrane adenylate cyclase in a GTP-dependent manner, with maximal stimulation also at 0.1 μM GTP (Fig. 2B). The dose-response relationship for activation of adenylate cyclase by Zn-α₂-glycoprotein (Fig. 3B) was similar to that for LMF (Fig. 3A).

To determine whether the human LMF was capable of fat depletion in vivo material was injected i.v. to male exbreeder NMRI mice over a 72-h period (Fig. 4), the animals were killed at 89 h, and the body composition and serum metabolite levels were determined (Table 1). There was a progressive decrease in body weight of the animals receiving LMF, which was significantly lower than that of PBS-treated controls, within 41 h of treatment. Total body weight decreased by 3.9 g during the 89-h period without a change in food and water intake (Table 1). Body composition analysis showed a large reduction (42%) in the body fat content of mice receiving LMF, with a tendency to increase the nonfat mass, although this did not reach significance. Despite the fat mobilization, there were significant reductions in the serum concentrations of nonesterified fatty acids, glycerol, and glucose (Table 1) in mice receiving LMF.

Chronic treatment of ob/ob mice with LMF produced a similar result. There was a decrease in total body weight, which became significant within 24 h of the first injection (Fig. 5) and remained below that of the control group over the 160 h of the experiment. Body composition analysis showed weight loss to arise from a decrease in carcass fat (26.03 ± 0.70 g in controls and 21.09 ± 0.99 g in LMF-treated animals), without an alteration in the water or nonfat mass (Table 2). Serum levels of glycerol and 3-hydroxybutyrate were significantly increased, whereas blood glucose levels were decreased and there was no effect on either triglyceride or NEFA levels (Table 2). There was a significant increase in the oxygen uptake in interscapular BAT from mice receiving LMF (Table 2). Thus, measurement of circulating NEFA or glycerol may not be expected to give an estimation of the overall rate of lipolysis because the values will be strongly influenced by an increased rate of metabolism in BAT. This can be seen by comparing the serum metabolite levels 60 h after the first injection of LMF (Table 3) with the values at 160 h. At 60 h, the serum levels of NEFA, glycerol, and triglycerides were all increased, whereas at 160 h, only serum glycerol was increased. These results suggest that prolonged administration of LMF induces an increased utilization of NEFA and triglycerides in ob/ob mice. Interestingly, blood glucose levels are depressed despite an increased metabolic flux

Fig. 1. Stimulation of lipolysis in freshly isolated murine epididymal adipocytes by human LMF (A) and human Zn-α₂-glycoprotein (B). Columns, mean; bars, SE. The data are representative of three separate experiments. Values for glycerol release from fat cells alone have been subtracted from the values given. Differences from controls were determined by Student's t test and are indicated as follows: *, P ≤ 0.05; **, P ≤ 0.01; and ***, P ≤ 0.005.
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Fig. 2. GTP dose dependency of stimulation of adenylate cyclase in isolated murine adipocyte plasma membranes by human LMF (10 μg; A) and by Zn-α2-glycoprotein (8 μg; B). Columns, means (n = 3); bars, SE. The data are representative of three separate experiments. Differences from basal values were determined by Student's t test and are indicated as follows: *, P ≤ 0.05; **, P ≤ 0.01.

from lipids, although this does not reach significance at 60 h. At 160 h, serum 3-hydroxybutyrate levels were significantly elevated, confirming an increased metabolism of fat. These results show that, in two model systems, human LMF produces a decrease in carcass weight specifically by depletion of adipose tissue.

To determine the effectiveness of LMF in cancer patients, a comparison has been made of the response of human and mouse white adipocytes to the lipid-mobilizing effect of human and mouse LMF and isoprenaline in vitro. Human white adipocytes responded to isoprenaline with a maximal response that was ~6-fold lower than murine white adipocytes (Fig. 6A). Murine white adipocytes also responded to murine LMF to a greater extent than human white adipocytes, although the difference in response (2-fold) was less than that for isoprenaline (Fig. 6B). The lipolytic response of murine adipocytes to human LMF was less than that to murine LMF (Fig. 6C). In contrast, both human and mouse white adipocytes responded to a similar extent to human LMF (Fig. 6C), with a maximal response of about half of that found for mouse LMF on mouse white adipocytes (Fig. 6B) but similar to that for isoprenaline on human adipocytes (Fig. 6A). High concentrations of human LMF seem to produce a down-regulation of the lipolytic response, an effect also observed with other stimulators of lipolysis, e.g., isoprenaline. These results confirm that LMF is capable of inducing lipolysis in human fat cells with the same low response as that observed with isoprenaline.

DISCUSSION

Lipolysis in adipocytes is initiated by HSL, which is regulated by reversible phosphorylation at a single serine residue catalyzed by cyclic AMP-dependent protein kinase A (17). Most hormones and other substances act directly on lipolysis by increasing or decreasing the adipocyte concentration of cyclic AMP. Both LMF and Zn-α2-glycoprotein have been shown to stimulate lipolysis in isolated murine epididymal adipocytes, and this stimulation is associated with an activation of adenylate cyclase in adipocyte plasma membranes in a GTP-dependent manner. The dose-response profiles for LMF and Zn-α2-glycoprotein are comparable: both require 0.1 μM GTP for maximal stimulation, and both produce similar levels of cyclic AMP.

Fig. 3. Dose dependency of stimulation of adenylate cyclase in isolated murine adipocyte plasma membranes by human LMF (A) and by Zn-α2-glycoprotein (B) in the presence of 0.1 μM GTP. Columns, means (n = 4); bars, SE. The data are representative of three separate experiments. Differences from basal values were determined by Student's t test and are indicated as follows: **, P ≤ 0.01; and ****, P ≤ 0.005.
with similar concentrations of agonists. These data, together with the ability of polyclonal antisera to Zn-α₂-glycoprotein to neutralize in vitro lipolysis by human LMF, the homology in amino acid sequence, and electrophoretic mobility (8), provide strong evidence that LMF is, indeed, Zn-α₂-glycoprotein. Previous reports have shown that Zn-α₂-glycoprotein is an adhesive protein (18) that is closely related to antigens of the major histocompatibility complex in amino acid sequence and domain structure (19), but there have been no reports of the capacity of Zn-α₂-glycoprotein to induce lipolysis. At present, the mechanism by which a large acidic protein can stimulate adenylate cyclase is not known because polypeptides having a similar role are small and basic.

This study also provides evidence for the ability of the human LMF to selectively mobilize body fat, both in exbreeder and in ob/ob mice, as well as the capacity to stimulate lipolysis in human white adipocytes. The effect of the LMF in vivo differs from that of a sulfated glycoprotein of Mᵋ, 24,000, which we have recently isolated both from the MAC 16 tumor and the urine of cachectic cancer patients, where the decrease in carcass weight arose predominantly from a decrease in the nonfat mass arising from a catabolic effect on skeletal muscle (20, 21). Interestingly, both factors produce a decrease in blood glucose, an effect also observed in mice bearing the MAC16 tumor unrelated to production of insulin-like growth factor I or insulin-like growth factor II (22).

Chronic administration of human LMF to both ex-breeder and ob/ob mice provided evidence for an increased fat catabolism and utilization. For ob/ob mice, a significant difference in body weight from the control group was observed after two injections of human LMF (70 μg of protein; Fig. 5). Although the normal plasma concentration of Zn-α₂-glycoprotein has not been reported in the mouse, the concentration in human plasma or serum has been shown to range between 50 and 140 μg/ml (23). Assuming that the value for the mouse is similar and that the plasma volume is 2 ml, administration of human LMF would increase the plasma concentration between 25 and 70%, assuming no loss by metabolism. Because the lipolytic effect of Zn-α₂-glycoprotein is dose related (Fig. 1), this may be sufficient to stimulate lipolysis in vivo. Thus, a 50% increase in the concentration of Zn-α₂-glycoprotein in vitro gives a significant change in the lipolytic response (Fig. 1). Zn-α₂-glycoprotein is normally expressed in liver, but an increased expression of the gene has been reported in both benign and malignant breast tissues (24). This may raise the plasma concentration above the threshold required to produce lipolysis.

The effect of human LMF in ob/ob mice has features in common

### Table 1: Effect of LMF isolated from human urine on body weight, body composition, food and water intake, and serum metabolite levels in exbreeder male NMRI mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Treated</th>
<th>P</th>
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<tbody>
<tr>
<td>Final body weight (g)</td>
<td>35.5 ± 2.0</td>
<td>31.6 ± 2.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Water (g)</td>
<td>22.0 ± 0.9</td>
<td>18.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Nonfat mass (g)</td>
<td>7.7 ± 0.8</td>
<td>9.6 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>5.9 ± 0.6</td>
<td>3.4 ± 0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>8.0 ± 0.6</td>
<td>8.0 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Water intake (ml/day)</td>
<td>4.5 ± 0.8</td>
<td>4.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>NEFA (meq/liter)</td>
<td>1.62 ± 0.09</td>
<td>0.95 ± 0.03</td>
<td>0.003</td>
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<tr>
<td>Glycerol (mM)</td>
<td>8.86 ± 0.51</td>
<td>6.73 ± 0.45</td>
<td>0.05</td>
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<tr>
<td>Triglyceride (mg/liter)</td>
<td>0.323 ± 0.036</td>
<td>0.201 ± 0.027</td>
<td>NS</td>
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<tr>
<td>Glucose (mg/100 ml)</td>
<td>223 ± 9</td>
<td>186 ± 0.08</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Material was administered to mice according to the schedule in Fig. 4. Values represent the mean ± SE for five mice per group. Differences from control values were determined by Student's t test.

** NS, not significant; meq, milliequivalent(s).
Fig. 5. Change in body weight of ob/ob mice produced by i.v. administration of LMF (35 µg; ○) isolated from human urine as described in "Materials and Methods" and control mice (X) administered PBS by i.v. injection. LMF was injected at times 0, 16, 24, 40, 48, 64, 72, 90, 96, 113, 120, 137, and 144 h and PBS was injected at the same time points; the animals were terminated 160 h after the first injection. The starting weights of the mice are given in Table 2. Data points, means for five animals per group; bars, SE. Differences from control values were determined by two-way ANOVA followed by Tukey’s test, and are indicated as follows: ****, P < 0.001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Treated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>66.7 ± 4.2</td>
<td>67.9 ± 2.9</td>
<td>NS*</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>73.1 ± 4.3</td>
<td>69.5 ± 4.3</td>
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<tr>
<td>Water (%)</td>
<td>50.3 ± 0.5</td>
<td>53.7 ± 1.1</td>
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<tr>
<td>Nonfat (%)</td>
<td>15.5 ± 0.9</td>
<td>17.4 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>34.6 ± 0.6</td>
<td>30.6 ± 0.7</td>
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<tr>
<td>NEFA (meq/liter)</td>
<td>1.47 ± 0.12</td>
<td>1.45 ± 0.45</td>
<td>NS</td>
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<tr>
<td>Glycerol (mg)</td>
<td>2.51 ± 0.28</td>
<td>5.31 ± 0.45</td>
<td>0.02</td>
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<tr>
<td>Triglyceride (mg/liter)</td>
<td>0.40 ± 0.05</td>
<td>0.49 ± 0.04</td>
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<tr>
<td>Glucose (mg/100 ml)</td>
<td>317 ± 11</td>
<td>260 ± 12</td>
<td>0.02</td>
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<tr>
<td>3-Hydroxybutyrate (mg)</td>
<td>0.30 ± 0.02</td>
<td>0.44 ± 0.01</td>
<td>0.001</td>
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<tr>
<td>Oxygen uptake (µmol BAT/h)</td>
<td>0.18 ± 0.06</td>
<td>0.55 ± 0.07</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Material was administered to mice according to the schedule in Fig. 5. Values represent the mean ± SE for five mice per group. Differences from control values were determined by Student’s t test.

**NS, not significant; meq, milliequivalents.**

with the administration of leptin (the OB protein; Refs. 25 and 26). Both produced weight loss and a reduction in body fat content, which was associated with a marked reduction in plasma glucose levels. However, weight loss produced by leptin was associated with a decrease in food and water intake, whereas there was no change in these parameters in mice administered LMF. The ability to reduce adipose tissue without affecting muscle mass suggests that LMF could be of use in the treatment of obesity in humans with increased susceptibility to maturity-onset diabetes.

The mode of degradation of adipose tissue by LMF is analogous to that for the lipolytic hormones and differs from that of the cytokines, the primary effect of which appears to be inhibition of the clearing enzyme lipoprotein lipase, which would prevent adipocytes from extracting fatty acids from plasma lipoproteins for storage, resulting in a net flux of lipid into the circulation (27). Treatment of animals with cytokines such as tumor necrosis factor causes a marked hypertriglyceridemia (28) that probably results from a stimulation of hepatic lipogenesis rather than inhibition of lipoprotein lipase (29). In contrast, chronic administration of LMF to exbreeder mice causes no change in plasma triglyceride levels, a situation similar to those found in animals bearing the MAC16 tumor (28) and in ovarian cancer patients, in whom triglycerides were reduced compared with normal individuals (30). However, in ob/ob mice, both long- and short-term administration of LMF caused an increase in serum glycerol concentrations, confirming an increase in lipolysis.

For LMF to reduce carcass lipid content, there must not only be an increase in lipolysis but also an increase in utilization of fat; otherwise, resynthesis of triglycerides will occur through the triacylglycerol/fatty acid substrate cycle. Although short-term (60 h) adminis
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Fig. 6. Effect of isoprenaline (A), murine LMF (B), and human LMF (C) on the induction of lipolysis in freshly isolated murine (○) and human (■) white adipocytes. Glycerol production over a 2-h period was determined as described in "Materials and Methods." Data points, means (n = 3); bars, SE.

Concentration of LMF to ob/ob mice produced a significant elevation of NEFA and triglyceride, confirming an increased lipid mobilization, there was no significant elevation of these serum metabolites after 160 h, but there was a significant increase in 3-hydroxybutyrate, commensurate with an increased lipid utilization. There was also a 3-fold increase in oxygen consumption by interscapular BAT, suggesting an increase in thermogenesis. Pharmacological studies indicate that the β-receptor subtype responsible for the stimulation of...
oxygen consumption in BAT is exclusively the β3 subtype (31). This suggests that the action of LMF on adipose tissue could be mediated through stimulation of a β3 receptor. However, although human white adipose tissue contains mRNA for the β3 adrenoceptor (32), the expression is very low (33). This may explain the low response of human white adipocytes to both isoprenaline and LMF and a similar maximal response to human LMF in mouse and human white adipocytes. These results suggest that LMF has the potential to induce lipid mobilization and catabolism in humans.

REFERENCES


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