Hyperoxia increases leptin production: a mechanism mediated through endogenous elevation of corticosterone

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Barazzone-Argiroffo, Constance, Patrick Muzzin, Yves R. Donati, Chen-Da Kan, Michel L. Aubert, and Pierre-François Piguet. Hyperoxia increases leptin production: a mechanism mediated through endogenous elevation of corticosterone. Am J Physiol Lung Cell Mol Physiol 281: L1150–L1156, 2001.—Leptin, a cytokine involved in the regulation of food intake, has been reported to be decreased in lung diseases such as chronic obstructive pulmonary disease and cystic fibrosis and increased in critically ill patients with sepsis. We investigated the role of leptin during hyperoxia in mice, which results in alveolar edema, severe weight loss, and death within 3–4 days. In oxygen-breathing mice, serum leptin was increased six- to sevenfold and its mRNA was upregulated in white adipose tissue. Leptin elevation could not be attributed to changes in circulating tumor necrosis factor-α but was completely dependent on endogenous corticosterone elevation because adrenalectomized mice did not exhibit any increase in leptin levels. Using leptin-deficient mice and wild-type mice treated with anti-leptin antibody, we demonstrate that weight loss was leptin independent. Lung damage was moderately attenuated in leptin-deficient mice but was not modified by anti-leptin antibody or leptin administration, suggesting that leptin does not play an essential role in the direct and short-term effects of oxygen-induced injury.

More recently, leptin has been shown to play an important role in inflammation and seems necessary for the induction of the T helper type 1 response (22). Acute inflammation elicited with endotoxin or by TNF-α injection is known to raise leptin levels (30). On the other hand, leptin has been shown to protect against the toxicity exerted by TNF-α because mice deficient for the ob gene [leptin deficient (ob/ob)] or its receptor are more sensitive to TNF-α or endotoxin (13, 33). High levels of leptin are related to a better survival rate in critically ill septic patients (8). Another study (9) performed in septic patients showed that serum leptin concentrations were significantly correlated with plasma cortisol but not with sepsis.

Several lung diseases (acute and chronic) are associated with severe weight loss, anorexia, and inflammation. Patients suffering from chronic lung disease such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis are underweight and exhibit high levels of circulating TNF-α and low levels of leptin (1, 32). However, leptin levels are not reported yet in nonseptic patients with acute lung injury. Weight loss in these patients has often been related to increased caloric loss due to high respiratory work (2). Intensivists are often confronted with patients ventilated for acute lung disease in whom it is very difficult to avoid weight loss even with adequate caloric support.

Taking this background into account, we have first examined circulating leptin levels and leptin gene expression during hyperoxia in mice because exposure of mice to high oxygen concentrations leads to an acute lung injury that is accompanied by severe and rapid weight loss (3, 5). Then, we tested whether leptin might be involved in oxygen-induced lung damage.

We report that during hyperoxia, leptin blood levels increase, probably because its synthesis is upregulated in adipose tissue. Serum leptin elevation is not mediated by circulating TNF-α but is secondary to increased levels of circulating corticosterone because adrenalectomized (ADX) mice do not increase their leptin levels during hyperoxia. Wild-type (WT) and ob/ob mice treated with anti-leptin antibody lose weight during...
hyperoxia, indicating that body weight loss is mainly leptin independent. We show that oxygen toxicity in ob/ob mice was attenuated, an effect that could not be reproduced with anti-leptin antibody administration in WT mice. The protective effect observed during oxygen toxicity in ob/ob mice could not be attributed to constitutive high corticosterone levels, whereas injection of hydrocortisone 21-acetate (HCS) aggravates rather than delays hyperoxia-induced lung injury. Rather, it is due to subtle metabolic and immunologic changes occurring in obese mice secondary to the lack of leptin.

MATERIALS AND METHODS

Mice. C57BL/6 female mice were purchased from Iffa Credo (Labresle, France) and bred in our animal facility for two generations. ob/ob mice and their littersmates (C57BL/6 background) were purchased from Taconic Farms. ADX or sham-operated mice (C57BL/6 females) were purchased from Iffa Credo. Experiments were performed with 2- to 3-mo-old mice. The animals were killed with an intraperitoneal injection of pentobarbital sodium and bled through the abdominal aorta. The thorax was opened, and the lungs were removed, weighed, frozen, and prepared for DNA or mRNA extraction. Pulmonary edema was evaluated by measuring the weight as previously described (4, 6). The white adipose tissue was removed from the periovarian region and frozen.

Reagents. Leptin blood level was assessed by RIA (mouse leptin RIA kit, Linco Research, St. Charles, MI). Corticosterone was determined by RIA with 125I-labeled corticosterone (Diagnostic Systems Laboratories, Webster, TX) as previously described (35). Mouse TNF-α and mouse IL-6 were determined by DuoSet ELISA (R&D Systems, Minneapolis, MN).

Hyperoxic exposure and in vivo treatment. The mice were placed in a sealed Plexiglas chamber and exposed to 100% oxygen or room air in the same conditions as previously described (6). Food and water were available ad libitum. All mice were weighed daily. The mice were killed at 72 h or between 84 and 96 h of exposure when the temperature dropped below 32°C, an event followed by death within 2 h. The Ethical Committee on Animal Experiments (Office Vétérinaire Cantonal of Geneva) approved this study protocol.

Anti-mouse TNF-α antibodies were derived from rabbits immunized with recombinant mouse TNF-α (27). Rabbit anti-TNF-α (1.5 mg) or nonimmune rabbit IgG as a control was injected intravenously on days 1 and 3.

Polyclonal anti-leptin antibody was generated by immunizing a specific pathogen-free New Zealand rabbit with recombinant mouse leptin (CovalAb, Oullins, France). The IgG fraction was obtained by precipitation with 50% ammonium sulfate. The bioactivity of this antibody was tested in vivo by measuring its inhibitory action on the satiety effect of recombinant mouse leptin (CovalAb, Oullins, France). The IgG fraction was injected intraperitoneally on day −1, and nonimmune IgG was injected as a control.

Mouse recombinant leptin was kindly provided by Novartis (Basel, Switzerland) and injected intraperitoneally twice a day at a dose of 1 μg/g body wt as described by Faggioni et al. (14).

In some experiments, HCS (Sigma, St. Louis, MO) was injected intraperitoneally on days 0, 1, 2, and 3 (200 μg/mouse, 7 mg·kg⁻¹·day⁻¹).

To differentiate between the effect of glucocorticoid or catecholamine absence in ADX mice, we inserted subcutaneously pellets of naldol (a catecholamine blocker, 21-day release, 0.5 mg/pellet; Innovative Research of America, Sarasota, FL) or RU-486 (a glucocorticoid receptor antagonist, 21-day release, 0.5 mg/pellet) in some WT mice (16).

RNA analysis. After removal, the lungs and adipose tissue were immediately frozen in liquid nitrogen and stored at −80°C. Total lung RNA was isolated with TRIzol reagent (GIBCO BRL), and total adipose tissue RNA was isolated with a RNeasy protocol with small modifications specific for adipose tissue (QIAGEN). Leptin mRNA was detected by Northern blot. The complete coding sequence of mouse leptin cDNA was labeled with the random-primer labeling system (Rediprime II, Amersham Pharmacia Biotech, Little Chalfont, UK). Northern blots of total RNA were hybridized with the complementary mouse leptin α-32P-labeled dCTP DNA probe (specific activity 3,000 Ci/mmol; Amersham International) (26). Mouse TNF-α mRNA was detected with a TNF-α32P-labeled dUTP riboprobe (specific activity 400 Ci/mmol) containing the 696 bp 5′-EcoRI fragment isolated from pAT153-trp-mTNF85 as previously described (10). Quantification was achieved by phosphorimager analysis (Molecular Dynamics, Sunnyvale, CA) with ImageQuant software (Molecular Dynamics). To evaluate gel loading and membrane transfer, the blots were stained with methylene blue. These blots were analyzed by densitometry, and small differences in loading were normalized by the density of the 18S rRNA bands. The results of mRNA abundance are expressed in arbitrary units ± SD as a ratio of the density of the signal to that of the 18S rRNA signal.

Detection of internucleosomal DNA fragmentation. The lungs were homogenized by polytron disruption in phosphate-buffered saline-10 mM EDTA (10 mg of tissue in 0.5 ml). The homogenate was then centrifuged at 13,000 rpm for 20 min at 4°C. The supernatant was kept and treated for 30 min at 37°C with 20 μg/ml of RNase A and for another 30 min with 200 μg/ml of proteinase K. After three phenol-chloroform extractions, 3 M sodium acetate (pH 4.8) was added (1:10), and DNA was precipitated with 1 volume of isopropanol. The pellet was centrifuged at 13,000 rpm for 10 min at 4°C, washed with 70% ethanol, dried, and resuspended in 10 mM Tris-0.1 mM EDTA, pH 8.0. The samples were run on a 1% agarose gel, and DNA fragmentation was revealed with ethidium bromide.

Statistical analysis. The values for all animals within each experimental group were averaged, and the SD of the mean was calculated. The significance of differences between different groups was determined by Kruskal-Wallis test with Dunn’s multiple comparison test. The significance between the survival of two groups was determined by Kaplan-Meier.

Table 1. Serum leptin, TNF-α, and IL-6 levels and weight loss during hyperoxia in C57BL/6 mice

<table>
<thead>
<tr>
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<th>n</th>
<th>Leptin, ng/ml</th>
<th>TNF-α, pg/ml</th>
<th>IL-6, pg/ml</th>
<th>Weight Loss, %</th>
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<tbody>
<tr>
<td>Air</td>
<td>50</td>
<td>4.0 ± 1.7</td>
<td>34.9 ± 5.2</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>Hyperoxia 72 h</td>
<td>17</td>
<td>8.9 ± 4.2a</td>
<td>34.8 ± 2.2</td>
<td>ND</td>
<td>8.2 ± 4.5*</td>
</tr>
<tr>
<td>Hyperoxia 84–90 h</td>
<td>12</td>
<td>27.0 ± 15.5a</td>
<td>35.2 ± 5.0</td>
<td>55 ± 36.1*</td>
<td>15.2 ± 2.4*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of animals. For tumor necrosis factor (TNF)-α and interleukin (IL)-6, n = 3–5 animals/group. ND, not done.

*P < 0.05 vs. control.
Fig. 1. Leptin mRNA levels in murine adipose tissue during hyperoxia. Total adipose tissue RNA was isolated, and 10 μg were electrophoresed and transferred onto nylon membranes and subsequently hybridized with α-32P-labeled dCTP DNA probe. Top: representative leptin mRNA signals under the conditions studied. Bottom: signals were quantified with scanning photodensitometry as described in MATERIALS AND METHODS. C, control (air breathing); Hox, hyperoxia. Values are means ± SD expressed in arbitrary units (au) of ratio of leptin to 18S rRNA signals from 5 animals. Leptin mRNA was present in adipose tissue of control animals; at 72 h, there was a significant increase in its level.

test. The significance between the values of one control group and one experimental group was determined by the unpaired Student’s t-test. Correlations were calculated with the Spearman correlation test. The significance level was set at P < 0.05.

RESULTS

Hyperoxia increases plasma leptin levels and mRNA expression in adipose tissue. Oxygen exposure is known to provoke an acute lung injury that leads to mouse death in 3–4 days, concomitant with a body weight loss of 10–15%. Plasma leptin levels did not change until 60 h of oxygen exposure and then markedly increased to reach levels that were six- to sevenfold higher than those measured in control mice (P < 0.05; Table 1). We then analyzed the expression of leptin mRNA in adipose tissue. At 72 h of hyperoxia, the oxygen-exposed mice showed a fourfold upregulation in leptin mRNA level compared with that in control animals (P < 0.003; n = 5; Fig. 1). Leptin mRNA was mildly expressed and unchanged during hyperoxia in the skeletal muscle and was not detectable in the lungs (data not shown).

Role of leptin in weight loss induced during oxygen-induced lung injury. Although it is known that the plasma leptin concentration correlates positively with body fat percentage and body mass index, the body weight did not diminish significantly until 48 h and was significantly decreased after 72 h (P < 0.05) when the leptin level was significantly elevated (Fig. 2). To determine whether the leptin increase was responsible for weight loss, we exposed ob/ob mice to hyperoxia. Because the initial body weight of ob/ob mice was very different from that of WT mice (45.6 ± 2.1 g vs. 20.4 ± 0.5 g), comparison of weight loss is not straightforward. Indeed, it is known that oxygen toxicity not only depends on the strain but also on the age of the animal, and ob/ob mice weighing ∼20–25 g would be only 4–5 wk old (19). Daily weight loss, expressed in grams, was equal in WT and ob/ob mice (Fig. 2) but was significantly different when measured in percent of initial body weight (10.4 ± 2.9% in WT vs. 4.2 ± 1.3% in ob/ob mice; P < 0.05).

The role of leptin was also investigated by treating oxygen-breathing WT mice with anti-leptin antibody; under these conditions, the weight loss was similar in the mice treated with the anti-leptin or control IgG when measured in either grams per day or percent of initial body weight, indicating that in WT mice, body weight is leptin independent (Fig. 2).

Role of leptin in hyperoxia-induced lung injury. We attempted to decipher the participation of leptin in hyperoxia-induced injury by using 1) ob/ob mice, 2) WT mice treated with anti-leptin antibody, and 3) WT mice treated with recombinant leptin.

First, the lung weight, reflecting alveolar edema and capillary leak after 72 h of oxygen exposure, was significantly higher in WT compared with ob/ob mice (P < 0.05; n = 10; Fig. 3A). We also compared the survival of ob/ob and WT mice. ob/ob mice survived slightly but not significantly longer than WT mice; mean survival was 92.7 ± 11 vs. 84.5 ± 6.1 h (95% confidence interval of the mean was 0.57–1.25; n = 10). We and others have shown that oxygen toxicity was related to apoptosis of lung cells (5); we then analyzed lung DNA fragmentation by gel electrophoresis. Figure 4 illustrates that WT but not ob/ob mice exhibit DNA fragmentation at
72 h of hyperoxia, whereas in ob/ob mice, nucleosomal ladders occurred only at 90 h (around the time of death; n = 3). In air-breathing mice, no DNA fragmentation was observed. These results might suggest that leptin aggravates pulmonary lesions. Second, we administered anti-leptin antibody to WT mice, which did not prevent hyperoxia-induced lung injury as measured by lung weight (n = 15; Fig. 3B). Third, we treated WT mice with recombinant leptin and found no statistical difference in total lung weight at 72 h of exposure (Fig. 3B). The data obtained with anti-leptin antibody or leptin administration do not argue in favor of an important role for leptin in the lesions of WT mice and suggest that the increased resistance to oxygen seen in ob/ob mice might be due not to the absence of leptin but to the indirect nutritional or immunologic long-term effects of leptin deficiency.

TNF-α does not account for leptin upregulation. TNF-α as well as other cytokines has been shown to regulate leptin levels (30). To determine whether the increase in leptin was due to an increase in circulating TNF-α, we measured the plasma TNF-α concentration with ELISA. Compared with control mice, no change was seen in active TNF-α during hyperoxic exposure (Table 1). The TNF-α concentration was <50 pg/ml when measured by ELISA. Blocking TNF-α in vivo has been shown to decrease leptin production in an endotoxin model (25). To evaluate whether TNF-α plays a role in the leptin elevation seen in the oxygen-exposed mice, we injected anti-TNF-α or control IgG on days 1 and 3 of hyperoxia at a dose that was effective in other models of lung injury in mice (28). No decrease in leptin levels was observed after this treatment (data not shown).

We also examined the possibility that TNF-α within adipose tissue could be responsible for leptin upregulation. TNF-α mRNA was moderately expressed in adipose tissue of WT mice and was significantly downregulated during hyperoxia (P < 0.001; Fig. 5). TNF-α mRNA was fivefold higher in ob/ob mice than in WT mice and was also downregulated during hyperoxia (P < 0.01). Thus the downregulation of the local TNF-α release might contribute to upregulate leptin production if the local TNF-α production really inhibits leptin synthesis.

IL-6 plasma levels and leptin production. IL-6 plasma levels were undetectable in air-breathing mice (WT; <0.1 pg/ml) and were markedly increased in mice exposed to hyperoxia for 84 h (n = 3; Table 1). ob/ob
air-breathing mice exhibited higher and dissimilar IL-6 levels compared with WT mice but did not show any increase during hyperoxia (20.5 ± 3.5 pg/ml; n = 5 air-breathing mice vs. 12.7 ± 6.4 pg/ml; n = 3 hyperoxic mice).

Corticosterone is responsible for leptin increase during hyperoxia. Because corticosterone has been shown to be regulated by leptin or, conversely, to regulate leptin levels (12, 20), we measured corticosterone levels in WT and ob/ob mice. Corticosterone increased gradually and significantly over time during hyperoxia in WT mice (Fig. 6). The correlation between corticosterone and the leptin level was highly significant as calculated by the Spearman correlation test (P < 0.0001). As already described (18), ob/ob mice exhibited a higher basal level of corticosterone than WT mice (253 ± 87 ng/ml in ob/ob mice compared with 98 ± 37 ng/ml in WT mice). The corticosterone level did not change significantly during hyperoxia in ob/ob mice (Fig. 6) and in anti-leptin antibody-treated WT mice.

We also administered 200 μg·mouse⁻¹·day⁻¹ of HCS intraperitoneally to WT mice. HCS administration worsened lung injury as assessed by lung weight (right lung weight 0.21 ± 0.05 g compared with 0.17 ± 0.023 g in saline-treated mice; n = 5), although not significantly (P = 0.21), and increased leptin levels compared with those in nontreated mice exposed to hyperoxia for the same time (Fig. 7B). Conversely, ADX mice showed no change in leptin levels during hyperoxia (Fig. 7B); corticosterone levels in these mice were measured and found to be very low (Fig. 7A) and were also protected during hyperoxia-induced injury. To discriminate between the effects due to glucocorticoids or catecholamines in ADX mice, we placed slow release pellets of RU-486 and nadolol in WT mice. Nadolol administration did not change the leptin level compared with placebo administration, whereas RU-486 diminished it partially (data not shown).

**DISCUSSION**

In this study, we report that circulating leptin increases dramatically during oxygen-induced lung injury, most likely by an increased synthesis in adipose tissue as suggested by an increase in the mRNA level. In contrast, the leptin mRNA level in the skeletal muscle, also detectable in accord with Friedman and Halaas (15), was unchanged. We failed to find detectable leptin mRNA within the lungs and did not find any upregulation of leptin receptor mRNA within the lung (data not shown).

Body weight loss in grams was similar in WT and ob/ob mice. However, when measured in percent of initial body weight, weight loss was clearly different and less important in ob/ob mice. How to interpret these results is debatable and still controversial in human studies (Golay A, unpublished observations). The percent of weight loss being different between ob/ob and WT mice could have been in favor of a leptin participation to weight loss. However, the similar weight loss (in grams and in percent) seen in WT mice treated with anti-leptin or control antibody argues against a leptin-dependent weight loss. Interestingly, the leptin increase seems specific to acute lung injury because bleomycin-induced lung injury (data not shown), a more chronic disease occurring in 7–14 days also accompanied by severe weight loss, or COPD was not followed by plasma leptin elevation (32).

The fact that leptin is produced mainly by adipose tissue during hyperoxia suggests that hyperoxia could either exert a direct effect on adipose tissue via oxygen toxic metabolites or exert an indirect effect via other mediators secreted by the lung or other organs. Differ-
ent hypotheses can be envisioned to explain the effects of hyperoxia on adipose tissue. 1) Hyperoxia-derived signals could act on the hypothalamus and in this way alter the adrenocortical axis (for example, sympathetic tone is known to regulate the adrenocortical axis). This possibility has been ruled out by the same level of leptin increase in mice exposed to hyperoxia and treated with nadolol. 2) Hyperoxia could differently upregulate other hormones or cytokines such as TNF-α and IL-6, insulin, and corticosterone in the lung or other tissues that might be responsible for the increase in leptin. We have explored several of the candidate molecules that might be relevant for lung diseases.

TNF-α is one of the proinflammatory cytokines known to regulate leptin production when injected into mice (30). Barazzone et al. (6) have previously shown that TNF-α mRNA was upregulated within the lungs only during the terminal phase of oxygen toxicity. In patients, the levels of circulating leptin are not always correlated with circulating TNF-α. Underweight patients suffering from COPD and cystic fibrosis exhibit, in opposite ways, high TNF-α and soluble TNF receptor levels and lower levels of plasma leptin than control patients (1, 32). Therefore, we tried to determine by different approaches whether TNF-α could be responsible for the increase in leptin synthesis. We could not measure any change in TNF-α blood levels during hyperoxia. Moreover, administration of anti-TNF-α antibody had no effect on the plasma leptin levels. Because leptin production by adipocytes is inhibited by TNF-α in vitro (36), we explored whether TNF-α from adipose tissue could influence local leptin production as during diabetes (17). For that reason, we measured TNF-α mRNA expression within the adipose tissue. We observed a decrease in TNF-α mRNA during hyperoxia, suggesting that the downregulation of TNF-α might favor leptin production. Taken together, our data do not argue for a significant role of circulating TNF-α in leptin upregulation but are consistent with the possibility that TNF-α produced in the adipose tissue might participate in leptin production. IL-6 can be produced by several organs, including adipose tissue, and is also one of the mediators that might be implicated in mice (23). The serum level of this circulating cytokine has been shown to be elevated during obesity (21), and this was confirmed by our results in ob/ob mice. In contrast to TNF-α, IL-6 blood levels increase dramatically during oxygen-induced injury, raising the possibility that this cytokine contributes to leptin production and weight loss.

The presence of leptin receptors in the lungs indicates that this tissue can be a target for leptin. Although the in vivo effects of leptin in the lungs are not reported, a study (34) has shown that this hormone acts as a proliferative factor for tracheal epithelial cells in vitro (34). Leptin might exert pro- or anti-inflammatory effects. On one hand, the circulating leptin level is increased in response to inflammatory agents such as lipopolysaccharide or cytokines and, furthermore, when injected leptin increases vascular permeability. On the other hand, leptin also protects against toxicity exerted by TNF-α because ob/ob mice are less resistant to TNF-α (33).

The role of leptin in alveolar damage was investigated by three separate approaches with different results. In overweight ob/ob mice, alveolar damage was delayed compared with that seen in WT mice. In contrast, blockade of leptin in WT mice did not alter the course of lung injury. Accordingly, leptin administration had no effect on the course of hyperoxic injury in WT mice. These observations suggest that the chronic or acute absence of leptin does not have similar effects on the course of an alveolar inflammation. This interpretation is in accord with that made during the study of the response of ob/ob mice to TNF-α or lipopolysaccharide discussed above. The peculiar response observed in ob/ob mice cannot be attributed to increased circulating steroid levels because corticosterone administration before the appearance of the injury did not protect the mice but even worsened the lesions. One possibility could be that obesity itself and its consequences such as changes in lipoproteins could be responsible for this small protective effect. Indeed, high levels of high-density lipoprotein (HDL) and cholesterol have been reported in ob/ob mice secondary to a defect in HDL catabolism by the liver (31). Because HDLs are able to protect endothelial cells from oxidative stress and apoptosis (29), it might be possible that the acute inflammatory response during hyperoxia in ob/ob mice is attenuated by high levels of circulating HDLs. In conclusion, we think that the acute elevation of leptin does not play an essential role in the development of hyperoxia-induced lung injury and that the effect of hyperoxia in ob/ob mice might be due not only to the absence of leptin but also to its related long-term consequences such as changes in biochemical, nutritional, and immunologic status compared with those in WT animals. Our data also underline that the long-term defect of a single gene might lead to complex modifications that are not comparable to acute blockade with the use of antibodies.

Corticosterone has been shown to stimulate leptin production in vitro and in vivo (11, 12, 24). Corticosterone increased up to fivefold during hyperoxia in WT mice, whereas in ob/ob mice in which the basal level is higher than in WT mice, (18), the corticosterone level did not further increase markedly during hyperoxia. We demonstrate a clear relationship between corticosterone elevation and leptin levels. ADX mice showed no change in leptin levels during hyperoxia compared with sham-operated mice. Furthermore, preliminary results suggest that glucocorticoids might contribute to aggravate the lesions of hyperoxia.

The present study demonstrated that hyperoxia stimulates leptin production via the stimulation of the adrenal gland but that leptin itself does not play a major role in oxygen-induced alveolar injury.

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LEPTIN INCREASES DURING HYPEROXIA IN MICE

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