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Augmented responses to ozone in obese carboxypeptidase E-deficient mice

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Johnston, Richard A., Todd A. Theman, and Stephanie A. Shore. Augmented responses to ozone in obese carboxypeptidase E-deficient mice. Am J Physiol Regul Integr Comp Physiol 290: R126–R133, 2006. First published July 7, 2005; doi:10.1152/ajpregu.00306.2005.—We reported previously that mice obese as a result of leptin deficiency (ob/ob) have enhanced ozone (O₃)-induced airway hyperresponsiveness (AHR) and inflammation compared with wild-type (C57BL/6) controls. To determine whether this increased response to O₃ was independent of the modality of obesity, we examined O₃-induced AHR and inflammation in Cpefat mice. These mice are obese as a consequence of a mutation in the gene encoding carboxypeptidase E (Cpe), an enzyme important in processing prohormones and proneuropeptides involved in satiety and energy expenditure. Airway responsiveness to intravenous methacholine, measured by forced oscillation, was increased in Cpefat vs. wild-type mice after air exposure. In addition, compared with air exposure, airway responsiveness was increased 24 h after O₃ exposure (2 ppm for 3 h) in Cpefat but not in wild-type mice. Compared with air-exposed controls, O₃ exposure increased bronchoalveolar lavage fluid (BALF) protein, IL-6, KC, MIP-2, MCP-1, and soluble TNF receptors (sTNFR1 and sTNFR2) as well as BALF neutrophils. With the exception of sTNFR1 and sTNFR2, all of these outcome indicators were greater in Cpefat vs. wild-type mice. Serum sTNFR1, sTNFR2, MCP-1, leptin, and blood leukocytes were elevated in Cpefat compared with wild-type mice even in the absence of O₃ exposure, similar to the chronic systemic inflammation observed in human obesity. These results indicate that increased O₃-induced AHR and inflammation are consistent features of obese mice, regardless of the modality of obesity. These results also suggest that chronic systemic inflammation may enhance airway responses to O₃ in obese mice.

Airway hyperresponsiveness; leptin; monocyte chemotactic protein-1; neutrophil; airway resistance

Obesity is an important public health problem that is reaching epidemic proportions (19, 42). Obesity is a known risk factor for cardiovascular disease, type II diabetes, and some forms of cancer (18). Recent epidemiological data indicate that obesity also increases the risk of asthma (13, 24, 35). The nature of the relationship between obesity and asthma remains to be determined, but it is likely that obesity either causes or exacerbates asthma, because longitudinal studies indicate that obesity antedates asthma and that the relative risk of incident asthma increases with increasing obesity (7, 8, 22, 23). In addition, obese asthmatics have a marked improvement in both their asthma severity and symptoms after weight loss (14, 16, 25, 51). Obesity may be particularly important for severe asthma because over 75% of subjects visiting the emergency room for asthma are obese or overweight (55).

One of the triggers for asthma is exposure to air pollution. The number of hospital admissions for asthma increases on days of high ambient ozone (O₃) concentrations (17, 56), and even O₃ concentrations below the current US Environmental Protection Agency standard are sufficient to initiate symptoms in children with asthma (21). Importantly, preliminary studies indicate that obesity exacerbates changes in pulmonary function induced by exposure to air pollution in children and adolescents (36, 39).

We (44, 49) have previously reported that airway responsiveness and airway inflammation following O₃ exposure are augmented in obese ob/ob vs. lean, wild-type (C57BL/6) mice. Baseline airway responsiveness was also increased in these obese mice. Ob/ob mice are genetically deficient in leptin, a satiety hormone. This deficiency reduces metabolism, increases food consumption, and causes the mice to become extremely obese (34). In contrast, human obesity is characterized by increased serum leptin (11), suggesting leptin resistance. Ob/ob mice also have small lungs; both absolute lung volumes and lung mass are decreased in ob/ob mice (49, 53). The reason for the reduced lung size is not yet known. It could result from the lack of leptin, which may promote lung growth (3, 58). Alternatively, increased abdominal fat mass may restrict lung growth during development; ob/ob mice are obese even at the time of weaning (34) when their lungs are still growing. Whatever the mechanism, this size difference may be important because it contributes to an increased inhaled dose of O₃ per gram of lung tissue in ob/ob vs. wild-type mice, which may account for their enhanced responses to O₃ (49).

The purpose of these studies was to examine O₃-induced airway hyperresponsiveness (AHR) and airway inflammation in another type of murine obesity, the Cpefat mouse. Cpefat mice have a single base-pair mutation in the gene encoding carboxypeptidase E (Cpe), an enzyme important in processing prohormones and proneuropeptides involved in appetite regulation and energy expenditure (34). The mutation abolishes virtually all Cpe activity. Consequently, the mice become obese (10, 34, 37). We report here that lung mass and displacement lung volume at functional residual capacity (FRC) are not different between wild-type (C57BL/6) and Cpefat mice, yet Cpefat mice display AHR even in the absence of O₃ exposure and have increased airway inflammatory responses to O₃ just as ob/ob mice do. Thus differences in lung size and/or altered O₃ dose cannot explain the increased responses to O₃ in Cpefat mice. Rather, some other aspect of their obesity must be
responsible for this phenomenon. Our data suggest that chronic systemic inflammation may be this factor.

MATERIALS AND METHODS

Animals

Animal protocols were approved by The Harvard Medical Area Standing Committee on Animals. Male and female Cpefat mice were purchased from Jackson Laboratory (Bar Harbor, ME) at 7 wk of age and used when at least 14 wk of age. Age- and sex-matched wild-type controls were purchased at the same time. Cpefat mice are available on both C57BLKS and C57BL/6 backgrounds. Cpefat mice used in this study were on a C57BL/6j background; thus wild-type C57BL/6j mice were used as controls.

Protocol

Three cohorts of wild-type and Cpefat mice were used. In the first cohort, bronchoalveolar lavage (BAL) was performed and blood was collected 4 h following the cessation of O3 (2 ppm for 3 h) or room air exposure. Mice were examined 4 h after exposure because we have reported that many BAL fluid (BALF) cytokines and chemokines of interest are elevated at this time (49). In the second cohort, the animals were anesthetized and instrumented for the measurement of pulmonary mechanics and airway responsiveness 24 h following O3 or room air exposure, according to previous reports (44, 49, 64). In addition, blood was collected and BAL was performed on these mice. In a third cohort, pressure-volume (PV) relationships, displacement lung volume at FRC, and lung mass were assessed in unexposed mice as described under PV Relationships, Displacement Lung Volume at FRC, and Lung Mass. In some mice, we measured tidal volume (Vt), breathing frequency, and minute ventilation (V˙E) by placing the animals in a whole-body plethysmograph (Buxco Electronics, Sharon, CT) as described previously (48, 50).

O3 Exposure

For O3 exposure, conscious mice were placed into individual wire mesh cages inside a stainless steel and Plexiglas exposure chamber. For room air exposures, a separate and identical exposure chamber was used. A PEEP of 3 cmH2O was held for 1 s. A second volume history maneuver was then applied, and the tracheal cannula was clamped at end expiration (defined as open-chested FRC). The lungs were immediately excised and lung volume measured by volume displacement. The lungs were also weighed to obtain lung mass.

Statistical Analysis

Comparisons of baseline airway and parenchymal mechanics and BALF parameters were assessed using factorial ANOVA, using genotype and exposure as the main effects. Fisher’s least significant difference test was used as a follow-up to determine the significance of differences between individual groups. Differences in R0∞ during MCh challenge were assessed by repeated-measures ANOVA. Comparisons of serum markers of inflammation, displacement lung volume at FRC, lung mass, quasistatic elastance, and the pattern of breathing were made using unpaired Student t-tests. Statistica software (StatSoft; Tulsa, OK) was used to perform all statistical analyses. The results are expressed as means ± SE, except where noted. A P value <0.05 was considered significant.

RESULTS

Body Mass

Cpefat mice, 14–16 wk of age, weighed ~50% more than wild-type mice of the same age and sex (Table 1).

Effect of Obesity on Pulmonary Mechanics at Baseline and Following O3 Exposure

Baseline pulmonary mechanics. Factorial ANOVA indicated a significant increase in G and H in Cpefat vs. wild-type mice regardless
of exposure ($P < 0.01$ in each case). O₃ exposure caused a significant ($P < 0.05$) increase in $\text{Raw}$ in $\text{Cpefat}$ but not wild-type mice. O₃ exposure did not alter $G$ or $H$ in either group (Table 1).

### Pulmonary responses to MCh.

In air-exposed mice, regardless of genotype, intravenous MCh increased $\text{Raw}$ (Fig. 1A), whereas $G$ and $H$ (Fig. 1, B and C) were unaffected by MCh. $\text{Raw}$ responses to MCh were significantly greater in $\text{Cpefat}$ vs. wild-type mice (Fig. 1A). O₃ exposure increased $\text{Raw}$ (Fig. 1A) responses to MCh in $\text{Cpefat}$ mice. In contrast, O₃ exposure had no effect on responses to MCh in wild-type mice. There were no MCh-induced changes in $G$ or $H$ in mice of either genotype with either room air or O₃ exposure (Fig. 1, B and C), although $G$ and $H$ remained elevated in $\text{Cpefat}$ compared with wild-type mice even with MCh exposure.

### Effect of Obesity on O₃-Induced Injury and Inflammation

Following room air exposure, there were no genotype-related differences in the total number of BALF cells or in the types of cells recovered from the BALF (Table 2). In wild-type mice 4 h post-O₃, the total number of BALF cells and macrophages were reduced, whereas neutrophils were significantly elevated compared with air-exposed controls. In $\text{Cpefat}$ mice 4 h post-O₃, the total number of BALF cells, macrophages, and neutrophils were increased significantly with respect to their air-exposed controls. Twenty-four hours following O₃ exposure, the total number of BALF cells, macrophages, neutrophils, and epithelial cells were elevated in both wild-type and $\text{Cpefat}$ mice compared with their respective air-exposed controls. Significantly more neutrophils were recovered from the}

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**Table 1. Baseline body mass and airway and parenchymal mechanics in wild-type (C57BL/6) and $\text{Cpefat}$ mice exposed to room air or O₃ (2 ppm) for 3 h**

<table>
<thead>
<tr>
<th>Mouse, exposure</th>
<th>Body Mass, g</th>
<th>$\text{Raw}$, cmH₂O/ml $^{-1}$s$^{-1}$</th>
<th>$G$, cmH₂O/ml</th>
<th>$H$, cmH₂O/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type, room air</td>
<td>27.6±2.0</td>
<td>0.23±0.02</td>
<td>3.24±0.23</td>
<td>20.43±1.42</td>
</tr>
<tr>
<td>$\text{Cpefat}$, room air</td>
<td>51.9±3.8#</td>
<td>0.24±0.02</td>
<td>4.48±0.44#</td>
<td>28.76±2.61#</td>
</tr>
<tr>
<td>Wild-type, O₃</td>
<td>26.3±2.6</td>
<td>0.23±0.01</td>
<td>3.52±0.26</td>
<td>21.18±0.79</td>
</tr>
<tr>
<td>$\text{Cpefat}$, O₃</td>
<td>48.5±1.4#</td>
<td>0.36±0.02*#</td>
<td>4.41±0.07#</td>
<td>30.14±0.69#</td>
</tr>
</tbody>
</table>

Results are means ± SE for 5–7 mice in each group. Measurements were made 24 h after cessation of exposure to room air or ozone (O₃, 2 ppm). $\text{Raw}$, airway resistance; $G$, lung tissue damping; $H$, lung tissue elastance. *$P < 0.05$ compared with genotype-matched, air-exposed controls; #*$P < 0.05$ compared with wild-type mice with an identical exposure.

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**Fig. 1.** Responses to intravenous methacholine (MCh) for airway resistance ($\text{Raw}$), lung tissue damping ($G$), and lung tissue elastance ($H$) in wild-type (C57BL/6) and $\text{Cpefat}$ mice exposed to either room air or ozone (O₃, 2 ppm) for 3 h. Responses were measured 24 h following cessation of exposure. $n = 5–7$ Mice for each group. *$P < 0.05$ compared with wild-type (C57BL/6) mice with an identical exposure. #*$P < 0.05$ compared with genotype-matched air-exposed controls. Cpe, carboxypeptidase E.
BALF of Cpefat vs. wild-type mice both 4 and 24 h post-O3. Lymphocytes and eosinophils were rarely observed under any genotype or treatment (data not shown).

**Effect of Obesity on Lung Size**

Because we have previously reported that reduced lung size may account for enhanced inflammatory responses to O3 in ob/ob mice (49), we measured lung mass and open-chested FRC (end-expiratory volume at a PEEP of 3 cmH2O) in unexposed wild-type and Cpefat mice. There was no difference in lung mass or FRC between wild-type and Cpefat mice. The lung mass averaged 0.28 ± 0.03 vs. 0.28 ± 0.01 g, and the FRC averaged 0.38 ± 0.03 vs. 0.32 ± 0.03 ml for wild-type and Cpefat mice, respectively. Nevertheless, lung PV curves were shifted to the right in Cpefat vs. wild-type mice (Fig. 3). Quasi-static lung elastance measured over the deflation portion of the curve from FRC to FRC plus 0.3 ml averaged 14.0 ± 0.5 cmH2O/ml in wild-type and 18.8 ± 1.4 cmH2O/ml in Cpefat mice (P < 0.05).

**Effect of Obesity on Breathing Pattern**

V˙E is an important determinant of the inhaled dose of O3 that may impact the degree of O3-induced injury and inflammation to the lungs. Thus V˙E was assessed in unexposed

Table 2. Bronchoalveolar lavage fluid total cell numbers and differentials in wild-type and Cpefat mice exposed to room air or O3 (2 ppm) for 3 h

<table>
<thead>
<tr>
<th>Mouse, exposure</th>
<th>Total Cells</th>
<th>Macrophages</th>
<th>Neutrophils</th>
<th>Epithelial Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type, room air</td>
<td>13.5 ± 1.0</td>
<td>12.2 ± 1.1</td>
<td>0.07 ± 0.01</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Cpefat, room air</td>
<td>17.7 ± 2.1</td>
<td>16.1 ± 2.2</td>
<td>0.08 ± 0.02</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Wild type, 4 h post-O3</td>
<td>7.1 ± 1.5*</td>
<td>5.8 ± 1.0*</td>
<td>0.3 ± 0.1*</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Cpefat, 4 h post-O3</td>
<td>26.1 ± 4.4*#</td>
<td>19.7 ± 4.9#</td>
<td>3.7 ± 1.9*#</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Wild type, 24 h post-O3</td>
<td>32.0 ± 3.3*</td>
<td>22.1 ± 2.6*</td>
<td>4.5 ± 0.9*</td>
<td>4.9 ± 1.0*</td>
</tr>
<tr>
<td>Cpefat, 24 h post-O3</td>
<td>38.9 ± 4.8*</td>
<td>20.4 ± 2.1</td>
<td>10.4 ± 1.9*#</td>
<td>7.4 ± 1.8*</td>
</tr>
</tbody>
</table>

Values are cell number × 10⁴; results are means ± SE for 6–12 mice in each group. Cells were counted 4 or 24 h following the cessation of exposure to room air or O3 (2 ppm). *P < 0.05 compared with genotype-matched, air-exposed controls; #P < 0.05 compared with wild-type mice with an identical exposure.
wild-type and Cpefat mice. There was no significant difference in $V_T$ between wild-type and Cpefat mice (Table 3). In addition, no differences existed in either the breathing frequency or VT between wild-type and Cpefat mice.

Effect of Obesity on Systemic Markers of Inflammation

Concentrations of several inflammatory proteins are elevated in the serum of obese humans (5, 6, 28, 60). To examine systemic inflammation in wild-type and Cpefat mice, we measured the serum levels of IL-6, MCP-1, sTNFR1, sTNFR2, and leptin, as well as the total number of blood leukocytes in air-exposed mice. Serum concentrations of sTNFR1, sTNFR2, MCP-1, and leptin were significantly greater in Cpefat vs. wild-type mice, whereas there were no differences in IL-6 (Fig. 4, A–E). The total number of blood leukocytes was also significantly elevated in Cpefat compared with wild-type mice (Fig. 4F).

Discussion

We have previously reported (44, 49) that responses to O3 are greater in obese ob/ob vs. lean wild-type mice. We (49) postulated that this difference might be related to the reduced lung size of ob/ob mice because it contributes to an increased inhaled dose of O3 per gram of lung tissue. We now report that obese Cpefat mice, which have lungs of normal size, also have increased airway responses to O3, suggesting that differences in lung size and/or altered O3 dose cannot account for this enhanced O3-induced responsiveness. Rather, some other factor common to both modalities of obesity must be responsible for this phenomenon. Our data suggest that chronic systemic inflammation may contribute.

Airway responsiveness was greater in obese Cpefat vs. lean, wild-type mice even in the absence of O3 exposure (Fig. 1), consistent with our previous findings in obese ob/ob mice (44, 49). In both Cpefat (Fig. 1) and ob/ob mice (44), this innate AHR was the result of differences in the airway response to MCh, whereas G or H, parameters reflecting the lung tissue, did not change with MCh in either obese or lean mice. Because of the relationship between $R_{aw}$ and airway diameter (2), low initial airway caliber can lead to AHR, yet there was no difference in baseline $R_{aw}$ between wild-type and Cpefat mice. However, Cpefat mice did have increased baseline G and H compared with lean controls (Table 1). As described by Fredberg (20) tidal stretching of the lung with breathing is a powerful bronchodilator. However, $V_T$ was the same in Cpefat and wild-type mice during spontaneous breathing (Table 3). Furthermore, the mice were all mechanically ventilated with the same $V_T$ during measurements of lung mechanics. Due to tethering of the airways by the surrounding lung tissue, airway diameter is strongly influenced by lung volume. Indeed, airway responsiveness increases when subjects breathe at low lung volume (15). Because of changes in abdominal load leading to altered chest wall compliance, obese humans breathe at a lower-than-normal FRC (43). We reasoned it was unlikely that changes in lung volume resulting from alterations in the chest wall could explain the innate airway responsiveness observed in these Cpefat mice, because these mice were all studied with an open chest and a fixed PEEP. Nevertheless, in ob/ob mice, lung volumes are reduced even when measured in open-chested animals (49, 53), apparently because of effects on lung growth (49, 53). To address this issue, we measured the lung volume at which we were ventilating our mice and performing our measurements and found that it was the same as the lung volume of lean, wild-type mice. Lung mass was also normal, whereas it is reduced in ob/ob mice (49). Nevertheless, there must be some impact of obesity on lung development in these Cpefat mice because lung PV curves were shifted to the right compared with lean, wild-type mice (Fig. 3) as manifested by the greater quasi-static lung elastance and the corresponding increases in other indices of lung tissue mechanics, G and H (Table 1). We would expect that increased lung elastic recoil per se would reduce rather than increase airway responsiveness, but we cannot rule out the possibility that some alteration in lung or airway anatomy in these Cpefat mice accounts for their increased airway responsiveness. It is also possible that the low-grade, systemic inflammation manifest in the Cpefat mice (Fig. 3) contributed to their AHR. Multiple stimuli that promote airway inflammation also promote AHR, although it is clear that AHR can occur in the absence of airway inflammation (49).

Following O3 exposure, Cpefat mice developed AHR, whereas wild-type mice did not (Fig. 1). Cpefat mice also developed a more robust inflammatory response to O3 than lean mice (Fig. 2). Based on our previous studies using the same protocol (49), we were somewhat surprised to see no O3-induced AHR in the wild-type mice. However, measured

Table 3. Baseline body mass, tidal volume ($V_T$), breathing frequency ($f$), and minute ventilation ($V_{E}$) of wild-type and Cpefat mice

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Body Mass, g</th>
<th>$V_T$, ml</th>
<th>$f$, breaths/min</th>
<th>$V_{E}$, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>32.2±0.8</td>
<td>0.25±0.04</td>
<td>321±42</td>
<td>75.1±11.6</td>
</tr>
<tr>
<td>Cpefat</td>
<td>54.1±1.2+</td>
<td>0.22±0.03</td>
<td>355±22</td>
<td>77.1±12.2</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE for 8 mice in each group. *P < 0.05 compared with wild-type mice.
by percent, the wild-type mice also recruited fewer neutrophils to their lungs than in the previous studies. The advanced age of the mice in this study may have contributed to an overall reduced response to O3. We have also reported both increased airway responsiveness and inflammation following O3 exposure in ob/ob compared with wild-type mice (44). Although we obtained essentially similar results in these two types of obese mice, there were two notable exceptions. First, whereas BALF obtained essentially similar results in these two types of obese O3-induced AHR. In mice, BALF neutrophils were increased in Cpefat whereas wild-type mice (Fig. 4), consistent with their obese status, reduction in Cpe activity somehow contributes to the responses observed in these obese Cpefat mice, because both V̇E and lung mass were the same as in lean mice. We cannot rule out the possibility that a difference in Cpe activity somehow contributes to the responses of Cpefat mice. However, this seems unlikely given the fact that both Cpefat mice which lack Cpe and ob/ob mice which are Cpe sufficient have similar pulmonary responses to O3. It is more likely that the increased responses are the result of some other factor common to both modalities of obesity.

We and others (9, 31, 50) have reported that in mice, acute O3-induced AHR is mechanistically linked to several aspects of O3-induced inflammation. Therefore, it is likely that the increased O3-induced AHR observed in the Cpefat vs. wild-type mice is the result of their greater inflammatory response. One explanation for the greater inflammatory response observed in Cpefat and ob/ob mice is that obesity promotes inflammation. Indeed, obesity is associated with chronic, low-grade systemic inflammation in both humans and animals. Plasma and/or adipose tissue expression of inflammatory markers, such as C-reactive protein, IL-6, IL-8, MCP-1, TNF-α, sTNFR1, and sTNFR2 are elevated in overweight or obese humans (5, 6, 28, 29, 52, 60) and weight reduction has been shown to significantly decrease this inflammation (5, 33). The total number of blood leukocytes, as well as monocyte and granulocyte phagocytosis and oxidative burst activity, are in-
creased significantly in obese humans (38). Importantly, elevated levels of systemic inflammatory markers, including IL-6, MCP-1, and TNF-α, correlate with other obesity-linked diseases, such as atherosclerosis and insulin resistance (1, 40, 46, 54, 59). Others have reported (62, 63) that TNF-α and MCP-1 are also increased in the adipose tissue of obese ob/ob mice as well as mice with diet-induced obesity. We now extend the list of serum inflammatory markers elevated in murine obesity to include sTNFR1, sTNFR2, and blood leukocytes (Fig. 3), and we demonstrate that systemic inflammation occurs in Cpefat mice as well as in other types of murine obesity. Thus the presence of chronic systemic inflammation in Cpefat mice may amplify subsequent inflammatory responses, such as those elicited by O₃ inhalation, leading to augmented changes in pulmonary mechanics and airway responsiveness.

We do not know precisely which aspect of this systemic inflammation response is essential. Leptin is proinflammatory (4, 45) and has the capacity to augment many aspects of O₃-induced pulmonary inflammation, such as changes in BALF cytokines, chemokines, and protein (49). However, leptin is unlikely to be contributing substantially to obesity-induced increases in BALF cytokines and chemokines, because these are augmented during O₃ exposure in both in Cpefat mice (Fig. 2) with high serum leptin and in ob/ob mice with no serum leptin (49).

In conclusion, we report that Cpefat mice display innate AHR, as well as increased airway responsiveness and inflammation following O₃ exposure. These increased effects of O₃ appear to be independent of changes in lung volume or lung mass. Taken together with our results from ob/ob mice, these data suggest that obesity augments airway responses to O₃. It is possible that the chronic systemic inflammation of obesity amplifies pulmonary responses to O₃.

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