HIGHLIGHTED TOPIC | Pulmonary Physiology and Pathophysiology in Obesity

Obesity, airway hyperresponsiveness, and inflammation

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Shore SA. Obesity, airway hyperresponsiveness, and inflammation. J Appl Physiol 108: 735–743, 2010. First published October 29, 2009; doi:10.1152/japplphysiol.00749.2009.—Epidemiological data indicate that obesity is a risk factor for asthma, but the mechanistic basis for this relationship is not established. Here we review data from human subjects and animal models investigating the relationship between obesity and airway hyperresponsiveness, a characteristic feature of asthma. We discuss obesity as a state of chronic systemic inflammation resulting from interactions between adipocytes and adipose tissue macrophages that are recruited to obese adipose tissue. Finally, we focus on the possibility that aspects of this inflammation, particularly obesity-related changes in TNF-α, leptin, and adiponectin, may contribute to airway hyperresponsiveness in obesity. Determining how obesity promotes asthma may uncover novel therapeutic strategies that are effective in the obese asthmatic subject.

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Obesity is an important risk factor for asthma. Numerous (>50) cross-sectional studies performed in adults and children throughout the world have examined the impact of obesity on asthma. Virtually all demonstrate an increased prevalence of asthma in the obese and overweight (5, 19, 44, 77). Importantly, 16 of 17 prospective studies involving more than 200,000 adults and children indicate that obesity antedates asthma (5, 19, 44, 77). Obesity also worsens asthma control (56, 64, 67). The observation that either surgical or diet-induced weight loss improves asthma outcomes (51, 85) provides additional support for a relationship between obesity and asthma.

The mechanistic basis for the relationship between obesity and asthma has not been established. Below we describe the relationship between obesity and airway hyperresponsiveness (AHR), a characteristic feature of asthma, and discuss the data suggesting a role for the chronic systemic inflammation that characterizes obesity in modifying airway responsiveness in the obese.

Obesity and airway responsiveness in human subjects

Table 1 summarizes studies that have examined the impact of obesity on airway responsiveness in adults or in children. The results of these studies are mixed. Some studies have shown that obesity is a risk factor for AHR. In the only prospective longitudinal cohort study in adults, Litonjua et al. (45) reported that high initial body mass index (BMI) was associated with an increased risk of developing AHR. Similarly, weight gain was linearly related to the risk of developing AHR. Three other large cross-sectional studies in adults, one from Europe, another from China, and a third from the USA, also noted a greater prevalence of AHR or symptomatic AHR in obese vs. normal weight adults (9, 12, 84). In contrast, others have reported no increase in airway responsiveness with increasing BMI (6, 71). Similarly, inconsistent results have been obtained in children (Table 1).

Several methodological issues deserve mention here. Some studies have reported a U-shaped relationship between BMI and AHR (9, 45), with underweight as well as obesity leading to increased AHR. Failure to account for such a relationship, for example, in simple comparisons of obese vs. nonobese subjects, could negate any potential impact of BMI on AHR. At least one study also noted a differing effect of obesity on AHR in female vs. male subjects (30). Grouping subjects of both sexes together could thus obscure or attenuate any sex-specific effects of obesity. Importantly, there are numerous studies describing a role for sex in the relationship between obesity and asthma (19, 77). The method by which subjects are accrued may also impact the results. For example, choosing to examine nonasthmatic subjects specifically (59, 68) would lessen the likelihood of detecting an effect of obesity on AHR, since these subjects may have been ascertained based on their lack of AHR. Finally, and perhaps most importantly, BMI was the measure of obesity in most of the studies in Table 1. BMI is often used as a surrogate for adiposity, simply because it is available, but is not an ideal measurement. For example, in children, forced vital capacity and forced expiratory volume in 1 s (FEV₁) increase with body weight (42). However, the effect is likely the result of lean body weight, since, after adjustment for height and weight, these measures of pulmonary function actually decrease with increasing percent total body fat pre-
dicted from skinfold thickness. In the obese, reductions in lung volumes do not correlate with BMI, but do correlate with fat mass, particularly truncal fat mass, as measured by dual-energy X-ray absorptiometry (10, 43). Thus using direct measures of adiposity and the distribution of adiposity, rather than BMI, might help to resolve the inconsistencies in the relationship between obesity and AHR.

The nature of the stimulus used to assess airway responsiveness may also be important. Most studies have used methacholine as the bronchoconstricting agonist (Table 1). While only three small studies have reported the impact of obesity with exercise as the bronchoconstricting agent (Table 1), all three have noted greater effects in obese vs. nonobese subjects (15, 21, 38). The pattern of bronchospasm, occurring soon after the exercise challenge, was consistent with that found in asthmatic subjects. The mechanistic bases for the bronchoconstriction induced by methacholine and that induced by exercise are not the same. Methacholine causes constriction of airway smooth muscle, whereas exercise, via changes in airway osmolarity, causes activation of mast cells and the subsequent release from these cells of several bronchoconstricting agents. Thus the relatively consistent differences between obese and nonobese subjects in exercise-induced bronchospasm could reflect greater effects of exercise on airway drying, or greater sensitivity of mast cells in obese subjects. Such changes would not be expected to impact methacholine-induced bronchoconstric-
tion. Notably, increased numbers of mast cells were reported in the lungs of obese vs. lean mice than had been sensitized and challenged with ovalbumin (OVA) (55).

The outcome indicator used to assess airway narrowing is also important to consider. Salome et al. (68) reported no difference in methacholine-induced changes in FEV₁ or respiratory system resistance in obese vs. nonobese normal subjects. In contrast, the obese subjects had greater increases in respiratory system reactance, consistent with greater airway closure and consequent hyperinflation. Indeed, a follow-up study by the same authors confirmed greater methacholine-induced airway closure in obese vs. lean subjects (11). Small airway closure, presumably in the dependent regions of the lung, has also been reported in obese subjects, even in the absence of any exogenously administered bronchoconstrictor (23, 25). The consequences of localized airway closure include dilation of the airways in the rest of the lung (since these areas now receive a greater portion of the tidal volume, leading to greater stretch of airway smooth muscle) (97). Simple measurements, such as FEV₁, are unlikely to capture the complexity of these heterogeneous airway changes. Instead, studies utilizing detailed measurements of lung and airway mechanics may be necessary to fully understand the relationship between obesity and AHR.

None of the studies that have examined interactions between BMI and asthma has taken diet into account. There is evidence that dietary antioxidants and omega-3 fatty acids can affect lung function (95), and obese individuals tend to consume not just more calories, but also a less healthy diet (89). It is possible that the observed heterogeneity in the effects of obesity on AHR observed across studies (Table 1) may reflect regional differences in dietary constituents.

There is only one report of the effect of weight loss on AHR in obese individuals (1). Although there was a trend toward an improvement in AHR after 6 mo on a weight reduction program, the effect was not significant, despite an average weight loss of 17.4% of pretreatment body weight and significant improvements in flow rates and symptoms. The study was small (50 patients) and may not have been sufficiently powered to observe an effect on AHR. The authors also did not phenotype the subjects with respect to their level of atopy or airway inflammation, and it is conceivable that there are patients with particular asthma phenotypes for whom weight loss does improve AHR. Indeed, within their population, the authors noted several individuals with fairly marked reductions in airway responsiveness after weight loss.

It is important to note that AHR is very common in the general population. There are numerous environmental, genetic, and epigenetic influences on AHR, and these may obscure any additional effect of obesity without the use of large sample sizes. In contrast, such effects are nullified in studies of genetically identical mice that are often born to the same mothers and are housed together. In this context, increased airway responsiveness has been consistently noted in obese mice (see below).

OBESE MICE EXHIBIT INNATE AHR

AHR to intravenous methacholine is observed in obese ob/ob and db/db that are genetically deficient in either the satiety hormone, leptin, or the leptin receptor, and in Cpefat mice that are obese because of a genetic deficiency in carboxypeptidase E, an enzyme involved in processing neuropeptides involved in eating behaviors, and in obesity induced by feeding mice a high-fat diet from the time of weaning (34, 35, 48, 66, 78, 82) (Fig. 1). The results indicate that AHR is a common feature of murine obesity. This hyperresponsiveness is independent of the bronchoconstricting agonist, since increased responses to serotonin are also observed (48). The hyperresponsiveness also seems to be a function of differences in the airways rather than the lung tissues, since, regardless of the modality of the obesity, AHR is observed when changes in airway resistance are used as the outcome indicator, but not with outcomes that reflect changes in the lung tissues (34, 35, 66, 82). While this may appear to differ from the situation in obese humans described by Salome et al. (68) (see above), it is important to note that measurements in mice were made with the chest wall open and an applied positive end-expiratory pressure of 3 cmH₂O. Such interventions limit the airway closure that likely explains the greater methacholine-induced increases in measures of the lung tissue observed in obese humans (68).

In mice, both the magnitude and duration of obesity may interact to affect AHR. Ob/ob and db/db mice gain weight very quickly after weaning and are massively obese by 8 wk of age (body weight averages 175 and 150% more, respectively, than lean controls). These mice exhibit AHR even at this early age, and the magnitude of their AHR is greatest (Fig. 1). Cpefat mice gain weight more slowly, but ultimately also become substantially obese: body weight averages 23, 61, and 84% more than wild-type controls at 7, 10, and 14 wk of age, respectively. The 7-wk-old mice are not hyperresponsive, whereas the older mice are (unpublished observations). Obesity is fairly mild in mice with diet-induced obesity, and body weight is comparable (~45% more than diet controls) at 23 and 35 wk of age (34). However, AHR is observed only in the older mice, suggesting that, with milder obesity, longer durations are required to elicit effects. Studies that incorporate not only the magnitude, but also the duration, of obesity may ultimately be required to sort out the impact of obesity on AHR in human subjects.

The mechanistic basis for the AHR observed in obese mice has not yet been established. The possibility that mechanical factors related to reductions in absolute lung volumes are involved has been previously discussed in detail (35, 76, 78). There is no overt cellular inflammation in the lungs of unchallenged obese mice (35, 48), although it is possible that normal resident immune cells are in an activated state. There is, however, increased pulmonary oxidative stress (unpublished observations), similar to the situation in the airways of obese asthmatic subjects (41). Oxidative stress contributes to many other aspects of the obese phenotype (29, 72), and oxidative stress has also been linked to asthma (40). If oxidative stress is important in the AHR observed in obese mice, it is unlikely to originate from the hyperglycemia that is a comorbidity of obesity in these models, since treating db/db mice for 2 wk with the anti-hyperglycemic agent, metformin, does not attenuate airway responsiveness in these mice (82). Below we consider data supporting the hypothesis that adipokines originating from inflamed adipose tissue may play a role in obesity-related AHR.
ADIPOKINES AND AHR

Microarray profiling of genes differentially expressed in the adipose tissue of obese vs. lean mice or humans indicates a marked obesity-related increase in expression of inflammatory genes (94, 99), including cytokines, such as TNF-α and IL-6, chemokines, such as IL-8 and monocyte chemoattractant protein-1, complement proteins, and other acute phase moieties. Together with hormones normally produced by adipocytes, including leptin and adiponectin, these adipose-derived proteins are collectively termed adipokines. The current paradigm is that these adipokines spill over into the blood. Indeed, there is substantial evidence of elevated levels of numerous proinflammatory molecules in the blood of obese vs. lean individuals that occur in proportion to the BMI and that decline with weight loss (4, 28, 32, 72, 87, 92, 93). Additional serum factors that are elevated in obesity may derive from effects of these adipokines on the vasculature (2). Circulating leukocytes are also increased (107), and it is increasingly appreciated that obesity is a state of low-grade systemic inflammation, with inflammatory activation at sites distant to the adipose tissue. Obesity-related elevations in many adipokines have been shown to correlate with the presence of obesity-related diseases, including Type 2 diabetes and atherosclerosis (18, 72), suggesting that this inflammation is functionally important. As described below, obesity-related changes in adipokines could also exacerbate airway responsiveness, precipitating asthma.

Adipose tissue macrophages (ATM) either alone or via interactions with adipocytes, appear to be the source of many of the inflammatory molecules produced by obese adipose tissue. While a few ATM exist in lean individuals, they are of...
the alternatively activated, M2 phenotype (49, 108) and produce few proinflammatory mediators. However, in obesity, the adipose tissue becomes infiltrated with macrophages, which can constitute upwards of 50% of the cells isolated from this tissue (94). These ATM are recruited from blood monocyte derived precursors and have an increased capacity to produce proinflammatory cytokines (49, 58, 86). Importantly, myeloid-specific knockout studies have established the importance of these ATM for some obesity-related conditions, including insulin resistance (3).

Because of the importance of ATM for the etiology of obesity-related conditions, some consideration of the factors contributing to their recruitment and activation is warranted. Necrosis of adipocytes is observed in obesity, and histological data indicate that ATM surround these necrotic cells (86). The adipose tissue of obese mice is hypoxic relative to lean mice (27, 65, 105), likely because expansion of adipose tissue mass precedes angiogenesis, leading to increasing distance between adipocytes and capillaries. One of the roles of macrophages is to phagocyte dead cells, and areas of macrophage infiltration correspond to areas of hypoxia, suggesting that hypoxia may initiate adipocyte cell death (65). Indeed, adipose tissue hypoxia appears to contribute to adipose inflammatory gene expression in obesity (27, 105), as well as to obesity-related reductions in adiponectin (27). These changes appear to at least partly result of increased expression of the hypoxia-dependent transcription factor, hypoxia-inducible factor-1α (104). In asthmatic subjects, systemic hypoxemia resulting from heterogeneous airway narrowing could exacerbate local adipocyte hypoxia, increasing cell death, and amplifying the attendant adipose-derived systemic inflammation. There is also increasing evidence that Toll-like receptor 4 (TLR4) activation may contribute to activation of ATM. Both adipocytes and macrophages express TLR4, and saturated fatty acids, especially C14:0, C16:0, and C18:0, stimulate TLR4 in these cells, leading to IL-6 and TNF-α expression (74). Also, high-fat diet feeding results in increased blood concentrations of endotoxin, a TLR4 ligand, likely as a result of its increased transport across the intestines, resulting from diet-induced changes in the intestinal microbiota (8).

Adipokines released into the serum from inflamed adipose tissue may circulate to the lungs and contribute to AHR [see recent reviews (75–77)]. For example, obesity increases the serum concentrations of TNF-α (28). Exogenous administration of TNF-α has been shown to induce AHR (90), while anti-TNF-α antibodies have been shown to inhibit allergen-induced AHR in mice (39). AHR induced by the air pollutant, ozone, is also attenuated in TNF receptor-deficient mice (79).

Other adipose-derived inflammatory moieties may also contribute to AHR. VEGF is also elevated in the serum of obese individuals (83), and VEGF expression in the airways of asthmatic subjects correlates inversely with airway caliber (26). Serum levels of plasminogen activator inhibitor-1 (PAI-1), an important inhibitor of both fibrinolysis and plasmin activation, are increased in the obese and decrease with weight loss (57). PAI-1 is a reasonable asthma candidate gene (50). PAI-1 is required for the AHR induced by LPS in mice (69), perhaps via effects on extracellular matrix turnover and remodeling, since PAI-1 is also required for the increased collagen and fibrin deposition that occurs in the airways after chronic allergen challenge in mice (50).

Below we focus on the possible roles of obesity-related increases in leptin and decreases in adiponectin in AHR.

**Leptin**

Leptin is an adipose-derived satiety hormone that is markedly elevated in obesity (34, 35). Leptin is also proinflammatory (18). Adipocyte production of leptin can be induced by infectious and inflammatory stimuli, including TNF-α and IL-1β (22). We have reported that allergen challenge to the airways of sensitized mice also increases serum leptin (80). Leptin stimulates proinflammatory cytokine production from monocytes and macrophages (20, 46, 52) and promotes formation of reactive oxygen species in neutrophils (7). Exogenous administration of leptin also augments cytokine and chemokine production in the lungs of mice after acute ozone exposure (78).

To address the relationship between leptin and AHR, we implanted microosmotic pumps, delivering a constant infusion of leptin or saline into lean, OVA-sensitized mice and challenged the mice with aerosolized OVA or PBS for several days (80). Compared with saline, delivery of leptin resulted in an approximate twofold increase in serum leptin. In mice challenged with aerosolized PBS, no effect of leptin was observed on airway responsiveness to methacholine, indicating that leptin alone does not cause AHR. However, leptin did augment the AHR induced by OVA aerosol challenge, even though it did not affect OVA-induced airway eosinophilia or T helper type 2 (Th2) cytokine expression (80). Taken together, the results suggest that leptin is capable of increasing airway responsiveness, but only in concert with other inflammatory agents. The data also indicate that leptin does not promote expression of Th2 cytokines, consistent with data from other investigators (47). Leptin receptors are expressed on CD4+ T lymphocytes, and leptin does promote survival, induce proliferation, and increase cytokine production from these cells, but the effect is on Th1, not Th2, cytokines (47, 63). Consistent with these data, a greater percentage of IFN-γ secreting CD4+ T cells is observed in blood of obese vs. lean children and
correlates with serum leptin (61). In contrast, leptin appears to inhibit proliferation of regulatory T cells (14) and could promote asthma in that manner.

It is possible that the observed effects of leptin on airway responsiveness (80) are mediated via the innate immune system. Exogenous administration of leptin to lean mice before acute O₃ exposure increases some aspects of their subsequent inflammatory responses (78), a response that is known to involve activation of TLRs (96). In contrast, reduction in endogenous leptin by fasting in lean mice does not affect O₃-induced generation of acute phase cytokines and chemokines (36), suggesting that leptin-related increases in O₃-induced inflammation require leptin concentrations above those normally observed in lean mice. Such increases are observed in obesity. However, even though leptin has the potential to augment airway responsiveness (80), it unlikely that leptin accounts for AHR observed in obese mice, since this AHR is observed both in ob/ob and db/db mice with leptin or leptin-receptor deficiency (48, 66, 78, 82), and in Cpedef mice and mice with diet-induced obesity that have marked increases in serum leptin (34, 35).

Adiponectin

In contrast to other adipokines, plasma adiponectin and adipose tissue adiponectin expression decline in obesity and rise again following weight loss (62, 73, 102). Obesity-related changes in adiponectin are likely to be functionally important, since exogenous administration of adiponectin protects obese mice against obesity-related diseases, including Type 2 diabetes and atherosclerosis (101). Adiponectin was originally identified as an energy-regulating hormone (13, 102), but also has effects on hematopoietic cells. Intriguingly, adiponectin has both pro- and anti-inflammatory effects, depending on the nature of the inciting stimulus (17). For example, adiponectin reduces TNF-α-induced NF-κB activation in endothelial cells (60) and decreases LPS-induced TNF-α production in macrophages (106). Adiponectin has also been shown to increase expression of certain anti-inflammatory moieties, including IL-10 and the endogenous IL-1 receptor antagonist (98). In contrast, adiponectin causes a dose-dependent increase in IL-6 release from synovial fibroblasts and macrophages (16, 91). Adiponectin receptors are expressed on airway epithelial cells, and adiponectin induces IL-8 release in these cells (54). Hence, the precise role of adiponectin may depend on the nature of the stimulus and the target cells affected.

To examine a possible role for adiponectin in the relationship between obesity and asthma, we implanted mini-Alzet pumps subcutaneously in lean OVA-sensitized mice. The pumps provided a continuous infusion of full-length murine recombinant adiponectin that resulted in an ~50% increase in adiponectin vs. mice implanted with pumps delivering buffer. When the mice were subsequently challenged with aerosolized OVA, there were increases in airway responsiveness, in BAL eosinophils, and in BAL and lung Th2 cytokines in the buffer-treated mice, but these changes were either markedly attenuated or completely absent in mice treated with adiponectin (81). Recent data from others support our findings: OVA sensitization and challenge result in greater eosinophilia in adiponectin deficient vs. wild-type mice (53).

We have also reported declines in the mRNA expression of the three currently identified adiponectin binding proteins, adiponectin receptor 1 (adipoR1), adiponectin receptor 2 (adipoR2), and T-cadherin (31, 100), in lungs of OVA-challenged mice (81), indicating that the allergic airway may also be adiponectin resistant. Decreased expression of adipoR1 and adipoR2 and declines in adiponectin-induced AMP kinase activation are also observed in skeletal muscle and adipose tissue of obese mice (37, 103), indicating that adiponectin resistance also characterizes the obese state. Thus, especially when obesity-related declines in serum adiponectin are considered, the obese asthmatic subject is likely to have substantial defects in this important immunomodulatory pathway that promote allergic airway responses, including AHR (Fig. 2). Nevertheless, adiponectin therapy for asthma seems an unlikely therapeutic option. The concentration of adiponectin in the blood is very high, even in the obese, and adiponectin is a large and complex molecule with multiple oligomers. However, it is conceivable that agonists for the receptors that mediate the beneficial effects of adiponectin described above could be developed. It is also important to note that thiazolidinediones, currently used as therapeutics in Type 2 diabetes, act in part by increasing circulating adiponectin levels (62) and may ultimately prove useful in the treatment in the obese asthmatic subject.

CONCLUSIONS

Obesity is an important risk factor for asthma, but the mechanistic basis for this relationship remains to be established. The adipose tissue of obese individuals is infiltrated with activated macrophages that interact with adipocytes to promote a state of systemic inflammation. Changes in many adipose-derived inflammatory moieties, including TNF-α, leptin, and adiponectin, have the capacity to promote AHR and may thus contribute to asthma in the obese.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the author.

REFERENCES


