

Obesity, smooth muscle, and airway hyperresponsiveness

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Both asthma and obesity are large and growing public health issues. Mounting evidence now implicates obesity as a major risk factor for asthma, thus linking these 2 major epidemics. Moreover, both in human subjects and in mice, obesity appears to predispose toward airway hyperresponsiveness. This review describes potential mechanisms whereby obesity might modify airway smooth muscle function to explain these observations. These mechanisms include both static and dynamic mechanical factors attributable to decreases in functional residual capacity and decreases in tidal volume that are observed in the obese. They include also obesity-related changes in lung development, chronic systemic inflammation (including increased serum levels of inflammatory cytokines and chemokines), and adipocyte-derived factors, including leptin, adiponectin, and plasminogen activator inhibitor. (*J Allergy Clin Immunol* 2005;115:925-7.)

Key words: *Leptin, adiponectin, plasminogen activator inhibitor, inflammation, TNF*

Obesity is an important public health problem. More than 50% of the adult US population is currently obese or overweight. Children are also increasingly affected: the prevalence of obesity in children has more than doubled in the last 20 years, and the epidemic shows no sign of abating. Obesity is a known risk factor for type II diabetes, hypertension, atherosclerosis, and some forms of cancer. Mounting evidence now also points to obesity as a risk factor for asthma. Asthma prevalence is increased in obese subjects (as reviewed by Weiss and Shore¹), and obesity appears to be particularly important for severe asthma because obese or overweight subjects account for 75% of emergency department visits for asthma.² Longitudinal studies indicate that obesity antedates asthma and that the relative risk of incident asthma increases with increasing obesity.^{3,4} Furthermore, morbidly obese asthmatic subjects studied after weight loss demonstrate decreased

Abbreviations used

AHR: Airway hyperresponsiveness
BMI: Body mass index
OVA: Ovalbumin
PAI-1: Plasminogen activator inhibitor

severity and symptoms of asthma.⁵ Thus rather than asthma predisposing toward obesity, obesity appears to either cause or worsen asthma.

Obesity appears to be a risk factor for airway hyperresponsiveness (AHR), as well as for asthma. For example, Litonjua et al⁶ reported an association between increased body mass index (BMI) and onset of AHR in a longitudinal study of aging in male subjects in the United States. Two other large cross-sectional studies confirm these observations.^{7,8} Although this association between BMI and AHR has not been universally observed in epidemiologic studies, it is noteworthy that obese mice also demonstrate innate AHR.⁹

Because airway smooth muscle is the key end effector of acute airway narrowing, it is logical to ask how obesity might influence airway smooth muscle function and airway responsiveness. There are many possibilities, but they are not mutually exclusive, and the dominant mechanism among them is yet to be singled out (Fig 1). The first of these possibilities rests on simple mechanical considerations, where both static and dynamic factors come into play. Concerning static factors, increased abdominal and chest wall mass in the obese causes lower than normal functional residual capacity.¹⁰ Because lung volume is a major determinant of airway diameter,¹¹ it is therefore likely that obesity-related changes in functional residual capacity unload the airway smooth muscle and thereby allow it to shorten excessively when activated. Concerning dynamic factors, the tidal action of spontaneous breathing imposes tidal strains on airway smooth muscle, and these tidal strains happen to be the most potent of all known bronchodilating agencies.^{12,13} The obese individual breathes at higher frequencies but substantially smaller tidal volume compared with the lean individual,¹⁴ and as a result, this potent bronchodilating mechanism is compromised and predisposes toward increased airway responsiveness compared with the lean individual. Although such mechanical considerations are likely to play

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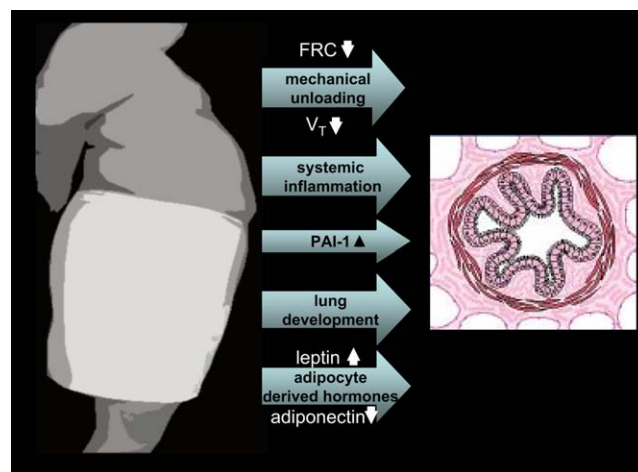


FIG 1. Obesity has the potential to affect airway function through a variety of agencies, including mechanical, inflammatory, humoral, enzymatic, and developmental. FRC, Functional residual capacity.

a role in the relationship between obesity and asthma, additional factors must also be involved because airway responsiveness is increased in obese compared with lean mice, even when the mechanical load is removed by opening the chest wall and the tidal volume is fixed by means of artificial ventilation.⁹

A second possible explanation for the influence of obesity on airway smooth muscle function concerns differences in the anatomy of the lungs and airways. For example, in children the mechanical load of obesity might affect lung growth, leading to reduced pulmonary function, a known risk factor for asthma. Indeed, leptin-deficient mice are morbidly obese very early in their development and have substantially smaller lungs than lean wild-type mice.⁹ Obesity might also lead to more accelerated airway remodeling with each asthma exacerbation. The observation that in obese asthmatic subjects weight loss results in improved pulmonary function but unaltered airway responsiveness⁵ is consistent with a role for obesity in airway remodeling, which is often not reversible.

A third possible influence of obesity on airway smooth muscle function involves the inflammatory microenvironment. In obese individuals, even in the absence of an overt inflammatory insult, there is chronic, low-grade systemic inflammation characterized by increased circulating leukocytes and increased serum concentrations of cytokines, cytokine receptors, chemokines, and acute-phase proteins.¹⁵⁻¹⁷ The origin of this inflammation appears to be, at least in part, the adipose tissue itself. Importantly, systemic inflammatory markers correlate with the presence of diseases common to obesity, including type II diabetes and atherosclerosis.¹⁶ With respect to airway smooth muscle, obesity-related increases in serum TNF- α ¹⁶ are particularly interesting: TNF receptors are expressed on airway smooth muscle, and exogenous TNF- α has been shown to increase *in vitro* contractility of mouse airways to a variety of contractile agonists.¹⁸

In both human and murine obesity, there are also changes in the serum concentrations of hormones and other factors derived from adipose tissue that could affect airway function, leading to AHR. These include leptin, adiponectin, and plasminogen activator inhibitor (PAI-1).^{15,17}

The hormone leptin acts in the hypothalamus to induce satiety and increase metabolism. Nevertheless, serum leptin concentrations are markedly increased in the obese,¹⁵ suggesting leptin resistance in obesity, similar perhaps to the insulin resistance observed in type II diabetes. In addition to its effects on the regulation of body weight, leptin is also proinflammatory.¹⁹ Hematopoietic cells express leptin receptors, and monocytes and macrophages respond to leptin with increased LPS-stimulated production of cytokines. CD4⁺ T cells exposed to leptin also demonstrate increased proliferative responses to T-cell mitogens. Coupled with the increased serum leptin observed in obesity, the proinflammatory effects of leptin suggest that this hormone might be relevant to asthma. In this context it is interesting to note that even after controlling for BMI, leptin is increased in the serum of male asthmatic compared with nonasthmatic children.²⁰ We did not observe AHR in lean mice in which we induced an approximate 2-fold increase in serum leptin levels by means of constant infusion through a subcutaneously implanted micro-osmotic pump, although the lack of effect could be related to the dose of leptin we used.²¹ Nevertheless, this dose of leptin was sufficient to increase airway responsiveness induced by ovalbumin (OVA) aerosol challenge in OVA-sensitized mice.²¹ The increase in OVA-induced airway responsiveness occurred in the absence of any effects of leptin on inflammatory cell influx or T_H2 cytokine expression but was associated with an increase in OVA-induced IgE production in the leptin-treated mice. Thus it is possible that the ability of leptin to augment OVA-induced AHR is the result of increased activation of mast cells.

Adiponectin is the most abundant gene product of adipose tissue. In contrast to many of the other adipokines, plasma adiponectin levels are decreased in obesity, and levels increase after weight loss.^{15,17} There is reason to believe that the decreased serum concentrations of adiponectin observed in the obese might contribute to the propensity toward AHR in this population. Although the primary effects of adiponectin are on metabolism, adiponectin also has anti-inflammatory properties. For example, in endothelial cells adiponectin reduces TNF- α -induced nuclear factor κ B signaling and reduces the subsequent expression of the adhesion molecules intercellular adhesion molecule, vascular cell adhesion molecule, and E-selectin.²² Importantly, adiponectin inhibits proliferation and migration of cultured vascular smooth muscle cells induced by mitogens.²² We do not know whether adiponectin has similar effects on airway smooth muscle, but increased smooth muscle mass is a prominent feature of asthma, and both the AdipoR1 and AdipoR2 receptors are expressed in cultured human airway smooth muscle cells (unpublished observations).

PAI-1 is the most important endogenous inhibitor of tissue plasminogen activator and uroplasminogen activator and is thus the major physiologic inhibitor both of fibrinolysis and of plasmin activation. Adipocytes produce and secrete PAI-1, and serum levels of PAI-1 are increased in the obese and decrease with weight loss.¹⁷ Increased serum PAI-1 levels, through effects on extracellular matrix turnover, could have effects in the airways that predispose toward hyperresponsiveness. Indeed, PAI-1 is induced in the lungs after LPS aerosol exposure and appears to be required for the airway remodeling and AHR that is induced by LPS in mice.²³ PAI-1 is also required for the increased collagen and fibrin deposition that occurs in the airways after allergen sensitization and chronic challenge.²⁴

In summary, the incidence of asthma is increased in the obese. The importance of understanding this relationship is underscored by the extremely high prevalence of obesity in inner-city children, who are at the greatest risk of asthma,²⁵ and by observations indicating that obesity is a strong predictor of the persistence of childhood asthma into adolescence.⁴ Potential mechanisms include obesity-related changes in lung volumes, systemic inflammation, and other adipocyte-derived factors that might alter airway smooth muscle function in such a way as to promote airway narrowing.

REFERENCES

- Weiss ST, Shore S. Obesity and asthma: directions for research. *Am J Respir Crit Care Med* 2004;169:963-8.
- Thomson CC, Clark S, Camargo CA Jr. Body mass index and asthma severity among adults presenting to the emergency department. *Chest* 2003;124:795-802.
- Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159:2582-8.
- Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at onset of puberty. *Am J Respir Crit Care Med* 2004;170:78-85.
- Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest* 2004;125:2046-52.
- Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study. *Thorax* 2002;57:581-5.
- Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. *European Community Respiratory Health Survey*. *Thorax* 2002;57:1028-33.
- Celedon JC, Palmer LJ, Litonjua AA, Weiss ST, Wang B, Fang Z, et al. Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. *Am J Respir Crit Care Med* 2001;164:1835-40.
- Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. *J Appl Physiol* 2003;95:938-45.
- Yap JC, Watson RA, Gilbey S, Pride NB. Effects of posture on respiratory mechanics in obesity. *J Appl Physiol* 1995;79:1199-205.
- Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol* 1987;62:1324-30.
- Fredberg JJ. Frozen objects: small airways, big breaths, and asthma. *J Allergy Clin Immunol* 2000;106:615-24.
- Gump A, Haughey L, Fredberg J. Relaxation of activated airway smooth muscle: relative potency of isoproterenol vs. tidal stretch. *J Appl Physiol* 2001;90:2306-10.
- Sampson MG, Grassino AE. Load compensation in obese patients during quiet tidal breathing. *J Appl Physiol* 1983;55:1269-76.
- Rajala MW, Scherer PE. Minireview: the adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology* 2003;144:3765-73.
- Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* 2003;27(suppl 3):S53-5.
- Nawrocki AR, Scherer PE. The delicate balance between fat and muscle: adipokines in metabolic disease and musculoskeletal inflammation. *Curr Opin Pharmacol* 2004;4:281-9.
- Chen H, Tliba O, Van Besien CR, Panettieri RA Jr, Amrani Y. TNF- α modulates murine tracheal rings responsiveness to G-protein-coupled receptor agonists and KCl. *J Appl Physiol* 2003;95:864-73.
- Huang L, Li C. Leptin: a multifunctional hormone. *Cell Res* 2000;10:81-92.
- Guler N, Kircerler E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: Does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004;114:254-9.
- Shore SA, Schwartzman IM, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. *J Allergy Clin Immunol* 2005;115:103-9.
- Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 2003;14:561-6.
- Savov JD, Brass DM, Berman KG, McElvania E, Schwartz DA. Fibrinolysis in LPS-induced chronic airway disease. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L940-8.
- Oh CK, Ariue B, Alban RF, Shaw B, Cho SH. PAI-1 promotes extracellular matrix deposition in the airways of a murine asthma model. *Biochem Biophys Res Commun* 2002;294:1155-60.
- Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr* 1998;132:699-703.