Humoral control of airway tone

The pathways involved in the control of airway tone in man are complex (figure). Airway smooth muscle can be activated by hormones and vasoactive peptides reaching the lungs from the bloodstream, by neurotransmitters released from nerve endings, and by molecules released locally from other cells within the airways. The physical properties and the chemical and biological content of inspired air can also influence airway function. The degree of airway narrowing or relaxation produced by these stimuli depends on the amount, contractility and length-tension relationship of the smooth muscle, the loads opposing shortening produced by surrounding structures, and by the thickness of the airway wall.[1]

In this editorial we will concentrate on one component of these control mechanisms by considering the role of certain of the circulating humoral factors in the regulation of airway tone in normal subjects and asthmatic patients (table). The potentially important actions of these substances on other functions of the airways not related directly to the control of airway tone will not be considered.

Vasoactive peptides

CATECHOLAMINES

Circulating adrenaline is released from the adrenal medulla into the circulation and may reduce bronchial smooth muscle tone directly by stimulating β_2 adrenergic receptors on airway smooth muscle or indirectly by reducing acetylcholine release from cholinergic nerves.[2] The lack of a bronchoconstrictor effect of β antagonists in normal subjects suggests that, in this group, basal concentrations of circulating adrenaline are probably not important in the regulation of resting bronchomotor tone. In contrast, β antagonists cause bronchoconstriction in some asthmatic patients which, in the absence of an important sympathetic nerve supply to airway smooth muscle, suggests a role for basal concentrations of circulating adrenaline in the maintenance of airway tone in asthma, perhaps particularly in those patients in whom resting airway calibre is already reduced.[1]

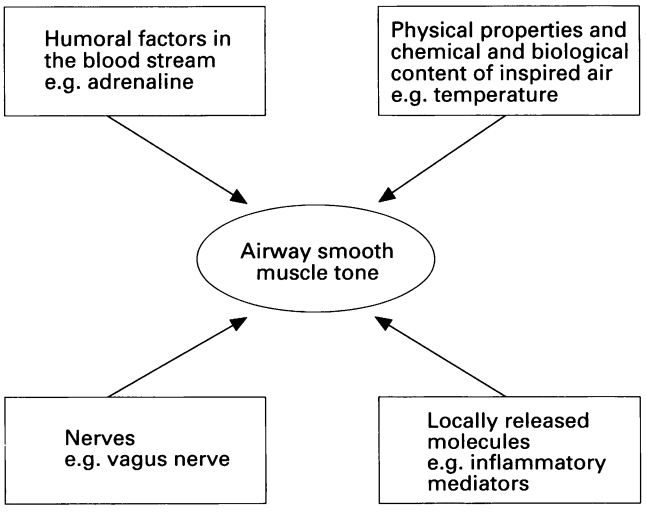
Basal adrenaline concentrations and the circadian variation in adrenaline concentrations in asthmatic patients has been reported in most studies to be similar to those found in normal subjects.[3–5] In a recent study Bates *et al*[6] found that plasma adrenaline levels at 22.00 hours were lower in patients with nocturnal asthma than in those without nocturnal asthma. However, correction of the nocturnal fall in plasma adrenaline does not alter the peak flow rate of patients with nocturnal asthma.[7] These findings, together with the report of nocturnal asthma occurring in a patient after adrenalectomy,[8] suggest that a fall in plasma adrenaline levels at night is not the dominant factor in nocturnal asthma.

Adrenaline is not released in response to allergen-induced or pharmacologically-induced bronchoconstriction per se and so does not appear to have an important homeostatic role in the regulation of airway calibre during bronchoconstriction to these stimuli.[9,10] Even during acute exacerbations of asthma there may be no increase in plasma adrenaline levels,[11] although very high adrenaline concentrations have been found in some patients with acute severe asthma.[12] The increased adrenaline concentrations achieved after strenuous exercises[13] can cause bronchodilation in both normal and asthmatic subjects[3,5,14] and may act to counteract bronchospasm induced by exercise in asthma.[15] Although a blunted catecholamine response to exercise in asthmatic patients has been reported by some investigators,[16] other studies have found no significant difference in either the peak plasma catecholamine level between normal and asthmatic subjects or in the response to increasing levels of exercise.[13,17]

Noradrenaline, which has β_1 and weak β_2 adrenergic activity in addition to α adrenergic effects, acts as a neurotransmitter in the sympathetic nervous system but overspills into the circulation. The infusion of noradrenaline, which produces circulating concentrations within the physiological and pathophysiological range, has no effect on airway calibre in either normal or asthmatic subjects.[3,5] The third catecholamine present in the blood, dopamine, also has no influence on bronchomotor tone in man.[18]

NATRIURETIC PEPTIDES

In 1981 de Bold and colleagues demonstrated that the injection of atrial, but not ventricular, extract into rats caused a natriuresis and diuresis.[19] It is now known that this extract contained a peptide, atrial natriuretic peptide (ANP), which is one of a family of hormones known to have an important role in salt and water homeostasis.[20] Other human natriuretic peptides include brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and urodilatin. Most natriuretic peptides are produced primarily in the heart, but are also released in other tissues



Factors influencing airway smooth muscle tone.

Circulating humoral factors and airway tone

Vasoactive peptides:
- Catecholamines: adrenaline, noradrenaline, dopamine
- Natriuretic peptides
- Angiotensin II
- Endothelins

Hormones
- Cortisol
- Thyroxine
- Progesterone
- Oestrogen

Inflammatory mediators
- Leukotrienes
- Prostenoids
- Histamine

including the kidneys, lungs, and central nervous system. Circulating ANP has effects on the kidney causing natriuresis and diuresis, and on vascular tissue causing vasodilatation. The actions of ANP also include inhibition of the release or action of several hormones including aldosterone, angiotensin II, and endothelin.[20]

Specific ANP receptors have been localised to the lung, including the airway smooth muscle,[21] of which some may be the ANP_C or clearance subtype,[32] although the receptor subtype(s) in human airway smooth muscle is unknown. In isolated human airway tissue ANP has a direct relaxant effect and confers protection against agonist-induced contraction.[23,24] Two principal mechanisms have been proposed for the inactivation of ANP: degradation by the enzyme neutral endopeptidase (NEP) and binding to a non-guanylyl cyclase clearance receptor (ANP_C receptor). NEP has been localised to the lung and it appears to be present in high concentrations in airway epithelium,[25] although it is also found in submucosal glands, airway smooth muscle, and nerves. NEP is widely distributed within the airways and plays a part in modulating the effect of ANP on airway smooth muscle.[23,24] Recent studies have suggested that an intravenous infusion of exogenous ANP has important actions on airway function including bronchodilatation and the modification of bronchial reactivity to inhaled histamine and to fog challenge.[26–31] The rise in plasma ANP levels during exercise[32] is similar to that obtained during the lowest rates of ANP infusion, and these results suggest that these elevations may lead to an attenuation of bronchospasm. Increased plasma ANP levels are found in patients with cardiac failure[33] and cor pulmonale,[34] and under these circumstances ANP may also play a protective role on the airways. Circulating ANP at physiological concentrations, however, appears unlikely to have any influence on bronchomotor tone in normal subjects.[28]

RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system is primarily involved in fluid and electrolyte homeostasis but is also activated in acute severe asthma[35] and during exercise.[36,37] Angiotensin II is formed from angiotensinogen by the action of renin on the angiotensin-converting enzyme (ACE), 60–80% of which occurs within the pulmonary vascular endothelium.[38] Alternative formation of angiotensin II occurs directly from angiotensinogen through cleavage by several proteases.[39]

Angiotensin II causes minor bronchoconstriction in isolated human and bovine bronchial rings but, interestingly, potentiates the effects of methacholine and endothelin-1 in vitro.[40,41] This effect may be prejunctional,[42] it may occur via the release of spasmogens, or it may be due to an interaction at the second messenger level intracellularly. Angiotensin II at subthreshold concentrations potentiates methacholine-induced bronchoconstriction in vivo in mild asthmatics,[41] suggesting a role for angiotensin II as a putative mediator in asthma, but its effect on other spasmogens may be variable. The effect of physiological concentrations of angiotensin II on basal bronchial tone of normal individuals is not known, whereas infusion of angiotensin II in mild asthmatics to plasma levels found in acute asthma causes bronchoconstriction.[35]

Exercise activates the renin-angiotensin system with increased levels of plasma renin, angiotensin II, and aldosterone,[36] and the addition of coexistent hypoxia causes a further rise in renin and angiotensin II which does not appear to be due to suppressed ACE activity.[37] These changes also occur during exercise in hypoxaemic patients with chronic airways obstruction.[43] These findings raise the possibility that increased angiotensin II levels during exercise could contribute to exercise-induced bronchospasm.

The renin-angiotensin system is activated in acute severe asthma but not in stable chronic asthma.[35] The mechanism of activation is unclear but nebulised and intravenous β_2 agonists cause an increase in the levels of renin and angiotensin II in mild asthmatics, more so following nebulisation, through an ACE dependent pathway.[44,45] This may occur via stimulation of β adrenoceptors on juxtaglomerular cells, but the levels of angiotensin II seen in acute severe asthma are higher, suggesting the existence of an alternative pathway of angiotensin II formation, possibly via inflammatory protease[39] or circulating catecholamines. The existence of a local renin-angiotensin system in the lung, as in other tissues,[46] is a possibility as renin secretion has been found from pulmonary tumours,[47] renin mRNA has been isolated from rat lung,[48] and AT_1 receptors have been identified in fetal rat lung.[49]

ENDOTHELINS

The human endothelin family comprises three structurally and pharmacologically distinct 21 amino acid peptides termed endothelin-1, endothelin-2, and endothelin-3. Endothelin-1 is produced by vascular endothelial cells and is present in the plasma of normal individuals. During acute severe asthma raised endothelin levels have been found in bronchoalveolar lavage samples.[50] It is one of the most potent bronchoconstrictor peptides yet isolated, producing prolonged and potent contractions in animal airways in vivo by both intravenous[51] and aerosol administration,[52] as well as in vitro.[53,54] Endothelin receptors have been found in human airway smooth muscle and are predominantly of the endothelin-B subtype.[55] The recent availability of endothelin-receptor antagonists should help to establish whether circulating and/or locally released endothelins have an important influence on the function of airway smooth muscle.

Hormones

CORTISOL

Pharmacological doses of intravenous cortisol have no short term effect on airway calibre in normal subjects.[56] Although glucocorticoids can potentiate the response to catecholamines in isolated bronchial tissue, this effect occurs only at supraphysiological concentrations.[57,58] These results suggest that endogenous cortisol is unlikely to have an important action on airway tone in normal individuals. In asthma the role of physiological concentrations of circulating cortisol in airway function is uncertain. In nocturnal asthma the nadir in the circadian variation in plasma cortisol occurs four hours before maximal bronchoconstriction,[59,60] although the delayed action of cortisol means that it could still have an influence on airway calibre. Kallenbach *et al*[61] found a reduced nadir of plasma cortisol levels in patients with nocturnal asthma compared with a group without nocturnal asthma, but this finding may have been influenced by previous corticosteroid therapy. Other studies have found no direct association between plasma cortisol concentrations and nocturnal asthma.[5] Furthermore, the infusion of physiological concentrations of hydrocortisone which eliminates the fall in plasma cortisol at night does not prevent the nocturnal fall in peak flow rate in most asthmatic patients,[60] suggesting that the circulating cortisol level is not the only factor in determining nocturnal asthma.

THYROID HORMONES

The relationship between asthma and thyroid disease provides indirect evidence for a role for thyroid hormones in

maintaining airway function. The development of hyperthyroidism can be associated with a deterioration in asthma control, with subsequent improvement in symptoms following appropriate treatment.[62-64] Conversely, the occurrence of hypothyroidism has been reported to be associated with improvement in asthma control, which relapses following subsequent thyroxine replacement.[65]

Several possible mechanisms have been suggested by which thyroid hormones could influence airway smooth muscle tone and responsiveness. Firstly, β adrenergic airway responsiveness may be downregulated as responsiveness is reported to be inversely related to thyroxine levels both in vitro in guinea pig tracheal specimens[66] and in vivo in non-asthmatic subjects.[67] Following treatment of hyperthyroidism or hypothyroidism, airway β adrenergic responses return to euthyroid levels.[67] It is unlikely that alterations in β adrenergic activity are due to changes in circulating catecholamine levels[68] or β adrenergic receptor numbers,[69] but it is possible that thyroxine acts at a post-receptor site within the smooth muscle. Secondly, Cockroft *et al*[70] reported a decrease in non-specific bronchial reactivity in an asthmatic patient after treatment of hyperthyroidism. Studies examining the effects of different circulating thyroid hormone levels on non-specific reactivity in non-asthmatic individuals have, however, produced conflicting results.[71-75] Thirdly, the metabolism of arachidonic acid is altered in vitro by the lungs of rats made hyperthyroid.[76] In particular, there is a reduction in the breakdown of the prostaglandins PGE_2 and $PGF_{2\alpha}$. The effects of increased thyroxine levels in man may result in alterations in the actions of prostaglandins on the airways. The involvement of thyroid hormones in lung function, however, may be unrelated to a direct effect on the airways. Respiratory muscle weakness, which may occur in hyperthyroidism,[72] could contribute to the dyspnoea that commonly accompanies thyrotoxicosis, and this action may heighten the degree of breathlessness experienced by a patient with pre-existing airways disease.

SEX HORMONES

Progesterone has an important role in reducing the contractility of uterine smooth muscle during pregnancy, and this effect may be due to its influence on gap junction formation between smooth muscle cells. It has been suggested that progesterone might cause similar effects on bronchial smooth muscle. Progesterone could influence airway smooth muscle tone by other mechanisms – indirectly by potentiating the effect of catecholamines[58] or through its immunosuppressive properties. Progesterone levels and airways responsiveness do not show a clear relationship during either pregnancy or the menstrual cycle, although changes in the levels of other hormones may obscure an effect of progesterone on the airways.[77 78] It is of interest that intramuscular progesterone has a beneficial effect in some women with severe premenstrual asthma.[79]

Oestrogen possesses both immunostimulatory and immunosuppressive properties and causes increased acetylcholine activity in the lungs of animals.[80] These actions could indirectly result in an increase or decrease in airway tone. A recent preliminary report suggested that oestrogen treatment may have steroid-sparing effects in postmenopausal asthmatic women[81] although, conversely, hormone replacement therapy has been associated with an increased risk of developing asthma.[92]

Circulating inflammatory mediators

Inflammatory mediators including histamine, cysteinyl leukotrienes, and thromboxane metabolites have been detected in the plasma and/or urine during acute asthma attacks.[83 84] It remains unclear, however, whether these circulating mediators have any influence on airway tone. Although both leukotriene and H_1-receptor antagonists cause mild bronchodilatation,[83 84] it seems likely that this effect is due mainly to the inhibition of locally produced mediators within the lungs rather than those reaching the airways from the systemic circulation.

Conclusions

The influence of certain circulating hormones and vasoactive peptides such as adrenaline and atrial natriuretic peptide on airway tone in man has become clearer over the last 10 years. Humoral factors appear to play a minor part in the physiological regulation of airway tone in normal individuals. Circulating adrenaline is the only hormone known to influence bronchomotor tone, and it is only during strenous exercise that concentrations are raised sufficiently to cause bronchodilation.

Circulating hormones play a more important part in the regulation of airway tone in diseased states of the airways such as asthma and, possibly, in other disorders such as cor pulmonale, congestive cardiac failure, respiratory failure, and thyroid diseases. Circulating adrenaline has a role in the maintenance of resting airway tone in asthma, perhaps particularly in those patients in whom resting airway calibre is already reduced. The increased concentrations of adrenaline and atrial natriuretic peptide achieved after vigorous exercise may act to counteract exercise-induced asthma. Although angiotensin II at subthreshold concentrations potentiates methacholine-induced bronchoconstrinction in vivo and at higher circulating levels causes bronchoconstriction, it has not been established in asthma whether the increased angiotensin II levels achieved during exercise or, more particularly, in acute severe asthma contribute to the bronchospasm.

For many hormones, however, little or nothing is known about their effects on airway tone or on other functions of the airways not directly related to the control of airway calibre.

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