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Airway Reactivity in Humans

Anesthetic Implications

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CONTENTS

BRONCHOSPASTIC DISEASES, a heterogeneous yet widespread group of disorders, have one essential component in common—airway hyperreactivity to physical, chemical, and pharmacologic stimuli.[1] This nonspecific airway hyperreactivity may be demonstrated with histamine,[2] cholinergic agonists,[2] prostaglandin $F_{2\alpha}$,[3] irritant gases,[4] chemically inert dusts,[4] and cold air.[5] Individuals with asthma or other bronchospastic disorders have persistent airway hyperreactivity which can result in intense bronchospasm during anesthesia. Many factors modify airway reactivity in humans. The older literature about the anatomy and regulation of tracheobronchial smooth muscle has been reviewed by Macklin[6] and Widdicombe,[7,8] and the regulation of bronchomotor tone during anesthesia by Aviado.[9] This review attempts to bring together recent information on reactivity of the airway of humans and the applicability of this information for the practicing anesthesiologist.

Neurohumoral Control

An imbalance in the neural control of airways has been suggested as a factor modifying airway reactivity.[8] Increased activity in those parts of the nervous system promoting airway constriction (parasympathetic and alpha-adrenergic systems) or decreased activity in those parts of the system promoting dilatation of the airway (beta$_2$-adrenergic and nonadrenergic inhibitory systems) (fig. 1) could lead to increases in airway tone and reactivity.

PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system promotes constriction of airway smooth muscle and appears to mediate the rapid reflex changes in airway caliber initiated by the presence of endotracheal tubes or other irritating substances[2] in the airway. The involvement of the parasympathetic nervous system in antigen-induced bronchoconstriction is controversial, since the protection afforded by atropine against this challenge has been highly variable in different studies.[10–12]

The parasympathetic innervation of the airways of humans predominates in the larger more central airways. Airway constriction may involve either the central or the peripheral airways.[13,14] Drugs which interrupt the parasympathetic nervous system are more effective when bronchoconstriction occurs in the larger, rather than the smaller airways.[15,16]

Because irritant-induced bronchoconstriction poses the major problem in the anesthetic management of the patient with bronchospastic disease, we must understand the pathway of the parasympathetic irritant reflex and the sites at which it can be interrupted (fig. 2).

Irritant receptors are found just beneath the tight junctions of the epithelial lining of the airway. The afferent connections of these receptors run in the vagus nerve. We know very little about the central pathways of this reflex. Parasympathetic efferent fibers also run in the vagus nerve. Postganglionic parasympathetic efferents stimulate cholinergic receptors located on the smooth muscle of the airway with resultant airway narrowing.

Both the afferent and efferent limbs of this reflex are interrupted by local anesthetics. The efferent limb is

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interrupted by cholinergic antagonists, such as atropine, which block the cholinergic receptors located on airway smooth muscle. Furthermore, systemically administered local anesthetics probably also block central reflex pathways. Both lidocaine[17,18] at nontoxic blood concentrations (1–4 μg/ml) and atropine[10,19] prevent irritant-induced airway constriction.

The major protective effect of potent inhalation anesthetics on airways also involves depression of the irritant-induced bronchoconstrictor reflex, presumably by interruption of central reflex connections. This has been studied for decades, and the ability of potent inhalation anesthetics to block airway reflexes is well-established.[20–24] Ketamine also depresses vagal pathways.[25]

While deep barbiturate anesthesia suppresses airway reflexes,[26] light anesthesia with ultrashort-acting intravenous barbiturates, such as those usually employed in the induction of anesthesia in clinical practice, produces relatively little depression.[27,28] Thiopental, in doses in clinical use, does not reliably protect against the development of irritant-induced airway constriction, such as that provoked by an endotracheal tube. Evidence to indicate that thiopental increases airway resistance and precipitates bronchospasm during clinical anesthesia has not been forthcoming. Methacholine produces parasympathomimetic effects by directly stimulating cholinergic receptors on airway smooth muscle and glands. Neostigmine, a cholinesterase inhibitor, also can provoke airway constriction.

Sympathetic Nervous System

The sympathetic nervous system is poorly represented in the lung by direct innervation, and norepinephrine, the major catecholamine released by nerve terminals, has relatively little $beta_2$ activity. The sympathetic nervous system appears to have marked influence by way of circulating epinephrine. Two types of adrenergic receptors are described in airway smooth muscle: alpha and $beta_2$ receptors.[29] Stimulation of alpha receptors constrict airway smooth muscle, while stimulation of $beta_2$ receptors relaxes it.

Alpha Adrenergic Input

Studies support the existence of alpha receptors in the airways of humans,[30] and, although alpha-receptor stimulation results in only mild bronchoconstriction, it may contribute to airway hyperreactivity. Henderson and co-workers[31] recently have demonstrated enhanced alpha-adrenergic responses in patients with allergic asthma when compared with responses in normal patients and patients with allergic rhinitis.

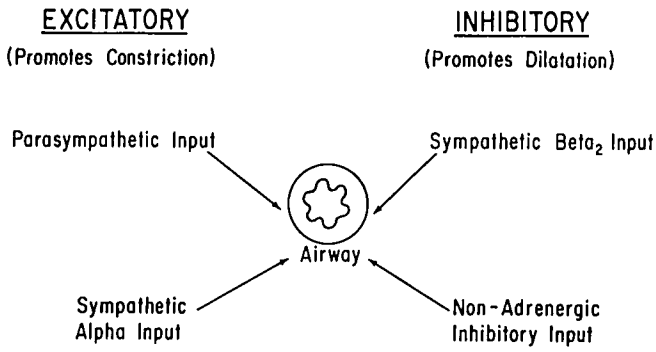

FIG. 1. Neurohumoral control defect.

$Beta_2$ Adrenergic Input

Beta-adrenergic agonists activate beta receptors, which activate adenyl cyclase to increase the intracellular concentration of 3′5′ cyclic adenosine monophosphate (cAMP), which in turn is degraded by the enzyme phosphodiesterase (PDE) (fig. 3). The intracellular concentration of cAMP is thought to regulate release of mediators in basophils and mast cells and to control tone in airway smooth muscle. A decrease in the intracellular concentration of cAMP leads to increased mediator release[32] and increased tone in airway smooth muscle.[33]

Szentivanyi's hypothesis[34] states that inherited or acquired beta-adrenergic blockade causes bronchial hyperreactivity in asthma. Clinical studies show that asthmatic patients indeed have decreased responsiveness of beta-adrenergic receptors to appropriate agonists in a number of organs and cells[34–37] and may exhibit tachyphylaxis or no response to $beta_2$ agonists during anesthesia. The reported induction of bronchospasm in asthmatic patients by beta-adrenergic blocking drugs[38] lends further support to the Szentivanyi hypothesis.

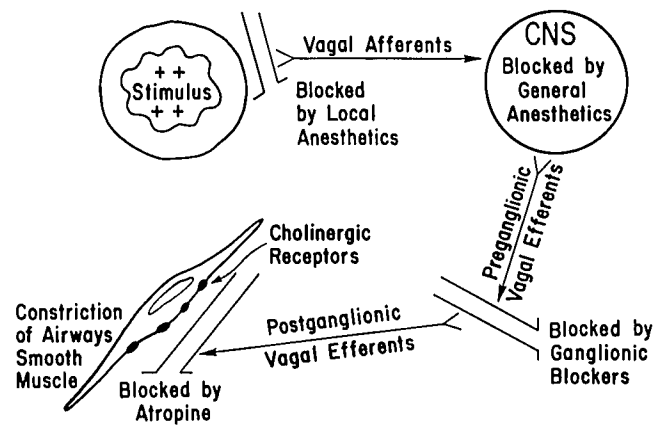

FIG. 2. Pathway of the parasympathetic irritant reflex. This reflex can be interrupted at multiple sites by specific compounds.

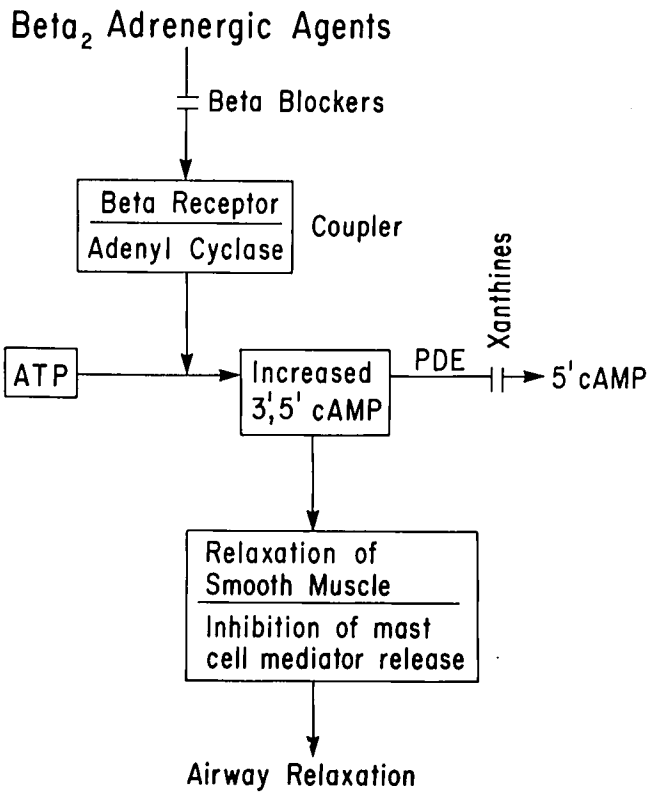

FIG. 3. Cyclic AMP pathways involved in bronchodilator action.

An objection to this theory arose when several investigators[39-41] noted that mononuclear leukocytes from both asthmatic and nonasthmatic patients, who were given beta-adrenergic drugs, had a depressed cAMP response to isoproterenol. This suggests that the apparent state of "beta-adrenergic blockade" was, in fact, drug-induced by prior exposure to beta-adrenergic agonists. However, atopic patients[42] and asthmatic dogs,[43,44] who have never received beta-adrenergic drugs, still have a depressed cAMP response to isoproterenol. Auto-antibodies to beta$_2$-adrenergic receptors have been identified in the serum of some patients with asthma, and could possibly explain some instances of defective beta-adrenergic response.[45,46]

Thus, substantial evidence supports the existence of a defect in the beta-adrenergic mechanism in cells of asthmatic patients, but its site remains to be identified. Because the beta-receptor-adenyl-cyclase system is composed of a receptor, a coupler, and a catalyst, a defect could occur at any of these sites, as well as in the systems responsible for the destruction of the cAMP.

The well-recognized sympathomimetic effects of ketamine have been attributed to baroreceptor desensitization,[47] central sympathetic stimulation,[48] and potentiation of endogenously released catecholamines, by inhibition of neuronal (cocaine-like effect)[49-51] or extraneuronal[52] uptake processes. In a dog model of airway hyperreactivity,[54] ketamine prevents antigen-induced increases in airway resistance more effectively than thiopental.[53] The sympathomimetic properties of ketamine appear to provide this protective effect since it is abolished by beta-adrenergic blockade with propranolol.[53]

Inhalation anesthetics could augment beta$_2$-adrenergic sympathetic responses and protect against the development of airway constriction. However, the contention that halothane causes bronchodilatation by stimulation of beta-adrenergic receptors in the airway[55] has never been substantiated.

Non-Adrenergic Inhibitory System

The autonomic nervous system ordinarily is described as consisting of parasympathetic and sympathetic systems. For some time, however, the smooth muscle of the gastrointestinal tract has been known to be innervated by nerves of another type which, when stimulated, cause smooth muscle relaxation.[56] This nonadrenergic, non-cholinergic inhibitory system reaches the lung by way of the vagus nerve. This system exists in humans and a variety of neurotransmitters have been considered to play a role.[58]

Electrical field stimulation of human airways *in vitro*[57] in the presence of atropine relaxes airway smooth muscle. This relaxation is blocked by the neurotoxin, tetrodotoxin,[59] demonstrating that the response is neurally mediated. However, in isolated bronchioles, the relaxation is not blocked by adrenergic antagonists, indicating an inhibitory system separate from adrenergic innervation. Although a deficiency of this system would explain airway hyperreactivity, further studies are needed to determine the importance, if any, of this system in bronchospastic disease in humans.

Bronchial Mucosal Permeability

The airway is protected by a layer of epithelial cells joined by tight junctions forming a formidable barrier to the passage of molecules. Hogg and co-workers have suggested that an anatomic defect in this barrier may be responsible for the asthmatic state,[60] presumably by allowing greater exposure of nerve endings as well as greater access of antigenic and nonantigenic substances to their sites of action. Airway viral infections[61] and exposure to irritants[62] increase the reactivity of the airways of normal subjects, as well as patients with bronchospastic disease. This is of considerable importance to the anesthesiologist since the hyperreactivity produced by viral illnesses is present for at least 3 weeks[61] following symptomatic recovery. Although epithelial damage increases airway reactivity, the interrelationship between epithelial damage, permeability changes, air-

way reactivity, and asthma remains unclear. No one has yet demonstrated an intrinsic anatomic defect in either humans or in animal models[63] with hyperreactive airways. Anesthetics may alter permeability of the bronchial epithelium, allowing greater or lesser access to subepithelial irritant receptors. However, little is known regarding this mechanism. Ether, but not halothane, increases permeability of the epithelium to tracer substances.[64]

Immunologic Component

The immunologic component of asthma is well-established in some cases[65] (fig. 4). However, although 90% of asthmatic children have an allergic history, this history can be elicited in only 30% to 50% of adult asthmatics.[65] Asthmatic individuals appear to have more allergies than the general population, but the interrelationship between allergy and nonspecific airway hyperreactivity remains an enigma. Allergy and nonspecific airway hyperreactivity are probably two separate and distinct entities in humans.[66] Bronchial responsiveness to antigen depends on both immunologic responsiveness and nonspecific airway hyperreactivity.

Biochemical Mediators

Many experiments have established histamine as a mediator of anaphylaxis; and histamine, acting at H_1 receptors on the surface of airway smooth muscle, elicits bronchoconstriction.[67] Although much has been written regarding histamine as a mediator in asthma, it is probably not the most important mediator in the disease, since antihistamines have been relatively ineffective in the prevention or treatment of bronchospasm.

Many of the drugs used in the clinical practice of anesthesia are associated with increases in histamine concentrations in the peripheral blood. Do drugs, such as curare,[68,69] constrict airways, and if so, will antihistamines prevent this response? It is not established that bronchoconstriction following administration of so-called "histamine releasers" is indeed primarily due to the histamine itself. Similarly, there is no evidence in the literature that bronchoconstriction elicited by these agents is treated effectively by histamine$_1$-receptor antagonists (classical antihistamines).

Histamine$_2$ receptors are thought to be responsible for the inhibitory feedback control of mediator release.[70] Therefore, histamine$_2$-receptor antagonists, like cimetidine, should theoretically worsen histamine-induced airway constriction. One study has shown that histamine$_2$-receptor blockade potentiated histamine$_2$-induced constriction,[71] presumably by this mechanism.

The capacity of the lung to synthesize a wide variety of prostaglandin-like substances has raised the possibility that such agents play a role in hyperreactive airway disease. In the majority of organs that were studied, including the lung, the essential precursor, arachidonic acid, derived from the breakdown of phospholipids in

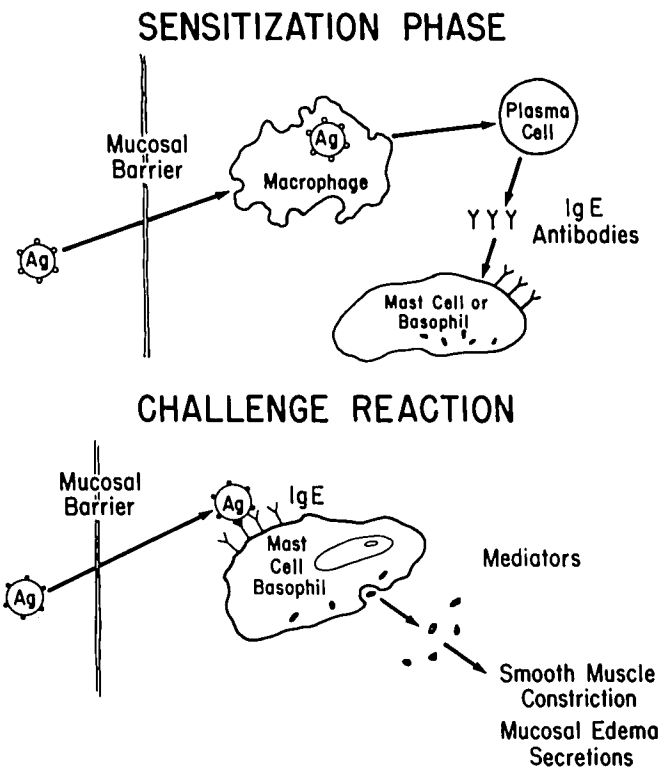

FIG. 4. In the sensitization phase (above) an atopic person is exposed to an antigen, which is able to cross the mucosal barrier of the airway. Phagocytes digest the outer layer of the antigen releasing water-soluble proteins which are absorbed onto plasma cells, which in turn produce specific antibodies. These antibodies attach to the surfaces of mast cells and basophils. In the challenge reaction (below) after a latent period, reexposure to the antigen results in the antigen attaching to the specific antibody on the mast cell and basophil surface. This bridging causes these cells to release mediators of immediate-type hypersensitivity.

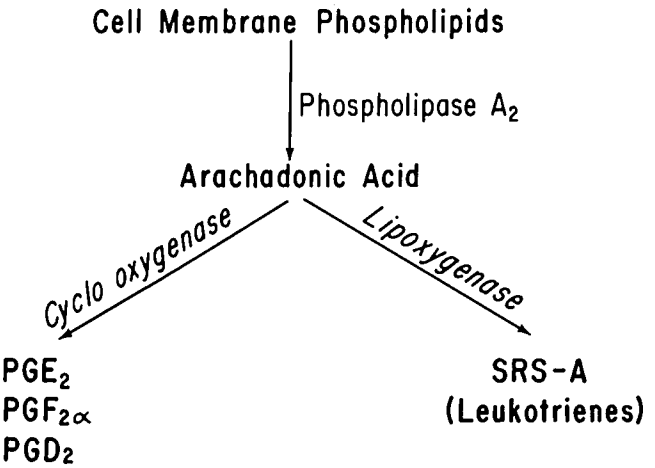

FIG. 5. Pathways for the production of primary prostaglandins and SRS-A.

the cell membrane, is converted along the cyclooxygenase pathway into primary prostaglandins (fig. 5). Prostaglandin $F_{2\alpha}$[3] is a potent bronchoconstrictor. Prostaglandin D_2, an even more potent bronchoconstrictor, recently has been found in humans, and is the principal mediator in systemic mastocytosis[72] (a disorder of unknown origin characterized by abnormal proliferation of tissue mast cells).

Another compound, thought to be important as a potential mediator of allergic bronchoconstriction, is slow reacting substance of anaphylaxis (SRS-A). Minute concentrations of SRS-A cause a characteristic slow contractile response on smooth muscle preparations. Forty years after its original detection, SRS-A has been identified as a mixture of leukotrienes.[73] These are also metabolites of arachidonic acid, but they are derived through a separate pathway, the lipoxygenase pathway (fig. 5), which is present only in certain tissues of the body including the lung, platelets, and white blood cells. We now look forward to the development of assays for these substances and to the synthesis of specific blockers so that the role of these agents in airway responses can be evaluated more critically. If these compounds are important in reactive airway disease, the development of specific antagonists and inhibitors of leukotriene biosynthesis will have an important role in the definitive treatment of reactive airway disease.

Even more relevant to the practice of anesthesia is the documentation of the release of leukotrienes (slow reacting substances) and other bronchoactive substances after nonallergic challenge *in vitro*[74–77] and more recently *in vivo*.[78] In addition to constricting airway smooth muscle, bronchoactive mediators liberated by allergic and perhaps nonallergic airway challenge impair mucociliary transport in the trachea.[79] It is conceivable that anesthetics may stabilize mast cell membranes and prevent mediator release. However, such an effect has only been demonstrated in *in vitro* studies with lidocaine, and the concentrations were 100 times greater than can be achieved safely *in vivo*.[80]

Other Considerations

Local anesthetics[81,82] and ketamine[83,84] directly relax airway smooth muscle, whereas thiopental produces a contractile response in some species.[85] However, the concentrations of drug needed to produce these effects are higher than achieved in blood during anesthesia. On the other hand, potent inhalation anesthetics, such as halothane and isoflurane, do have a small direct relaxant effect on constricted airways in the intact animal in clinically useful concentrations.[20]

Although abnormal contractile behavior of airway smooth muscle may result from mediator release or abnormalities of neurohumoral regulation, an intrinsic defect may exist in the smooth muscle itself. Significant differences in both contraction[86] and relaxation[86,87] have been demonstrated in muscles from antigen-sensitized animals. However, the importance of these changes is difficult to evaluate since these animals lacked nonspecific airway hyperreactivity.[86,87]

Increased free intracellular calcium-ion concentrations might account for many of the abnormalities seen in bronchospastic disease in humans,[88] including heightened smooth muscle contractility, increased mediator release, and increased activity in neural pathways. The nature and regulation of the calcium channels involved in these processes are unknown at present. It is possible that calcium channel antagonists, such as nifedipine and verapamil, which inhibit calcium influx or movements in smooth muscle, mast cells, and nerves might be of use in treating bronchospastic disease in humans.[89–92] Although the therapeutic value of these drugs is unproven, they may be particularly helpful in patients with both reactive airway and cardiovascular disease, who are unable to tolerate beta-adrenergic antagonists.

Exercise-induced asthma actually is misnamed. Bronchospasm precipitated by exercise is a manifestation of nonspecific airway hyperreactivity. Transmucosal heat loss is implicated in the initiation of bronchospasm in patients with asthma; and cold dry air, whether inhaled in exercise or by hyperventilation, is a potent stimulus for bronchoconstriction in asthmatics.[5,93] On this basis, warm humidified gases should benefit asthmatic patients during anesthesia. Anticholinergic drugs are usually ineffective in preventing bronchospasm provoked by exercise, cold air, or mist, whereas cromolyn sodium (an inhibitor of mediator release) attenuates responses to these challenges.[94–98] This again suggests that mediator release plays a role in so-called "irritant responses" in humans.

Summary

Airway hyperreactivity occurs as a consequence of multiple pathologic mechanisms. Although it is not possible to predict with certainty which patients will react during anesthesia with severe airway constriction and by what mechanism, it is possible to characterize certain subgroups of patients.

Bronchospasm in early childhood usually is precipitated by viral infections and exposure to allergens. Edema and inflammation play a greater role in bronchospastic disease in children than in adults, and anti-inflammatory drugs and mediator inhibitors may be more effective treatments.

In later life, allergy plays a lesser role; and nonallergic stimuli become more important as triggers. Nonallergic

stimuli are capable of releasing bronchoactive mediators. This may explain why local anesthetics and cholinergic antagonist drugs seem more effective in preventing airway constriction than at reversing it. Acute airway constriction that has persisted for any length of time responds better to drugs that act directly on airway smooth muscle.

In patients with chronic obstructive pulmonary disease with a bronchospastic component, irritant reflex mechanisms usually predominate; blocking either the afferent or efferent limb of the irritant reflex effectively prevents and treats the bronchospasm. Airway viral infections render normal people hyperreactive for at least three weeks following symptomatic recovery.

Laryngoscopy and endotracheal intubation provides a potent reflex stimulus and, in addition, may provoke the release of bronchoactive mediators. If mediators play a major role in eliciting bronchoconstriction, suppression of airway reflexes by increasing the anesthetic depth may not be effective treatment. We understand the chemical structure and some effects of SRS-A. We look forward to the development of a sensitive assay for detection of this important mediator and further definition of its role in asthma. If SRS-A is important in reactive airway disease, specific antagonists and inhibitors of leukotriene biosynthesis have important therapeutic implications in the treatment of reactive airway disease.

In the anesthetic management of patients with hyperreactive airways, the aim of the anesthesiologist is to prevent the development or reverse the occurrence of airway constriction. Anesthetics may accomplish this by blocking parasympathetic irritant reflexes, by directly relaxing the smooth muscle of the airway, by inhibiting release of mediators, and by augmenting beta$_2$-adrenergic sympathetic responses. An understanding of factors modifying airway reactivity and mechanisms of actions of drugs on airways will lead to safer anesthetic management of the patient with reactive airway disease.

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References

1. Menkes HA: Airway reactivity and the need for a simple test. Am Rev Respir Dis 121:619–620, 1980
2. Boushey HA, Holtzman MJ, Shelley JM, Nadel JA: Bronchial hypperreactivity. Am Rev Respir Dis 121:389–413, 1980
3. Mathe AA, Hedqvist P, Holmgren A, Svanborg N: Bronchial hypperreactivity to prostaglandin $F_{2\alpha}$ and histamine in patients with asthma. Br Med J 1:193–196, 1973
4. Nadel JA, Salem H, Tamplin B, Tokiwa Y: Mechanisms of bronchoconstriction during inhalation of sulfur dioxide. J Appl Physiol 20:164–167, 1965
5. Deal EC, McFadden ER, Ingram RH, Breslin FJ, Jaeger JJ: Airway responsiveness to cold air and hyperpnea in normal subjects and in those with hay fever and asthma. Am Rev Respir Dis 121:621–628, 1980
6. Macklin CC: The musculature of the bronchi and lungs. Physiol Rev 9:1–60, 1929
7. Widdicombe JC: Regulation of tracheobronchial smooth muscle. Physiol Rev 43:1–37, 1963
8. Widdicombe JC, Sterling GM: The autonomic nervous system and breathing. Arch Intern Med 126:311–329, 1970
9. Avido DM: Regulation of bronchomotor tone during anesthesia. ANESTHESIOLOGY 42:68–80, 1975
10. Rosenthal RR, Norman PS, Summer WR, Permutt S: Role of the parasympathetic nervous system in antigen-induced bronchospasm. J Appl Physiol 42:600–606, 1977
11. Fish JE, Rosenthal RR, Summer WR, Menkes H, Norman PS, Permutt S: The effect of atropine on acute antigen-mediated airway constriction in subjects with allergic asthma. Am Rev Respir Dis 115:371–379, 1977
12. Yu DYC, Galant SP, Gold WM. Inhibition of antigen-induced bronchoconstiction by atropine in asthmatic patients. J Appl Physiol 32:823–828, 1972
13. Despas PJ, Leroux M, Macklem PT: Site of airway obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium-oxygen mixture. J Clin Invest 51:3235–3243, 1972
14. Farshter RD, Wilson AF: Relationship between the site of airflow limitation and localization of the bronchodilator response in asthma. Am Rev Respir Dis 122:27–32, 1980
15. Ingram RH, McFadden ER: Localization and mechanisms of airway responses. N Engl J Med 297:596–600, 1977
16. Hensley MJ, O'Cain CF, McFadden ER, Ingram RH: Distribution of bronchodilatation in normal subjects: beta agonist versus atropine. J Appl Physiol 45:778–782, 1978
17. Downes H, Gerber N, Hirshman CA: I.V. lidocaine in reflex and allergic bronchoconstriction. Br J Anaesth 52:873–878, 1980
18. Downes H, Hirshman CA: Lignocaine aerosols do not prevent allergic bronchoconstriction. Anesth Analg (Cleve) 60:28–32, 1981
19. Hirshman CA, Downes H: The Basenji-Greyhound dog model of asthma: Influence of atropine on antigen-induced bronchoconstriction. J Appl Physiol: 50:761–765, 1981
20. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H: Mechanism of action of inhalational anesthesia on airways. ANESTHESIOLOGY 56:107–111, 1982
21. Hickey RF, Graf PD, Nadel JA, Larson CP: The effects of halothane and cyclopropane on total pulmonary resistance in the dog. ANESTHESIOLOGY 31:334–343, 1969
22. Hirshman CA, Bergman NA: Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg (Cleve) 57:629–633, 1978
23. Lloyd TC: Reflex effects of lung inflation and inhalation of halothane, ether and ammonia. J Appl Physiol 45:212–218, 1978
24. Coon RL, Kampine JP: Hypocapnic bronchoconstriction and inhalation anesthetics. ANESTHESIOLOGY 43:635–641, 1975
25. McGrath JC, MacKenzie JE, Millar RA: Effects of ketamine on cental sympathetic discharge and the baroreceptor reflex during mechanical ventilation. Br J Anaesth 47:1141–1147, 1975
26. Jackson DM, Richards IM: The effects of pentobarbitone and chloralose anesthesia on the vagal component of bronchoconstriction produced by histamine aerosol in the anesthetized dog. Br J Pharmacol 61:251–256, 1977
27. Bernstine ML, Berker E, Cullen M: The bronchomotor effects of certain intravenous barbiturates on vagal stimulation in dogs. ANESTHESIOLOGY 18:866–870, 1957

28. Steinhaus JE, Gaskin L: A study of intravenous lidocaine as a suppressant of cough reflex. ANESTHESIOLOGY 24:285–290, 1963
29. Ahlquist RP: A study of the adrenergic receptors. Am J Physiol 153:586–600, 1948
30. Kneussl MP, Richardson JB: Alpha-adrenergic receptors in human and canine tracheal and bronchial smooth muscle. J Appl Physiol 45:307–311, 1978
31. Henderson WR, Shelhamer JH, Reingold DB, Smith LJ, Evans R, Kaliner M: Alpha-adrenergic hyperresponsiveness in asthma. N Engl J Med 300:642–647, 1979
32. Kaliner M, Austen KF: Cyclic AMP, ATP and reverse anaphylactic histamine released from rat mast cells. J Immunol 112:664–674, 1974
33. Stephens NL: Airway smooth muscle: biophysics, biochemistry, and pharmacology, Asthma: Physiology, Immunopharmacology and Treatment. Edited by Lichtenstein LM, Austen KF. New York, Academic Press, 1977, p 160
34. Szentivanyi A: The beta adrenergic theory of atopic abnormality in bronchial asthma. J Allergy 42:203–232, 1968
35. Cookson DV, Reed CE: A comparison of the effects of isoproterenol in normal and asthmatic subjects. Am Rev Respir Dis 88:636–643, 1963
36. Middleton E, Finke SR: Metabolic response to epinephrine in bronchial asthma. J Allergy 42:288–299, 1968
37. Shelhamer SH, Metcalf DD, Smith LJ, Kaliner M: Abnormal beta adrenergic responsiveness in allergic subjects. Analysis of isoproterenol-induced cardiovascular and plasma cyclic adenosine monophosphate responses. J Allergy Clin Immunol 66:52–60, 1980
38. Macdonald AG, Ingram CG, McNeil RS: The effect of propranolol on airway resistance. Br J Anaesth 39:919–926, 1967
39. Conolly ME, Greenacre JK: The lymphocyte B adrenoceptor in normal subjects and patients with asthma. The effect of different forms of treatment on receptor function. J Clin Invest 58:1307–1316, 1976
40. Morris HG, Rusnak SA, Barnes K: Leukocyte cyclic adenosine monophosphate in asthmatic children. Effects of adrenergic therapy. Clin Pharmacol Ther 22:352–357, 1977
41. Galant SP, Duriseti L, Underwood S, Insel PA: Decreased beta-adrenergic receptors on polymorphonuclear leukocytes after adrenergic drug therapy. N Engl J Med 299:933–936, 1978
42. Busse WW, Lee TP: Decreased adrenergic response in lymphocytes and granulocytes in atopic eczema. J Allergy Clin Immunol 58:586–596, 1976
43. Peters JE, Chan SC, Hanifin JM, Hirshman CA: The Basenji-Greyhound dog model of asthma: Defective leukocyte cyclic nucleotide response. Clin Res 29:171A, 1981
44. Rinard GA, Rubinfeld AR, Brunton LL, Meyer SE: Depressed cyclic AMP levels in airway smooth muscle from asthmatic dogs. Proc Natl Acad Sci USA 76:1472–1476, 1979
45. Venter JC, Fraser CM, Harrison LC: Autoantibodies to B_2 adrenergic receptors: A possible cause of adrenergic hyporesponsiveness in allergic rhinitis and asthma. Science 207:1361–1362, 1980
46. Fraser CM, Venter JC, Kaliner M: Autonomic abnormalities and auto anti-bodies to beta-adrenergic receptors. N Engl J Med 305:1165–1170, 1981
47. Dowdy EG, Kaya K: Studies of the mechanism of cardiovascular responses to CI-581. ANESTHESIOLOGY 29:931–943, 1968
48. Wong DHW, Jenkins LC: An experimental study of the mechanism of action of ketamine on the central nervous system. Can Anaesth Soc J 21:57–67, 1974
49. Montel H, Starke K, Gorlitz BD, Shumann HJ: Tierexperimentelle Untersuchungen zur Wirkung desketamins auf periphe sympathische Nerven. Anaesthesist 22:111–116, 1973
50. Nedergaard O: Cocaine-like effect of ketamine on vascular adrenergic neurons. Eur J Pharmacol 23:153–161, 1973
51. Hill GE, Wong KC, Shaw L, Sentker CR, Blatnick RA: Interactions of ketamine with vasoactive amines at normothermia and hypothermia in the isolated rabbit heart. ANESTHESIOLOGY 48:315–319, 1978
52. Lundy PM, Frew R: Ketamine potentiates catecholamine responses of vascular smooth muscle by inhibition of extraneuronal uptake. Can J Physiol Pharmacol 59:520–527, 1981
53. Hirshman CA, Downes H, Farbood A, Bergman NA: Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth 51:713–718, 1979
54. Hirshman CA, Malley A, Downes H: The Basenji-Greyhound dog model of asthma: Reactivity to Ascaris Suum, citric acid, and methacholine. J Appl Physiol 49:953–957, 1980
55. Klide AM, Aviado DM: Mechanism for reduction in pulmonary resistance induced by halothane. J Pharmacol Exp Ther 158:28–35, 1967
56. Burnstock G: Comparative studies in purinergic nerves. J Exp Physiol 194:103–134, 1975
57. Richardson J, Beland J: Nonadrenergic inhibitory nervous system in human airways. J Appl Physiol 41:764–771, 1976
58. Matsuzaki Y, Hamasaki Y, Said SI: Vasoactive intestinal peptide: A possible transmitter of nonadrenergic relaxation of guinea pig airways. Science 210:1252–1253, 1980
59. Kao CY: Tetrodotoxin, saxitonin and their significance in the study of the excitation phenomena. Pharmacol Rev 18:997–1049, 1966
60. Hogg JC, Paré PD, Boucher RC: Bronchial mucosal permeability. Fed Proc 38:197–201, 1979
61. Empy DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA: Mechanisms of bronchial hyperractivity in normal subjects after upper respiratory tract infections. Am Rev Respir Dis 113:131–139, 1976
62. Golden JA, Nadel JA, Boushey HA: Bronchial hyperirritability in healthy subjects after exposure to ozone. Am Rev Respir Dis 118:287–294, 1978
63. Taylor S, Downes H, Hirshman CA, Peters J, Leon DA: Mannitol as a marker of bronchial permeability. ANESTHESIOLOGY 55:360A, 1981
64. Richardson J, Bouchard T, Ferguson CC: Uptake and transport of exogenous proteins by the respiratory epithelium. Lab Invest 35:307–314, 1976
65. Aas K: Heterogeneity of bronchial asthma. Allergy 36:3–14, 1981
66. Nathan RA, Kinsman RL, Spector SL, Horton DG: Relationship between airway response to allergens and nonspecific bronchial reactivity. J Allergy Clin Immunol 64:491–499, 1979
67. Chand N, Eyre P: Classification and biological distribution of histamine receptor subtypes. Agents Actions 5:277–295, 1975
68. Crago RR, Bryan AC, Laws AIC, Winestock AE: Respiratory flow resistance after curare and pancuronium measured by forced oscillations. Can Anaesth Soc J 19:607–614, 1972
69. Moss J, Rosow CE, Savarese JJ, Philbin DM, Kniffen KJ: Role of histamine in the hypotensive action of *d*-tubocurarine in humans. ANESTHESIOLOGY 55:19–25, 1981
70. Lichtenstein LM, Gillespie E: Inhibition of histamine release controlled by the H_2 receptor. Nature 244:287–288, 1973
71. Nathan RA, Segall N, Glover GC, Shocket AL: The effects of H_1 and H_2 antihistamines on histamine inhalation challenges in asthmatic patients. Am Rev Respir Dis 120:1251–1258, 1979
72. Roberts LJ, Sweetman BJ, Lewis RA, Austen KF, Oates JA: Increased production of prostaglandin D_2 in patients with systemic mastocytosis. N Engl J Med 303:1400–1404, 1980
73. Morris HR, Taylor GW, Piper PJ, Tippins JR: Structure of slow-reacting substance of anaphylaxis from guinea pig lung. Nature 285:104–106, 1980

74. Rouzer CA, Scott WA, Cohn P, Blackburn P, Manning JM: Mouse peritoneal macrophages release leukotriene C in response to a phagocytic stimulus. Proc Natl Acad Sci USA 77:4928–4932, 1980
75. Orange RP, Austin KF: Slow reacting substance of anaphylaxis. Adv Immunol 10:105–144, 1969
76. Parker CW: Prostaglandins and slow-reacting substance. J Allergy Clin Immunol 63:1–14, 1979
77. Cade JF, Clancy KL, Walker SE, Pain MCF: Slow-reacting substance from alveolar macrophages—a mechanism of asthma. Aust J Exp Biol Med Sci 59:449–454, 1981
78. Hirshman CA, Peters J, Butler J, Hanifin J, Downes H, Lynn RK: Leukotrienes mediate nonallergic airway constriction *in vivo*. Am Rev Respir Dis 124:65A, 1982
79. Ahmed T, Greenblatt DW, Birch S, Marchette B, Wanner A: Abnormal mucociliary transport in allergic patients with antigen-induced bronchospasm: Role of slow reacting substance of anaphylaxis. Am Rev Respir Dis 124:110–114, 1981
80. Weiss EB, Hargraves WA, Viswanath SG: The inhibitory action of lidocaine in anaphylaxis. Am Rev Respir Dis 117:859–869, 1978
81. Downes H, Loehning RW: Local anesthetic contracture and relaxation of airways smooth muscle. ANESTHESIOLOGY 47:430–436, 1977
82. Weiss EB, Anderson WH, O'Brian KP: The effect of a local anesthetic, lidocaine on guinea pig trachealis muscle *in vitro*. Am Rev Respir Dis 112:393–400, 1975
83. Lundy PM, Gowdey CW, Calhoun EH: Tracheal smooth muscle relaxant effect of ketamine. Br J Anaesth 46:333–336, 1974
84. Wanna HT, Gergis SD: Procaine, lidocaine and ketamine inhibit histamine-induced contracture of guinea pig tracheal muscle *in vitro*. Anesth Analg (Cleve) 57:25–27, 1978
85. Adriani J, Rovenstine EA: The effect of anesthetic drugs upon bronchi and bronchioles of exised lung tissue. ANESTHESIOLOGY 4:253–262, 1943
86. Souhrada J: Changes in airway smooth muscle in experimental canine asthma. Respir Physiol 32:79–90, 1978
87. Antonissen LA, Mitchell RW, Kroeger EA, Kepron W, Tse KS, Stephens NL: Mechanical alterations of airway smooth muscle in a canine asthmatic model. J Appl Physiol 46:681–687, 1979
88. Middleton E: Antiasthmatic drug therapy and calcium ions. Review of pathogenesis and role of calcium. J Pharmacol Sci 69:243–251 1980
89. McFadden ER: Calcium-channel blocking agents and asthma. Ann Intern Med 95:232–233, 1981
90. Cerrina J, Denjean A, Alexandre G, Lockhart A, Duroux P: Inhibition of exercise-induced asthma by a calcium antagonist, nifedipine. Am Rev Respir Dis 123:156–160, 1981
91. Patel KR: Calcium antagonists in exercise-induced asthma. Br Med J 282:932–933, 1981
92. Williams DO, Barnes PJ, Vicker HP, Rudolph M: Effect of nifedipine on bronchomotor tone and histamine reactivity in asthma. Br Med J 283:348, 1981
93. Chen WY, Weiser PC, Chai H: Air cooling: Stimulus for exercise-induced asthma. Scand J Respir Dis 60:144–150, 1979
94. Allegra L, Bianco S: Nonspecific broncho-reactivity obtained with an ultrasonic aerosol of distilled water. Eur J Respir Dis 61(Suppl 106):41–49, 1980
95. Hartley JPR, Davies BH: Cholinergic blockade in the prevention of exercise-induced asthma. Thorax 35:680–685, 1980
96. Breslin FJ, McFadden ER, Ingram RH: The effects of cromolyn sodium on the airway response to hyperpnea and cold air in asthma. Am Rev Respir Dis 121:6–11, 1980
97. Dahl R, Henriksen JM: Effect of oral and inhaled sodium cromoglycate in exercise-induced asthma. Allergy 35:363–365, 1980
98. Woenne R, Kattan M, Levison H: Sodium cromoglycate-induced changes in the dose-response curve of inhaled methacholine and histamine in asthmatic. Am Rev Respir Dis 119:927–931, 1979