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Review Article

Regulation of Bronchomotor Tone during Anesthesia

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THE PHARMACOLOGY of the bronchial smooth muscle has received considerable attention in recent years, in part because two new bronchodilator and antiasthmatic drugs have been recently approved for commercial distribution in the United States. One of them, metaproterenol, is a *beta*-adrenergic receptor stimulant administered by inhalation in aerosol form. The other is cromolyn sodium, which interferes with the antigen–antibody reaction and is inhaled in powder form. These new drugs are discussed in detail elsewhere.[1–3] The pharmacology of the older sympathomimetic drugs and that of the corticosteroids when used in the treatment of bronchial asthma have also been reviewed.[4,5]

The effects of drugs used in the practice of anesthesiology have not been investigated as thoroughly as those of the antiasthmatic drugs. This is understandable, since bronchospasm is not a common complication of anesthesia. Nevertheless, when it occurs, it is an important problem, often necessitating immediate treatment. Correct treatment requires a knowledge of etiology. This article reviews a new classification of bronchomotor mechanisms formulated by Aviado and Salem[3] for the bronchodilators and antiasthmatic drugs. The manner in which bronchospasm may develop in the anesthetized patient and the effects of anesthetic agents are discussed within this classification.

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Classification of Bronchomotor Mechanisms

The classic grouping of bronchomotor mechanisms into autonomic (such as cholinergic) and nonautonomic or musculotropic (such as histaminergic) is no longer practical. Although it is generally true that the vagus nerve elicits bronchoconstriction and the sympathetic nerve bronchodilation, each autonomic component can be influenced through visceral receptors, the medullary center, autonomic ganglia, and the neuroeffector junction. Chemical agents that influence one of these areas also affect the others. A well-known example is acetylcholine, which exerts a primary action on the parasympathetic neuroeffector junction and also, in appropriate dose, excites the other areas and may even influence the release of histamine. On the other hand, histamine, which acts directly on the bronchial muscle even after denervation or blockade of autonomic receptors, can elicit a reflex increase in vagal tone. There are numerous other examples to demonstrate that the discussion must be based on a different grouping.

The classification of bronchomotor mechanisms used in this review is related to anatomic location and pharmacologic response. It is based also on the results obtained from investigation of the bronchopulmonary effects of nicotine and cigarette smoke, which have proven to be useful tools in identifying the eight groups of mechanisms. Some of these mechanisms have been demonstrated only in animal experiments, and their occurrence in the human lung remains hypothetical.

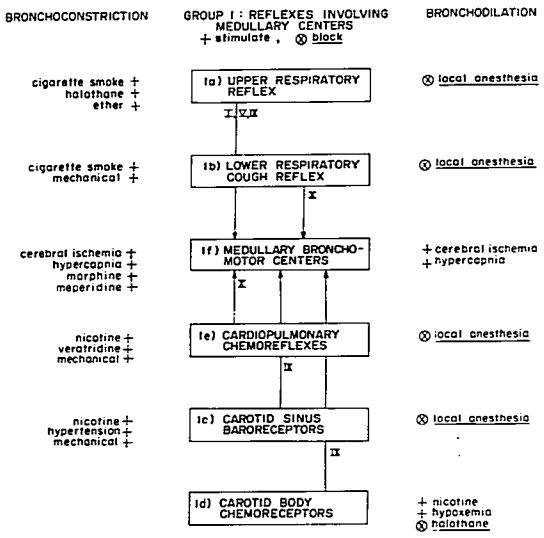

FIG. 1. Bronchomotor reflexes involving medullary centers.

GROUP 1: REFLEXES INVOLVING THE MEDULLARY CENTERS

The first group of regulatory mechanisms involves the areas most remote from the bronchial muscle and includes reflex mechanisms and responses of medullary centers (fig. 1). They are discussed together in order to combine all those bronchomotor mechanisms that depend on the central nervous system.

1a. Upper respiratory reflex mediating bronchoconstriction. In 1870, Kratschmer[6] described the response of a rabbit subjected to cigarette smoke, chloroform vapor, carbon dioxide gas, and other similar irritants. The effects consisted of breath-holding, bradycardia, and biphasic fall and rise in aortic blood pressure. The phenomenon is referred to as the Kratschmer reflex. Subsequent investigation by Allen[7] established the reflex nature of the response because olfactory, trigeminal and glossopharyngeal denervation eliminated the reaction. Kaufman *et al.*[8] demonstrated an increase in airway resistance measured by body plethysmography in subjects with the nose and nasopharynx exposed to an aerosol of free crystalline silica. After unilateral interruption of the second division of the trigeminal nerve, performed for treatment of tic douloureux, there was no bronchoconstriction. The efferent arm of the reflex is the vagus nerve, and the response can be blocked by prior administration of atropine.[9]

1b. Lower respiratory cough reflex. The administration of cigarette smoke or other irritant vapor directly to the lower respiratory passages leads to the cough reflex. Contraction of the respiratory muscles is synchronized by a cough center in the medulla. Bronchoconstriction accompanies the coughing. It has been postulated that bronchospasm triggers the cough receptors, and that this may in turn cause further bronchospasm as a reflex response mediated by the afferent and the efferent vagus.[10] The initial bronchospasm is an axon reflex, which is discussed under Group 2.

1c. Carotid sinus baroreceptors mediating bronchoconstriction. The stretch receptors or

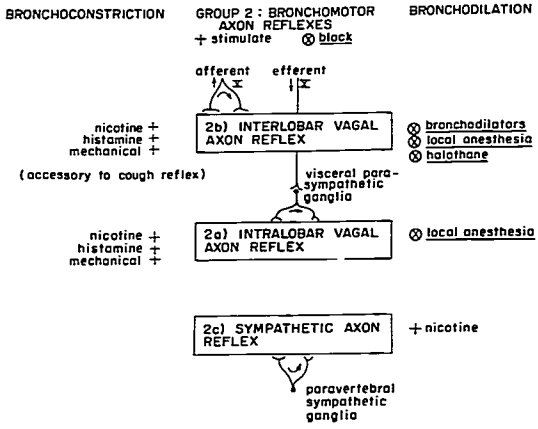

FIG. 2. Bronchomotor axon reflexes.

baroreceptors in the carotid sinuses influence bronchomotor tone. A rise in mean blood pressure causes bronchoconstriction.[11] In the course of exposing an animal to excessive amounts of cigarette smoke or to an injection of nicotine, the rise in aortic blood pressure is accompanied by bronchoconstriction, part of which effect is contributed by the carotid sinus reflex. In this situation denervation of the baroreceptors does not eliminate the bronchoconstriction, because of the participation of various mechanisms, including the lower respiratory cough reflex (see above) and the other actions of cigarette smoke and nicotine (see below). The existence of the carotid sinus–bronchomotor mechanism in man has not been substantiated.

1d. Carotid body chemoreceptors mediating bronchodilation. There have been reports that stimulation of the carotid body chemoreceptors in the dog causes a reflex increase in vagal tone.[12] It has been demonstrated that the increase in vagal tone can be produced by chemical excitation of the baroreceptors in the carotid sinuses, for instance, by large doses of sodium cyanide or lobeline, an alkaloid related to nicotine.[13] However, after selective cutting of the baroreceptor nerve fibers and exposing the carotid body chemoreceptors to the same stimuli, the response is bronchodilation, conforming to the general pattern whereby the chemoreceptors increase sympathetic nerve activity.

1e. Cardiopulmonary chemoreflexes mediating bronchoconstriction. Another group of reflexes involving medullary centers consists of the Bezold-Jarisch reflex, which elicits bradycardia, hypotension and apnea. The receptors are in the coronary and pulmonary circulation and are stimulated by veratrum alkaloids, nicotine, and other substances.[14] It has been demonstrated that the reflex is accompanied by bronchospasm, which can be blocked by prior administration of atropine.

1f. Medullary centers mediating bronchoconstriction or bronchodilation. There are areas in the medulla which, when stimulated by implanted electrodes, produce either bronchoconstriction or bronchodilation. The areas do not only control bronchomotor tone, but also serve for regulation of heart rate through the vagus and sympathetic nerves.[15] Such locations are stimulated by large doses of nicotine as well as by cerebral ischemia. The areas that increase vagal tone are more sensitive to chemical excitation than those that increase sympathetic activity.

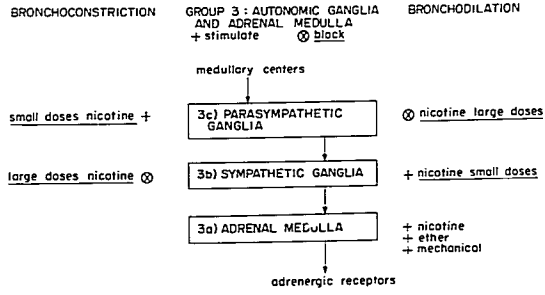

FIG. 3. Mechanisms in autonomic ganglia and adrenal medulla regulating bronchomotor tone.

GROUP 2: BRONCHOMOTOR AXON REFLEXES

The original concept of axon reflexes proposed by Langley[16] is that a nerve fiber can transmit an impulse antidromically, so that one terminal will originate the impulse and another terminal will manifest a response. The classic example is the triple reaction following intradermal injection of histamine. The flare, red spot, and wheal are mediated by an axon reflex, which is absent when the sensory nerves to the skin have undergone degeneration.[17] A series of axon reflexes has been postulated, involving the vagal afferents, the vagal efferents, and the sympathetic efferents to the pulmonary blood vessels during embolization and congestion.[18] A group of axon reflexes (fig. 2) for the airways has also been described. It consists of the following[19–22]:

2a. Intralobar vagal axon reflex. Pleural application of histamine or nicotine to one lobe causes bronchoconstriction in the same lobe.[21] The effect is not influenced by acute or chronic denervation of the lobe, but is blocked by atropine. However, the bronchoconstriction is prevented by pleural administration of lidocaine, indicating its reflex nature. Since the amount of histamine or nicotine administered topically is too small to be absorbed and influence the bronchial muscle directly, an axon reflex involving the parasympathetic ganglia in the lung has been postulated to explain the response. The ganglia remain even after degeneration of the preganglionic components of the vagus.

2b. Interlobar vagal axon reflex. Pleural application of histamine or nicotine to one lobe, as indicated in the preceding paragraph, elicits bronchoconstriction in the adjoining lobe, which is blocked by administration of lidocaine or atropine, or chronic denervation.[21] Acute denervation of the lobe does not interefere with the response, so that this differs from the lower respiratory cough reflex (Group 1b). It is called an "axon" reflex because of its disappearance after chronic degeneration of the nerves of the lung.

The interlobar and intralobar vagal axon reflexes are the means by which an isolated stimulus can lead to bronchoconstriction of the adjoining airways. The bronchoconstriction characteristic of the cough reflex is probably initiated by these axon reflexes.

2c. Sympathetic axon reflex. Injection of nicotine into the bronchial artery of the dog produces bronchodilation even after acute denervation of the lungs. However, after chronic denervation, bronchodilation is absent, indicating the axon-reflex nature of the response.[22] Administration of beta-blocking drugs also prevents the bronchodilation, indicating that the reaction is related to adrenergic nerves.[20]

GROUP 3: BRONCHOMOTOR MECHANISMS INVOLVING THE AUTONOMIC GANGLIA AND THE ADRENAL MEDULLA

The bronchomotor responses originating from reflexes and medullary centers described under Group 1 are mediated through autonomic outflow channels, which include the autonomic ganglia and the adrenal

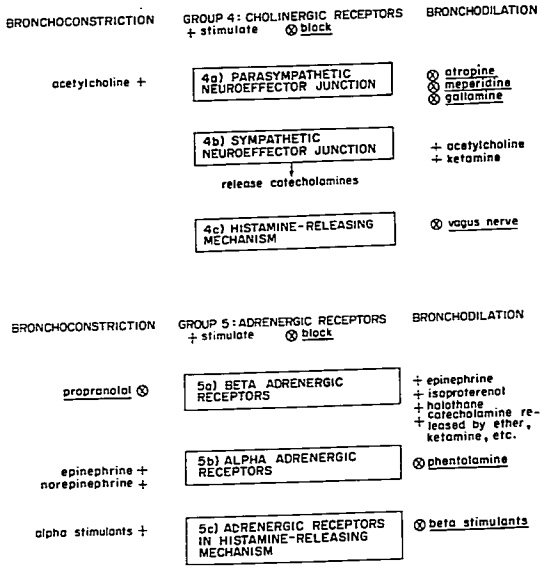

FIG. 4. Cholinergic receptors regulating bronchomotor tone.

FIG. 5. Adrenergic receptors regulating bronchomotor tone.

medulla (fig. 3). There are chemical agents which exert their effects initially on the ganglia and the adrenals. The classic example is the action of nicotine on what have been referred to as "nicotinic receptors" in these areas.[23]

3a. Adrenal medulla causing bronchodilation. Stimulation of the splanchnic nerve or injection of nicotine into the adrenal artery causes release of catecholamines, predominantly epinephrine from the adrenal medulla. The end result is bronchodilation by excitation of adrenergic beta receptors (see Group 5).

3b. Sympathetic ganglionic stimulation causing bronchodilation. Nicotine in minimal effective doses causes excitation of sympathetic ganglia, which leads to bronchodilation, vasoconstriction, and tachycardia. Large doses of nicotine, however, cause blockade of transmission in these ganglia. (The term "nicotinic action" refers to stimulation by small doses and blockade by large doses of nicotine.)

3c. Parasympathetic ganglionic stimulation causing bronchoconstriction. Nicotinic action also occurs in the parasympathetic ganglia, which are stimulated and blocked by the corresponding amounts of nicotine. The effect of excitation is bronchoconstriction and that of blockade is bronchodilation.

GROUP 4: CHOLINERGIC RECEPTORS IN THE AIRWAYS

Acetylcholine can influence several areas that regulate bronchomotor tone (fig. 4). The sympathetic ganglionic synapse and adrenal medulla discussed in Group 3 and the carotid body chemoreceptors in Group 1 are stimulated by acetylcholine, but are not in the lung parenchyma. The cholinergic areas within lung parenchyma, arranged in the order of their importance, are as follows.

4a. Cholinergic receptors in parasym-

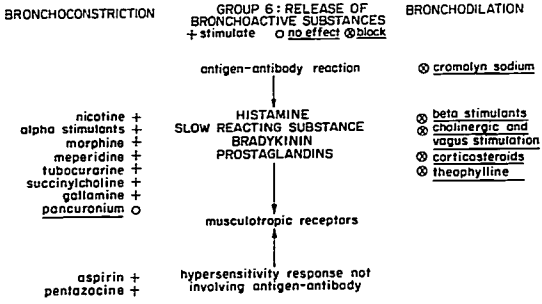

FIG. 6. Release of bronchoactive substances influencing bronchomotor tone.

pathetic neuroeffector junction. Bronchoconstriction resulting from injection or inhalation of acetylcholine is elicited by excitation of cholinergic receptors in the junction between the vagal postganglionic nerve ending and bronchial smooth muscle. These receptors are blocked by atropine and form the most important group of cholinergic receptors in the airways.

4b. Cholinergic receptors in sympathetic neuroeffector junction. After administration of atropine, application of acetylcholine causes bronchodilation, which, according to the Burn and Rand hypothesis, is due to release of catecholamines at the sympathetic neuroeffector junction.[24]

4c. Cholinergic receptors in histamine-releasing mechanism. Electrical stimulation of the vagus nerve in the perfused lung causes inhibition of the release of histamine.[25] These observations have not included the application of acetylcholine, although it is safe to assume that the release of histamine can be inhibited by cholinergic receptors.

GROUP 5: ADRENERGIC RECEPTORS IN THE AIRWAYS

The sympathetic neuroeffector junction in the airways consists of the postganglionic nerve terminal, which releases catecholamines that combine with adrenergic receptors (fig. 5). However, the identity of the neurohumoral transmitter is in question. Norepinephrine, which is the accepted transmitter for the blood vessels and heart, does not mimic the effect of stimulation of the sympathetic nerve supplying the bronchial muscle. Although bronchodilation results from sympathetic stimulation, administration of norepinephrine does not relax the bronchial smooth muscle. Epinephrine is a potent bronchodilator and is probably the catecholamine that serves as the neurohumoral transmitter in the airways.[26]

5a. Beta-adrenergic receptors in the bronchial muscle. The bronchodilation associated with administration of epinephrine is classified as a *beta*-receptor response, which is prevented by a *beta*-blocking drug.

5b. Alpha-adrenergic receptors in the bronchial muscle. After blockade of *beta*-receptors, the administration of epinephrine causes bronchoconstriction. This is explained by stimulation of *alpha*-adrenergic receptors, since alpha-adrenergic blocking agents prevent the bronchoconstriction.

5c. Adrenergic receptors in the histamine-releasing mechanism. The adrenergic drugs, including epinephrine, have been demonstrated to influence release of histamine from the lungs.[27] *Beta*-receptor stimulation causes inhibition of the release, whereas *alpha* activation produces release of histamine and other humoral agents. Additional details of the release of humoral agents are discussed under Group 6.

GROUP 6: RELEASE OF HISTAMINE AND OTHER BRONCHOACTIVE SUBSTANCES

What was originally supposed to be a simple phenomenon, the release of histamine as part of the antigen–antibody reaction, has

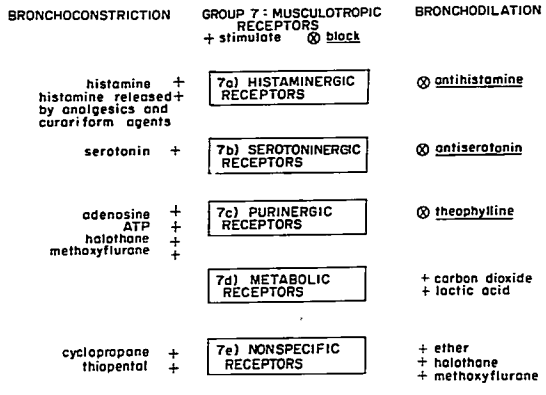

FIG. 7. Musculotropic receptors in the airway.

now become complex. Histamine release can be triggered by inhalation of cigarette smoke[28] or by administration of chemical agents, a process that is inhibited by cholinergic drugs (see Group 4) and either inhibited or reinforced by adrenergic receptors (see Group 5). The major sources of histamine are the mast cells, which also release heparin, slow-reacting substance, and enzymes that participate in the formation of angiotensin II and prostaglandins (fig. 6). No subgroups are identified here because they have been included under cholinergic, adrenergic, and musculotropic receptors. The significance of the bronchoactive substances released in the lung has been reviewed recently by Orange and Austen[29] and Sadavongvivad.[30]

GROUP 7: MUSCULOTROPIC RECEPTORS IN THE BRONCHIAL MUSCLE

The classic group of musculotropic receptors includes those that mediate bronchoconstriction and those that mediate bronchodilation (fig. 7). The subgroups relate to the humoral agents mentioned above (see Group 6), as well as to other substances released from blood cells.

7a. Histaminergic receptors causing bronchoconstriction. Histamine of either endogenous or exogenous origin causes bronchoconstriction. Bronchial arterial injection of histamine causes a reflex increase in vagal tone, which not only exaggerates the bronchoconstriction but also reduces the further release of histamine in the lung.[31] The site of the histaminergic receptor that triggers the reflex has not be localized. In the opinion of the reviewer it is in the bronchial smooth muscle, which is activated by bronchospasm. Until the receptor is clearly identified the reflex response to histamine is treated as a separate subgroup.

7b. Serotoninergic receptors causing bronchoconstriction. Bronchospasm resulting from administration of serotonin or 5-hydroxytryptamine is unaffected by antihistaminic drugs. However, most drugs that block serotonin also exert an antihistaminic effect, so that it has been difficult to clarify the role of serotoninergic receptors in regulation of bronchomotor tone. The major source of serotonin is the blood platelets, and part of the bronchospasm occurring during pulmonary embolism is believed to originate from this subgroup of receptors.

7c. Purinergic receptors causing bronchoconstriction or bronchodilation. In 1972, Burnstock[32] reviewed the pharmacologic effects of adenosine, adenosine triphosphate, and related purines, and introduced the term "purinergic" to cover the receptors that

FIG. 8. Accessory mechanisms influencing airway resistance.

mediate their action. A discussion of the airways was avoided for lack of information. Investigation in the author's laboratory has indicated that theophylline, which is related to the purines in structure, produces bronchodilation. Adenosine triphosphate, on the other hand, produces bronchospasm. The pulmonary blood vessels behave in a similar manner, showing vasodilation in response to theophylline, and vasoconstriction to adenosine triphosphate.[33]

It is proposed that theophylline blocks purinergic receptors, resulting in relaxation of the bronchial and pulmonary vascular smooth muscles.

7d. Metabolic receptors. This last group of specific receptors includes those that respond to carbon dioxide and metabolites, including lactic acid. The end result is relaxation of the bronchial muscles.[34]

7e. Nonspecific receptors causing bronchoconstriction or bronchodilation. The other bronchoactive substances, both endogenous and exogenous in origin, are listed in figure 7. The mechanism of their smooth-muscle effect has not been identified but does not involve the other specific receptors, because the agents that block receptors 7a, 7b, 7c, and 7d do not influence the activity of 7e. Hawkins[35] tabulated the effects of several hundred chemical compounds on the bronchi; his work is the only available compilation of bronchoactive substances.

GROUP 8: MECHANISMS THAT INFLUENCE AIRWAY RESISTANCE

The final group includes mechanisms other than those covered in the first seven groups. The examples contained in figure 8 include alterations in bronchial secretion, bronchial circulation, and interstitial fluid in the airways, all of which lead to corresponding changes in airway resistance than can overshadow any primary change in smooth-muscle caliber. Specific clinical situations relating to them are discussed elsewhere in this article.

Pharmacologic Agents Used in Anesthesia

It is evident from figures 1–8 that many anesthetics and adjuvant drugs act on the bronchopulmonary areas, particularly Group 4 cholinergic receptors, Group 5 adrenergic receptors, Group 6 release of bronchoactive substances, and Group 7 musculotropic receptors.

INHALATIONAL ANESTHETICS

In most instances, the inhalational anesthetics produce bronchodilation. Failure to elicit bronchodilation in all cases is not unique for inhalational anesthetics but is true of bronchodilators in general. The ability to demonstrate a reduction in airway resistance is dependent on the existence of some preexisting bronchomotor tone. Lack of bronchomotor tone would render the airways insensitive to bronchodilating agents. A discussion of halothane, the most widely investigated inhalational anesthetic, illustrates the difficulties in identifying the influence of anesthetics on bronchomotor regulation.

Halothane. Inhalation of an anesthetic concentration of halothane produced bronchodilation in man[36] and dogs.[37,38] The negative results in other cases can be explained by either minimal bronchomotor tone or interference with one or more of the mechanisms known to be influenced by halothane. The major component of bronchodilation elicited by halothane is mediated through (Group 5a) *beta*-adrenergic receptor stimulation, which is decreased by *beta*-blocking drugs. This mechanism has been demonstrated with the *in-situ* dog lung.[37] Boissier *et al.*[39] found it in the guinea pig

lung *in situ*, which after administration of a *beta*-blocking drug shows bronchospasm in response to halothane. The bronchospasm is not blocked by atropine or antihistaminic drugs but is abolished by theophylline, indicating that (Group 7) purinergic receptors are involved. Bronchospasm has not been reported to be elicited by halothane in the dog after *beta*-receptor blockade.

The results derived from excised guinea pig lung are different from those described above for the lung *in situ*. Caujolle and Pham-Huu-Chanh[40] demonstrated bronchoconstriction in the isolated perfused guinea pig lung. Fletcher *et al.*[41] observed relaxation of the guinea pig tracheal chain. This observation indicates that a third set of receptors (Group 7e) the nonspecific musculotropic receptors, are participating.

Other investigations of halothane indicate that it is an antagonist to the following bronchospastic agents: histamine in the dog[42] and hypocapnia in the dog[42] and in man.[36] Halothane depresses the cough reflex in man,[43] which may reflect either depression of the cough center or depression of (Group 2a) axon reflex bronchoconstriction, which is an important intermediate event in the elicitation of the cough reflex. The site of action has not been identified, as this would require cross-circulation experiments performed on the head separately from the body. The investigation of extracorporeal circulation in man performed by Patterson *et al.*[44] indicates that halothane administered to the systemic circulation, including the cerebral, did not influence bronchomotor tone, so that participation of bronchomotor centers in the medulla can be excluded. Millar[45] reported inhibition of (Group 1c) carotid body chemoreceptors by halothane. The reduction of airway resistance in two patients was interpreted by Brakensiek and Bergman[46] to indicate blockade of reflex bronchospasm, but this may be attributable to the action of halothane on musculotropic receptors.

Ether. There is a prevalent opinion that ether anesthesia causes bronchodilation, which is a combination of (Group 5a) *beta*-adrenergic stimulation from (Group 3a) the release of catecholamines in the adrenal medulla, and (Group 7e) nonspecific musculotropic bronchodilation.[47] No measurement of airway resistance in patients during ether anesthesia has been reported. In the dog, increase in respiratory rate resulting from ether anesthesia probably accounted for the failure to demonstrate bronchodilation.[38]

Methoxyflurane. In the anesthetized dog, administration of this anesthetic had no significant effect on airway resistance.[38] Methoxyflurane, like halothane, caused bronchoconstriction in the isolated guinea pig lung[40] but relaxation of the guinea pig tracheal chain.[41] The mechanisms involved include (Group 7c) purinergic receptors and (Group 7c) nonspecific musculotropic receptors.

Cyclopropane. This is the only inhalational anesthetic known to produce an increase in airway resistance. The effect has been demonstrated in bronchial slices[48] and in the dog lung *in situ*,[38] and is classified as (Group 7e) nonspecific musculotropic response. This classification is based on unpublished experiments by the author, who could not confirm in the dog the interaction between atropine and cyclopropane observed *in vitro* by others.[48] The reaction of bronchodilation to cyclopropane was reported by Hickey *et al.*[42] only, but this group has failed to confirm what others have reported for various anesthetic agents.

Intravenous Anesthetics and Adjuvants

No important depression of the bronchomotor centers (Group 1) results from intravenous injection of barbiturates and ketamine. Their effects on the airways are largely dependent on Group 4 cholinergic Group 5 adrenergic, and Group 7 musculotropic receptors. Laryngospasm has been reported to occur during administration of thiopental sodium and ketamine.[48] The mechanism had not been clarified and is beyond the scope of a review dealing primarily with smooth muscle of the airways.

Adriani and Rovenstine[49] examined the sodium salt of thiopental and other intravenous barbiturates in the excised lung tissue of rats, dogs and man. They reported bronchoconstriction. However, no subsequent attempt had been made to identify the specific musculotropic mechanisms. Since in other organs the barbiturates do not stimulate

cholinergic, histaminergic and purinergic receptors, it is safe to suggest that these drugs act on (Group 7e) nonspecific musculotropic receptors.

Corssen *et al.*[50] reported that ketamine was a safe dissociative anesthetic agent for administration to asthmatic patients. It produced relief of bronchospasm, which was confirmed in reports by Betts and Parkins[51] and Huber *et al.*[52] The latter investigators measured airway resistance and reported decreased in nine of ten asthmatic patients, and no significant change in seven non-asthmatic patients. It has been suggested that the bronchodilation is due to (Group 5a) *beta*-adrenergic stimulation, resulting from the elevation of catecholamine levels. Another mechanism involved is based on the observation of Traber *et al.*[53] that atropine blocks tachycardia resulting from ketamine. It is proposed that (Group 4b) cholinergic receptors in the sympathetic neuroeffector injection may be the mechanism responsible for the bronchodilation, but direct proof is lacking.

Other Central Nervous System Depressants

Analgesics and tranquilizers that depress certain areas in the brain, including the respiratory center, have negligible effects on the medullary centers regulating bronchomotor tone. The influence of these drugs on the airways is exerted on peripheral mechanisms.

Morphine sulfate. The bronchoconstrictor action of morphine was first identified by Jackson in the dog, in 1916.[54] Since morphine is known to increase central vagal tone and release histamine, the relative importance of these two mechanisms was examined by Shemano and Wendel[55] in the dog. They concluded that, since vagotomy or an antihistamine drug markedly reduced the bronchoconstriction, morphine was acting through both mechanisms. In the light of the bronchomotor mechanisms reviewed above, the sequence of events is as follows: (Group 6) release of histamine; (Group 7a) histaminergic bronchoconstriction; (Group 2b) histamine-induced axon reflex which also increases vagal tone; (Group 1f) direct action on medullary bronchoconstrictor center. Reports of the effects of morphine in man have been entirely descriptive in nature. Higgins, in 1915, showed that morphine causes bronchiolar constriction,[56] and there have been subsequent reports[57] of asthmatic attacks resulting from its use.

Meperidine hydrochloride. This analgesic, originally introduced in 1939, was known to have a spasmolytic action on bronchial smooth muscles, induced by a cholinergic drug and by histamine.[58,59] However, in experiments on the intact dog, no difference between morphine and meperidine was found and the spasmolytic action of the latter could not be detected.[55] Barach[60] has reviewed the clinical use of meperidine to treat asthmatic patients, in whom a spasmolytic action could be demonstrated.

Pentazocine. A group of asthmatic patients who were sensitive to aspirin were also sensitive to pentazocine. Delaney[61] reported one such patient who developed bronchospasm after ingestion of a 25-mg dose. There has been no report of a similar occurrence in a non-asthmatic individual.

Diazepam. Following the introduction of diazepam as an antianxiety agent, it was used in preanesthetic medication. Catchlove and Kafer,[62] in administering the drug to patients with chronic obstructive pulmonary disease, questioned its safety, because they observed an increase in arterial blood carbon dioxide tension. Heinomen and Muittari[63] did not observe an increase in carbon dioxide tension in asthmatic patients receiving diazepam, provided ventilation was controlled. In this situation, no increase in airway resistance occurred. There is no information concerning the effect of this drug on asthmatic patients without controlled ventilation.

Local Anesthetics

An effective method to prevent bronchospasm arising from intubation and surgical manipulation in the cardiopulmonary area is to administer local anesthetics topically or by infiltration.[64] In the isolated tracheal chain preparation, procaine and most other local anesthetics produce relaxation of the smooth muscle.[65] This response would properly belong to (Group 7e), nonspecific musculotropic

bronchodilators, although there is no information to exclude blockade of specific musculotropic receptors. Intravenous injection of procaine has been used to relieve bronchospasm induced reflexly by intubation, and lidocaine had been administered intravenously for alleviation of bronchospasm induced by *d*-tubocurarine.[66]

Neuromuscular Blocking Drugs

The classic examples of (Group 6) histamine-releasing agents include the curariform drugs. One serious manifestation of this action is bronchospasm.

d-Tubocurarine. Landmesser[67] demonstrated for the first time that the bronchoconstrictor effect of *d*-tubocurarine in the dog can be blocked by an antihistaminic drug. In a few cases of bronchospasm occurring in curarized patients circulatory collapse has also developed.[68,69] This adverse reaction appears to occur in those individuals who are hypersensitive to the curarizing drug or to histamine. An absence of bronchomotor effect during anesthesia with halothane, which has a bronchodilator action,[70] was observed in normal individuals who had been curarized.

Succinylcholine chloride. Although succinylcholine is not as potent as *d*-tubocurarine in releasing histamine in animal tissue, there have been reports of bronchospasm resulting from the use of succinylcholine. The mechanism appears to be hypersensitivity, either to the small amount of histamine released or to the drug itself. Scattered observations indicate that the bronchospasm can be so severe as to resist the dilating action of atropine[71] or ether,[72] that there is no cross-sensitization to pancuronium,[73] and that it occurs in nonallergic individuals.[74]

Gallamine triethiodide. This agent may release histamine and has been reported to cause bronchospasm in patients.[75] In the heart, gallamine has two additional actions: blockade of cholinergic receptors and release of catecholamines.[76] It is not known whether the same mechanisms in the bronchomotor system are influenced by gallamine.

Pancuronium bromide. This bisquarternary steroid component is devoid of histamine-releasing activity. Nana *et al.*[77] tested the drug in asthmatic patients and did not encounter any cases of bronchospasm. Although no case of hypersensitivity has been encountered, it is too soon to exclude the possibility. A patient in status asthmaticus receiving pancuronium developed severe tachycardia,[78] although the drug has been claimed to have an insignificant cardiovascular effect.

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