Pharmacology of the Airways

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Cassandra Bailey, Paul J. Wojciechowski, and William E. Hurford

Key Points

- Short-acting beta-2 adrenergic agonists are administered for the acute relief of bronchospasm, wheezing, and airflow obstruction. Long-acting beta-2 adrenergic agonists are for long-term control of symptoms.
- Inhaled anticholinergics are first-line therapy in COPD. They are useful for both maintenance therapy and in acute exacerbations.
- Inhaled corticosteroids are used to control inflammation in asthma and COPD. In asthma, they can be used as monotherapy. In COPD, they are used in conjunction with long-acting beta-adrenergic agonists.
- Systemic corticosteroids are used for the reduction of inflammation in asthma and COPD exacerbations and are not typically prescribed as maintenance therapy.
- Phosphodiesterase 4 inhibitors can be used in patients with severe COPD, chronic bronchitis, and a history of exacerbations.
- Leukotriene modifiers, mast cell stabilizers, and methylxanthines are alternative therapies used in asthma when symptoms are not well-controlled on first-line therapy.
- Volatile and intravenous anesthetics provide a degree of bronchodilation that may be useful in treating intraoperative bronchoconstriction.
- Helium/oxygen mixtures, antihistamines, and magnesium sulfate are alternative therapies used when bronchospasm does not respond to conventional therapies.

Introduction

This chapter reviews the pharmacology of agents commonly encountered in anesthetic practice that are either administered to treat pulmonary diseases or administered into the airway for action at end organs other than the lung but have effects on the airway. Drugs that modify the state of the autonomic nervous system (ANS) and the airway will be reviewed along with medications that modify or suppress inflammation of the airway. Lastly, the action of anesthetic agents on the airway will be reviewed along with the actions of several adjunctive agents.

Pharmacologic agents administered via the lungs take advantage of the unique interface between air and blood allowing for rapid uptake of drugs into the bloodstream or immediate utilization by cells that populate the airway. The delivery of medications to the lungs can have systemic effects, direct effects on the airway, or both. For example, inhaled anesthetics are delivered via the lungs to act in the brain and have bronchodilatory effects. Conversely, beta-adrenergic agonists delivered via aerosol exert direct effects on bronchial smooth muscle with few systemic effects. Drugs administered directly to the airway are ideal for treating pulmonary parenchymal diseases such as asthma and chronic obstructive pulmonary disease (COPD).

C. Bailey (✉) · P. J. Wojciechowski · W. E. Hurford
Department of Anesthesiology, University of Cincinnati, Cincinnati, OH, USA
e-mail: barryca@ucmail.uc.edu

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Influence of the Autonomic Nervous System on the Airway and Modulation of the Response

Traditionally, the ANS has been divided into two major parts, the parasympathetic and sympathetic nervous systems. The parasympathetic nervous system regulates airway caliber, airway glandular activity, and airway microvasculature [1–4]. The vagus nerve provides the preganglionic fibers which synapse with postganglionic fibers in airway parasympathetic ganglia [1–4]. Acetylcholine activates the muscarinic (M3) receptor of postganglionic fibers of the parasympathetic nervous system to produce bronchoconstriction [5]. Anticholinergics can provide bronchodilation even in the resting state since the parasympathetic nervous system produces a basal level of resting bronchomotor tone [3, 4, 6]. Activated eosinophils may play a role in airway hyperresponsiveness through release of major basic protein that prevents acetylcholine from binding the M2 receptors, leading to inhibition of negative feedback control and increasing release of acetylcholine [7].

Although the sympathetic nervous system plays no direct role in control of airway muscle tone, beta-2 adrenergic receptors are present on airway smooth muscle cells and cause bronchodilation via G-protein and secondary messenger mechanisms [1–5]. The abundance of these receptors in the airway allows for pharmacologic manipulation of airway tone [8].

The ANS also influences bronchomotor tone through the nonadrenergic noncholinergic (NANC) system [2, 4, 9, 10]. The exact role of NANC in humans is not well defined; it has excitatory and inhibitory neuropeptides that influence inflammation and smooth muscle tone, respectively [2, 9]. Vasoactive intestinal peptide (VIP) and nitric oxide (NO) are the main inhibitory transmitters thought to be responsible for airway smooth muscle relaxation [2, 9]. Substance P (SP) and neurokinin A (NKA) are the main excitatory transmitters and have been shown to cause neurogenic inflammation, including bronchoconstriction [2, 9]. The precise role of NANC in healthy and diseased human lung is unclear. Further study is needed to fully elucidate the role that this group of neuropeptides has in the regulation of bronchial smooth muscle responsiveness.

Inhaled Adrenergic Agonists

The mainstay of therapy for bronchospasm, wheezing, and airflow obstruction is beta-adrenergic agonists. Beta-adrenergic agonists used in clinical practice are typically delivered via inhalers or nebulizers, are beta-2 selective, and are divided into short- and long-acting therapies [11]. Short-acting beta-2 agonist therapy is effective for the rapid relief of wheezing, bronchospasm, and airflow obstruction [11]. Longer-acting beta-2 agonists are used as maintenance therapy providing improvement in lung function and reduction in symptoms and exacerbations [11]. Please refer to Table 8.1 for a selection of beta-2 selective agonists that play a role in the management of airway diseases and symptoms both in and out of the operating room.

Table 8.1 Pharmacologic influence on the autonomic nervous system

Systemic adrenergic agonists	Inhaled adrenergic agonists	Inhaled cholinergic antagonists	Systemic cholinergic antagonists
	Short-acting	Short-acting	
Terbutaline	Albuterol	Ipratropium	Atropine
Epinephrine	Levalbuterol		Scopolamine
Albuterol	Metaproterenol		Glycopyrrolate
	Pirbuterol		
	Long-acting	Long-acting	
	Salmeterol	Tiotropium	
	Formoterol		
	Arformoterol		

Adapted from Fanta et al. [11]

Mechanism of Action

Short-acting beta-2 agonists bind to the beta-2 adrenergic receptor located on the plasma membrane of smooth muscle cells, epithelial, endothelial, and many other types of airway cells [8, 12]. Figure 8.1 demonstrates how a ligand binding to the receptor causes a G-stimulatory protein to activate adenylate cyclase-converting adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [8, 12]. It is unknown precisely how cAMP causes smooth muscle relaxation; however, decreases in calcium release and alterations in membrane potential are the most likely mechanisms [8]. Longer-acting beta-2 agonists have the same mechanism of action as short-acting beta-2 agonists; however, they have unique properties that allow for a longer duration of action. For example, salmeterol has a longer duration of action because a side chain binds to the beta-2 receptor and prolongs the activation of the receptor [12, 13]. The lipophilic side chain of formoterol allows for interaction with the lipid bilayer of the plasma membrane and a slow, steady release prolonging its duration of action [12].

Clinical Applications

Beta-2 agonists have a central role in the management of obstructive airway diseases allowing for control of symptoms and improvement in lung function. Short-acting beta-2 agonists such as albuterol, levalbuterol, metaproterenol, and pirbuterol are prescribed for the rapid relief of wheezing, bronchospasm, and airflow obstruction [11]. Clinical effect is seen in a matter of minutes and lasts up to 4–6 h [12]. Scheduled, daily use of short-acting beta-2 agonists has

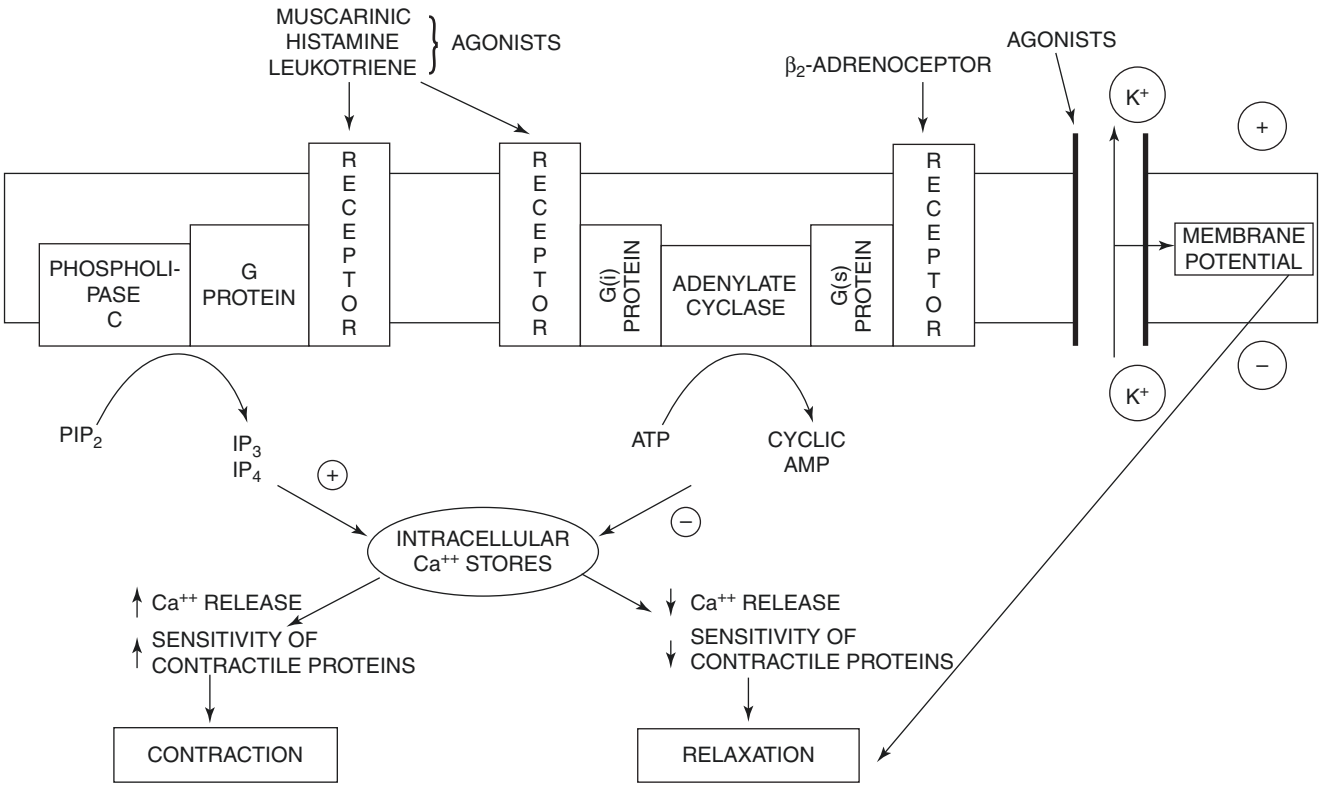

Fig. 8.1 Effects of agonists at the beta-2 receptor and at the muscarinic receptor. Stimulation of the beta-2 receptor will cause a decrease in calcium release and relaxation of smooth muscle. Blockade of the muscarinic receptor will prevent the release of calcium and smooth muscle contraction. ATP, adenosine triphosphate; AMP, adenosine monophosphate; IP, inositol phosphate; PIP2, phosphoinositide bisphosphate. (Reprinted with permission of the Thoracic Society. Copyright© American Thoracic Society. Johnson [8]. Official Journal of the American Thoracic Society)

fallen out of favor, and they are now used primarily as rescue therapy [14–16]. Long-acting beta-2 agonists can be prescribed for control of symptoms when rescue therapies (i.e., short-acting beta-2 agonists) are used frequently within a week [11, 17]. In asthma, combination therapy including a long-acting beta-2 agonist and an inhaled corticosteroid (IC) are effective in reducing symptoms, reducing the risk of exacerbation, and improving lung function while minimizing the dose of IC [11, 18]. In COPD, combination therapy composed of inhaled long-acting beta-2 agonists, IC, and long-acting muscarinic antagonists can improve lung function and reported patient outcomes; however more studies are needed before triple therapy can be fully recommended [19].

Side Effects

Systemic absorption of inhaled beta-2 agonists is responsible for a myriad of side effects, most of which are not serious. Most commonly, beta-2 agonist therapy leads to tremors and tachycardia secondary to direct stimulation of the beta-2 adrenergic receptor in skeletal muscle or vasculature, respectively [11, 12, 20, 21]. In severe asthma, beta-2 agonists may cause a temporary reduction in arterial oxygen tension of 5 mmHg or more secondary to beta-2-mediated vasodilation in poorly ventilated lung regions [12, 22]. Hyperglycemia, hypokalemia, and hypomagnesemia also can occur with beta-2 agonist therapy, but the severity of these side effects tends to diminish with regular use [12]. Tolerance to beta-2 agonists can occur with regular use over a period of weeks and, while not affecting peak bronchodilation, can be evidenced by a decrease in the duration of bronchodilation and the magnitude of side effects (tremor, tachycardia, etc.) [12, 23, 24]. Tolerance likely reflects beta-2 adrenergic receptor downregulation [12]. Last, beta-2 agonist therapy withdrawal after regular use can produce transient bronchial hyperresponsiveness [12].

Safety Concerns

Evidence has associated the use of long-acting beta-2 agonist therapy without concomitant use of a steroid inhaler with fatal and near-fatal asthma attacks [11, 25]. In light of this evidence, it seems prudent to save long-acting beta-2 agonists for asthmatic patients that are poorly controlled on inhaled steroids alone or for those patients with symptoms sufficiently challenging to warrant the potential extra risk associated with use of the agents [11, 25].

Systemic Adrenergic Agonists

Systemic administration of adrenergic agonists for asthma was used more frequently in the past. Oral, intravenous, or subcutaneous administration of beta-specific or nonspecific adrenergic agonists is now reserved for rescue therapy.

Mechanism of Action

The mechanism of action of systemically administered adrenergic agonists is the same as it is for inhaled agents. Binding of the drug to the beta-2 adrenergic receptor on smooth muscle cells in the airway is responsible for the bronchodilatory effects [8]. Specifically, beta-2 receptor stimulation induces a G-stimulatory protein to convert ATP to cAMP and in turn reduces intracellular calcium release and alters membrane potential [8, 12].

Clinical Applications

Terbutaline can be given orally, subcutaneously, or intravenously (IV), albuterol (salbutamol) can be given intravenously, and epinephrine is usually given subcutaneously or intravenously. Regardless of the route of administration, all three will produce bronchodilation. Comparison of intravenous and inhaled formulations of terbutaline failed to demonstrate any difference in bronchodilation, and, with the propensity for IV formulations to cause side effects, inhaled therapy should be considered the first-line treatment [26, 27]. This principle not only applies to terbutaline but also to all beta-adrenergic agonists that are available in IV and inhaled forms [17]. If inhaled therapy is not readily available or if inhaled therapy is maximized and symptoms persist, then subcutaneous epinephrine or terbutaline can be administered with improvement in symptoms and spirometry values [28]. In summary, subcutaneous or IV beta agonists should be reserved only for rescue therapy.

Side Effects

The side-effect profile of systemic adrenergic agonists is similar to that for inhalational adrenergic agonists. The most common side effects are tremor and tachycardia [11, 12]. Arterial oxygen tension can be transiently decreased, and hyperglycemia, hypokalemia, and hypomagnesemia can also be present [11, 12]. Escalating oral, subcutaneous, or IV doses can be associated with a greater incidence of side effects for the same degree of bronchodilation compared to inhaled beta-adrenergic agonists [11, 12].

Inhaled Cholinergic Antagonists

The use of anticholinergics (antimuscarinics) for maintenance therapy and treatment of acute exacerbations in obstructive airway diseases is common. The parasympathetic nervous system is primarily responsible for bronchomotor tone, and inhaled anticholinergics act on muscarinic receptors in the airway to reduce tone [2]. The parasympathetic nervous system plays a role in determining resting heart rate, and suppression of the parasympathetic nervous system can cause tachyarrhythmias. The use of inhaled anticholinergics (see Table 8.1) in COPD as maintenance and rescue therapy is considered first-line, standard treatment [29]. Anticholinergics are not used for first-line maintenance therapy in asthma and are only recommended for use in acute exacerbations or as therapy steps up [11, 17, 29, 30].

Mechanism of Action

The targets of therapy for anticholinergics are the muscarinic receptors located in the airway. There are three subtypes of muscarinic receptors found in the human airway [31]. Muscarinic 2 (M2) is present on postganglionic cells and is responsible for limiting production of acetylcholine and protects against bronchoconstriction [31]. M2 is not the target of inhaled anticholinergics but is antagonized by them [31]. Muscarinic 1(M1) and muscarinic 3 (M3) receptors are responsible for bronchoconstriction and mucus production and are the targets of inhaled anticholinergic therapy [31]. Acetylcholine binds to the M3 and M1 receptors and causes smooth muscle contraction (see Fig. 8.1) via increases in cyclic guanosine monophosphate (cGMP) or by activation of a G-protein (Gq) [5, 6, 31]. Gq activates phospholipase C to produce inositol triphosphate (IP3), which causes release of calcium from intracellular stores and activation of myosin light-chain kinase causing smooth muscle contraction [5, 6, 31]. Anticholinergics inhibit this cascade and reduce smooth muscle tone by decreasing release of calcium from intracellular stores [5, 6].

Clinical Applications

Inhaled antimuscarinics are approved for the treatment of obstructive airway diseases. Ipratropium is classified as a short-acting anticholinergic and is commonly used as maintenance therapy for COPD and as rescue therapy for both COPD and asthmatic exacerbations [29, 31]. It is not indicated for the routine management of asthma [11, 17, 29, 30]. Patients treated with ipratropium experience an increase in exercise tolerance, decrease in dyspnea, and improved gas exchange [31]. Tiotropium is an example of inhaled long-acting antimuscarinic available for COPD maintenance therapy. Tiotropium has been shown to reduce COPD

exacerbations, respiratory failure, and all-cause mortality [32]. Combination bronchodilators with both LABA and LAMA are available and improve symptoms and reduce exacerbations greater than with a single bronchodilator. Tiotropium also improves the effectiveness of pulmonary rehabilitation [19]. The newer long-acting muscarinic antagonist, inhaled glycopyrronium, has a faster onset of bronchodilation on the first day when compared to tiotropium. A randomized controlled trial showed comparable improvements in lung function and health status when combination glycopyrronium with LABA and ICs was compared to tiotropium with LABA and ICs. This study also demonstrated benefits of triple therapy compared to combination LABA/ICs [33]. In asthmatics who are poorly controlled on ICs and LABA, the addition of tiotropium reduces severe exacerbations [34].

Side Effects

Inhaled anticholinergics are poorly absorbed and therefore serious side effects are uncommon. Most commonly, patients experience dry mouth and urinary retention and can experience pupillary dilation and blurred vision if the eyes are inadvertently exposed to the drug [31]. Inhaled anticholinergic medications have been shown to increase the risk of serious cardiovascular events including cardiovascular mortality [35]. Tachyarrhythmias and atrial tachycardias are side effects, and inhaled anticholinergics should be used with caution in patients with known concomitant cardiovascular disease.

Systemic Cholinergic Antagonists

The systemically administered anticholinergics atropine and glycopyrrolate act via the same mechanisms as inhaled anticholinergics. While these anticholinergics can be administered by IV or inhalation, significant systemic absorption occurs, and their use is generally limited by side effects. Atropine, in particular, is limited in use because of its tertiary ammonium structure [29]. It has a tendency to cause tachycardia, gastrointestinal upset, blurred vision, dry mouth, and central nervous system effects secondary to its ability to cross the blood–brain barrier [29]. Glycopyrrolate has a quaternary ammonium structure and is insoluble in lipids, similar to ipratropium and tiotropium, and has fewer systemic side effects than atropine [29, 31]. Intravenous glycopyrrolate is also clinically limited in use secondary to side effects [36]. Glycopyrrolate has been studied as inhaled therapy, however, and is an effective bronchodilator with an intermediate duration of action [37–40]. Clinically, it has never been popular as a mainstay of therapy for obstructive airway diseases. Atropine and glycopyrrolate are both used clinically to reduce secretions.

Influence of Inflammation on the Airway and Modulation of the Response

Asthma and COPD, the most common obstructive airway diseases, have a component of inflammation as part of their pathogenesis. Although inflammation is a common pathogenesis, the characteristics and prominent cellular elements involved in the inflammatory process for each disease are distinct [41]. In COPD, neutrophils, macrophages, CD8+ T lymphocytes, and eosinophils are more prominent in the inflammatory composition [41]. In asthma, eosinophils play a more prominent role followed by mast cells, CD 4+ T lymphocytes, and macrophages in the inflammatory composition [41]. Inflammatory cell types present in sputum, biopsy specimens, and bronchoalveolar lavage fluid can help predict the response to anti-inflammatory therapy [41]. For example, eosinophilia in induced sputum of a patient presenting with a COPD exacerbation predicts an increase in steroid responsiveness [41–43]. Treatment aimed at reducing eosinophilia in COPD patients has been shown to reduce exacerbations and hospitalization [44, 45]. Patients presenting to the operating room with obstructive airway diseases have a high likelihood of being prescribed and taking or being exposed to one of the anti-inflammatory therapies in Table 8.2 for control of their disease.

Table 8.2 Pharmacologic influence on inflammation

Inhaled corticosteroids	Leukotriene modifiers	Mast cell stabilizers	Methylxanthines
Monotherapy	Antagonists		
Beclomethasone	Montelukast	Cromolyn sodium	Theophylline
Budesonide	Zafirlukast	Nedocromil	Aminophylline
Ciclesonide	Pranlukast (not in the United States)		
Flunisolide			
Fluticasone	Inhibitors		
Mometasone	Zileuton		
Triamcinolone			
Combination therapy			
Budesonide/formoterol			
Fluticasone/salmeterol			

Adapted from Fanta et al. [11]

Inhaled Corticosteroids

In the treatment of asthma, the use of ICs reduces the inflammatory changes associated with the disease, thereby improving lung function and reducing exacerbations that result in hospitalization and death [11, 46–48]. On the contrary, the use of ICs as monotherapy in COPD is discouraged [31]. In COPD, ICs are used as a part of combination therapy along with long-acting beta-adrenergic agonists (LABA) and possibly long-acting antimuscarinic antagonists [19]. The combination of drugs acts synergistically and is useful for reducing inflammation [31]. Currently, combination therapy of ICs and LABA is recommended for use in severe to very severe COPD [31, 49]. Triple therapy with ICs, LABA, and LAMA improves lung function and reduces exacerbations more than ICs combined with only LABA [19].

Mechanism of Action

The glucocorticoid receptor alpha (GRα) located in the cytoplasm of airway epithelial cells is the primary target of ICs [50, 51]. Passive diffusion of steroids into the cell allows for binding of the steroid ligand to GRα, dissociation of heat shock proteins, and subsequent translocation to the nucleus [51]. Figure 8.2 shows how the steroid–receptor complex can have a multitude of actions when it enters the nucleus [51]. The complex can bind to promoter regions of DNA sequences and either induce or suppress gene expression [51]. Additionally, the steroid–receptor complex can interact with transcription factors already in place, such as the ones responsible for proinflammatory mediators, without binding to DNA and repressing expression of those genes [50, 51]. Corticosteroids may inhibit the transcription of proinflammatory mediators and upregulate production of anti-inflammatory proteins [52]. The steroid–receptor complex also can affect chromatin structure by association with transcription factors that influence the winding of DNA around histones, reducing access of RNA polymerase and other transcription factors, and thus reducing expression of inflammatory gene products [50, 51]. Corticosteroids are able to modulate B2-adrenoreceptor and their function by protecting against desensitization and development of tolerance, increasing the efficiency of receptor coupling, and mitigating the risk of inflammation-induced receptor down-regulation and uncoupling [52].

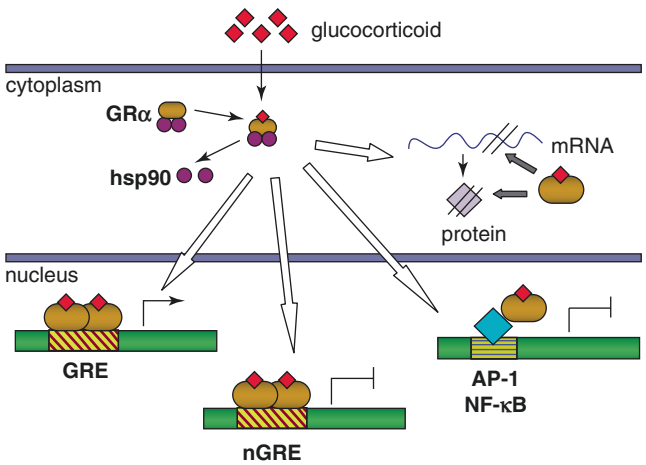

Fig. 8.2 Action of glucocorticoids. Glucocorticoids can bind to promoter regions inducing or repressing gene expression, act on promoters with transcription factors in place, or influence the structure of chromatin. GRα, glucocorticoid receptor alpha; hsp90, heat shock proteins; mRNA, messenger ribonucleic acid; GRE, glucocorticoid responsive elements; nGRe, negative glucocorticoid responsive elements; NF-KB, nuclear factor kappa beta; AP-1, activator protein-1. (Reprinted from Pujols et al. [51] with permission)

Clinical Applications

ICs are used in asthma as part of a multimodal treatment regimen and are added to a therapeutic regimen when there is an increase in severity or frequency of asthma exacerbations [11]. There is good evidence to show that ICs can reduce both hospitalizations and death in asthma [47, 48]. The use of ICs in COPD is limited to use in severe to very severe COPD and in combination with LABA [19, 31]. Although no improvement in mortality has been consistently demonstrated with combination therapy (ICs/LABA), an ICs combined with LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations [19]. Triple therapy with the addition of LAMA is more effective in reducing exacerbations. In COPD, the benefits of corticosteroids have been shown to be greater in patients with eosinophilic airway inflammation [19]. Research is ongoing looking at the use of eosinophil counts as potential biomarkers to direct treatment decisions. Further investigation is needed, but the use of eosinophil counts may lead to an improved risk–benefit ratio for inhaled corticosteroid treatment in severe COPD [53].

Side Effects and Safety Concerns

Side effects have been reported with the use of ICs in asthma and COPD. A recent meta-analysis reported an increase in pneumonia and serious pneumonia but not pneumonia-related deaths when ICs was used in the treatment of COPD [54]. Patients at higher risk of pneumonia are smokers, age 55 years or older, BMI less than 25 kg/m^2, or have a history of prior pneumonia or exacerbations [55]. Other reported side effects in COPD and asthma include oropharyngeal candidiasis, pharyngitis, hoarseness, easy bruising, osteoporosis,

cataracts, elevated intraocular pressure, dysphonia, cough, and growth retardation in children [11, 31, 49]. As with any pharmacotherapy, the risks and benefits of therapy must be weighed, and the patient must be carefully monitored for adverse effects. This is especially true with the use of ICs in obstructive lung diseases.

Systemic Corticosteroids

Systemic corticosteroids given in intravenous or oral form are used for treatment of asthma and COPD exacerbations. The mechanism of action is the same as it is for ICs, activation or suppression of gene products at a transcriptional level and alteration of chromatin structure [50, 51]. Patients that are hospitalized with a COPD exacerbation will typically receive corticosteroids to suppress any inflammatory component that may be contributing to the flare-up. Therapy with oral prednisolone is equally as effective as IV administration [56]. A study done at the Veterans Affairs medical centers in the United States published in 1999 reported that corticosteroid therapy shortened hospital length of stay and improved forced expiratory volume in 1 second vs. placebo. The study also compared a 2-week regimen vs. an 8-week regimen of corticosteroids and found no difference [57]. The REDUCE randomized clinical trial compared 5 days to 14 days of therapy with 40 mg prednisone daily for treatment of COPD exacerbations. The trial showed that 5-day treatment was noninferior [58]. Current guidelines state that duration of therapy for systemic corticosteroids should not be more than 5–7 days [19]. In asthma, corticosteroids are recommended for exacerbations that are either severe, with a peak expiratory flow of less than 40% of baseline, or a mild to moderate exacerbation with no immediate response to short-acting beta-adrenergic agonists [17]. The recommended duration of therapy is 3–10 days without tapering [17]. Alternatively, some patients with asthma and COPD will be receiving long-term oral corticosteroid therapy because their disease is difficult to manage. Side effects of systemic corticosteroids are well described and numerous. Hypertension, hyperglycemia, adrenal suppression, increased infections, cataracts, dermal thinning, psychosis, and peptic ulcers are reported complications of corticosteroid therapy [59].

Leukotriene Modifiers

Leukotriene modifiers can be used for the treatment of asthma. They are prescribed primarily for long-term control in addition to short-acting beta-adrenergic agonists or in conjunction with ICs and short-acting beta agonists. Leukotriene modifiers are taken by mouth, produce bronchodilatation in hours, and have maximal effect within days of administration [11]. Their role in the management of COPD is not defined. Future investigations will need to focus on the role these medications can play in the outpatient management of COPD [60].

Mechanism of Action

Arachidonic acid is converted to leukotrienes via the 5-lipoxygenase pathway [61]. Leukotrienes C_4, D_4, and E_4 are the end products of the pathway and cause bronchoconstriction, tissue edema, migration of eosinophils, and increased airway secretions [61]. Leukotriene modifiers come in two different varieties, leukotriene receptor antagonists and leukotriene inhibitors [11]. Figure 8.3 shows how the binding of leukotrienes C_4, D_4, and E_4 at the type 1 cysteinyl leukotriene receptor is blocked by the leukotriene receptor antagonists montelukast, zafirlukast, and pranlukast (not available in the United States) [11, 61]. The leukotriene inhibitor zileuton antagonizes 5-lipoxygenase (Fig. 8.3), inhibiting the production of cysteinyl leukotrienes [11, 61].

Clinical Applications

Leukotriene modifiers improve lung function, reduce exacerbations, and are used as long-term asthma therapy [11, 17, 62, 63]. Clinical trials have reported that ICs are superior to leukotriene modifiers for long-term control and should be the first-line choice [17, 64, 65]. Leukotriene modifiers provide an additional pharmacologic option for the control of asthma. Addition of leukotriene modifiers to ICs will improve control of symptoms of asthma as opposed to ICs alone [66].

Side Effects

Overall, leukotriene antagonists are well-tolerated without significant side effects. Links between Churg-Strauss syndrome and the use of leukotriene antagonists have been reported, but it is not clear whether these reports reflect unmasking of a preexisting condition or whether there is a direct link between the two [11, 61]. Zileuton is known to cause a reversible hepatitis in 2–4% of patients [11]. Liver function tests should be checked frequently at first and periodically thereafter to monitor for hepatocellular damage [11, 61].

Mast Cell Stabilizers

Cromolyn sodium and nedocromil are the two prototypical agents in this category that are used in the treatment of asthma. These agents are delivered by powder inhaler and are not first-line therapy for asthma. They do provide an alternative treatment when the control of asthma is not optimal on other conventional therapies [17].

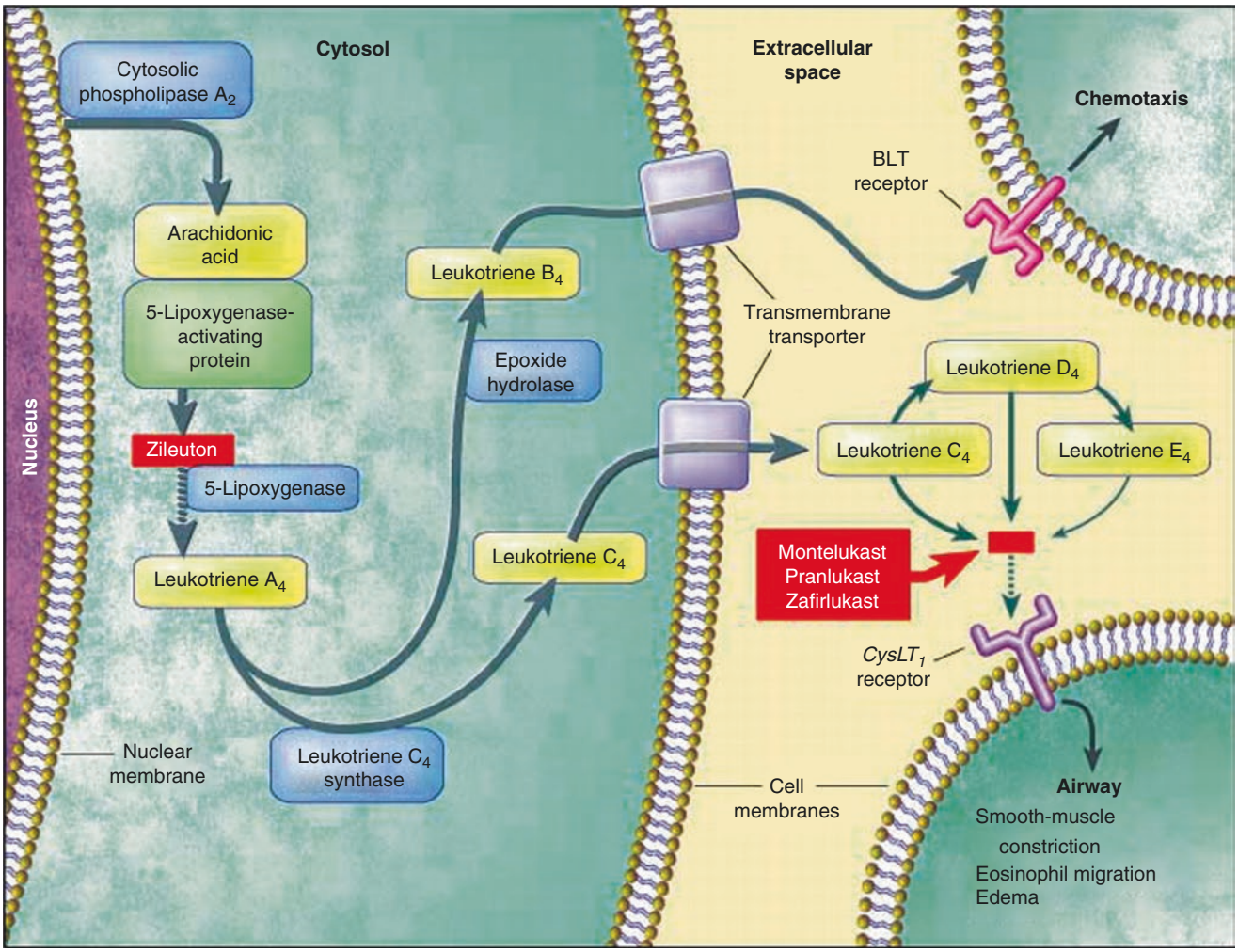

Fig. 8.3 Generation of leukotrienes and action of leukotriene-modifying drugs. Leukotriene antagonists block the action of leukotrienes at the cysteinyl leukotriene receptor (CysLT1), and leukotriene inhibitors block the conversion of arachidonic acid to leukotriene A4. BLT leukotriene receptor B. (Reprinted from Drazen et al. [61] with permission, © 1999 Massachusetts Medical Society. All Rights Reserved)

Mechanism of Action

Cromolyn sodium and nedocromil stabilize submucosal and intraluminal mast cells [17, 67]. These drugs interfere with the antigen-dependent release of mediators, such as histamine and slow-reacting substance of anaphylaxis, that cause bronchoconstriction, mucosal edema, and increased mucus secretion [67].

Clinical Applications

Large systematic reviews of the available literature and consensus statements favor the use of ICs over cromolyn sodium or nedocromil as first-line agents to control symptoms of asthma [17, 68]. Alternatively, cromolyn sodium and nedocromil may be used as preventative treatment before exercise or known allergen exposure causing symptoms of asthma [17].

Side Effects

There are no major side effects reported with the use of cromolyn sodium and nedocromil. The most commonly reported side effects are gastrointestinal upset and coughing or irritation of the throat [67].

Methylxanthines

The role of theophylline, a prototypical methylxanthine, has changed since the introduction of ICs and LABA. Theophylline was a common choice for the control of asthma and COPD because of its bronchodilatory and anti-inflammatory effects [69]. Currently, theophylline is recommended only as an alternative therapy and is not a first-line choice for asthma or COPD [17, 70, 71].

Mechanism of Action

Theophylline is thought to act via multiple pathways causing improvement in symptoms in obstructive lung diseases. Theophylline is a nonselective inhibitor of phosphodiesterase and increases levels of cyclic AMP and GMP causing smooth muscle relaxation [69]. Antagonism of the A_1 and A_2 adenosine receptors also causes smooth muscle relaxation via inhibition of the release of histamine and leukotrienes from mast cells, another reported action of theophylline [69]. In asthma, theophylline reduces the number of eosinophils in bronchial specimens and, in COPD, reduces the number of neutrophils in sputum, having an anti-inflammatory effect in both conditions [69]. In addition, theophylline activates histone deacetylase and reduces the expression of inflammatory genes [69]. Theophylline and aminophylline are reported to improve diaphragmatic function; however data have not demonstrated this effect consistently [69, 72].

Clinical Applications

Theophylline has been relegated to an alternative therapy in both asthma and COPD. This has occurred largely because of its significant side-effect profile and the subsequent need for monitoring of blood levels [17, 69–71]. Patients that are already on an ICs and a LABA and still have symptoms may benefit from the addition of theophylline, especially if leukotriene modifiers and other alternatives are not tolerated [17, 70, 71]. Theophylline is not recommended for use in COPD exacerbations due to significant toxicity.

Side Effects

Theophylline can cause significant and life-threatening side effects if not dosed carefully and monitored appropriately. Toxicity is dose related, and side effects tend to be more prominent when blood levels exceed 20 mg/L [69]. The most common side effects include headache, nausea, vomiting, restlessness, abdominal discomfort, gastroesophageal reflux, and diuresis [69]. The most significant side effects include seizures, cardiac arrhythmias, and death [69]. Adverse effects from theophylline may be avoided if the clinician follows the patient carefully, monitors blood levels regularly, and educates the patient on the signs and symptoms of overdose.

Phosphodiesterase 4 Inhibitors

Mechanism of Action

Phosphodiesterase 4 (PDE4) is an enzyme that breaks down cyclic AMP. The enzyme is present in inflammatory and immune cells such as eosinophils, macrophages, and T lymphocytes. Inhibition of PDE4 has anti-inflammatory effects. Roflumilast, a PDE4 inhibitor, has been shown to decrease the expression of T cell adhesion molecules and decrease release of inflammatory mediators and cytokines [73].

Clinical Applications

Roflumilast is available for management in COPD in patients whose disease is not adequately controlled with long-acting bronchodilators. It is recommended for patients with severe airflow limitation, symptoms of chronic bronchitis, and history of exacerbations [74].

Side Effects

PDE4 inhibitors have a significant side-effect profile, which has limited their use. The main side effects are nausea, weight loss, and diarrhea. Less frequent side effects include insomnia, anxiety, and depression. In clinical trials, the side effects appeared to be dose dependent. Other PDE4 inhibitors are being studied for use in asthma and COPD [73, 74].

Influence of Anesthetics on the Airway

Volatile Anesthetics

Volatile anesthetics have a host of effects on the respiratory system. Volatile anesthetics reduce bronchomotor tone. All commonly used volatile anesthetics (see Table 8.3), except desflurane, produce a degree of bronchodilatation that may be helpful in patients with obstructive lung disease or in patients that experience any degree of bronchoconstriction [75, 77]. Rooke and colleagues in 1997 reported that sevoflurane produced a greater reduction in respiratory system resistance than isoflurane or halothane 10 min after the induction of anesthesia [75].

Mechanism of Action

The precise mechanisms by which volatile anesthetics induce bronchodilatation are not completely clear. Animal studies

Table 8.3 Anesthetics with a favorable influence on bronchomotor tone

Volatile anesthetics[a]	Intravenous anesthetics[b]
Isoflurane	Propofol
Sevoflurane	Ketamine
Halothane	Midazolam

[a]Adapted from Rooke et al. [75]
[b]Adapted from Cheng et al. [76]

suggest that volatile anesthetics inhibit tracheal smooth muscle contraction by decreasing intracellular calcium, mediated by an increase in intracellular cAMP and by suppression of protein kinase C which, in the absence of volatile anesthetics, sensitizes contractile elements to calcium and inhibits myosin light-chain phosphatase [78]. The effect is seen to a greater degree in distal airway smooth muscle secondary to the T-type voltage-dependent calcium channel, which is sensitive to volatile anesthetics [79].

Clinical Applications

Volatile anesthetics are administered to provide amnesia and blunt the response to surgical stimulation but can be of use in patients who have obstructive airway diseases or experience bronchoconstriction in the operating room. Multiple case reports provide examples of how volatile agents were used solely for the treatment of status asthmaticus [80–83].

Side Effects

The main concern with the use of volatile anesthetics is the rare occurrence of malignant hyperthermia. Hypotension can also be a concern with volatile anesthetics; however the blood pressure is usually easily restored with small amounts of IV fluids or vasopressors. Nausea and vomiting is a known side effect of volatile anesthetics, and prophylactic antiemetics should be considered based on patient risk factors. Deep levels of anesthesia associated with high concentrations of volatile anesthetics may be undesirable, and prolonged administration outside the operating room is problematic.

Intravenous Anesthetics

Intravenous anesthetics can have positive effects on bronchomotor tone when used for induction or intravenous anesthesia in the operating room. Ketamine, propofol, and midazolam (see Table 8.3) have relaxant effects on airway smooth muscle [76]. Etomidate and thiobarbiturates do not affect bronchomotor tone to the same extent [84]. The choice of intravenous anesthetics for induction and maintenance of anesthesia may be important for a patient with hard to manage bronchospasm or reactive airway disease.

Mechanism of Action

The precise mechanism of reduction of bronchomotor tone for the intravenous anesthetics is largely unknown. Ketamine is thought to have a direct relaxant effect on smooth muscle [85]. Propofol is thought to reduce vagal tone and have a direct effect on muscarinic receptors by interfering with cellular signaling and inhibiting calcium mobilization [86, 87]. The preservative metabisulfite in propofol prevents the inhibition of vagal-mediated bronchoconstriction [88].

Clinical Applications

Choosing an agent such as propofol or ketamine can be beneficial in patients with bronchospasm or obstructive airway disease [76, 84]. The use of these intravenous agents for induction or maintenance of anesthesia over other agents can be useful in minimizing the intraoperative effects of bronchospasm.

Side Effects

Although each of the intravenous anesthetics carries a unique side-effect profile, the major effects are not related to the airway. The use of ketamine is associated with increased salivation, and coadministration of a small dose of anticholinergic can attenuate secretion production. Propofol is associated with hypotension that usually is easily corrected with IV fluids and vasopressors.

Local Anesthetics

Local anesthetics are primarily used to suppress coughing and blunt the hemodynamic response to tracheal intubation [89, 90]. Although animal models have demonstrated some ability of local anesthetics to relax bronchial smooth, in clinical practice the use of local anesthetics as pure bronchodilators is limited by toxicity and the ready availability of more potent bronchodilators such as short-acting beta-adrenergic agonists [85].

Influence of Adjunctive Agents on the Airway

Heliox

Helium (administered as a mixture of helium and oxygen [heliox]) has the advantage of having a low Reynolds' number and less resistance during turbulent airflow especially in large airways [6]. Helium and oxygen mixtures are recommended as alternative therapies in asthma to support patients when traditional therapies have initially failed to make improvements [17, 70]. A recent trial in patients with COPD exacerbations failed to demonstrate a statistically significant reduction in the necessity for endotracheal intubation in patients treated with noninvasive ventilation and helium/

oxygen mixtures [91]. The use of helium–oxygen mixtures is limited by a progressive reduction in efficacy at higher inspired oxygen concentrations.

Antihistamines

Histamine release from mast cells and basophils is responsible for airway inflammation and bronchoconstriction in asthma [92]. Antihistamines are not standard therapy for asthma, but the use of antihistamines and leukotriene modifiers for allergen-induced bronchoconstriction has shown promise for diminishing the early and late responses to allergens [92, 93]. Patients that have allergen-induced asthma or patients that experience an allergic reaction in the operating room may benefit from antihistamines to attenuate the role that histamine plays in bronchoconstriction.

Magnesium Sulfate

Magnesium sulfate is not a standard therapy for asthma exacerbations. Magnesium sulfate is thought to produce additional bronchodilation when given in conjunction with standard therapy for asthma exacerbations. Currently, intravenous magnesium therapy is reserved as an alternative therapy when the patient has not responded to standard therapy [17, 70, 94]. The combination of nebulized magnesium sulfate and beta-adrenergic agonists has also been studied and shows potential benefit in asthma exacerbations [95]. Overall, magnesium sulfate, IV or nebulized, is not a first-line therapy for asthma exacerbations and should be reserved for situations when the patient is not responding to conventional therapy [17, 70].

Summary

Patients with obstructive lung diseases presenting to the operating room for thoracic surgical procedures usually will be receiving pharmacotherapy to modify their symptoms or disease process. Understanding the role of pharmacotherapy in obstructive lung disease is essential to proper preoperative evaluation, perioperative risk reduction, and intraoperative management.

Clinical Case

A 65-year-old-man with COPD who quit smoking 2 years ago now presents to the preoperative clinic for evaluation before a right upper lobe lobectomy for a lung nodule. The patient has no other medical history and a recent cardiac stress test is normal.

Questions

Preoperative evaluation:

- How often does he need rescue inhalers? Has the frequency increased recently?
- When was the last time he was in the hospital with a COPD exacerbation?
- What medications for the treatment of COPD is the patient receiving?
- When was the last time he needed systemic corticosteroids for an exacerbation?
- Has there been any recent change in sputum or use of antibiotics?

Intraoperative Management:

- What medications will provide quickest relief of wheezing?
- Are prophylactic systemic corticosteroids indicated?
- What role do helium/oxygen mixtures and magnesium sulfate play in the management of wheezing?

Answers

Preoperative evaluation:

- Asking patients about the use of rescue inhalers gives some indication of how well their symptoms are controlled at baseline. Any increase in frequency of inhaler use may indicate disease progression or potential acute exacerbation.
- Inquiring about previous hospitalizations and the extent of illness (i.e., intubation, ICU admission) is important in determining the severity of disease.
- This patient will likely present on an IC and long-acting beta-adrenergic agonist combination along with an antimuscarinic such as ipratropium.
- The most recent use of systemic corticosteroids not only provides information as to how well the disease is being controlled but also gives the evaluator an idea if the patient is prone to adrenal suppression during surgical stress.
- Discussing the use of antibiotics and changes in sputum allows the evaluator to know if the patient is experiencing an exacerbation or if the patient is at risk for infection with multidrug-resistant bacteria.

Intraoperative management:

- Intraoperative wheezing can be due to endotracheal intubation, light anesthesia, or allergic reaction. Short-acting

beta-2 adrenergic agonists, followed by inhaled anticholinergics, will give the most prompt relief. The additional use of intravenous and inhaled anesthetics may also be an effective treatment of bronchoconstriction. Epinephrine may be used for severe bronchoconstriction.

- Prophylactic IV corticosteroids are not indicated. Steroids should be given if the patient has recently received steroids and stress doses are needed or the patient experiences an allergic reaction and steroids are administered to reduce the inflammatory response associated with the exposure.
- Helium/oxygen mixtures and magnesium sulfate are only indicated when the patient fails to adequately respond to maximum conventional therapy.

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