The Bronchodilators

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Cover Illustration by Catherine Twomey

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INTRODUCTION

The cardinal manifestations of the major obstructive lung diseases (emphysema, chronic bronchitis, and asthma) include wheezing, breathlessness, chest tightness, and cough and are generally attributed to variable airflow limitation and associated air trapping. The importance of inflammation in the pathophysiology of asthma has been established, and successful control of all but mild intermittent asthma involves the use of a corticosteroid. Pharmacologic agents that cause bronchodilation by modulation of the autonomic nervous system play a key role in the management of symptoms, even though they do not change the natural history of the obstructive lung diseases. Airflow obstruction in chronic obstructive pulmonary disease (COPD) is structural as well as inflammatory, with inflammation mediated more by neutrophils, which are less responsive to steroids. Because obstruction generally is less reversible in COPD, control of symptoms with bronchodilators is even more important in this progressive obstructive disease. This manual discusses 2 classes of bronchodilators that play a key role in the management of the obstructive lung diseases, the β-adrenergic-receptor agonists and the cholinergic antagonists.

PHYSIOLOGIC MEDIATORS OF BRONCHIAL TONE

The baseline tone of the airways is governed by a circadian pattern, with tone being highest during the night and early morning hours. This pattern is surmised to be one of the etiologies of the classic manifestation of predawn worsening of asthmatic symptoms. The human lung is richly innervated by the cholinergic system, with the muscarinic receptor subtype M3 mediating smooth muscle contraction. The parasympathetic system is the primary mediator of basal bronchial tone and probably controls most of the mucus secretion under neural control. In contrast, the direct sympathetic innervation of smooth muscle is limited. β2 Receptors residing on bronchial smooth muscle respond primarily to circulating epinephrine, with little direct sympathetic innervation. The primarily β1,2 and α-agonist norepinephrine has no effect on bronchial tone in asthmatics or controls. Obstructive lung diseases for the most part are not disorders of the autonomic control system of the lung, although the general importance of this system is demonstrated by the dramatic efficacy of sympathetic agonists and muscarinic antagonists.

β-ADRENERGIC–RECEPTOR AGONISTS

HISTORICAL PERSPECTIVE

β2-Adrenergic-receptor agonists are the cornerstone bronchodilatory treatment for asthma, despite a lack of high-quality data regarding the long-term safety and efficacy of this class of agents. However, the utility of β2-agonists as the primary bronchodilator in asthma (and to less extent in COPD) is supported by the weight of years of clinical experience. In traditional Chinese medicine, the botanical ma huang has been used for more than 2000 years for the short-term treatment of respiratory ailments and asthmatic symptoms. The efficacy of this treatment results from the sympathomimetic alkaloids the plant contains.

The history of sympathetic agonism for obstructive lung diseases is an excellent example of empiric use of drugs that directly lead to the elucidation of the physiology of the underlying condition, followed by the development of increasingly precise receptor-directed therapeutics. At the beginning of the twentieth century, the nonselective α-agonist and β-agonist adrenaline (epinephrine) was administered by the subcutaneous route and later was delivered by aerosolization using a squeezebulb. Initially, interest in the sympathomimetic amines focused upon vasoconstrictive rather than bronchodilatory effects, and there were no significant advances in the pulmonary use of this class of agents until the development of isoproterenol in the 1940s. Isoproterenol had specificity for the β receptor, and indeed, characterization of its effects was key in the subsequent identification of the α and β receptors. Inhaled isoproterenol became the standard-of-care bronchodilator, although its use was complicated by a short duration of action (~1 hour after inhalation) and, more concerning, tachycardia and arrhythmias mediated by β1 receptors. Metaproterenol, a