Respiratory system: applied pharmacology

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Abstract

Knowledge and application of respiratory pharmacology is essential for both anaesthetists and intensive care physicians. Patients often present with co-existing respiratory disease for which they may be taking prescription medications. Respiratory function is often altered by anaesthetic drugs and interventions, therefore an in-depth understanding of respiratory pathophysiology and pharmacology is required in order to safely treat these patients. This article describes the basics of the bronchial tone, the ability of the lung to handle and metabolize drugs in addition to discussion of the drugs that can be used to alter bronchial tone and pulmonary vascular resistance.

Keywords β_2-agonists; acute respiratory distress syndrome (ARDS); anticholinergics; asthma; bronchodilators; corticosteroids; pulmonary hypertension; respiratory pharmacology; respiratory physiology; theophyllines

Royal College of Anaesthetists CPD Matrix: 1A01; 1A02; 2A12; 2C04; 3C00; 3G00

Learning objectives

After reading this article, you should be able to:

- explain the physiology of bronchial smooth muscle tone
- explain the role of the lung in drug metabolism
- describe the different classes of bronchodilators
- describe the role of immunomodulation in respiratory pharmacology
- discuss some of the current national guidance for the management of asthma
- discuss the classes of drugs used to treat pulmonary hypertension

Anaesthetists and intensivists commonly treat patients with co-existent respiratory pathology. Many of the drugs used in anaesthesia alter normal respiratory physiology or pathophysiology. Therefore, in order to ensure safe and effective clinical care for patients with respiratory disease, it is essential that practitioners have a detailed understanding of applied respiratory pharmacology.

Bronchial physiology and pathophysiology

Neurohumoral control of bronchial tone results from the interaction of a number of competing pathways. The efferent innervation consists of parasympathetic (cholinergic); sympathetic (adrenergic); non-adrenergic non-cholinergic (NANC) neurones alongside circulating catecholamines and local factors. The afferent pathways are predominantly those arising in sensory receptors.

Parasympathetic ganglia are found in abundance throughout the walls of the bronchi and bronchioles with the post-ganglionic fibres directly innervating the mucus glands along with the airway and vascular smooth muscle. The post-ganglionic fibres innervate post-junctional muscarinic (M_3) receptors located within the mucous glands and bronchial smooth muscle, stimulation of which, causes the predominant bronchoconstrictive response of bronchial smooth muscle by the mechanisms shown in Figure 1 in addition to secretion of mucus from goblet cells.

There is no direct sympathetic innervation of the bronchial smooth muscle, however, autoradiography demonstrates the abundant presence of the β_2-adrenoceptor with increasing density from trachea to alveolus. These receptors are also found on mast cells.[1] Receptor stimulation leads to both relaxation of bronchial muscle and reduction in mast cell mediator release (Figure 1). Adrenergic neurones may interact with and reduce parasympathetic activity through a direct action.

The NANC or the 'non-cholinergic parasympathetic' system releases mediators that contribute to bronchial tone. The predominant inhibitory NANC mediator leading to bronchodilation is nitric oxide (NO), which is synthesized by both endothelial and inducible nitric oxide synthase (eNOS and iNOS). Other peptide hormones (e.g. vasoactive intestinal peptide – VIP) have also been implicated. Stimulatory mediators include: substance P, neuropeptide Y and neurokinins. Locally released mediators also contribute to bronchial tone, usually as a result of membrane receptor interaction and may cause constriction or relaxation (e.g. endothelin, histamine, leukotrienes and prostaglandins).

In health, basal airway tone is set by parasympathetic control although the bronchial tree is at near maximal dilatation to allow for efficient gas exchange. Any sympathetic stimulation typically produces a trivial airway response.[2] In diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS), the respiratory system undergoes physiological changes that render it more vulnerable to insults from increasing mediator release and nervous system alteration, which contributes to the clinical presentations of these conditions.

Drug delivery and the lung

Many of the drugs used to treat respiratory disease, and indeed several anaesthetic drugs, can be delivered to the lungs and system circulation by inhalation. The advantage is the drugs are delivered rapidly to their site of action avoiding first-pass hepatic metabolism. Particle size is important; smaller particles (3 μm diameter) reach the alveoli, whereas larger particles are

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Please cite this article in press as: Brand J, Arrowsmith JE, Respiratory system: applied pharmacology, Anaesthesia and intensive care medicine (2017), https://doi.org/10.1016/j.mpaic.2017.09.001

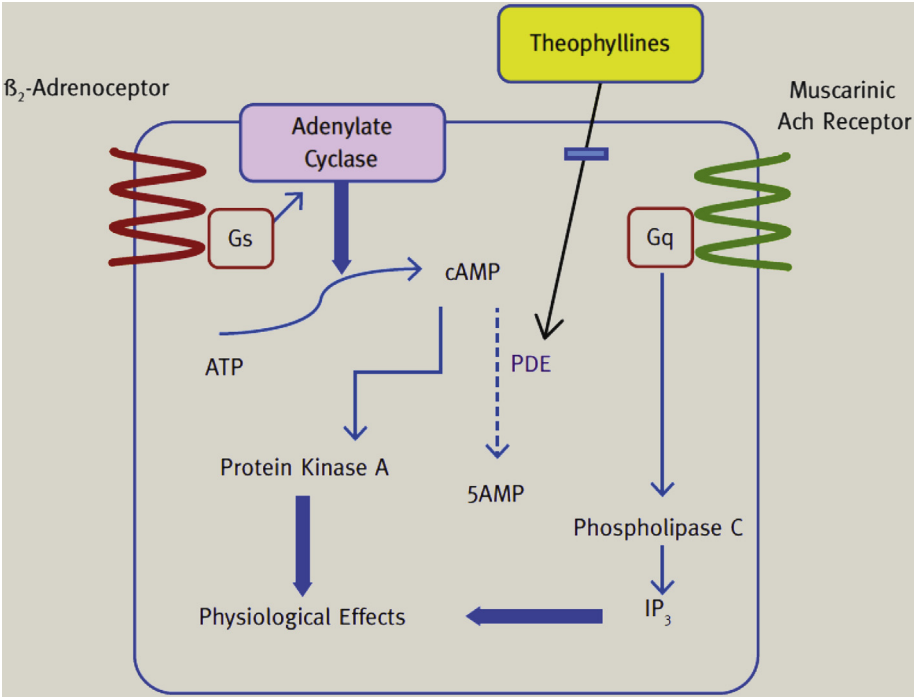

Figure 1 Intracellular signalling mechanisms associated with bronchial smooth muscle. Muscarinic receptors act by Gq G-protein coupled receptors (GPCR). Stimulation of these receptors induces a conformational change that activates phospholipase C and inositol triphosphate (IP_3). The IP_3 then induces an increase in intracellular calcium concentration leading to a contractile response. This is the primary target of the muscarinic antagonists that prevent this activation leading to bronchial smooth muscle relaxation. β-adrenoceptors are also GPCRs, although they are coupled to Gs proteins, the activation of which by an agonist results in an increase of intracellular cyclic adenosine monophosphate (cAMP) that activates protein kinase A to induce phosphorylation of myosin light chains leading to smooth muscle relaxation. The non-specific phosphodiesterase inhibitors (PDEs) act to amplify the above pathway by inhibiting the breakdown of cAMP, thereby increasing the concentration available within the above signalling pathway. Ach, acetylcholine.

deposited throughout the length of the bronchial tree, making targeted drug delivery possible. Most aerosol delivery systems produce a variety of particle sizes (1–35 μm diameter) to ensure an equal distribution of the drug throughout the pulmonary tree. The delivery systems used in clinical practice are: metered-dose inhalers (MDI), dry powder inhalers, nebulizers and vapour/gas.

Drug metabolism and the lung

The lungs process a wide variety of endogenous enzymes thereby inferring that they have involvement in drug metabolism. The lungs have an abundance of active mixed function oxidase and cytochrome p450 systems, suggesting that drug handling within the lung draws parallels with the hepatic system. For example, both steroids and isoproterenol are predominantly metabolized in the lung.[3] Drug uptake within the lung is also high, removing a number of systemically administered drugs. However many of these drugs are not metabolized and are retained in the tissues where they either undergo a slow release, displacement or are removed by the reticuloendothelial system. This uptake and slow distribution may result in the lung toxicity associated with drugs such as amiodarone.[4] The relative metabolic activity is likely to be low due to anatomical location of the lung enzyme systems.

Pharmacological bronchodilation

β_2-adrenoceptor agonists are sympathomimetic amines that are widely used as bronchodilators through their action on bronchial smooth muscle adrenoceptors (Figure 1). They also reduce the release of histamine and other pro-inflammatory cytokines,[1] although this is not useful for long-term control due to rapid desensitization. They are considered first-line treatment in exacerbations of both asthma and COPD, although asthmatics usually exhibit a more rapid response time following administration.[5] Acute bronchoconstriction is initially treated with high-dose short-acting agents (e.g. salbutamol). These agents have an onset of action within 1–5 minutes and last for up to 5 hours. Longer acting agents (e.g. salmeterol) are reserved for long-term control and prevention. These act within 30 minutes of administration and, due to their lipophilic nature and reduced diffusing capacity, last for up to 12 hours. The drugs are usually administered by aerosol inhalation of either a powder, MDI or nebulized solution. Oral formulations are commonly used in paediatric patients unable to use delivery devices whilst intravenous (IV) formulations are reserved for emergency situations where inhaled therapy cannot be reliably administered. The drugs undergo metabolic transformation in the liver by hydroxylation and sulphation. Their adverse effects are predominantly a direct result of cardiac β_1-adrenoceptor stimulation – tachycardia, arrhythmias, prolongation of QT interval and hypertension. Tremor of skeletal muscle is very common, particularly at higher doses, as is a lactic acidosis. Exacerbations of both ketoacidosis and hyperthyroidism have also been reported. Hypokalaemia is a common adverse effect resulting from receptor-induced intracellular potassium flux; therefore particular attention must be paid when using these

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