

CHAPTER 2 – Bronchodilator Response

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2.1 Introduction

A wide range of drugs are currently available for the treatment of respiratory disorders (Table 2.1). Many drugs are delivered via the inhaled route with the advantages of more rapid onset of action, reduced doses and side effects. However drugs such as methylxanthines and the more recently introduced leukotriene antagonists are still delivered via the oral route. However whichever route of administration is used, drug receptor interactions remain the same.

Table 2.1 Drugs commonly used in the treatment of respiratory disorders

Bronchodilator drugs	β_2 adrenoreceptor stimulants
	Anticholinergic agents
Anti-inflammatory agents	Corticosteroids
	Cromoglicate
Leukotriene antagonists	
Anti-microbial agents	Antibacterial drugs
	Antifungal drugs

All of the above quoted drugs are listed in the British National Formulary (BNF) [1] in which they are divided according to their site of action in the human body or to their particular action.

2.2 Pharmacodynamics

Nearly all drugs exert their effect by interaction with receptors. Receptors are proteins that serve as recognition sites for various stimuli with specific receptors responding to specific stimuli. Drugs that act as stimuli for receptors are termed agonists. Most drug receptors are located on the cell membrane, with the exception of corticosteroid receptors which are located within the cell.

Drug receptor interactions

Several terms are used to describe drug-receptor interaction.

Efficacy. The tendency of a drug-receptor complex to cause a specific response.

Affinity. The tendency of a drug to combine with a particular receptor.

Agonists. A drug that has both affinity for a receptor and elicits a response is called an agonist. A drug that produces a less than maximal effect is termed a partial agonist.

Antagonists. A drug that has affinity for a receptor but is not able to induce an effect is known as an antagonist. Antagonists can be either competitive or non-competitive.

Competitive antagonism exists when an agonist and an antagonist compete for a common receptor. Competitive antagonism is surmountable in that increasing the concentration of the agonist will overcome the actions of the antagonist. e.g. histamine and antihistamine.

In *non-competitive antagonism* the antagonist prevents the agonist from producing an effect at its receptor site by acting on any of the steps that lead to the ultimate response. In this case an increase in concentration of the agonist has no effect.

2.2.1 Autonomic Nervous System

The autonomic nervous system is the involuntary, unconscious control mechanism of the body. It is divided into the parasympathetic and sympathetic branches which maintain a balance of opposing effects on the body's smooth muscle and glands.

The autonomic system is generally considered an efferent system, where impulses travel from the brain and spinal cord out to the various neuroeffector sites. Three different efferent nervous pathways supply the airway smooth muscle: *cholinergic*, *adrenergic* and *non adrenergic non cholinergic* (NANC). There are however afferent nerves within the respiratory system that convey impulses to the spinal cord from the periphery. Afferent nervous signals that originate in respiratory tissue come from stretch, irritant and J receptors. These nerve signals may control smooth muscle tone of the airway in a reflex manner and may trigger reflex actions such as cough and hyperpnea.

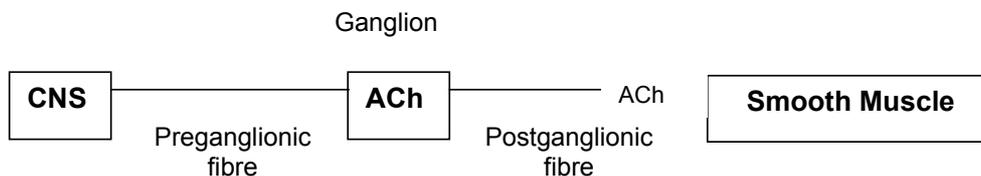
The autonomic nervous system with both its parasympathetic and sympathetic subdivisions regulates airway function. Primarily the *parasympathetic* division influences airway smooth muscle, where acetylcholine, released from postganglionic neurons results in contraction of

smooth muscle in the airway. Noradrenaline, released from the postganglionic neurons of the *sympathetic* branch of the autonomic nervous system, relaxes smooth muscle in the airways.

2.2.2 Parasympathetic Innervation

Stimulation of parasympathetic efferent fibres in the airways causes an increase in smooth muscle tone. The nerve that innervates the respiratory system is the vagus nerve. Parasympathetic nerve endings are found throughout the respiratory tree, however their number decreases in the smaller airways.

Figure 2.1 A simplified model of a parasympathetic nerve pathway



The pre ganglionic fibre (efferent neuron), conducts an impulse from the central nervous system to the post ganglionic fibre and then to the effector organ (airway smooth muscle).

Acetylcholine is both the neural transmitter at the synapse between the pre and post ganglionic nerve fibres and the effector tissue. It is contained in small agranular vesicles in the nerves and is released upon stimulation of the nerve. When released acetylcholine quickly depolarises the post-synaptic membrane, allowing transmission of the nerve signal to the post ganglionic fibre. There is continuous release of ACh by these cholinergic fibres creating the basal tone of the airway.

Acetylcholine, once released into the neuromuscular junction, binds reversibly with a surface receptor on the smooth muscle, activating complex cellular mechanisms that result in smooth muscle contraction. The action of acetylcholine at the receptor site is of limited duration as it is hydrolysed in less than a millisecond by the enzyme cholinesterase into choline and acetic acid. Drugs can use this neurotransmitter mechanism to stimulate (parasympathomimetics) nerve endings or to block (parasympatholytics) the transmission of impulses.

2.2.3 Parasympathomimetic Agents

These agents mimic the action caused by acetylcholine at its receptor sites and can be either *direct* or *indirect* acting.