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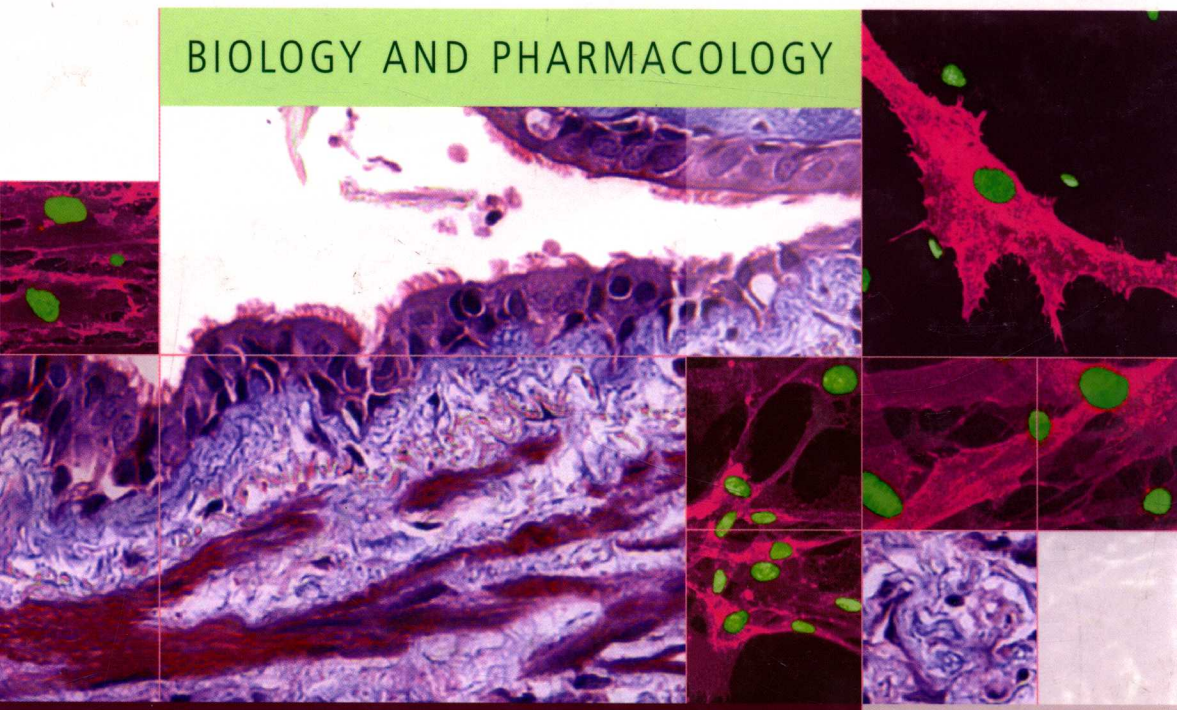
Airway Smooth Muscle in Asthma and COPD

BIOLOGY AND PHARMACOLOGY



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Airway Smooth Muscle in Asthma and COPD:

Biology and Pharmacology

Edited by

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Airway Smooth Muscle

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Contents

1

Biophysical basis of airway smooth muscle contraction and hyperresponsiveness in asthma

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1.1 Introduction

It is self-evident that acute narrowing of the asthmatic airways and shortening of the airway smooth muscle are inextricably linked. Nonetheless, it was many years ago that research on the asthmatic airways and research on the biophysics of airway smooth muscle had a parting of the ways (Seow and Fredberg, 2001). The study of smooth muscle biophysics took on a life of its own and pursued a deeply reductionist agenda, one that became focused to a large extent on myosin II and regulation of the actomyosin cycling rate. The study of airway biology pursued a reductionist agenda as well, but one that became focused less and less on contractile functions of muscle and instead emphasized immune responses, inflammatory cells and mediators, and, to the extent that smooth muscle remained

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of interest, that interest centred mainly on its synthetic, proliferative and migratory functions (Amrani and Panettieri, 2003; Black and Johnson, 1996; 2000; Black *et al.*, 2001; Holgate *et al.*, 2003; Kelleher *et al.*, 1995; Zhu *et al.*, 2001). Inflammatory remodelling of the airway wall was also recognized as being a key event in the asthmatic diathesis (Dulin *et al.*, 2003; Homer and Elias, 2000; James *et al.*, 1989; McParland *et al.*, 2003; Moreno *et al.*, 1986; Paré *et al.*, 1991; Wang *et al.*, 2003).

To better understand the impact of inflammatory remodelling processes upon smooth muscle shortening and acute airway narrowing, computational models of ever increasing sophistication were formulated, but, remarkably, the muscle compartment of these models remained at a relatively primitive level, being represented by nothing more than the classical relationship of active isometric force versus muscle length (Lambert and Paré, 1997; Lambert *et al.*, 1993; Macklem, 1987; 1989; 1990; 1996; Wiggs *et al.*, 1992). As discussed below, this description is now considered to be problematic because the very existence of a well-defined static force–length relationship has of late been called into question, as has the classical notion that the muscle possesses a well-defined optimal length. Rather, other factors intrinsic to the airway smooth muscle cell, especially muscle dynamics and mechanical plasticity, as well as unanticipated interactions between the muscle and its load, are now understood to be major factors affecting the ability of smooth muscle to narrow the airways (An *et al.*, 2007; Fredberg, 2000a; Fredberg *et al.*, 1999; Pratusevich *et al.*, 1995; Seow and Fredberg, 2001; Seow and Stephens, 1988; Seow *et al.*, 2000).

The topics addressed in this chapter are intended to highlight recent discoveries that bring airway biology and smooth muscle biophysics into the same arena once again. Here we do not provide an exhaustive review of the literature, but rather emphasize key biophysical properties of airway smooth muscle as they relate to excessive airway narrowing in asthma. This is appropriate because, in the end, if airway inflammation did not cause airway narrowing, asthma might be a tolerable disease. But asthma is not a tolerable disease. In order to understand the multifaceted problem of airway hyperresponsiveness in asthma, therefore, an integrative understanding that brings together a diversity of factors will be essential.

1.2 Airway hyperresponsiveness

It was recognized quite early that the lung is an irritable organ and that stimulation of its contractile machinery in an animal with an open chest can cause an increase

in lung recoil, an expelling of air, a rise in intratracheal pressure, and an increase in airways resistance (Colebatch *et al.*, 1966; Dixon and Brodie, 1903; Mead, 1973; Otis, 1983). The fraction of the tissue volume that is attributable to contractile machinery is comparable for airways, alveolated ducts and blood vessels in the lung parenchyma (Oldmixon *et al.*, 2001); the lung parenchyma, like the airways, is a contractile tissue (Colebatch and Mitchell, 1971; Dolhnikoff *et al.*, 1998; Fredberg *et al.*, 1993; Ludwig *et al.*, 1987; 1988). Although airway smooth muscle was first described in 1804 by Franz Daniel Reisseisen (as related by Otis (1983)) and its functional properties first considered by Einthoven (1892) and Dixon and Brodie (1903), until the second half of the last century this muscle embedded in the airways was not regarded as being a tissue of any particular significance in respiratory mechanics (Otis, 1983). A notable exception in that regard was Henry Hyde Salter, who, in 1859, was well aware of the 'spastic' nature of airway smooth muscle and its potential role in asthma (Salter, 1868). The airway smooth muscle is now recognized as being the major end-effector of acute airway narrowing in asthma (Lambert and Paré, 1997; Macklem, 1996). There is also widespread agreement that shortening of the airway smooth muscle cell is the proximal cause of excessive airway narrowing during an asthmatic attack (Dulin *et al.*, 2003), and swelling of airway wall compartments and plugging by airway liquid or mucus are important amplifying factors (Lambert and Paré, 1997; Yager *et al.*, 1989). It remains unclear, however, why in asthma the muscle can shorten excessively.

'Airway hyperresponsiveness' is the term used to describe airways that narrow too easily and too much in response to challenge with nonspecific contractile agonists (Woolcock and Peat, 1989). Typically, a graph of airways resistance versus dose is sigmoid in shape (Figure 1.1); the response shows a plateau at high levels of contractile stimulus. The existence of the plateau, in general, is interpreted to mean that the airway smooth muscle is activated maximally and, thereby, has shortened as much as it can against a given elastic load. Once on the plateau, therefore, any further increase in stimulus can produce no additional active force, muscle shortening, or airway resistance.

To say that airways narrow too easily, on the one hand, means that the graph of airways resistance versus dose of a nonspecific contractile stimulus is shifted to the left along the dose axis, and that airways respond appreciably to levels of stimulus at which the healthy individual would be unresponsive; this phenomenon is called hypersensitivity. To say that airways narrow too much, on the other hand, means that the level of the plateau response is elevated, or that the plateau is abolished altogether, regardless of the position of the curve along the dose axis; this phenomenon is called hyperreactivity. As distinct from hypersensitivity, it is

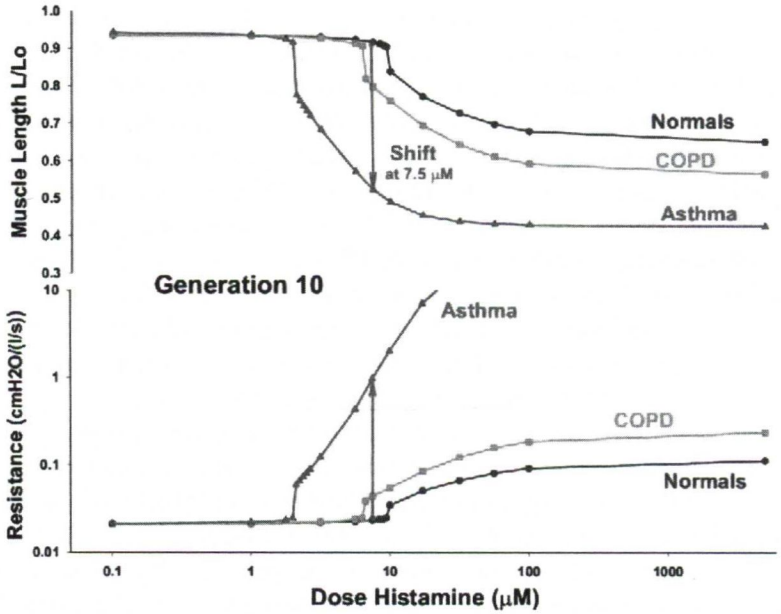

Figure 1.1 Computation of airway hyperresponsiveness in asthma. A computational result showing airway length (top) and airway resistance (bottom) as a function of agonist concentration for a 10th-generation airway (Mijailovich, 2003). The cases shown depict airways from a normal, an asthmatic and a COPD (Chronic obstructive pulmonary disease) lung. In this computation, the effects of tidal breathing and deep inspirations (6/min) upon myosin binding dynamics are taken into account explicitly (Mijailovich, 2003). As explained in the text, such an airway exhibits both hyperreactivity and hypersensitivity. (Reproduced courtesy of the American Journal of Respiratory and Critical Care Medicine 167, A183.)

this ability of the airways to narrow excessively, with an elevated or abolished plateau, that accounts for the morbidity and mortality associated with asthma (Sterk and Bel, 1989).

It has long been thought that the factors that cause hypersensitivity versus hyperreactivity are distinct, the former being associated with receptor complement and downstream signalling events but the latter being associated with purely mechanical factors, including the contractile apparatus, the cytoskeleton (CSK), and the mechanical load against which the muscle shortens (Armour *et al.*, 1984; Lambert and Paré, 1997; Macklem, 1996; Wiggs *et al.*, 1992). Macklem has pointed out that, once the muscle has become maximally activated, it is the active force and the load that become all-important, and the plateau response becomes essentially uncoupled from underlying biochemistry, signalling and cell biology