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Airway smooth muscle and bronchospasm: Fluctuating, fluidizing, freezing

Ramaswamy Krishnan, Xavier Trepat, Trang T.B. Nguyen, Guillaume Lenormand, Madavi Oliver, Jeffrey J. Fredberg*

Program in Molecular and Integrative Physiological Sciences, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, United States

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ABSTRACT

We review here four recent findings that have altered in a fundamental way our understanding of airways smooth muscle (ASM), its dynamic responses to physiological loading, and their dominant mechanical role in bronchospasm. These findings highlight ASM remodeling processes that are innately out-of-equilibrium and dynamic, and bring to the forefront a striking intersection between topics in condensed matter physics and ASM cytoskeletal biology. By doing so, they place in a new light the role of enhanced ASM mass in airway hyper-responsiveness as well as in the failure of a deep inspiration to relax the asthmatic airway. These findings have established that (i) ASM length is equilibrated dynamically, not statically; (ii) ASM dynamics closely resemble physical features exhibited by so-called soft glassy materials; (iii) static force–length relationships fail to describe dynamically contracted ASM states; (iv) stretch fluidizes the ASM cytoskeleton. Taken together, these observations suggest that at the origin of the bronchodilatory effect of a deep inspiration, and its failure in asthma, may lie glassy dynamics of the ASM cell.

1. Introduction

Asthma is characterized by airways that constrict too easily (airway hypersensitivity) and too much (airway hyper-responsiveness, AHR) (Woolcock and Peat, 1989). It is the excessive airway narrowing associated with AHR, rather than the hypersensitivity, that accounts for the morbidity and the mortality that is attributable to the disease (Macklem, 1989; Sterk and Bel, 1989; McParland et al., 2003). AHR is thought to arise as a result of ongoing and irreversible remodeling of the airway wall (Pare et al., 1997; King et al., 1999b; Martin et al., 2000; Brusasco and Pellegrino, 2003; McParland et al., 2003; Bai et al., 2004; Fredberg, 2004). Among the various contributing factors that come into play in the remodeled airway (Woolcock and Peat, 1989), AHR might be accounted for either by increased mass of airway smooth muscle (ASM) or by decreased load against which the ASM must contract, but it is widely believed that increased ASM mass is the main culprit (Wiggs et al., 1992; Lambert et al., 1993; Macklem, 1998).

Importantly, this conclusion has been based upon considerations that are mainly theoretical, deriving almost entirely from structural evidence that has been incorporated into detailed mathematical models describing the mechanics of airway narrowing (Wiggs et al., 1992; Lambert et al., 1993; Macklem, 1996). We have recently come to learn, however, that phenomena accounting for AHR are mainly dynamic and are therefore unaccounted for by these previous theoretical analyses, which are entirely static. Moreover, these new results confirm the long-held conclusion that increased ASM mass is the functionally dominant derangement, but mechanisms accounting for this derangement differ dramatically from those previously presumed. Within such a dynamic framework, increased ASM mass not only explains AHR but also accounts for the failure of a deep inspiration (DI) to relax the asthmatic airway (Oliver et al., 2007), much as had been described long ago by Salter (1859). Indeed, new results imply that the failure of a DI to relax the asthmatic airway may be the proximal cause of AHR in asthma.

We begin this review by highlighting Salter's early observations, and then go on to describe four iconoclastic findings that have changed in a fundamental way how we now think about airway smooth muscle and its role in bronchospasm.

1.1. HH Salter and the pivotal role of deep inspirations in asthma

In 1859, Henry H. Salter highlighted the existence of ASM and its importance in asthma (Salter, 1859). He noted in particular that during a spontaneous asthma attack the asthmatic loses the ability to dilate the airways with a deep inspiration, almost as if the airways had narrowed and then become frozen in the narrowed state. He wrote,

* Corresponding author. Tel.: +1 617 432 0198.
E-mail address: jeffrey_fredberg@harvard.edu (J.J. Fredberg).

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> "...the spasm may be broken through, and the respiration for the time rendered is perfectly free and easy, by taking a long, deep, full inspiration. In severe asthmatic breathing this cannot be done; but in the slight bronchial spasm that characterizes hay asthma I have frequently witnessed it. It seems that the deep inspiration overcame and broke through the contracted state of the air tubes, which was not immediately re-established..."(Salter, 1859).

It is now well established that of all known bronchodilatory agencies or drugs, the single most efficacious is a simple sigh or DI (Nadel and Tierney, 1961; Green and Mead, 1974; Gump et al., 2001). During the spontaneous asthmatic attack – but *not* during induced obstruction in the laboratory – this most beneficial of all known bronchodilating agencies becomes ablated altogether (Fish et al., 1981; Lim et al., 1987; Ingram, 1995; Skloot et al., 1995). It was suggested subsequently that the failure of this potent homeostatic phenomenon may be the proximal cause of the excess morbidity and mortality that is attributable to the disease (Nadel and Tierney, 1961; Fish et al., 1981; Lim et al., 1987; Skloot et al., 1995; Moore et al., 1997; Fredberg, 2000). This mystery then went on to attract the attention of an impressive pedigree of luminaries – Salter (1859), Nadel (Nadel and Tierney, 1961), Fish et al. (1981), Mead (Green and Mead, 1974), Macklem (Ding et al., 1987), Ingram (Lim et al., 1987), Permutt (Skloot et al., 1995), Paré (Moore et al., 1997), Brusasco (Crimi et al., 2002), Solway (Dowell et al., 2005; Chen et al., 2006) – but the mechanism has remained elusive.

2. Four iconoclastic discoveries

2.1. Muscle length is equilibrated dynamically, not statically

To explain acute airway narrowing and why it becomes excessive during asthma, the classical theory assumes static mechanical equilibrium: isometric active force generated by the ASM is balanced by the passive reaction force developed by the external load against which the muscle had shortened. According to this formulation, if the external load fluctuates with time, during lung inflation for example, the muscle would regulate its force at every instant as dictated by its static force–length characteristic. The key ideas here are force balance and its static nature: the smaller the elastic load, or the bigger the active isometric force, the smaller will be the caliber of the airway lumen at equilibrium, where the isometric force-generating capacity of ASM is set principally by muscle mass, muscle contractility, and muscle position on its static force–length characteristic (Lambert and Wilson, 1973; Moreno et al., 1986; Wiggs et al., 1992; Macklem, 1996; Thomson et al., 1996; Lambert and Pare, 1997).

These classical ideas predict the static equilibrium length toward which activated airway smooth muscle would tend if given enough time, but the biologically relevant prediction is quite different. In spontaneous normal breathing there is not nearly enough time for such an equilibration to occur, and the fluctuations associated with action of tidal breathing itself strongly perturbs the muscle (Fredberg et al., 1999a). We can put the potency of tidal fluctuations into perspective with the following observations. The expected physiologic range of tidal muscle stretch is from about 4% of muscle length during spontaneous breathing at rest to 12% during a sigh and greater still during exercise (Gump et al., 2001). In isolated activated muscle, however, tidal stretches of only 3% of muscle length are enough to inhibit active force generation by 50% (Fredberg et al., 1997). As such, isometric force generating capacity of airway smooth muscle fails to describe muscle forces in normal physiologic circumstances (Raboudi et al., 1998). The old view of homeostasis and equilibrium is now replaced by a dynamic world of fluctuation and nonequilibrium behavior.

The bronchodilating effect of spontaneous breathing is so effective that airway narrowing never approaches dangerous levels in healthy people, even when challenged with high concentrations of nonspecific bronchoconstricting agents. In healthy volunteers who inhale bronchoconstricting substances, such as histamine, there is a reflex increase in the frequency and depth of spontaneous sighs, and these fluctuations cause prompt and nearly complete dilation of the airway (Orehek et al., 1980; Lim et al., 1987, 1989). Even when healthy volunteers inhale some of the most potent known bronchoconstrictors, such as leukotrienes, bronchospasm is profoundly blunted unless deep inspirations are prohibited (Drazen and Austen, 1987). Taking into account the levels at which endogenous dilators are found in the airway, these observations suggest that the tidal muscle stretches that are attendant to spontaneous breathing comprise the first line of defense against bronchospasm, and that imposed tidal fluctuations of muscle length may be the most potent of all known bronchodilating agencies (Fredberg, 1998, 2000, 2004; Fredberg and Shore, 1999b).

2.1.1. Freezing at static equilibrium

During an asthmatic attack, this potent bronchodilating mechanism fails. Indeed, there is ample evidence from the work of Ingram (Lim et al., 1987) to show that, if anything, deep inspirations during an asthmatic attack only serve to make matters worse. In this connection, experiments conducted years ago led Fish et al. (1981) to the striking observation that airway obstruction in asthma behaves as if it were caused by an intrinsic impairment of the bronchodilating effect of a deep inspiration, as opposed to an inappropriate end responsiveness of the airway itself. At about the same time, similar observations led Orehek et al. (1980) to speculate that asthma triggers a vicious cycle in which asthmatic airway obstruction increases the frequency of deep inspirations, and deep inspirations, in turn, make the obstruction worse.

This impairment of the bronchodilating effect of a deep inspiration was long thought to be a characteristic of only spontaneous asthmatic obstruction and the late phase response to allergen challenge (Lim et al., 1987; Ingram, 1995). Therefore, it came as a surprise to learn only recently that an impairment of this kind is easily evoked in completely healthy individuals. Two laboratories have shown that if healthy, nonasthmatic, nonallergic subjects do nothing more than to voluntarily refrain from deep inspirations but otherwise maintain normal tidal volume, minute ventilation, and functional residual capacity, within 15 min their airways become hyper-responsive to a degree that is virtually indistinguishable from that observed in asthmatic subjects (Skloot et al., 1995; Moore et al., 1997; King et al., 1999a). Although in ordinary circumstances a normal individual subjected to bronchial provocation can reinstate a dilated airway with a single deep inspiration, if DIs are prohibited for 15 min and eventually reinstated, the subsequent ability of deep inspirations to dilate the airways becomes profoundly impaired, just as it does in spontaneous asthmatic obstruction. Put simply, it is as if the airway smooth muscle, when activated, is all the time flirting with disaster (Fredberg, 1998), and the mere removal of deep inspirations, which would seem superficially to be a rather trivial matter, is sufficient nonetheless to precipitate a cascade of events that is much more serious. The airway smooth muscle can somehow become frozen into a stiff and shortened state, even in healthy volunteers with no airway inflammation, no history of airway inflammation or allergy, and airways and airway smooth muscle that are perfectly normal. This stiff and shortened state has been recently demonstrated experimentally in isolated ASM strips subjected to physiological loading conditions (Fig. 1) (Oliver et al., 2007).