Pulmonary Pharmacology & Therapeutics 26 (2013) 3–12

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Airway contractility and remodeling: Links to asthma symptoms

Adrian R. West [a], Harley T. Syyong [b], Sana Siddiqui [c,1], Chris D. Pascoe [b], Thomas M. Murphy [d], Harm Maarsingh [e], Linhong Deng [f,g], Geoffrey N. Maksym [a], Ynuk Bossé [b,*]

[a] School of Biomedical Engineering, Dalhousie University, Nova Scotia, Canada
[b] University of British Columbia, James Hogg Research Center, St. Paul's Hospital, 985 West 10th Ave, Vancouver, British Columbia, Canada
[c] Meakins-Christie Laboratories, McGill University Montréal, Québec, Canada
[d] Duke University Medical Center, Durham, NC, USA
[e] University of Groningen, Groningen, Netherlands
[f] Institute of Biomedical Engineering and Health Sciences, Changzhou University, Changzhou, Jiangsu, China
[g] Ministry of Education Key Laboratory of Biorheological Science and Technology, Bioengineering College, Chongqing University, Shapingba, Chongqing, China

ARTICLE INFO

Article history:
Received 19 July 2012
Received in revised form
14 August 2012
Accepted 16 August 2012

Keywords:
Airway smooth muscle
Asthma
Airway hyperresponsiveness
Contractility
Tone
Spasmogens
Remodeling

ABSTRACT

Respiratory symptoms are largely caused by obstruction of the airways. In asthma, airway narrowing mediated by airway smooth muscle (ASM) contraction contributes significantly to obstruction. The spasmogens produced following exposure to environmental triggers, such as viruses or allergens, are initially responsible for ASM activation. However, the extent of narrowing of the airway lumen due to ASM shortening can be influenced by many factors and it remains a real challenge to decipher the exact role of ASM in causing asthmatic symptoms. Innovative tools, such as the forced oscillation technique, continue to develop and have been proven useful to assess some features of ASM function *in vivo*. Despite these technologic advances, it is still not clear whether excessive narrowing in asthma is driven by ASM abnormalities, by other alterations in non-muscle factors or simply because of the overexpression of spasmogens. This is because a multitude of forces are acting on the airway wall, and because not only are these forces constantly changing but they are also intricately interconnected. To counteract these limitations, investigators have utilized *in vitro* and *ex vivo* systems to assess and compare asthmatic and non-asthmatic ASM contractility. This review describes: 1- some muscle and non-muscle factors that are altered in asthma that may lead to airway narrowing and asthma symptoms; 2- some technologies such as the forced oscillation technique that have the potential to unveil the role of ASM in airway narrowing *in vivo*; and 3- some data from *ex vivo* and *in vitro* methods that probe the possibility that airway hyperresponsiveness is due to the altered environment surrounding the ASM or, alternatively, to a hypercontractile ASM phenotype that can be either innate or acquired.

1. Introduction

Asthma symptoms are triggered by exposure to environmental factors, such as viruses, allergens and pollutants (Fig. 1). In any case, diverse and intricate inflammatory processes take place and lead to the release of spasmogens, such as leukotrienes, histamine, endothelin-1 and others. Acting collectively, these spasmogens activate the airway smooth muscle (ASM), which then strives to shorten. Due to its nearly circumferential arrangement within the airway wall, ASM shortening causes narrowing of the airway lumen, which causes respiratory symptoms by increasing resistance to airflow. The salutary effect of drugs relaxing or inhibiting contraction of the ASM, such as the β_2-agonists or anti-cholinergics [73] in the treatment of asthma is the testimony of the importance of ASM in the elaboration of asthma symptoms.

Another characteristic feature of asthma is airway hyper-responsiveness (AHR). AHR is defined as a non-specific increase in sensitivity (leftward shift of the dose-response curve) and reactivity (increased slope of the dose-response curve and elevated maximal achievable response) to an inhalational challenge with a spasmogen. Apart from being a good diagnostic test for asthma, the measurement of airway responsiveness is also a useful predictor for asthma control, future risk of exacerbations and decline in lung function [16]. The measurement of airway responsiveness is also relevant for the understanding of asthma symptoms, as it reasonably reproduces the airway response that will take place in response to endogenously-produced spasmogens.

* Corresponding author. Tel.: +1 7789977004.
E-mail address: ynuk.bosse@hli.ubc.ca (Y. Bossé).
[1] Present address: Receptor Pharmacology Unit, National Institute on Aging, Baltimore, MD, USA.

1094-5539/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pupt.2012.08.009

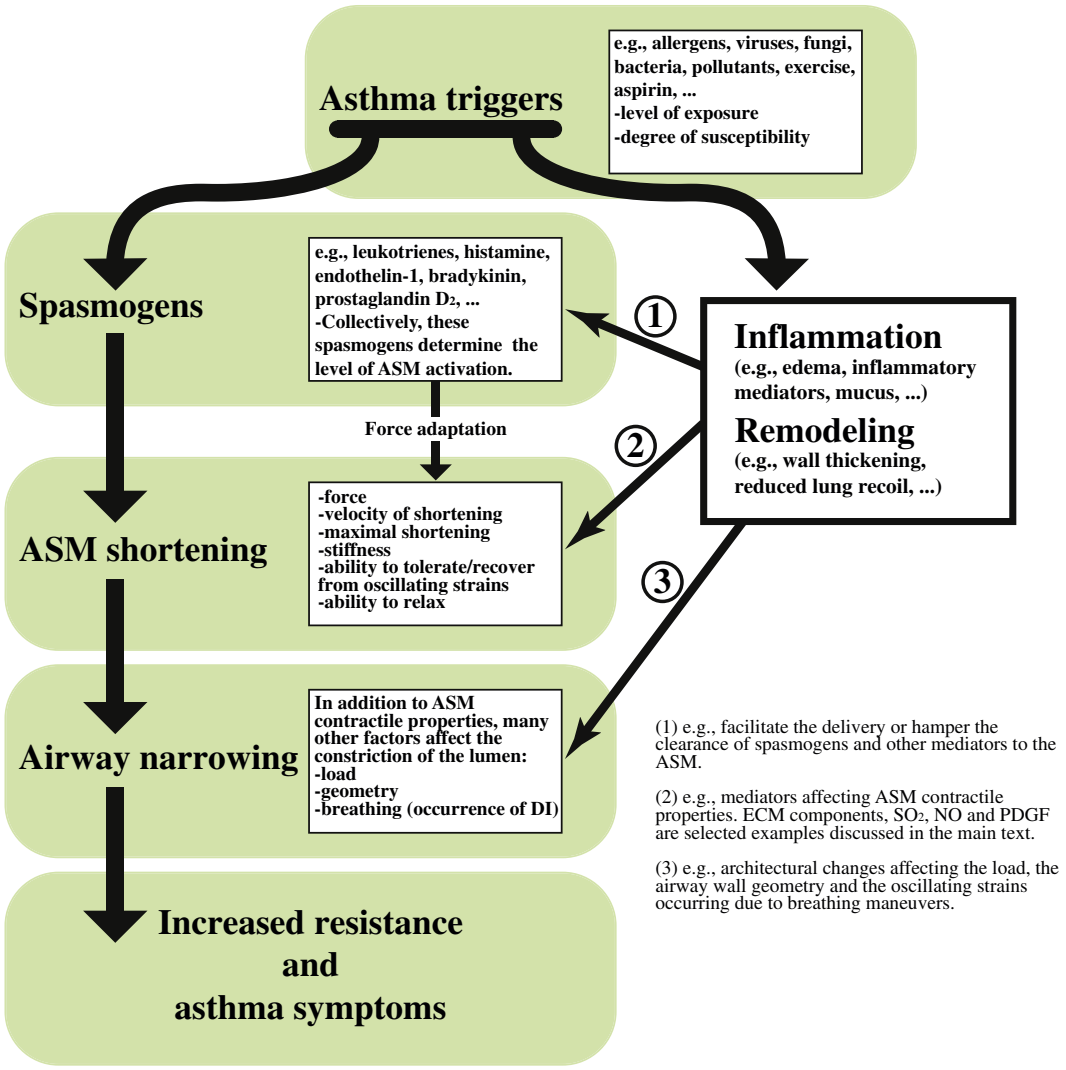

Fig. 1. Diagram showing the airway responsiveness component on the left, the inflammatory/remodeling component on the right, and various ways by which they contribute and interconnect to affect asthma symptoms following exposure to asthma trigger(s). The inflammatory/remodeling component can affect symptoms either directly or indirectly by modifying airway responsiveness at different levels (enumerate 1–3 in the diagram). Thus, the inflammatory/remodeling component can affect airway responsiveness (positively or negatively) directly or indirectly by affecting both the size of the ASM tissue and any of its contractile property.

While airway responsiveness is unequivocally mediated by ASM activation and shortening, the cause of AHR is unclear. It is not established if the excessive responsiveness is due to altered ASM, or normal ASM in an altered environment. Indeed, many non-muscle factors can contribute to AHR (reviewed in Ref. [14]). For example, changes in the extracellular matrix, the geometry of the airways and the load impeding ASM shortening can all lead to AHR.

The severity of asthma symptoms depends on the magnitude of exposure to the environmental trigger(s), the amount of spasmogens produced for a given exposure, the contractility of the ASM, as well as to non-muscle factors that increases airway narrowing passively, or by affecting ASM contractility. In this review, we first give a brief overview of the techniques that are currently used to assess lung function and how these kinds of measurements are related to airway and ASM mechanics. We then highlight recent work in the field that provides possible mechanistic links between asthma symptoms and either innate/acquired ASM hyper-contractility or normal ASM contractility in an altered environment.

2. *In vivo* measurement of airway functions

Classically, in the clinical setting lung functions are measured by spirometry. Force expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), force vital capacity (FVC), mean flow in between chosen lung volumes, such as the forced expiratory flow in between 75 and 25% FVC (FEV_{25-75}), are certainly amongst the most frequent outcomes obtained by spirometry. Together and sometimes expressed in relation to each other, such as the FEV_1/FVC ratio, these lung functions are quite informative, they correlate well with asthma symptoms, and they are useful to guide clinicians in their therapeutic approach. Combined with some other interventions, they can also give some clues regarding ASM function. The reversibility of airway obstruction measured by the change in FEV_1 prior and after inhaling a bronchodilator (e.g., β_2-adrenoceptor agonist) is a good example illustrating the role played by the ASM in airflow limitation. The degree of airway responsiveness measured by the progressive decrease in FEV_1 during the inhalation of increasing doses of a spasmogen during bronchial challenge testing also provides an indication of the role played by ASM contraction in