The Role of Transient Receptor Potential Vanilloid 1 (TRPV1) in Enalapril-Induced Airway Hyperresponsiveness in Mouse Model

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ABSTRACT

Airway hyperresponsiveness is an important pathophysiological feature of asthma. Transient Receptor Potential Vanilloid-1 (TRPV1) receptor expression is increased under asthma and activation of TRPV1 plays a key role in the manifestation of airway hyperresponsiveness. Various inflammatory mediators (prostaglandin E2, bradykinin etc.) enhance sensitivity and reduce the activation threshold of TRPV1 receptor. Enalapril is an Angiotensin-converting enzyme (ACE) inhibitor often associated with airway hyperresponsiveness in asthmatic hypertensive patients through an increase in bradykinin level. Therefore, the present investigation is carried out to find out the role of TRPV1 in enalapril-induced airway hyperresponsiveness using trypsin and egg-albumin induced asthma model mice. Enalapril, baicalein, celecoxib and capsazepine were administered for 8 days and airway hyperresponsiveness was measured in terms of tidal volume, respiratory rate, and airflow rate. There was significantly lower tidal volume and airflow rate and higher respiratory rate in enalapril treated asthmatic mice compared to only asthmatic mice. Mice pretreated with capsazepine, celecoxib, and baicalein before 2 h of enalapril administration showed significantly increased tidal volume and airflow rate, and decreased respiratory rate compared to enalapril-treated asthmatic mice. Thus, it is concluded that TRPV1 might be involved in enalapril-induced airway hypersensitiveness in asthmatic mice. The cycloxygenase and 12-lipoxygenase pathways might be involved in activation of TRPV1 by enalapril.

KEYWORDS: Airway hyperresponsiveness; asthma; TRPV1; enalapril; bradykinin; ACE inhibitors.

Introduction

Angiotensin-converting enzyme inhibitors, which block the renin–angiotensin–aldosterone system, are used to treat hypertension and congestive heart failure. Although these agents are well tolerated and have few incidences of serious adverse reactions, they are often associated with increased incidences of cough and airway hyperresponsiveness (AHR) (Lindgren and Andersson, 1989). The mechanism of ACE inhibitor-induced cough and airway hyperresponsiveness remains unresolved, but likely involves the mediators bradykinin and substance P, agents that are degraded by ACE and therefore accumulate in the upper respiratory tract or lung when the enzyme is inhibited, and prostaglandins, the production of which may be stimulated by bradykinin. Bradykinin-induced sensitization of airway sensory nerves has been proposed as a potential mechanism of ACE inhibitor-induced coughing and airway hyperresponsiveness (Fox et al., 1996; Subissi et al., 1990).

Airway hyperresponsiveness is defined by an exaggerated obstructive response of the airways to a variety of pharmacological, chemical, and physical stimuli and is a hallmark clinical symptom of asthma (Postma and Kerstjens, 1998). Airway sensory nerves play a key role in airway hyperresponsiveness (Spina, 1996). TRPV1, a nonselective cation channel, is expressed on the C-fibres of airway sensory nerves and might be involved in the regulation of airway functions, especially in diseased conditions (Geppetti et al., 2006; Jia and Lee, 2007). The TRPV1 channel plays a pivotal role in the manifestation of various symptoms of airway hypersensitivity in patients of airway inflammatory diseases (Lee and Gu, 2009) and modulation of its activity represents a potential target for the pharmacological therapy of AHR in airway diseases (Delescluse et al., 2012). It has been recently demonstrated that bradykinin, acting at B2 bradykinin receptors, excites sensory nerve endings by activating TRPV1 receptors via production of 12-lipoxygenase metabolites of arachidonic acid (Shin et al., 2002).