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Apelin Increases Airway Responsiveness and Inflammation in a Mouse Model of Asthma

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Abstract

There is evidence that inflammatory exacerbations in asthma may be mediated by specific endogenous peptides. Apelin, an endogenous hypotensive and angiogenic peptide, is increased in atopic asthma. However, it is unclear how apelin affects allergic inflammation observed in asthma. We studied the role of exogenously administered apelin in airway hyper reactivity and inflammation in allergic mice. Mice were divided into control (CON) and allergen sensitized-challenged (SEN) groups. Mice were sensitized (i.p.) on days 1,6 with 0.2µg ovalbumin (OVA) followed by 5% OVA aerosol challenges on days 11-13. Apelin was given i.p. as a single bolus dose (4mg/kg) on day 14 to SEN mice. Whole body plethysmography (measuring airway responsiveness as enhanced pause, Penh) and bronchoalveolar lavage (BAL) studies were then performed. Airway responsiveness to MCh (48mg/ml) was highest in SEN+APELIN group (126.43±30.61 vs. 36.95±11.44% in SEN, $p<0.05$, n=3). Differential BAL cell analysis showed that treatment with apelin increased eosinophils (68.67±1.86% in SEN vs 80.67 ±1.20% in SEN+APELIN, $p<0.05$) and neutrophils (8.33±0.88% in SEN vs 13.33±0.88% in SEN+APELIN, $p<0.05$) in sensitized mice, thus potentiating the allergic inflammation. Although further studies are needed to evaluate detailed cellular mechanisms, the role of apelin and apelinergic system appears to be proinflammatory in this model of asthma.

Keywords: Apelin; Asthma; Airway responsiveness; Airway inflammation

Abbreviations: IP: Intra-Peritoneal; SEN: Sensitized; CON: Control; PENH: Enhanced Pause

Introduction

Apelin, also termed as APLN, is a peptide encoded by the apelin gene [1]. The apelinergic system comprises of apelin and its G-protein coupled receptor APJ [2] which was originally identified by O'Dowd et al. [3]. For long, APJ, a receptor sharing similarities with the angiotensin II receptor (AT1R), was labeled an orphan GPCR since it was not activated by any of the known ligands [3]. The identification of the cognate ligand apelin stripped the orphan title of the human apelin receptor (APJ) and opened up possibilities leading to novel biological studies. Apelin exists as a 36 amino acid peptide (apelin-36), along with other isoforms including apelin-17, apelin-13,apelin- 28,apelin-31 and apelin 12 [3-6] Apelin and APJ are found abundantly in various tissues of organs such as heart, lung, stomach, kidneys, in most parts of the brain and adipose tissue [4,5,7,8].

Over the years it has been reported that apelin possesses hypotensive properties [9-11] along with a broad range of physiological effects, however the main physiological function of apelin and its receptor APJ remains unclear to this date. This may be due to the different binding properties of different sized apelin isoforms to its receptors [12]. Apelin is believed to exhibit regulatory effects on the cardiovascular system, energy metabolism, fluid homeostasis, inflammation (anti-inflammatory) and angiogenesis [6,2].

The APJ gene and its regulation has not yet been fully understood and the role of apelin and APJ gene in asthma is a justifiable new aspect to be looked into since acute and repeated stress has been linked to the up- regulation of the APJ gene [13]. Hence the aim of this study was to understand the role of apelin in our mouse model of asthma [14]. An unrestrained whole body plethysmograph (Buxco electronics, Troy, NY) was used to assess the airway hyper-responsiveness by measuring the respiratory air flow pressure curves of individual mice to different concentrations of methacholine (MCh).

Conclusion

The effect of apelin on airway responsiveness was measured using methacholine (MCh) by whole body plethysmography. Data was obtained as enhanced pause (Penh) based on the protocol described by Ponnoth et al. [15]. Penh correlates to airway obstruction, and higher the Penh values, greater is

the airway obstruction. Inhalation of MCh exhibited a dose-dependent increase in bronchoconstrictor responses with apelin treatment increasing the response in (126.43±30.61 vs. 36.95±11.44% in SEN, $p<0.05$, n=3). These data indicate apelin increased bronchoconstriction induced by MCh in asthmatic mice. Our next experiment consisted of studying the cellular content in the bronchoalveolar lavage (BAL) fluid taken from the lungs of the experimental mice to determine the effect of apelin in the recruitment of inflammatory cells in the asthmatic mice. Differential cell analysis showed that sensitized mice had significant inflammation compared to controls, and apelin further increased the inflammation. The differential count studies were done 24 hours after the airway responsiveness studies. Cell counts for eosinophils, macrophages and neutrophils were obtained. Differential BAL cell analysis showed that treatment with apelin increased eosinophils (68.67±1.86% in SEN vs 80.67±1.20% in SEN+APELIN, $p<0.05$) and neutrophils (8.33±0.88% in SEN vs 13.33±0.88% in SEN+APELIN, $p<0.05$) in sensitized mice, thus potentiating the allergic inflammation. Thus our major finding for this study is that although apelin has been shown to be anti-inflammatory in certain conditions, it appears to have a pro-inflammatory role in allergic study. Airway hyper responsiveness correlated to eosinophilia increased with apelin. Further studies are required to elucidate the mechanisms behind the apelin-mediated increases in inflammation, as also deducing the role for endogenous apelin in asthma [16-19].

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