International Immunopharmacology 63 (2018) 110–118

Contents lists available at ScienceDirect

International Immunopharmacology

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

Alleviating airway inflammation by inhibiting ERK-NF-κB signaling pathway by blocking Kv1.3 channels

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ARTICLE INFO

Keywords:
Asthma
Airway inflammation
Kv1.3 channel
T lymphocyte
ERK
NF-κB

ABSTRACT

Allergic asthma is a chronic inflammatory disease of the airways. T lymphocytes play an important role in the pathogenesis of asthma. The voltage-gated Kv1.3 potassium channel is a target for the preferential inhibition of T_{EM} cells. In this study, we investigate the effects of PAP-1, a selective inhibitor of Kv1.3 channel, on the treatment of the neutrophilic asthma model. PAP-1 (40 mg/kg) was injected intraperitoneally into ovalbumin (OVA)-lipopolysaccharide (LPS)-challenged BALB/c mice. We found that the expression of the Kv1.3 channel in the lung tissues, and the intensity of the Kv current in the asthmatic mice increased clearly compared with those in normal control. PAP-1 significantly reduced airway hyperresponsiveness (AHR), inflammatory cell count in the bronchoalveolar lavage fluids (BALF) and serum, and attenuated airway inflammation in a histological examination of the asthmatic mice. Moreover, PAP-1 inhibited the OVA-LPS-induced imbalance of Th1/Th2, Treg/Th17 lymphocytes, and reduced levels of IL-4 and IL-17, inducing an increase in the production of IFN-γ and IL-10. Furthermore, the activation of the extracellular signal-regulated kinase (ERK)/nuclear factor-κB (NF-κB) pathway in the lungs of the asthmatic mice was suppressed by PAP-1. We also found that PD-98059, an inhibitor of ERK, had a similar effect with PAP-1 in terms of regulating the imbalance of Th1/Th2, Treg/Th17 cytokines. However, PD-98059 could not further influence cytokine changes when the cells were treated with PAP-1. The results suggest that ERK acts as a downstream regulator of inhibitors of the Kv1.3 channel in neutrophilic asthma. In conclusion, the inhibitor of the Kv1.3 channel has therapeutic potential for treating asthma.

1. Introduction

Asthma is a chronic inflammatory disease of the airways. The most widely used mouse model of asthma involves allergic sensitization by intraperitoneal injections of ovalbumin (OVA) and aluminum hydroxide, challenged by an aerosol or intranasal instillation of OVA. Pulmonary inflammation here is mediated by Th2 cells [1]. However, studies have shown that some severe asthmas, and glucocorticoids-dependent or -resistant asthmas, are mediated by Th17 cells with the infiltration of neutrophils [2–4]. Therefore, it is important to seek reliable drugs for the treatment of Th17-mediated neutrophilic asthma.

Voltage-gated Kv1.3 potassium channel is a target for the preferential inhibition of T_{EM} cells [5], and has been reported to be involved in the pathogenesis of T-cell-mediated autoimmune diseases, such as autoimmune encephalomyelitis, rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis [6–9]. Koshy et al. investigated the effects of ShK-186, a selective Kv1.3 channel blocker, for the treatment of asthma, and found that ShK-186 can reduce Th2-mediated response [10]. Although a large number of biological and pharmacological activities of the Kv1.3 channel have been reported, its mechanisms and possible effects on Th17-mediated neutrophilic asthma are still unknown. Several studies have shown that the Kv1.3 channel mediates autoimmune diseases through the activation of the extracellular signal-regulated kinase (ERK)-nuclear factor (NF)-kappaB (NF-κB) signaling pathway [11, 12].

ERK, a member of the mitogen-activated protein kinase (MAPK) family, is a key molecule that transfers signals from the cell surface to the nucleus. Phosphorylated ERK mediates the degradation of IκBα and the activation of transcription factors, such as NF-κB. Some researches have claimed that the activation of the ERK signaling pathway is related to the response of IL-17 [4, 13].

In this study, we investigate the expression and function of the Kv1.3 channel in lung tissues and the bronchoalveolar lavage fluid (BALF) in the Th17-mediated neutrophilic asthmatic mouse model. Furthermore, 5-(4-phenoxybutoxy) psoralen (PAP-1) is a potent and selective small molecule Kv1.3 blocker [14, 15], we investigate

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https://doi.org/10.1016/j.intimp.2018.07.009
Received 11 February 2018; Received in revised form 29 June 2018; Accepted 10 July 2018

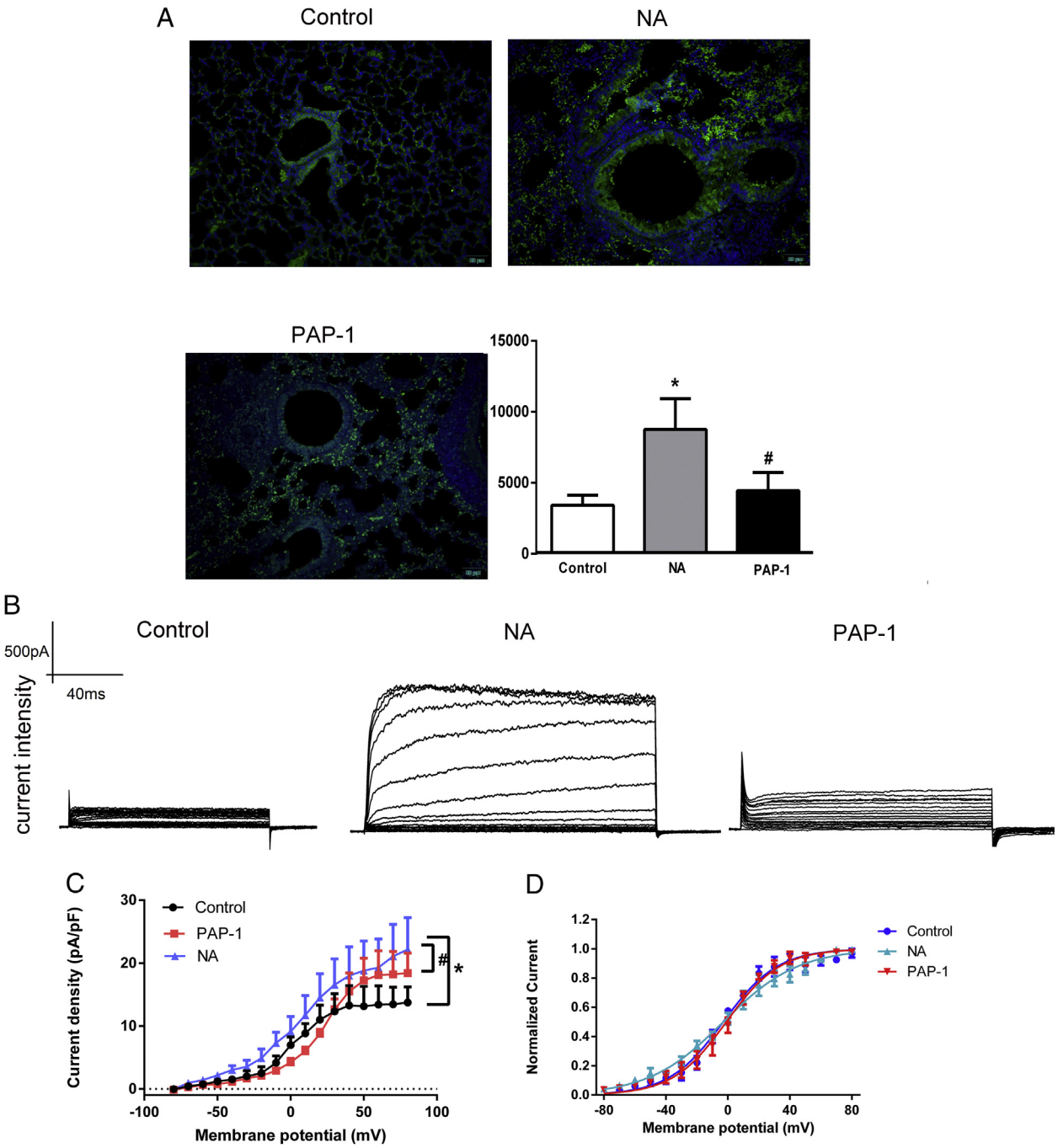

Fig. 1. The expression and activities of Kv1.3 increase in the lung tissues and BALF of in OVA-LPS-induced neutrophilic asthmatic mice. (A) Kv1.3 protein in lung tissues increased in the OVA-LPS-induced neutrophilic asthmatic mice model detected by immunofluorescence. (B) Representative currents obtained by step pulses from −80 to 80 mV in 10 mV steps. (C) The peak current to voltage relation (I–V curve) of I_{kv}. The intensity of the I_{kv} increased clearly in the OVA-LPS-induced neutrophilic asthmatic mice model, which was significantly reduced in PAP-1-treated mice. (D) The voltage-dependence of KV activation was estimated by fitting normalized conductance against clamp voltages using the Boltzmann distribution equation. There was no difference in the voltage-dependence of I_{kv} in different groups.

BALF: Bronchoalveolar lavage fluid. MFI: Mean fluorescence intensity. NA: neutrophilic asthmatic group. Each value represents the mean ± SD ($n = 8$).

$^{*}P < 0.01$ versus the control group.

$^{\#}P < 0.01$, versus the NA group.

mechanisms of PAP-1, and its effects on the Th17-mediated neutrophilic asthmatic mouse model.

2. Materials and methods

2.1. Animals and groups

Female BALB/c mice (eight-12 weeks old, 20 ± 2 g) were obtained from the China Medical University (Shenyang, Liaoning, China). The animals were used in accordance with the regulations of the Ethics