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Appropriate transient receptor potential vanilloid 4 (Trpv4) inhibition protects mice against lipopolysaccharide stress.

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Abstract

Background: TRPV4 as a therapeutic target was used in endotoxemia research. However, conflicting results have been reported. It was reported that HC067047 as a TRPV4 inhibitor caused a reduction in LPS-induced mortality. Oppositely, TRPV4 inhibited with HC06047 could not attenuate LPS-induced symptoms and exaggerated pathology. The mechanism of conflict is still unknown.

Material and methods: We assessed the pathological state in their experiments and further assessed the levels of TRPV4 expression with their respective treatment. Then the cell models with various levels of TRPV4 expression were used to explore the mechanism of conflicting results. The effect of TRPV4 expression on the apoptosis was observed under same LPS-dose stress. Meanwhile, F-actin contents were assessed with FITC-phalloidine staining.

Results: Our experiments verified their results and further showed that TRPV4 expression differed between the two reports. We speculated that the different TRPV4 expression might have caused the conflicting results. Cell models of varying TRPV4 expression included normal TRPV4 expression and overexpression models. Results showed that TRPV4 overexpression significantly increased the apoptosis when compared with normal expression cells with the same lipopolysaccharide dose ($P<0.05$). HC067047 enhanced apoptosis in normal expression cells ($P<0.05$) and reduced apoptosis in overexpression cells ($P<0.05$). Research about the mechanism showed that HC06047 blocked TRPV4 signals, caused actin stress fiber accumulation, and induced apoptosis in normal expression cells. Oppositely, HC06047 inhibited relatively overactive TRPV4, attenuated excessive actin depolymerization, and reduced apoptosis ratios in overexpression cells.

Conclusion: Underactive and/or overactive TRPV4 may be inhibitory to maintenance of cell function against lipopolysaccharide -induced stress.

Keywords: TRPV4, Apoptosis, HC06047, Lipopolysaccharide, Actin cytoskeleton.

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Introduction

Transient Receptor Potential Vanilloid 4 (TRPV4) is a non-selective cation channel and is widely expressed in mammalian tissues [1]. It is known as an osmosensor [2], a thermosensor [3], and/or a chemoreceptor [4] and appears to play an important role in a multitude of disease processes [5,6]. TRPV4 as a therapeutic target has been investigated in septic diseases [5].

Sepsis is characterized by increasing vascular permeability and reducing blood pressure [7]. TRPV4 is expressed in the vasculature [8]. It has been reported that TRPV4 can influence the septic process and may be a potential therapeutic target [5]. Interestingly, there are conflicting results on the potential role of TRPV4 in sepsis pathogenesis [5,9,10]. Dalsgaard et al. reported that TRPV4 inhibition with HC067047 reduced mortality in a Lipopolysaccharide (LPS)-induced sepsis model [10]. In contrast, Sand et al. found that TRPV4 inhibited with HC067047 could not attenuate LPS-induced symptoms and exaggerated pathology [9]. The LPS doses used by Dalsgaard et al. and Sand et al. were 50 mg/kg LPS and 12.5 mg/kg, respectively. The two groups used the same dose of TRPV4 inhibitor with 10 mg/kg HC067047. The same dose of HC67047 used in different LPS-dose induced mice might have caused conflicting results. However, the mechanism behind the conflicting results is still unclear.

We assessed the pathological state in their experiments in order to examine the reasons behind this discrepancy. 12.5 mg/kg LPS did not kill the experimental mice [9], but Dalsgaard et al. reported that all of the mice died three days after 50 mg/kg LPS treatment [10]. It has been suggested that different LPS doses can induce different levels of sepsis. The principal aspect of sepsis is a systemic inflammatory response to infection. TRPV4 activators are produced in inflammatory processes [11,12]. The activators induced an increase in TRPV4