PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

ET-1 and cytokines in airway inflammation

ArticleInfo		
ArticleID	:	1609
ArticleDOI	:	10.1186/rr-2001-68524
ArticleCitationID	:	68524
ArticleSequenceNumber	:	20
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–9–18 Received : 2001–4–11 Accepted : 2001–9–18 OnlineDate : 2001–9–18
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	129312211

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Keywords

Asthma, BAL, bosentan, cytokine, endothelin, inflammation

Context

Endothelin (ET)-1 has been implicated in the development of eosinophilic airway inflammation although its role is unknown. It has been demonstrated to increase both mucus secretion and vascular leakage, and has been detected in bronchoalveolar lavage (BAL) fluid in asthmatics. The aim of this study was to determine the role of ET-1 in the synthesis of other inflammatory cytokines, including tumor necrosis factor (TNF)-a, interleukin (IL)-1?, IL-4, IL-8, interferon (IFN)-? and leukotriene (LT) B4.

Significant findings

ET-1 mRNA increased 15 min following Sephadex (SDX) provocation, which correlated with the early phase of inflammation, and declined after 2 h. Increases in the mRNA levels of IL-1?, IL-8 and TNF-a mRNA followed 12-24 h later. IFN-? and IL-4 mRNA levels were not detectable in the lung tissues during the course of this study. A substantial amount of LT B4 was detected in the BAL fluid 15 min following provocation and was maintained for 2 h. IL-8 and TNF-a protein expression in BAL fluid was biphasic, with peaks at 3 h and 24 h. The concentration of ET-1 in the BAL fluid did not increase until 6 h following SDX provocation, this delay may be due to abluminal secretion of ET-1. Rats were treated with bosentan, a highly specific ET antagonist, prior to SDX provocation. As expected if synthesis of ET-1 preceded the synthesis of other proinflammatory cytokines, bosentan pretreatment attenuated expression of TNF-a, IL-4, IL-1?, IL-8 and IFN-? in BAL fluid.

Comments

Understanding the initial steps of the inflammatory pathway may allow for the development of new anti-inflammatory treatments. In this report, the investigators detected a very early increase in ET-1 mRNA in lung tissue, and determined that ET-1 expression precedes the synthesis of other proinflammatory cytokines. The early increase in ET-1 could, in addition to stimulating the expression of proinflammatory mediators, act as a chemoattractant to cause an influx of inflammatory cells.

This study utilized intratracheal installation of SDX particles to induce airway eosinophilia and inflammation, although previous studies have shown that it is intravenous administration of SDX that causes airway hyperreactivity. In addition, the authors suggest that increases in both TNF-a and IL-4 protein levels, without a significant increase in mRNA expression, are due to release of preformed protein. This current experimental model may not, therefore, fully represent allergic airway inflammation as seen in asthma and the results should be interpreted carefully.

Methods

Intratracheal installation of SDX, male Wistar rats, BAL, ELISA, mRNA isolation, radioimmunoassay

Additional information

References

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