Anti-atherosclerotic Potentials of Montelukast & a Possible Link to Its Anti-asthma Efficacy in Asthmatic- Dyslipidemic Guinea Pigs "A Comparative Study with Fluticasone"

Thesis

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INTRODUCTION

An increasing body of literature suggests a connection between asthma, on one hand, and obesity and atherosclerosis on the other. It is increasingly recognized that obese people are more prone to develop asthma ***(Peters-Golden et al., 2006).*** Nearly half of the people who suffer from asthma are classified as, either overweight or obese, with a body mass index of greater than 25 ***(Beuther and Sutherland, 2007).*** The severity of asthma was also found to be greater among those in the overweight and obese groups ***(Peters-Golden et al., 2006).***

High cholesterol in children was also linked with asthma risk regardless of body weight ***(Al-Shawwa et al., 2006).*** Among OVA-challenged mice, leukocyte numbers, particularly those of eosinophils, in the bronchoalveolar space increased by 3- to 5-fold with cholesterol supplementation. Interleukin-5 and cysteinyl leukotrienes in the bronchoalveolar lavage fluid were also found to be significantly higher in mice fed a 2% cholesterol diet compared to those on the control diet ***(Yeh and Huang, 2001).***

Multiple logistic regression models also revealed that asthmatic patients were 43% more likely to have heart diseases than non asthmatics ***(Dorga et al., 2007).*** Indeed, asthma has been reported in several studies to contribute to enhanced risk for atherosclerosis ***(Micheal et al., 2005).***

A possible explanation for the association of asthma, obesity and atherosclerosis may be the fact that all these disorders share a common underlying pathology: inflammation. Indeed it is now well established that obesity is a state of chronic low-grade systemic inflammation ***(Shore, 2008).*** Adipose tissue is recognized as a rich source of proinflammatory adipokines ***(Lau et al., 2005).*** Elevated levels of many adipokines are observed in the serum in proportion to the body mass index (BMI) and have been shown to correlate with atherosclerosis**.** Furthermore these proinflammatory adipokines have been also shown to be associated with asthma, and this may play a role in the relationship between obesity and asthma ***(Shore, 2008)***

Mast cells are inflammatory cells widely distributed throughout the body and were recently suggested to be one of the components of adipose tissues ***(Chaldakov et al., 2007)***. Mast cells are involved in many physiological processes of the body ***(Rao and Brown, 2008)*** and play a pathophysiological role in different conditions, such as asthma, atherosclerosis and obesity (***Kaartinen et al., 1998; Okayama et al., 2007; Liu et al., 2009)***. They exert their biological effects by releasing preformed inflammatory mediators including the neutral proteases tryptase, chymase, carboxypeptidase A and histamine ***(Pejler et al., 2009)*** and de novo-synthesized mediators such as leukotrienes ***(Okayama et al., 2007)***.

Recently, a potential link between leukotrienes (one of the mast cells mediators) production and atherosclerosis has been proposed. A cross link between asthma and atherosclerosis has received attention, given the finding that polymorphisms in the 5-lipoxygenase and 5-lipoxygenase–activating protein genes, 2 key genes in the regulation of leukotriene synthesis, predict a high risk for atherosclerosis and its main clinical sequelae; stroke and myocardial infarction ***(Dwyer et al., 2004; Helgadottir et al., 2004; Helgadottir et al., 2005).***

The expression of leukotriene biosynthetic enzymes and leukotriene receptors has been identified in coronary atherosclerotic plaques and the levels of biosynthetic enzymes have been correlated with the clinical symptoms of unstable plaques ***(Whatling et al., 2007).*** Within atherosclerotic lesions in humans, the 5-lipoxygenase enzyme was found in macrophages, dendritic cells, mast cells and neutrophilic granules ***(Spanbroek et al., 2003).***

In support of a role of increased production of leukotrienes for the observed association of asthma with atherosclerotic disease are the reports showing that asthmatic patients receiving 5-lipoxygenase pathway modifiers have lower blood risk factors including inflammatory biomarkers and lipid levels associated with cardiovascular disease ***(Hooman et al., 2007).***

The association of asthma with obesity and atherosclerotic disease has attracted much attention not only regarding its pathophysiolohgical aspect, but

also extensive studies have been directed towards differences in responses to anti-asthma drugs in the obese and cardiac asthmatic patients. Conflicting results have been published regarding the efficacy of anti-asthma drugs in asthmatic obese patients.

Obesity appears to alter the efficacy of standard asthma medications**.** Two recent reports ***(Peters-Golden et al., 2006; Boulet and Franssen, 2007)*** indicate that overweight and obese patients with asthma may not respond as well as their lean counterparts to inhaled glucocorticoids (GCs),which is contradictory to another report stating that fluticasone produced a significantly greater clinical response for normal, overweight, and obese subjects compared with montelukast ***(Sutherland et al., 2010)***.

An equally important issue that has also been raised is the potential beneficial effects of the anti-asthma drugs against coronary heart disease. While recent evidence indicates a role for leukotriene antagonist in atherosclerotic disease ***(Song et al., 2009)***, much debate has been raised concerning the role of corticosteroids in such diseases ***(Girod and Brotman, 2004).***

Although cortisol is involved in the development of coronary artery disease ***(Bhallaccharyya et al., 2008),*** and corticosteroids appear to elevate all lipoprotein cholesterol levels ***(Henkin et al., 1992)***, yet retrospective observations suggest that inhaled corticosteroids may reduce atherothrombotic mortality by altering systemic inflammation**,** very low doses of inhaled corticosteroids may be associated with a reduction in the risk of acute myocardial infarction ***(Huiart et al., 2005;Fimognari et al., 2008).***

Given this newly generated interest relating the pathophysiology of asthma to cardiovascular diseases and the proatherogenic role of leukotrienes together with the suggestions that anti-asthma medications may have some beneficial value in asthmatics with respect to cardiovascular diseases risk ***(Spanbroek et al., 2003),*** new insights on the potential role of anti-asthma drugs on the atherogenic profile should be investigated especially in patients suffering from both diseases.

AIM OF THE WORK

The present study was designed to investigate whether a reciprocal relationship exists between asthma, obesity, and atherosclerosis.

Using an animal model of chronic OVA challenge – induced asthma, the study attempted to determine whether induction of asthma might be associated with concomitant metabolic or vascular atherogenic changes. Conversely, the study also investigated whether induction of obesity and dyslipidemia, using a model of high fat diet, might result, not only, in vascular atherogenic changes but might also induce simultaneous asthmatic airway changes.

The impact of the leukotriene antagonist montelukast on the possible association of the airway and vascular changes was investigated in an attempt to determine the role played by leukotrienes and mast cells in such an association

In view of the conflicting data concerning the response to anti-asthma drugs in the obese together with the debate regarding the beneficial or harmful cardiovascular effects of corticosteroids in patients with coronary artery disease, the anti-asthma efficacy and potential anti-atherosclerotic effects of montelukast were compared to those of the inhaled corticosteroid fluticasone. An attempt was made to detect any significant difference between the two drugs that could advocate the use of one agent over the other in asthmatic patients with coronary heart disease.

Research Questions:

1. Does feeding animals a high fat diet per se induce airway functional or histological changes?
2. Does feeding animals a high fat diet aggravate asthmatic airway changes induced by chronic OVA challenge?
3. Does chronic exposure to OVA challenge per se induce metabolic and vascular atherogenic changes?
4. Does chronic OVA challenge aggravate high fat diet- induced metabolic and vascular atherogenic changes?

5. Is there a difference in the anti- asthma effect of the test drugs between animals fed a high fat diet and those fed normal chow fed?
6. What are the possible effects of the test drugs on the high fat diet- induced metabolic and vascular atherogenic changes in asthmatic dyslipidemic animals?

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