

Role of Leptin in Correlation between Obesity and Asthma

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Abstract— Obesity and asthma have dramatically increased over recent decades. Obesity seems to be a risk factor for the development of asthma and it makes existing asthma more severe and depends on factors such as age and sex. Severity of asthma in obesity is suggested to higher level of leptin. The complex interrelation between obesity and asthma is an example of the interaction between genes, plasma leptin level and the environment in the pathogenesis of both disorders. Obesity, by means of inflammatory mechanisms or changes in lifestyle, can trigger asthmatic symptoms in susceptible individuals. The combination of diet, genes and plasma leptin level may alter the normal patterns the tone of the airways (giving rise to asthma).

Key words: Leptin, Obesity, Asthma, Pro-Inflammatory Mediators

I. INTRODUCTION

Obesity is nutritional disorder and chronic inflammatory state⁽¹⁾ which has increased markedly over the last two decades. The prevalence of obesity risen by 110% when compared to period 1976-1980 with 1999-2000 which indicate independent risk factor for mortality⁽²⁾. This trend is not only limited to U.S. but also in the other developed and affluent countries⁽³⁾. In obesity, five times higher leptin level was observed and it increases exponentially with increasing fat mass⁽⁴⁾. Higher leptin level reflect states of energy imbalance⁽⁵⁾ and leptin resistance⁽⁶⁾. Mutation of mouse *ob* gene results in a syndrome that includes obesity, increased body fat deposition, hyperglycemia, hyperinsulinemia, hypothermia and impaired thyroid and reproductive function in both male and female homozygous *ob/ob* obese mice⁽⁷⁾. Obesity and increasing weight gain might be risk factor for the development of asthma especially in women⁽⁸⁾. Levy et al., 2004 and Akerman et al., 2004 were found positive correlation between body mass index (BMI) and asthma severity⁽⁹⁻¹⁰⁾. Therefore, we proposed that leptin might be a link between Asthma and Obesity.

Leptin is an adipocyte hormone that functions as the afferent signal in negative feedback loop regulating body weight. Leptin circulates as a 16-kD protein in mouse and human plasma⁽¹¹⁾. Five of the known leptin receptor isoforms, OB-R_a, OB-R_b, OB-R_c, OB-R_d, OB-R_f contain transmembrane domains⁽¹²⁻¹³⁾. OB-R_b is most prominent and it is single transmembrane-spanning receptor that belongs to the class I family of cytokine receptors⁽¹⁴⁾. Leptin binding to OB-R receptors activate Janus kinase (JAK)-STAT-signaling transduction cascade⁽¹⁵⁾. Increase in the normal functioning of adipose tissue in obese subjects reflects a systemic pro-inflammatory state which leads to elevated serum concentrations of various cytokines, and soluble fractions of their receptors and chemokines⁽¹⁶⁾ which are common factor for Airway hyper responsiveness (AHR) (Figure 1).

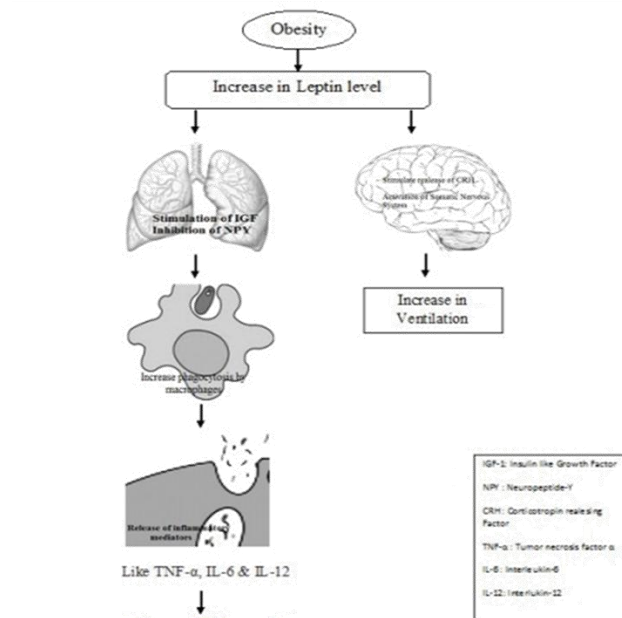


Fig. 1: Role of Leptin as a Pro-inflammatory mediator

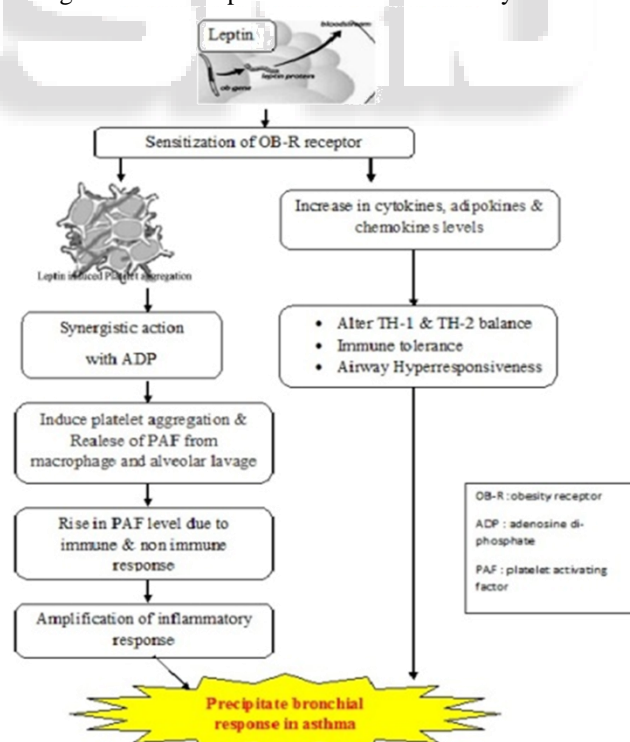


Fig. 2: Role of Leptin as a Pathogenesis of asthma

Many of these mediators are synthesized and secreted by cells from adipose tissue which includes IL-6, IL-10, eotaxin, tumor necrosis factor (TNF)- α , TGF- β 1, C-reactive protein, leptin, and adiponectin⁽¹⁷⁻¹⁹⁾. Leptin impairs immune function in both *ob/ob*⁽²⁰⁾ and *db/db* mice⁽²¹⁾. These

impairment have been observed principally in cell-mediated immune response, in resistance to viral and bacterial infections and in macrophage function⁽²²⁾. Leptin has been shown to act directly on CD4⁺ helper T cells including their proliferation and increasing cytokine production⁽²³⁾. Impairment of cell-mediated immune reaction & imbalance the TH1 & TH2 (Figure 2) which are causative factor for asthma. Platelet aggregation due to activation of cytokine releases platelet activating factor (PAF) and complement system. PAF is one factor for Hypersensitivity reaction at bronchial level⁽¹⁴⁾. Leptin stimulates proliferation of T-lymphocytes and promotes helper type 1 immune response. Serum leptin increases as BMI increases⁽²⁴⁾.

Mice that are genetically deficient of leptin or the leptin receptor have been experimentally produced. When normal mice are given injections of bovine serum albumin (BSA) in to their joints or nerve sheath myelin into their circulation, they develop arthritis or experimental autoimmune encephalomyelitis (animal model for human multiple sclerosis) respectively.

When leptin deficient mice are injected with BSA or myelin they develop a greatly attenuated form of these disorders⁽²⁵⁻²⁶⁾. These studies suggest that leptin may play a role in organ specific inflammatory disorders. Asthmatic patient however have been found to have elevated leptin levels⁽²⁷⁻²⁸⁾.

II. CONCLUSION

From our proposed hypothesis, it is clear that in obesity as leptin level increases, pro-inflammatory mediators like IL-6, IL-12, TNF- α etc can exaggerate the asthma. Leptin also found to be releasing PAF by leptin receptor in respiratory tract and causing hyper-responsiveness which make existing asthma more severe.

In conclusion, this new outlook illustrating the pathophysiology of asthma in obesity and considering and with evidences, one can provide novel therapeutic measures putting into consideration the advantages of this natural morphological defensive mechanism. Clearly, more research is needed to further elucidate these two phenomena and the multiple interrelationships that exist between them.

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