The Yin Yang of Hormones that Control Glucose Homeostasis in Asthma

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Abstract
Asthma is a chronic inflammatory disease whose prevalence has increased in the last 50 years. Several hormones can determine the course of asthma pathogenesis. Furthermore, some endocrine disorders, including diabetes and obesity, have been identified as important factors that influence the prevalence of asthma. These endocrine disorders are characterized by presenting an imbalance in blood hormones levels that regulate glucose metabolism, including hyperglycemic and hypoglycemic hormones. This review gives an update of the state-of-the-art concerning the effect of hormones that control glucose homeostasis on asthma pathogenesis and development. Here, we proposed that while hyperglycemic hormones, including insulin and leptin aggravate asthma, the hyperglycemic hormones, as glucagon, glucocorticoids and epinephrine, have a protective effect on asthma.

Keywords: Asthma; Glucagon; Glucocorticoid; Glucose metabolism; Hormones; Insulin

Introduction
Asthma is one of the main chronic diseases of contemporary man, affecting people in countries at all stages of economic and social development and is a major public health burden worldwide. The global prevalence of asthma has markedly increased over the last 50 years. Around 300 million people have asthma worldwide, and each year 250 thousand people die due to this disease [1,2]. Asthma is a chronic inflammatory disease of the lungs characterized by variable airway obstruction in association with airway hyperresponsiveness (AHR) that leads to symptoms including recurrent episodes of wheezing, chest tightness and coughing [3,4].

The inflammatory response observed in airways of asthmatic patients is characterized by accumulation of mast cells, eosinophils and type 2 CD4+ T cells (Th2 cells). Th2 cells are central to the pathogenesis of asthma, since Th2-type cytokines orchestrate the allergic inflammatory response in asthma, including IgE synthesis, Th2 cells, eosinophils and mast cells survival, eosinophil and mast cell maturation and basophil recruitment [3,5]. Moreover, the infiltration of type 17 CD4+ T cells (Th17 cells) in the airway walls of some asthmatic patients and the severity of AHR is correlated with the presence of these cells. This evidence suggests the role of Th17 cells in driving airway inflammation and pathological changes in some cases of asthma. In fact, activation of Th17 cells is closely associated with asthma severity, neutrophil recruitment and development of steroid-resistance in asthmatic subjects [6,7]. Moreover, asthmatics show structural changes in the airway wall called airway remodeling. These changes including epithelial shedding increased airway smooth muscle mass and mucus-producing goblet cells in the epithelium or submucosal glands and subepithelial fibrosis [4].

In type 1 diabetes, glucagon and insulin secretion from pancreatic α- and β-cells, respectively, become dysregulated with hypersecretion of glucagon and hyposecretion of insulin resulting in hyperglycemia [8]. Uncontrolled type 1 diabetic patients present a lower prevalence of allergic diseases, including asthma [9,10]. One hypothesis to explain this negative correlation between type 1 diabetes and asthma is that autoimmune diseases, including diabetes, involve a Th1 response while allergic diseases are associated with the Th2 phenotype [11,12]. We showed that alloxan-diabetic rats presented decrease in the allergen-induced acute protein leakage and eosinophil infiltration in skin, intestine and pleural space. This suppression of allergic responses in diabetic rats was correlated with reduction in IgE synthesis and number of local mast cells [13-16].

Hypoglycemic Hormones and Asthma
The maintenance of glucose homeostasis requires a tight regulation of glucose utilization by liver, muscle and fat, besides the glucose production and release in the blood by liver. This homeostatic process is controlled by two classes of hormones: i) hypoglycemics that induce uptake of glucose to peripheral tissues; ii) hyperglycemics that stimulate hepatic glycogenolysis and gluconeogenesis [17]. Among the hyperglycemic hormones, stands insulin that is produced by pancreatic β-cells and acts by inhibiting hepatic glycogenolysis and glycogenolysis and stimulating glucose storage by liver, muscle and fat as promoting glucose uptake and utilization by muscle and adipose tissues [18].

In diabetic patients, treatment with inhaled insulin induces decrease in forced expiratory volume in 1 second (FEV-1) [19]. Moreover, uncontrolled insulin-dependent diabetic patients present a less incidence of asthma [9,10]. In inflammatory and structural cells involved in asthma pathogenesis, insulin is able to modulate T cell differentiation promoting a shift towards a Th2-type response, which is central to the pathogenesis of asthma, with an increase in the number of Th2 cells and Th2-cytokine profile [20]. Furthermore, insulin promotes mast cell survival and a more robust antigen-triggered mast cell degranulation [21,22], and enhances contractility and proliferation of airway smooth muscle [23], through a mechanism dependent on PI3K pathway activation [21,24]. In keeping with this, hyporesponsiveness to antigen observed in the airways and pleural space of diabetic rats was reversed by treatment of the animals with insulin [25,26]. In association, these evidences indicate that insulin seems to aggravate asthma symptoms.

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Although insulin is the major hypoglycemic hormone, it is known that other hormones can reduce the circulating levels of glucose. These hormones are produced by adipose tissue, including adiponectin and leptin, and gastrointestinal tract, as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) [27,28]. Animal models of untreated type 1 and type 2 diabetes present leptin deficiency accompanied by insulin resistance [29,30], and central or peripheral leptin administration was able to restore normoglycemia in animal models of type 1 and type 2 diabetes [31-35]. This hypoglycemic effect of leptin in diabetes is associated with lower circulating glucagon levels, decreases glucocorticoid gene expression and improves insulin sensitivity and release [35]. Furthermore, leptin is able to suppress glucose production in non-diabetic animals by a mechanism associated with decrease of hepatic glycogenolysis without affecting glucose uptake [36].

Receptors for both leptin and adiponectin are expressed in lungs [37], however only some experimental evidences supported that leptin and adiponectin could have a role in the pathogenesis of asthma. Leptin has a pro-inflammatory profile in cells that have an important role in asthma, including mast cell activation, CD4+ T cells proliferation and activation of dendritic cells polarizing naïve CD4+ T cells into Th17 and matrix degrading effects [50,51], and induces maturation and arthritis [48,49], activates synovial fibroblast inducing cytokine release [38-41]. Furthermore, leptin increases inflammatory cells mobilization to bronchoalveolar fluid and airway hyperreactivity following allergen challenge [42].

In addition to leptin, another important hormone produced by adipose tissue that influences glucose homeostasis is adiponectin. Adiponectin induces decrease of systemic glucose levels by increasing glucose uptake, reducing hepatic glucose production and improving insulin sensitivity [43-45]. Unlike leptin, adiponectin seems to present an anti-asthmatic profile since adiponectin knockout mice presented an increase of allergic airway inflammation [46], and adiponectin administration was able to reduce allergen-induced airway hyperreactivity and inflammation in mice [47]. However, adiponectin may have an important pro-inflammatory action in severe asthma and, especially, in steroid-resistance in asthmatic subjects since this hormone is highly expressed in synovium of patients with rheumatoid arthritis [48,49], activates synovial fibroblast inducing cytokine release and matrix degrading effects [50,51], and induces maturation and activation of dendritic cells polarizing naïve CD4+ T cells into Th17 phenotype [52].

GIP and GLP-1 modulate glucose homeostasis through an “incretin” effect, which is a potentiation of glucose stimulated insulin secretion in an additive manner [53,54]. However, until now there is no information about the role of these incretins on allergic diseases, including asthma, and on inflammatory cells which are central in development of asthma.

**Hyperglycemic Hormones and Asthma**

The hyperglycemic hormones are secreted during fasting to maintaining blood glucose levels and preventing hypoglycaemia. Glucagon is secreted by pancreatic α-cells, and considered as the body’s primary defence against low blood glucose levels [55]. Glucagon induces hyperglycemia through stimulation of synthesis and mobilization of hepatic glucose, by activating glycogenolysis and gluconeogenesis and inhibition of glycolysis and glycogenesis [56,57]. Here, we showed that mice treated i.p. with glucagon for 7 consecutive days presented a reduction in the plasma insulin levels (Figure 1), which could be partly explained by the hyperglycemic effect of this hormone too. Moreover, although fasting plasma glucagon levels are not elevated in patients with type 1 and type 2 diabetes [58,59], significant elevations were shown with serial sampling in both type of diabetes [60,61].

In asthmatic patients, glucagon presents a relaxant action on the airway smooth muscle inducing an improvement in the lung function [62,63], however this effect of glucagon needs to be further elucidated since some studies did not show any significant bronchodilator effect of glucagon on these patients [64,65]. Despite this controversy about the bronchodilator effect of glucagon in asthmatics, the lungs of rats express glucagon receptor (GcgR), and glucagon relaxes guinea pig bronchiolar smooth muscle in vitro independently of β-adrenergic receptor stimulation [66,67]. We showed that glucagon inhibited the allergen-evoked histamine release from rat subcutaneous tissue fragments in vitro (Figure 1), indicating a putative mast cell-stabilizing properties by...
this hormone. Moreover, i.p. daily treatment with glucagon for 7 days induced a decrease in peritoneal and mesenteric mast cell numbers in a clear association with reduction of plasma insulin levels (Figure 1). Other important inflammatory cells for development of asthma that may have its activity negatively modulated by glucagon are lymphocytes, since these cells express GcGR. However, although lymphocytes express GcGR, this hormone was not able to change the proliferation of these cells induced by anti-CD3 or LPS [68]. Nevertheless, glucagon can act reducing Th2 cytokine production by lymphocytes since the activation of GcGR induces an increase in the intracellular cAMP levels [67], and forskolin, an adenylate cyclase activator that elevates cAMP, induces apoptosis of T cells in vitro [69].

Beyond glucagon, others hormones including epinephrine and glucocorticoids increasing blood glucose levels in response to hypoglycemia and stress situation [17]. Epinephrine is mainly produced in the adrenal medulla by a methylation reaction from norepinephrine catalyzed by the enzyme phenylethanolamine N-methyltransferase. Epinephrine induces hyperglycemia through activation of glycogenolysis and hepatic gluconeogenesis, stimulation of glucagon and inhibition of insulin release, and induction of insulin resistance. As glucagon, epinephrine increases glycogenolysis and gluconeogenesis by increasing the intracellular levels of cAMP through the activation of β-adrenergic receptors [70,71]. Although, epinephrine is less potent in inducing hyperglycemia than glucagon, epinephrine becomes essential in the control of glucose homeostasis when glucagon is less potent in inducing hyperglycemia than glucagon, epinephrine is less potent in inducing hyperglycemia than glucagon, epinephrine becomes essential in the control of glucose homeostasis when glucagon actions are impaired, [72].

Airway smooth muscle expresses all subtypes of epinephrine receptors, with predominance of the β2 receptors. The activation of these receptors in airway smooth muscle promotes opposite effects; while α receptors induces contraction, the β receptors relax the muscle. An imbalance in the expression of these receptors on airway smooth muscle could be involved in the etiology of bronchial asthma [73]. Moreover, it was observed that asthmatic patients present a decrease in levels of endogenous epinephrine and this fact could explain the high effectiveness associated to the administration of exogenous epinephrine on asthma [74]. Furthermore, epinephrine was used as a standard treatment for severe asthma before the development of β2 receptors selective agonists. Nowadays, epinephrine is used when asthmatic patients do not respond to the conventional treatment [75,76] and the inhaled β2 agonists associated with inhaled corticosteroids became the standard therapy for asthma [77]. In addition, activation of β receptors inhibits the function of various inflammatory cells involved in asthma pathogenesis, including IgE-evoked release of histamine, PGD2 e cysteinyl-leukotrienes by mast cells [78]; ovalbumin-induced airway eosinophil infiltration and adhesion of eosinophils to lung fibroblast [79,80]; IL-4 and IL-13 production by human T cells [81,82]; pro-inflammatory and pro-fibrotic mediators release and matrix production by lung fibroblasts [83,84].

Glucocorticoids are produced in the adrenal cortex under the control of hypothalamic-pituitary-adrenal (HPA) axis [85]. Moreover, the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes can modulate the biological effects of glucocorticoids in target tissues since 11β-HSD type 1 amplifies local glucocorticoids action by conversion of cortisone to cortisol [86]. Glucocorticoids increase blood glucose by increasing hepatic glucose production, decreasing insulin-dependent glucose uptake into peripheral tissues, and inhibiting insulin release from pancreatic β-cells [87]. Furthermore, disruption of glucocorticoid receptor (GR) in hepatocytes leads to hypoglycemia during prolonged starvation, and inactivation of GR in hepatocytes reduces blood glucose levels in streptozotocin-induced diabetes [88].

Currently, glucocorticoids are recommended as first-line therapy for all patients with persistent asthma [89]. Glucocorticoids have its anti-inflammatory effect on several structural and inflammatory cells involved in asthma pathogenesis [90]. In inflammatory cells, glucocorticoids inhibit activation and proliferation of T cells and induce apoptosis of T cells, B cells, eosinophils and mast cells [91]. Moreover, glucocorticoids suppress the activity of the transcription factor GATA-3, that regulates the expression of genes encoding cytokines involved in asthma pathophysiology including IL-4, IL-5 and IL-13, in Th2 cells which results in decreased production of these cytokines by these cells [92]. However, the action of glucocorticoids on Th17 cells is not well established yet. Although glucocorticoids are able to reduce the production of IL-17 in asthmatics [93], this hormone does not inhibit cytokine production by Th17 cells in vitro, and the treatment with dexamethasone in vivo did not minimize inflammation and hyperreactivity of the airways of mice that received Th17 cells and were challenged with ovalbumin [94]. Furthermore, glucocorticoids inhibit the release of Th2 cytokines, including IL-4 and IL-5, and lipid mediators by eosinophils and mast cells [95]. We previously described that alloxan-induced diabetic rats presented an increase in the circulating corticosterone levels [14,95]. Besides, the decrease in the mast cell numbers and reactivity and antigen-induced IgE production as well as reduction of local and systemic antigenic response noted in alloxan-induced diabetes were reversed by surgical removal of adrenal glands and by treatment with the glucocorticoid receptor blocker RU486 [13,96].

In structural cells, glucocorticoids inhibit airway smooth muscle proliferation in vitro [97]. It also has been demonstrated that treatment with budesonide, an inhaled glucocorticosteroid, prevents airway smooth muscle thickening, contractile protein expression and tracheal hypercontractility in guinea pigs sensitized and challenged with ovalbumin [98]. Glucocorticoids are also able to inhibit airway smooth muscle contraction promoted by histamine, bradykinin or acetylcholine in vitro in a mechanism that involves increase in the intracellular levels of cAMP in airway smooth muscle cells [99]. Moreover, it was demonstrated that glucocorticoids increase the expression of β2 receptor in human lungs in vitro and in nasal mucosa in vivo, which could prevent the down-regulation of these receptors after prolonged administration with β agonists and thus enhance the effects of these agonists [77]. Besides, glucocorticoids inhibit cytokine generation by airway smooth muscle cells and epithelial cells [100,101]; however it is not defined if this hormone has a damaging or protective effect on epithelial cells, because some studies demonstrated that glucocorticoids increase apoptosis and epithelial shedding while others observed that the therapy with inhaled glucocorticoids restored epithelium integrity [101]. The anti-inflammatory action of glucocorticoids on pulmonary fibroblasts remains undefined. This is because, although glucocorticoids inhibit the production of fibronectin by stimulated lung fibroblast, it partially reduced the airway wall thickening and matrix deposition in a rat model of airway remodeling induced by allergen [102], decreased proliferation and liberation of inflammatory mediators by pulmonary fibroblasts, and reduced basement membrane thickness in airway biopsies from asthmatic patients [103], this hormone presents an anti-apoptotic effect on fibroblasts [103] and does not alter the ECM deposition in the reticular basement membrane in the airways [104].

Finally, an adrenal suppression has been reported in untreated allergic and asthmatic patients [104]. This phenomenon could be associated with the modulation of HPA axis activity by inflammatory
response noted in these patients, since corticotropin-releasing factor (CRF) knockout mice showed a decrease in endogenous glucocorticoid production in close-relationship with increase in airway inflammation with mechanical dysfunction of the lungs and increased levels of IL-4, IL-5 and IL-13 [105]. Together, these evidences demonstrated that patients with severe asthma exhibit a relative adrenal insufficiency that may be associated with worsening of disease.

As described previously, adipose tissue produces hormones that regulate blood glucose levels called adipokines. Even as adipose tissue releases adipokines that reducing blood glucose levels, as leptin and adiponectin, adipocytes produce hyperglycemic hormones too, including resistin [106]. The production of resistin is increased in feeding and obesity [107], and its hormone plays a significant role in obesity-induced insulin resistance [108]. The hyperglycemic effect of resistin is associated with decrease of glucose uptake in skeletal muscle cells [109] and severe hepatic insulin resistance [110]. Moreover, reduction in resistin levels by deleting the resistin gene, infusing resistin antibodies or resistin antisense oligodeoxynucleotides protect against obesity-induced hyperglycemia by restoring hepatic insulin responsiveness [108,111,112].

Steppan et al. [113] showed that asthmatic patients present elevated plasma resistin levels and they propose that resistin is associated with increase of asthma severity. However, atopic asthmatics had lower resistin levels compared to non-atopic asthmatic patients and control group, and resistin was negatively associated with eosinophil numbers and serum IgE levels [114]. Hence, the effect of resistin on asthma is unclear yet and need further studies.

### PI3K x cAMP on Airway Responsiveness and Inflammation in Asthma

Hormones that control glucose homeostasis act by distinct signaling pathways. While some hypoglycemic hormones, including insulin and leptin, activate PI3K, the major hyperglycemic hormones, as glucagon and epinephrine, induce increase in the intracellular levels of cAMP [70,71,115]. The activation of PI3K plays an important role in the pathogenesis of asthma by stimulating recruitment of mast cells, neutrophils and eosinophils; increasing survival of mast cells and neutrophils; activating mast cells, neutrophils and T cells; inducing proliferation of T cells and airway smooth muscle cells and differentiation of Th0 cells in Th2 and Th17 cells; promoting airway smooth muscle cell contraction [21,24,116-120] (Figure 2). Moreover, PI3K-knockout mice showed reduction in allergen-induced AHR, airway inflammation and remodeling [121,122], and aerolization of PI3K inhibitor decreased pulmonary eosinophil accumulation and AHR in murine asthma model [123].

Modulation of cAMP levels is a key therapeutic target in asthma, since the increase in cAMP induces relaxation of airway smooth muscle cells. Furthermore, CAMP stimulates apoptosis of mast cells and T cells; inhibits proliferation and activation of T cells and recruitment and activation of eosinophils [69,124-126] (Figure 2). This difference

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**Figure 2:** The opposing effects of PI3K and cAMP could explain the divergence between the role of hyperglycemic and hypoglycemic hormones in asthma physiopathology. Glucagon and epinephrine exert their action through an increase of cAMP intracellular levels. The elevation in cAMP on effectors cells of asthma promotes a range of effects that can reduce airway inflammation and hyperresponsiveness, and therefore improve asthma framework. On the other hand, most of insulin and leptin actions involve PI3K activation that induces a pro-inflammatory status in airways of asthmatics, which will aggravate the airway responsiveness. (→): stimulation; (←): inhibition.
in signaling pathways between hypoglycemic and hyperglycemic hormones could be associated with the opposite effect of these hormones in asthma [127-131].

Conclusion

The focus of this review has been on hormones that control glucose homeostasis on asthma pathogenesis and development. The fact that some diseases which are characterized by hyperglycemia have an imbalance between hypoglycemic and hyperglycemic hormones and the dichotomy between the effect of these hormones on asthma could explain, at least partly, why diseases like type 1 and type 2 diabetes present opposite incidence of asthma. In addition, a greater knowledge about the role of these hormones in asthma physiopathology may be important for the development of new therapeutic strategies for asthma.

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