

Down-Regulation of Allergic Responses in Conditions of Experimental Diabetes: A Role for Glucocorticoids?

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Key Words

Atopy • Diabetes • Glucocorticoids • Mast cells • Hypothalamic-pituitary-adrenocortical axis

Abstract

The prevalence of atopic diseases and diabetes is increasing worldwide, though the co-occurrence of both diseases in the same individual is less frequent than predicted. Previously published studies suggest that the Th1/Th2 concept could explain the inverse relationship between allergic diseases and type 1 diabetes. However, down-regulation of the IgE-mast cell system can also markedly contribute to the lack of responsiveness to local and systemic allergen challenges in diabetic conditions. Moreover, dysregulation of the hypothalamic-pituitary-adrenocortical axis and elevated endogenous glucocorticoid levels play a pertinent role in some of the pathological-related processes associated with poorly controlled or uncontrolled diabetes.

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Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia [1, 2]. Although diabetes has long been considered a disease of minor significance, it is now considered one of the major threats to human health in the 21st century. Significant changes in the human environment, behavior and lifestyle resulted in rising incidence rates of diabetes nowadays [3]. According to the World Health Organization, the existence of different clinical presentations as well as genetic and environmental etiologic factors led to five types of diabetes recognized and termed as (i) insulin-dependent diabetes mellitus (type 1 diabetes); (ii) non-insulin-dependent diabetes mellitus (type 2 diabetes); (iii) gestation-related diabetes, (iv) malnutrition-related diabetes and (v) other types of diabetes [2, 4, 5].

Diabetes is a consequence of defects in insulin secretion, insulin action or both, translated into abnormalities of carbohydrate, fat and protein metabolism, resulting in hyperglycemia [6, 7]. Symptoms of chronic hyperglycemia include polyuria, polydipsia and polyphagia as well as weight loss. Although variable among patients, long-term complications of diabetes can also include changes

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in arteries (atherosclerosis), basement membranes of small vessels (microangiopathy), kidneys (nephropathy), retina (retinopathy) and nerves (neuropathy) [8–10]. Glycation of tissue proteins and other molecules and excessive production of polyol compounds from glucose are among the detrimental effects induced by chronic hyperglycemia [9, 10].

Enhanced susceptibility to bacterial and fungal infections is thought to occur in poorly controlled diabetes, a phenomenon which might reflect an altered capacity of the diabetic patient to mount an inflammatory response, and the occurrence of immunoregulatory disorders, probably associated with severely decreased insulin secretion rather than increased blood glucose levels [11–13]. In addition, a direct correlation between hyperglycemia and the incidence of infection in diabetic patients has also been proposed [14, 15].

Disturbances in the inflammatory cycle evoked by diabetes mellitus with a reduction in granulocyte migration to the inflamed lesion are not uncommon. They have been clinically recognized [16]. Experimental models of diabetes have been developed in order to investigate this point, with alloxan being one of the most widely used agents to chemically induce diabetes [17]. Administration of alloxan to different animal species produces, via necrosis of the islets, several features common to those observed in human diabetes [18–20]. A number of studies state that diabetic animals present a decreased response to bradykinin and vasoactive amines as well as swelling induced by dextran, carrageenan and cellulose sulfate, indicating alterations in the microcirculatory reactivity [21–23]. Moreover, neutrophils from diabetics have also been shown to present functional abnormalities, e.g. less phagocytizing capacity [24] and chemotactic responses [25, 26], which might be extended to other inflammatory cells than those involved in allergic processes.

Diabetes versus Allergy

A lower prevalence of allergic diseases such as asthma, atopic dermatitis, eczema and conjunctivitis in uncontrolled type 1 diabetic patients [27–31] has been reported. In a multicenter case-control study, the prevalence of atopic diseases in children with type 1 diabetes was strikingly decreased, particularly regarding asthma, compared to age-matched controls (EURODIAB), and symptoms were also less severe in diabetic children. Although many epidemiologic studies attested the mutual exclusion between atopy and diabetes, the reason for this phe-

nomenon has not been elucidated. The concept of a Th1/Th2 balance as the basis for the mechanism of disease development has been raised. As already stated, autoimmune diseases such as type 1 diabetes involve a cellular T-helper response characteristic of the Th1 phenotype, and allergic diseases are associated with the Th2 phenotype [32–35]. There is substantial evidence that each of the Th1 and Th2 pathways controls a unique group of immune responses, via the production of different cytokines and the involvement of transcription factors, promoting the development of cells of the same subset while suppressing the expansion and effector cells of the other subset [36]. Thus it is plausible to speculate that an imbalance in the Th1/Th2 ratio might contribute to the negative correlation between type 1 diabetes and atopic diseases. In line with this idea, IL-4 has been regarded as a principal cytokine inducing differentiation of naive T-cell precursors into Th2 cells and switching B cells to produce IgE. A study in multiplex Caucasian families showed significant evidence of linkage and association of the *IL4R* gene with type 1 diabetes [37]. A haplotype of the *IL-4R* gene which appears to be protective against ■■■ and associated with a strong risk for type 1 diabetes was identified. Additionally, it was reported that peripheral and thymic T cells from spontaneous non-obese diabetic (NOD) mice [36] secreted significantly less IL-2 and IL-4 compared with cells from their respective controls. Moreover, exogenously added rIL-4 not only restored the NOD thymic and peripheral T-cell-proliferative responses but also protected NOD mice from developing diabetes [36, 38]. Although the Th1/Th2 paradigm has been widely accepted to explain disease development and/or immune responses for the last decades, Th17, another population of T cells being characterized by their production of the cytokine IL-17, has been reported recently [39, 40]. Although the precise role of Th17 in diabetes remains to be clarified, evidence suggests that IL-17 production is crucial to the development of autoimmune diseases [39, 41]. On the other hand, IL-17-mediated inflammatory mediators do not seem to contribute to the development of eosinophilia in allergic asthma in rodents [40]. Thus, an increase in Th17 cells associated with type 1 diabetes might contribute to a lower incidence of allergic diseases. Additionally, environmental factors may also have a direct effect on the decreased incidence of atopy in type 1 diabetic patients [31].

For ethical reasons, experimental diabetes has been widely induced with chemical agents such as alloxan and streptozotocin, reported to exert toxic effects on the β -cells of the islets of Langerhans, reproducing typical signs

of human type 1 diabetes [17]. While trying to elucidate why allergic dysfunctions in patients with type 1 diabetes are smaller than predicted, rats with alloxan-induced diabetes were found to have significantly reduced allergen-induced acute protein leakage as well as late eosinophil infiltration into the pleural and bronchoalveolar spaces [42–44]. Decreased bronchial hyperreactivity and blood eosinophilia were also detected in diabetic mice [Carvalho et al., in prep.]. Interestingly, the suppression of allergic responses in alloxan-diabetic rats directly correlated with a selective and time-dependent reduction in the number of local mast cells [42]. In addition, isolated fragments of the ileum, trachea and skin from diabetic sensitized animals were shown to be refractory to antigen challenge in vitro [45, 46]. Since mast cells exhibit a morphological and functional heterogeneity at different body sites [47, 48], these findings indicate that both connective tissue and mucosal mast cell subtypes are affected by alloxan-induced diabetes. Mast cells are generally found around blood vessels, predominantly in tissues forming an interface between the host and the external environment, e.g. the skin, airways and gastrointestinal tract [49], with mast cell number being dependent on both the rate of production of mast cell precursors and the survival of mature mast cells within the tissue [50]. In response to antigen, mast cells can release cytoplasmic granule-associated mediators, e.g. vasoactive amines, and have also been shown to produce lipid mediators, e.g. cysteinyl-leukotrienes and platelet-activating factor [51]. Mast cells can also secrete a wide range of cytokines, which contribute to the initiation and perpetuation of IgE-dependent allergic inflammation at different sites [49]. In studies using the adoptive transfer system, in genetically mast-cell-deficient mice, it was demonstrated that mast cells were essential for the leukocyte recruitment in the skin after challenge with IgE and specific antigen [52]. In line with the above observations, the reconstitution of the mast cell population in animals with alloxan-induced diabetes, by means of adoptive transfer system, led to restoration of the inflammatory process [45], suggesting that down-regulation of mast cells could be responsible at least in part for the lack of responsiveness of diabetic animals to antigen challenge. Additional studies showed that reactivity of mast cells from diabetic animals to immunological and non-immunological stimulation in vitro was lower than that from control cells, suggesting a direct correlation between hyporesponsiveness of diabetic mast cells and elevated basal levels of cAMP [53]. Mast cells from alloxan-diabetic rats also exhibited a drastic increase in the apoptotic rate and over-

expressed the pro-apoptotic protein Bax, indicating that the hyporesponsiveness of mast cells was associated with apoptosis in diabetic conditions [54].

The resistance of alloxan-diabetic animals to allergen provocation was also extended to the condition of systemic anaphylaxis [55, 56], when a substantial reduction in the mortality rate, intestinal hemorrhage and plasmatic levels of histamine were evidenced [57]. In addition, diabetes was shown to affect the sensitization stage of the anaphylactic reaction, since the augmentation in total and ovalbumin-specific serum levels of IgE was impaired in diabetic sensitized rats [57]. In 1983, Ptak et al. [58] demonstrated that immune cells recovered from spleen and lymph nodes lost their ability to form IgE when transferred from naive to alloxinated diabetic mice, whereas immune cell suspensions from diabetic animals regained the capacity to generate IgE upon transfer to normal recipients. These findings suggest that a soluble factor present in the blood circulation of diabetic mice interferes directly or indirectly with IgE-producing cells.

Role of Steroids in the Lack of Responsiveness of Diabetics to Antigen Stimulation

Glucocorticoids are potent physiologic inhibitors of inflammatory processes and for decades have been used due to their wide therapeutic properties [59, 60] associated with inhibition of gene transcription, resulting in a smaller production of a wide range of effectors such as cytokines [60, 61], including the stem cell factor – an important mediator for the control of the mast cell population in tissues [62]. At baseline and during inflammatory or immune responses, the number of mast cells seems to be regulated by local concentrations of factors that influence their local survival and proliferation, e.g. stem cell factor and IL-3 [47, 63, 64], as well as by factors that regulate tissue homing, survival and maturation of circulating mast cells. Glucocorticoids have the ability to deplete mast cells at different body sites, including the skin, lung and intestines [63, 65–67]. Thus, glucocorticoid-induced inhibition of cytokine production by cells of the microenvironment space might be a plausible explanation for the mast cell depletion noted in diabetes.

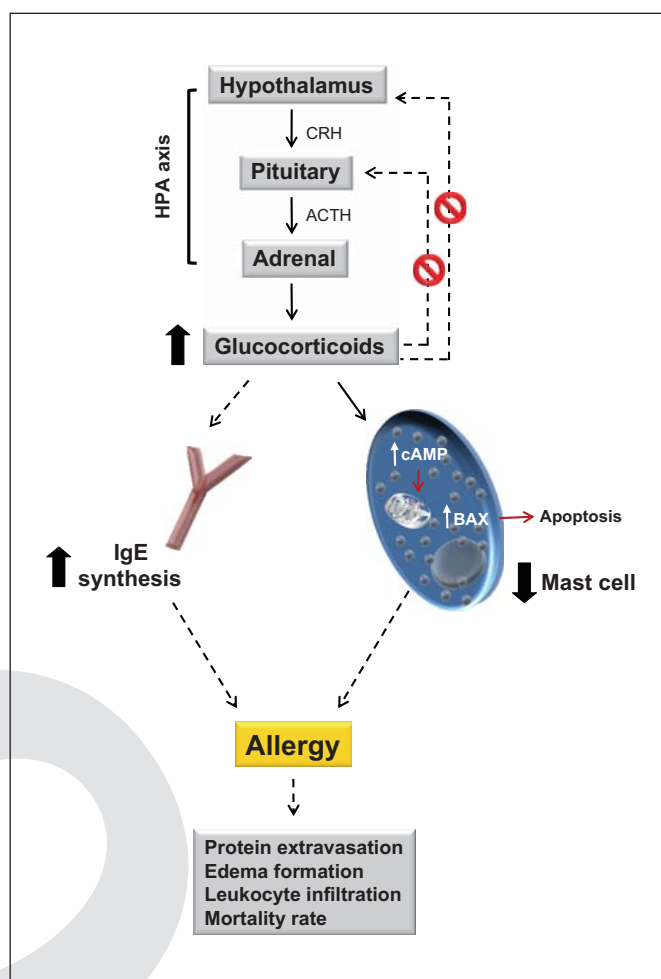
Hyperactivity of the hypothalamic-pituitary-adrenal axis followed by hypercortisolism is frequently observed in patients with type 1 and 2 diabetes [68–71]. In diabetes, dysfunction of the hypothalamic-pituitary-adrenal axis

Table 1. Comparison of serum corticosterone levels (means $\pm$ SEM) of normal and 21-day diabetic rats treated daily with dexamethasone (0.02 mg/kg, s.c.) for 5 days

Condition	Treatment	Serum corticosterone, ng/ml	n
Normal	–	64.3 $\pm$ 27.2	8
	+	72.1 $\pm$ 18.2 ^a	8
Diabetic	–	272.2 $\pm$ 11.3 ^b	9
	+	246.1 $\pm$ 28.2	10

Basal serum corticosteroid levels were significantly higher in diabetic animals compared with controls (^a $p < 0.01$). Normal animals exhibited a graded response to dexamethasone treatment (^b $p < 0.05$), whereas the response in diabetic animals seems to plateau at the high level.

Fig. 1. The hyporesponsiveness to allergic challenges in diabetes may be explained by the following mechanism. Establishment of a diabetic state causes hypothalamic-pituitary-adrenal (HPA) axis dysfunction due to impaired negative feedback sensitivity, followed by an increase in the circulating levels of glucocorticoids. This leads to suppression of increased IgE synthesis and to apoptosis-triggered mast cell depletion, which together contribute to the lower responsiveness to local and systemic allergen challenges noted under diabetes. Dashed lines represent suppressive effects. ACTH = Adrenocorticotrophic hormone; CRH = corticotropin-releasing hormone.



seems to involve complex interactions with impaired glucocorticoid negative-feedback sensitivity, as evidenced in table 1. Other factors such as hypoinsulinemia, hyperglycemia and/or hypoleptinemia may also increase central drive of the axis [72, 73]. We and others described a rise in serum corticosterone levels in parallel with an increase in the adrenal-gland/body weight rate following diabetes caused by alloxan treatment in rats [5, 43]. The decreases in the mast cell number and reactivity as well as of antigen-induced IgE production noted in alloxan-induced diabetes were reversed by surgical removal of adrenal glands and by treatment with the steroid blocker RU486 [54, 74]. Likewise, bilateral adrenalectomy restored the antigen-induced inflammatory responses in the hindpaw and pleural space of alloxan-diabetic rats [75]. Altogether, these findings reinforce the hypothesis that glucocorticoids are involved in the dysfunction noted in diabetic animals.

Conclusion

The focus of this review is the decline in the occurrence of atopic diseases in diabetic individuals and vice versa. There is evidence demonstrating that the mutual antagonistic effect of Th1 and Th2 cells can contribute to the negative association between allergy and diabetes, possibly by means of selective cytokine networks. Additionally, as illustrated in figure 1, we also suggest that impaired response of the IgE mast cell system, which is closely related to the elevated circulating levels of endogenous glucocorticoids, is implicated in the hyporesponsiveness to allergen challenge detected in diabetic individuals.

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