

Mast cell changes in experimental diabetes: focus on attenuation of allergic events

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The prevalence of atopic diseases and diabetes is increasing worldwide though the concurrence of these pathologies in individual patients is found less frequent than it would be predicted. Moreover, co-existence of diabetes and allergy is generally marked by attenuation of their respective symptoms, and effective treatment of one disease exacerbates the other. This review gives an update of the state-of-the-art concerning the intercurrency of allergy and diabetes, particularly focusing on the consequences to the allergen-evoked vascular and cellular changes. It is proposed that the reduction in mast cell numbers and reactivity may be a pivotal mechanism behind the mutual exclusion phenomenon.

Key words: diabetes - allergy - mast cells - glucocorticoids

Diabetes mellitus represents a heterogeneous group of disorders which have hyperglycemia as a common feature (Tisch & McDevitt 1996, Bell & Polonsky 2001). Although diabetes has long been considered a disease of minor significance, it is considered now as one of the main threats to human health in 21st century. Great changes in the human environment, behavior, and lifestyle resulted in the raising rates of diabetes (Zimmet et al. 2001). According to the World Health Organization, the existence of different clinical presentations and genetic and environmental etiologic factors have led to five types of diabetes recognized and termed as i) insulin-dependent diabetes mellitus (IDDM, type 1 diabetes), ii) non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes), iii) gestational-related diabetes (GDM), iv) malnutrition-related diabetes, and v) other types (Muir et al. 1992, Atkinson & Maclaren 1994, Hoet & Tripathy 1996, Bell & Polonsky 2001).

Diabetes is consequence of defects in insulin secretion, insulin action or both, which is translated into abnormalities of carbohydrate, fat and protein metabolism, resulting in hyperglycemia (Klip et al. 1992, Taskinen et al. 1996) Symptoms of chronic hyperglycemia include polyuria, polydipsia, and polyphagia as well as weight loss. Although varying among patients, long term complications of diabetes can also include changes in arteries (atherosclerosis), basement membranes of small vessels (microangiopathy), kidneys (nephropathy), retina (retinopathy), and nerves (neuropathy) (Vlassara et al. 1984, Yabe-Nishimura 1998, Brownlee 2001).

It has generally been stated that uncontrolled type 1 diabetic patients are more susceptible to bacterial and fungal infections than normal controls, though the cause has not yet been determined (Larkin et al. 1985). In order to investigate this point, experimental models of diabetes have been developed from which chemical induction with alloxan has been the most widely used (Rerup 1970). Administration of alloxan to different animals produces, via necrosis of the islets, several features common to those observed in human diabetes (Lukens 1948, Gaulton et al. 1985, Quan et al. 2001). There is some evidence that diabetics present a deficiency in mounting an inflammatory response, probably associated with severe reduction in insulin secretion rather than increased blood glucose levels (Garcia Leme et al. 1973, Garcia Leme & Farsky 1993). This is still a controversial point as other investigators have suggested a direct correlation between hyperglycemia and the incidence of infection in diabetic patients (Rayfield et al. 1982). A number of studies shows that diabetic animals present a decreased response to intradermally administered bradykinin and vasoactive amines as well as swelling induced by dextran, carrageenan, and cellulose sulphate, indicating alteration in the microcirculatory reactivity (Garcia-Leme et al. 1974, Fortes et al. 1984, Akamine et al. 2003). Moreover, neutrophils from diabetics have also been shown to present functional abnormalities such as less phagocytizing capacity (Wertman & Henney 1962) and chemotactic responses (Mowat & Baum 1971, Fortes et al. 1991, Mello et al. 1992), which might be extended to other inflammatory cells as those involved in allergic processes.

Diabetes vs allergy

It is noteworthy that allergic disorders, including asthma, atopic dermatitis and eczema, have an uncommon occurrence in diabetic patients (Tinkelman & King 1979, Bottini & Fontana 1999, Douek et al. 1999, Olesen et al. 2001, Cardwell et al. 2003), though the reason for this mutual

exclusion is still debatable. The possibility does exist that the Th1/Th2 paradigm could be a potential explanation. As already stated, autoimmune diseases such as type-1 diabetes involves a cellular T-helper response characteristic of the Th1 phenotype, and allergic diseases are associated with Th2 phenotype (Romagnani 1991, Abbas et al. 1996). There is substantial evidence that Th1 and Th2 pathways each control a unique group of immune responses, by means of differences in cytokines produced and transcription factors involved, promoting the development of cells of the same subset while suppressing the expansion and effector cells of the other subset (Rapoport et al. 1993). Thus it is reasonable to speculate that an imbalance between the Th1/Th2 subtypes might contribute to the negative association between type-1 diabetes and atopic diseases. In line with this idea and considering IL-4 as a major cytokine to induce differentiation of naive T-cell precursors into Th2 cells and B cell switch to produce the immunoglobulin E, a study with multiplex Causasian families shows significant evidence of linkage and association of the *IL4R* gene with type 1 diabetes (Mirel et al. 2002). The existence of a halotype of IL-4R gene, which appears to be protective and associated with individuals exhibiting the strongest risk for type 1 diabetes, has been identified. Additionally, it has been reported that peripheral and thymic T cells from spontaneous non-obese diabetic (NOD) mice (Rapoport et al. 1993) as well as from mice rendered diabetic by streptozotocin (Wood et al. 1999) significantly secrete less amount of IL-2 and IL-4 when compared with cells from their respective controls. Moreover, exogenously added rIL-4 not only did it restore the NOD thymic and peripheral T cell proliferative responses but also protects NOD mice from developing diabetes (Rapoport et al. 1993).

Down-regulation of allergic inflammation in experimental diabetes

While investigating the reason why clinical asthma appeared less severe when diabetes mellitus was superimposed, Vianna and Garcia-Leme (1995) demonstrated that compared with controls, animals that were turned diabetic after alloxan injection presented a marked decrease in the number of cells recovered from bronchoalveolar lavage after antigen challenge (Vianna & Garcia-Leme 1995). In accordance with the above observation, using the model of pleural allergic response in rats (Lima et al. 1990, 1991, Silva et al. 1992), we found that sensitized animals rendered diabetic after alloxan reacted to antigenic challenge with 50% reduction in the number of eosinophils recruited to the pleural cavity (Diaz et al. 1996, 1997). The less pronounced eosinophil accumulation did not relate to an intrinsic cell locomotor abnormality since eosinophils from diabetic rats presented similar chemotactic responses in vitro as compared to matching controls (Diaz et al. 1996). Moreover, antigen-induced protein leakage (de Oliveira Barreto et al. 2003) as well as neutrophil infiltration (unpublished data) were also clearly suppressed in diabetic sensitized rats. Interestingly, we showed that suppression of allergic responses in diabetic rats well correlated with a selective and time-dependent reduction in the number of pleural mast cells ($50\% \pm 2.2\%$, $p < 0.01$;

mean \pm SEM), while other leucocytes were not altered. As compared to naive animals, the reduction in mast cell numbers was first noted 48 h following alloxan administration and remained unaltered for at least 60 days (Diaz et al. 1996). Furthermore, the amount of histamine stored in diabetic mast cell granules was not different from that found in controls, clearly indicating that alloxan induced a decrease in the number of mast cells rather than their degranulation (Diaz et al. 1996, de Oliveira Barreto et al. 2003). Altogether these findings suggested that down-regulation of mast cells could be responsible for at least part of refractoriness of diabetic animals to antigen challenge. Since mast cells played a critical role not only in eosinophil recruitment but also in other key features of the allergic inflammatory response (Metcalf et al. 1997), we further evaluated how diabetes-associated mast cell disturbance could effect the suppression of allergen-mediated inflammation under diabetic conditions. The reconstitution of the pleural mast cell population in diabetic animals, by means of adoptive transfer system, restored the antigen-induced plasma leakage (de Oliveira Barreto et al. 2003). Additionally, the transfer of diabetic sensitized mast cells to normal animals caused a lower pleural exudatory response compared to the response produced by non-diabetic mast cells, indicating that not only the number of mast cells and also their reactivity were significantly reduced in experimental diabetes. In fact, purified mast cells from diabetic rats were hyporesponsive to antigen and compound 48/80 stimulation in vitro as attested by histamine release (de Oliveira Barreto et al. 2003), in direct correlation with increase in the intracellular levels of cAMP (Barreto et al. 2004). This was an indicative that augmentation in the amount of cAMP nucleotide could be accounted for by the refractoriness of mast cells under diabetic conditions.

The resistance of diabetic animals to allergen provocation was also extended to the condition of systemic anaphylaxis (Ganley 1962, Dhar et al. 1967), when a substantial reduction in mortality rate, intestinal haemorrhage and plasmatic levels of histamine were evidenced (Carvalho et al. 2003). Moreover, in the case of diabetic animals fragments of trachea, skin, and intestine showed refractoriness to the antigen challenge in vitro (de Oliveira Barreto et al. 2003), providing evidence that similarly to what was noted in the case of free mast cells, those located in tissues seemed to be negatively regulated in diabetes. In addition, the diabetic state was also shown to affect the sensitization stage of the anaphylactic reaction, since the augmentation in total and ovalbumin specific serum IgE levels was suppressed in diabetic sensitized rats (Carvalho et al. 2003). Coherently, Ptak et al. (1983) demonstrated that immune cells recovered from spleen and lymph nodes when transferred from naive into diabetic mice lost their ability to form IgE, whereas the immune cell suspensions from diabetic animals regained the capacity to generate IgE upon transfer to normal recipients (Ptak et al. 1983). These findings suggested that a soluble factor present in the blood circulation of diabetic mice interfered directly or indirectly with IgE-producing cells.

Balance between steroid and insulin levels in diabetes

Hyperactivity of the hypothalamic-pituitary-adrenal axis with consequent hypercortisolism was frequently observed in patients with type 1 and type 2 diabetes (Cameron et al. 1984, Roy et al. 1990, 1998, Chan et al. 2002), and seemed to be associated with increased expression of hypothalamic corticotrophin-releasing hormone (CRH) mRNA (Chan et al. 2003). We described an increase in the adrenal-gland/body weight rate in parallel to an elevation in serum corticosterone levels following diabetes caused by alloxan treatment in rats. The reduction of mast cell number and reactivity as well as of antigen-induced IgE formation, noted in alloxan diabetes, was reversed by surgical bilateral adrenalectomy and by treatment with the steroid blocker RU 486 (Diaz et al. 2001, Carvalho et al. 2003, Barreto et al. unpub. data), indicating a causative link between the negative regulation of mast cell-IgE system and enhanced serum glucocorticoid levels. These findings were consistent with previous reports which had demonstrated the effect of glucocorticoids in inducing depletion of mast cells in different body sites including skin, lung, and intestine (Pipkorn et al. 1989, Goldsmith et al. 1990, Finotto et al. 1997). Glucocorticoids were shown to have their anti-inflammatory activity due to inhibition of gene transcription, resulting in a smaller production of a wide range of effectors such as cytokines (Schleimer 1993, Barnes 2004), including the stem cell factor (SCF) (Finotto et al. 1997), IL-3 and IL-4 (Braun et al. 1997). Thus, the inhibition by glucocorticoids of the cytokine production by cells of the microenvironment space might be a plausible explanation for mast cell depletion noted in diabetes.

As opposed to glucocorticoids, insulin is considered a pro-inflammatory hormone (Strauss 1984) capable of sensitizing rats to the anaphylactoid reaction caused by dextran, and restoring the reactivity to antigen challenge when given to diabetic rats (Diaz et al. 1996). In fact, we have noted that treatment with insulin restores the baseline levels of mast cells in the pleural cavity of diabetic rats (Diaz et al. 2001), a phenomenon which may be explained by its known proliferative activity verified in different cell systems (Strauss 1984). Similar findings obtained by Cavalher-Machado et al. (2004), show that insulin might also modulate mast cell degranulation at the early-phase response to antigen provocation, which represents an alternative insight for a better understanding of the mechanisms accounted for the decreased risk of asthma among type-1 diabetic patients (Cavalher-Machado et al. 2004). In this context, our group has reported that treatment of alloxanated rats with insulin impaired the increase in the systemic levels of corticosterone, indicating that insulin can directly control glucocorticoid secretion (Diaz et al. 2001). These data are in line with those of Meehan et al. (1988) who reported that insulin, when injected into diabetic animals by intracerebro ventricular via, impaired the increase in the systemic levels of glucocorticoids (Meehan et al. 1988). Likewise, glucocorticoids are shown to be effective in inhibiting insulin secretion by pancreatic β cells (Ludvik et al. 1993) and in inducing tolerance to insulin in diabetic patients (Isoniemi et al. 1993). Thus, our

findings support the concept that insulin and glucocorticoids have antagonistic effects on different biological systems and can also regulate the level of each other.

Conclusion

The focus of this review has been the decline in incidence 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 negative association between allergy and diabetes, possibly by means of selective cytokine networks. Additionally, we also provide evidence that a defective response of IgE-mast cell system, in close relationship with increased glucocorticoid levels, is implicated in the refractoriness to allergen challenge detected in diabetics.

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