

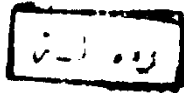
ROLE OF IMMUNOLOGY IN ENDOCRINE DISORDERS

ESSAY

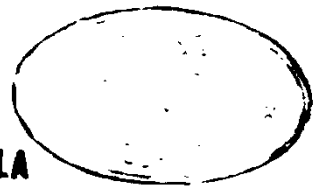
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَعَلَيْكَ مَا تَكُنْ تَعْلَمُ وَكَانَ فَضْلُكَ عَلَيْنَا عَظِيمًا

(صدق الله العظيم)

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INTRODUCTION

INTRODUCTION AND AIM OF THE WORK

Immune response may play an important role in both production and complications of endocrine diseases at the level of the endocrine gland, the circulating hormone, or the target cell (including the hormone receptor site). Examples of these disorders, Hashimoto's thyroiditis, Graves' disease, idiopathic primary hypothyroidism, primary adrenal insufficiency, insulin-dependent diabetes mellitus and certain forms of hypoparathyroidism and gonadal insufficiency. It appears that the immune response plays a direct role in the pathogenesis of the hormone-deficiency disease by producing damage to an endocrine gland. In other endocrine disease, such as Graves' disease or the syndrome of insulin resistance due to anti-insulin receptor antibodies, hormone receptors on target tissues become the target of the altered immune response resulting in production of either glandular overactivity or hormone resistance. The immune response may also play an important role in some of the complications of endocrine diseases. The most obvious example is diabetes mellitus with development of insulin allergy. For this reason this essay is an attempt to explain the role of immunology in endocrine disorders.

BASIC IMMUNOLOGY

TOLERANCE AND AUTOIMMUNITY

Immunologic tolerance is failure of the immune systems to respond to a specific antigen after previous exposure to that antigen (i.e. it is an absence of functional response rather than the lack of any response at all). Tolerance may in fact, be due to a continuing active response that results in specific immunologic unreactivity. (Talal 1980). Many different mechanisms may lead to specific unresponsiveness. these include, specific elimination of clone of B and T cells at early phases in their developmental history when they pass through a state in which they are particularly sensitive to tolerance induction and is called clonal abortion theory. (Paul 1980).

Another mechanism that results in specific immunologic unreactivity which depends on the dose of antigen administered. a low zone tolerance the antigen dose is smaller than the requirement to cause immune response, while a high zone tolerance is obtained when a high dose of antigen is administered. At low antigen dose T-cells alone are rendered unresponsive whereas both B and T cells are rendered unresponsive at a high antigen dose. (Hudson & Hay 1980).

Classic tolerance or central failure (clonal deletion), there are deletion of immunocompetent cells due either to death of these cells or to an irreversible inhibition of surface membrane receptors for antigen. Antigen-binding cells cannot be demonstrated, the unresponsive state cannot be transferred by either T or B lymphocytes, and suppressor cell activity cannot be demonstrated. (Talal 1980).

Effector cell blockade a mechanism which is proposed to account for the phenomenon of tolerance is the blockade of receptors at surface of antigen-reactive cells, particularly antibody-forming cells. (Cohen et al., 1979).

Antibody dependent mechanism is also involved, in which although the antigen binding cells are present and not deleted as in clonal deletion yet tolerance can still be present even when antigen binding cell exist and antibody is present an example to it is the "Tread mille-effect" which means inability to measure free antibody despite its continued biosynthesis and this may be due to complexing of antibody with the circulating antigen, so free antibody cannot be measured. Antibody can also contribute to an unresponsive state by competing with lymphocyte receptors for available antigen. (Talal 1980).

Autoimmunity is breakdown of self tolerance and it indicates immunologic self injury. It does not imply etiology. (Talal 1980).

Autoimmune diseases include clinical disorders resulting from an immune response against self antigens (autoantigens) in which self destructive process occurs, directed by ownimmune system. Autoimmune disease must be differentiated from autoimmune response (phenomenon) that occurs during life when some cells of body changed by age, infection or mutation and the immune system responds by forming antibodies or by producing T-cells against them without a harmful effect, while autoimmune disease is a pathological condition arising from an immune response. (Stiller et al., 1975).

Autoimmunity is characterized by inappropriate or excessive activity of immune effector cells. Thus B-cells may begin producing autoantibodies, immune complexes may deposit in blood vessels, T-lymphocytes may infiltrate and destroy tissues and the complement system may activate phagocytic mononuclear cells. Most of autoimmune diseases are mediated by humoral auto-antibodies and less by sensitized T-cells reacting with autoantigens. (Talal 1980).

Some requirements must be present in auto-immune diseases as presence of autoimmune reaction, and the reaction is not secondary to tissue damage but primary, and absence of any other well defined cause of the disease. (Robbin and Cotram 1979).

Autoimmune diseases may arise by several mechanisms as helper T-cells by-pass, emergence of sequestered antigen and loss of function of suppressor T-cells. (Roitt 1978).

By-pass of helper T-cell tolerance may be carried by modification of normal antigen by drugs as alpha methyl dopa and autoimmune haemolytic anemia or by viruses as influenza and measles. Also modification of auto-antigen may arise from enzyme degradation, this exposes antigenic determinants to react with T-lymphocytes (Roitt 1978). By-pass of helper T-cell may be due to cross reacting antigen, where some microorganisms carry antigenic determinants similar to that of tissue component as in rheumatic fever, where antibodies to streptococcal antigens react with constituents of cardiac muscle and certain connective tissues. (Robbin & Cotram, 1979).

Sequestered or hidden antigens as thyroglobulin, spermatozoa, or lens protein are normally secluded from

contact with lymphocytes due to their presence in non vascular sites. Accordingly autoimmunity would arise when for whatever reason (as injury, inflammation) these antigens suddenly come in contact with immune system which regards them as foreign antigen and forms antibodies against them. Against this mechanism, it was found that thyroglobulin circulates in small amounts without causing an autoimmune damage. (Pinchra & Fenzi 1979).

Concentration of this order of thyroglobulin produces low zone tolerance where T-cells are tolerant while B-cells are not as B-cells are stimulated by the antigenic determinants on human thyroglobulin through T-cells cooperation which are tolerant to thyroglobulin so B-cells will not normally be activated. So a small proportion of B-cells in normal individuals bind human thyroglobulin and this may also be true for many different body constituents. (Roitt 1978).

Disordered immunologic regulation mechanisms may explain many examples of autoimmunity and according to it the potential for autoimmunity present in normal individual is not expressed because of the normal functioning immunologic regulatory mechanisms. The interaction between various T-cell subpopulations is mainly responsible for this regulation, so a

disequilibrium resulting either in the generation of helper T-cells or in a deficiency of suppressor T-cells could trigger these potentially autoreactive B-cell clones to autoantibodies production (Talal 1980).

Any procedure non specifically activates lymphocytes as the use of mitogens, adjuvants, some microbes could stimulate the formation of autoantibodies, so it has been recently put forward stimulation of pre-existing population of lymphocytes (B-cells) capable of making antiself antibodies. (Weir 1981).

Hypersensitivity

Hypersensitivity is a state in which the individual develops an excessive reactivity to the introduction of antigen leading to tissue damage. (Roitt 1978).

Four classic types of hypersensitivity were proposed. Type I (or Immediate hypersensitivity). The antigen reacts with specific class of antibody (IgE) bound to mast cells or circulating basophils through a specialized region of Fc piece with degranulation of these cells and release of vasoactive amines as (histamine, slow-reacting substance of anaphylaxis (SRS-A), bradykinin and others), which lead to acute local or

systemic anaphylaxis e.g. of local type atopic allergy as hay fever and extrinsic asthma and e.g. of systemic anaphylaxis is acute anaphylaxis following parenteral injection of foreign serum. (Roitt 1978, Weir 1981).

Type II (cytotoxic) reactions. These involve the combination of IgG or IgM antibodies with specific antigen on the surface of the target cell resulting in complement activation and lysis of the cell. Examples of this type are autoimmune hemolytic anemia and Goodpasture's syndrome (antibodies against glomerular and alveolar basement membranes) (Roitt 1978, Pinchra and Fenzi 1979).

Type III reactions (immunocomplex mediated) these result from the formation of complexes between antigen and humoral antibody. The localization of these complexes in tissues leads to activation of complement followed by prominent inflammatory changes classical examples of these types of reactions are the Arthus phenomenon and serum sickness. (Pinchra and Fenzi 1979).

Type IV reactions (Cell-mediated, delayed hypersensitivity). These carried out when sensitized T-cells come in contact with a specific antigen with release of lymphokines that share the killer T-cells in causing