PITUITARY GONADAL ASPECTS IN INSULIN DEPENDENT DIABETIC FEMALES

M.D.THESIS

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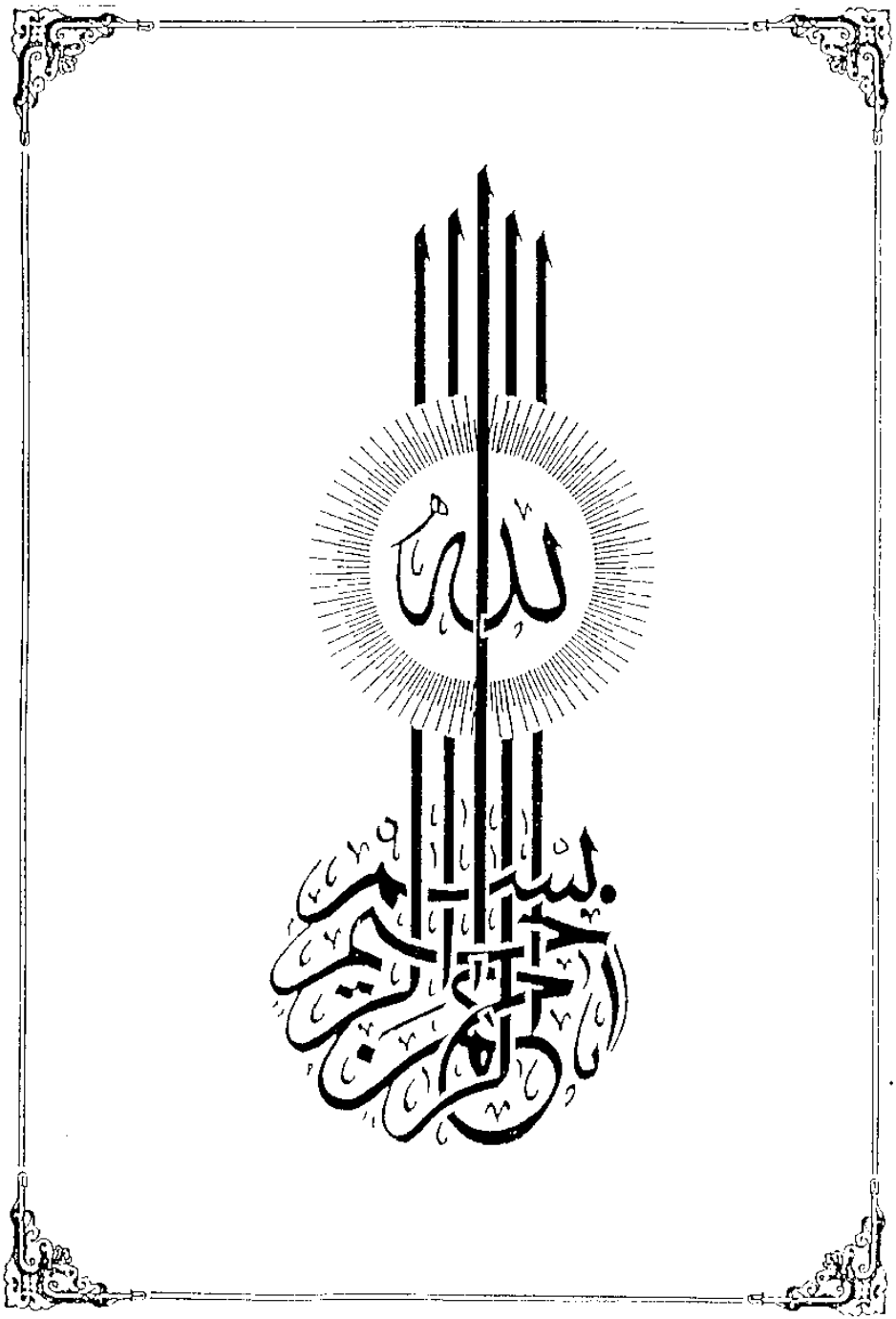

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AIM OF THE WORK

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Women with Type I Insulin Dependent Diabetes Mellitus have an increased risk of developing menstrual disorders throughout their fertile years . The site of dysfunction may be located any where along the hypothalamic-pituitary-gonadal axis . The aim of this work is to study the hypothalamic pituitary gonadal aspects as regard LH , FSH , Prolactin , Estradiol , and Progesterone in diabetic females with menstrual disturbances , trying to localize and define the site of dysfunction and the possible pathogenesis of such dysfunction .

REVIEW OF LITERATURE

IMMUNOLOGIC AND GENETIC FACTORS IN AUTOIMMUNE DISEASES

IMMUNOLOGIC FACTORS:

The complex mechanisms whereby autoimmunity develops and is pathologically perpetuated in animal models and human disease has been the subject of intensive investigations over the past several years . Recent investigation have emphasized two mechanisms that can lead to the production of autoantibodies : i)impaired immunoregulation , which causes the formation of autoantibodies against a family of ubiquitous autoantigens , ii) and the idiotype cascade , which can faster the production of autoantibodies (Shaenfeld et al ,1984) .

IMMUNOREGULATION : The immune system control its latent tendency to produce autoantibodies by the regulatory influence of the two principles families of lymphocytes , T cells and B cells . There are two major divisions of T lymphocytes ; helper (inducer) cells and suppressor cells . B cells with potential to produce autoantibodies are held in a dormant state by the action of suppressor cells , a lack of "help" from inducer cells , or both , and that in autoimmunity , an imbalance between the two kinds of T cells perturbs the immunoregulatory network , thereby activating the dormant , autoreactive B cells . A reduction in

suppressor cells is consonant with the immunoregulatory hypothesis of autoimmunization (Shaenfeld et al,1984) . Increased helper-cell activity has been found in procainamide-induced lupus (Miller et al ,1982) . The drug or its metabolite may inhibit cyclic AMP , an effect that stimulates helper cells . Methyldopa, which can cause drug-induced autoimmune hemolytic anemia, activates cyclic AMP , an effect that inhibits suppressor cells (Kirtland et al,1980) . Hence , autoimmunity may result from either stimulatory or inhibitory effects of a drug on immunoregulatory cells . A primary B cell abnormality which by the production of lymphocytotoxic antibodies specific for suppressor cells self-perpetuates its own hyperactivity by removing negative influences (Anthony et al,1980) .

Phamacologic modification of regulatory lymphocytes may also contribute to the pathogenesis of spontaneous autoimmune diseases.In systemic lupus the lymphocytes respond subnormally to adenosine , an activator of cyclic AMP adequately may contribute to both impaired suppressor cell function and excessive activation of helper cells . Of further interest is the finding of autoantibodies against lipomodulin , an inhibitor of phospholipase A2 , in systemic lupus , rheumatoid artheritis and dermatomyositis (Shaenfeld et al,1984) . By inhibiting the enzyme,lipomodulin decreases the availability of arachidonic acid and thus reduces the formation of prostaglandins . That effect

can in turn impair prostaglandin-dependent suppressor cells (Chouab et al,1984) . Anti-lipomodulin autoantibodies , therefore have the potential to disrupt immunoregulatory circuits through their metabolic effects

IDIOTYPES : It is unlikely that abnormalities of immunoregulatory T cells can fully explain the specific immunopathology of autoimmune diseases . Idiotypes are serologically identifiable configurations in the antigen- binding region of an antibody . The variable portions of the heavy and light chains of an antibody molecule form a cavity whose convolutions accomodate the relevant antigen (Fig. 1) . In view of the unique structure of the antibody variable region , it is not surprising that it is immunogenic . The rabbit antiserum was made by immunization with a foreign protein and is thus a heterologous anti-idiotype . There are also autologous anti-idiotypes (auto-anti-idiotypes) . They arise during the course of a normal immune response . There is considerable evidence that idiotypes and auto-anti-idiotypes constitute the B-cell component of the immunoregulatory network (Iden,1981) . These principles are relevant to the formation of an important class of auto-antibodies , of which the antireceptor auto-antibodies in myasthenia gravis , diabetes mellitus , and Graves disease are representatives . The anti-idiotype may stimulate the receptor by mimicking the physiologic effects of the ligand or it may block the receptor .

In a rare variant of diabetes mellitus, associated with acanthosis nigricans, there are autoantibodies to insulin receptors (Flier,1976). It was found that mice immunized with bovine or pork insulin produced both anti-insulin antibodies and auto-anti-idiotypes that were anti-(anti-insulin) antibodies. The anti-(anti-insulin) antibodies may be reactive with insulin receptors, and, as a result, had insulin-like activity (Schechter et al,1982).

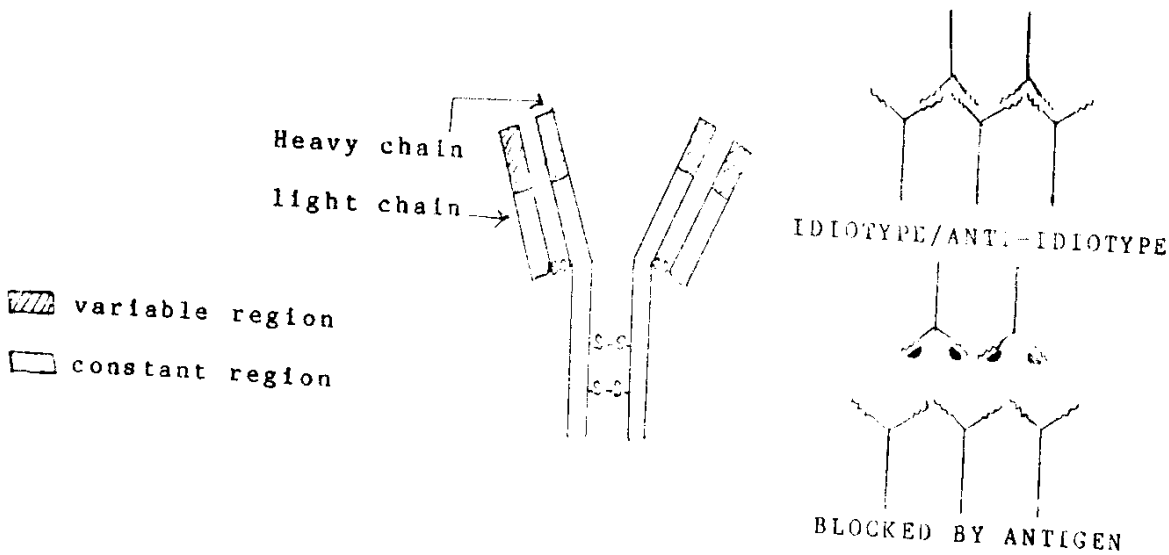

FIGURE 1. IMMUNOGLOBULIN MOLECULE (LEFT) AND BLOCKING OF IDIOTYPE-ANTIIDIOTYPE REACTION BY ANTIGEN (RIGHT)

GENETIC FACTORS :

The genetic loci of great interest in autoimmunity are associated with the major histocompatibility complex (MHC) . The short arm of chromosome 6 contains the human MHC genes , which encode cell-surface polypeptides termed HLA and DR antigens . HLA (class I) antigens are functionally relevant to the cytotoxic T lymphocytes that mediate immune lysis , as in the destruction of virus- infected cells . DR (class II) antigens ,by contrast , are necessary for antigen recognition by helper lymphocytes , responsiveness or unresponsiveness to a given antigen depends on a particular assemblage of DR genes (Shaenfeld et al ,1984) . Class I and II are likely polymorphic . Each of the many alleles is designated by a number e.g. DR2 or HLA-B6 .

In several autoimmune diseases there are statistically significant associations with the DR3 antigen , the HLA-B8 antigen , or both . Other MHC antigens are also linked to particular diseases , either by over-representation or underpresentation . Type I diabetes mellitus has an association with either DR3 or DR4 or with both (Schwartz et al ,1980) .

Four linked genes for the compelment components BF (factor B),C 2 , C4A , and C4B (class III antigens) lie close to the DR region of the MHC . Certain allelic forms of these components occur frequently in some autoimmune diseases .

Furthermore , polymorphic variants of the C4 gene , analogous to the DR4 genetic variants , may reveal unsuspected links between class III MHC antigens and these disorders (Whiteheed et al ,1984). Serologic methods have diaclosed that BFf1 , an allelic form of BF , is eight times more frequent in patients with Type I diabetes than in the general population (Alper et al ,1982) . In that disease the combination HLA-B18/DR3/BFf1 is a genetic marker Such groupings have been termed extended haplotypes (Alper et al,1982) .

A novel way relating the MHC to autoimmunization has been proposed by Hanafusa et al,1983 . They found that thyroid epithelium does not express DR antigens , but demonstrated DR antigens in patients with Graves disease . These findings can explain how T lymphocytes recognize thyroid autoantigens : the aberrant production of DR antigens exposes the MHC class II structures that helper lymphocytes require for antigen recognition . The thyroid epithelial cell thus becomes an antigen-presenting cell . New evidence has demonstrated that interferon induces human epithelial cells to cause the aberrant expression of DR antigens (Pober et al,1983) . In principle , therefore, a local viral infection , by eliciting the production of interferon, could permit recognition of thyriod autoantigens by T cells (Bottazzo et al ,1983).

Genes that specify phenotypic markers of immunoglobulins also correlate with certain autoimmune diseases . One of these phenotypes , termed Gm , is a polymorphic serologic marker on the Fc portion of immunoglobuline . Its variants , or allotypes , are associated with Graves disease , myasthenia gravis and Type I diabetes mellitus (Nakao et al,1980) . Idiotypes also provides serologic markers of antibodies . Some idiotypes are genetically determined . Recurrent idiotypes have been found in several autoantibody systemes : cold aggluinins , rheumatoid factors and anti-acetylcholine-receptor antibodies . In all cases the autoantibodies were from unrelated patients , an indication that the corresponding immunoglobuline genes were widely dispersed .

It seems ,then ,that certain genetic markers (DR,HLA , B F, Gm , and idiotypes) of the main elements of immune system bear on susceptibility to autoimmune diseaes .

The suppressor-cell function of normal person with DR3 is impaired in vitro , and the numbers of immnuoglobulin-secretory B-cells in their circulation are increased relative to the numbers in DR3-negative subjects . The DR3 allele is also associated with an abnormality of phagocytosis by monocytes , especially when associated with certain Gm allotypes .

Another apparent genetic abnormality of immunoregulation is the impaired function of suppressor T lymphocytes that occurs in