REASSESSMENT OF HUMAN IgA SYSTEM

Essay

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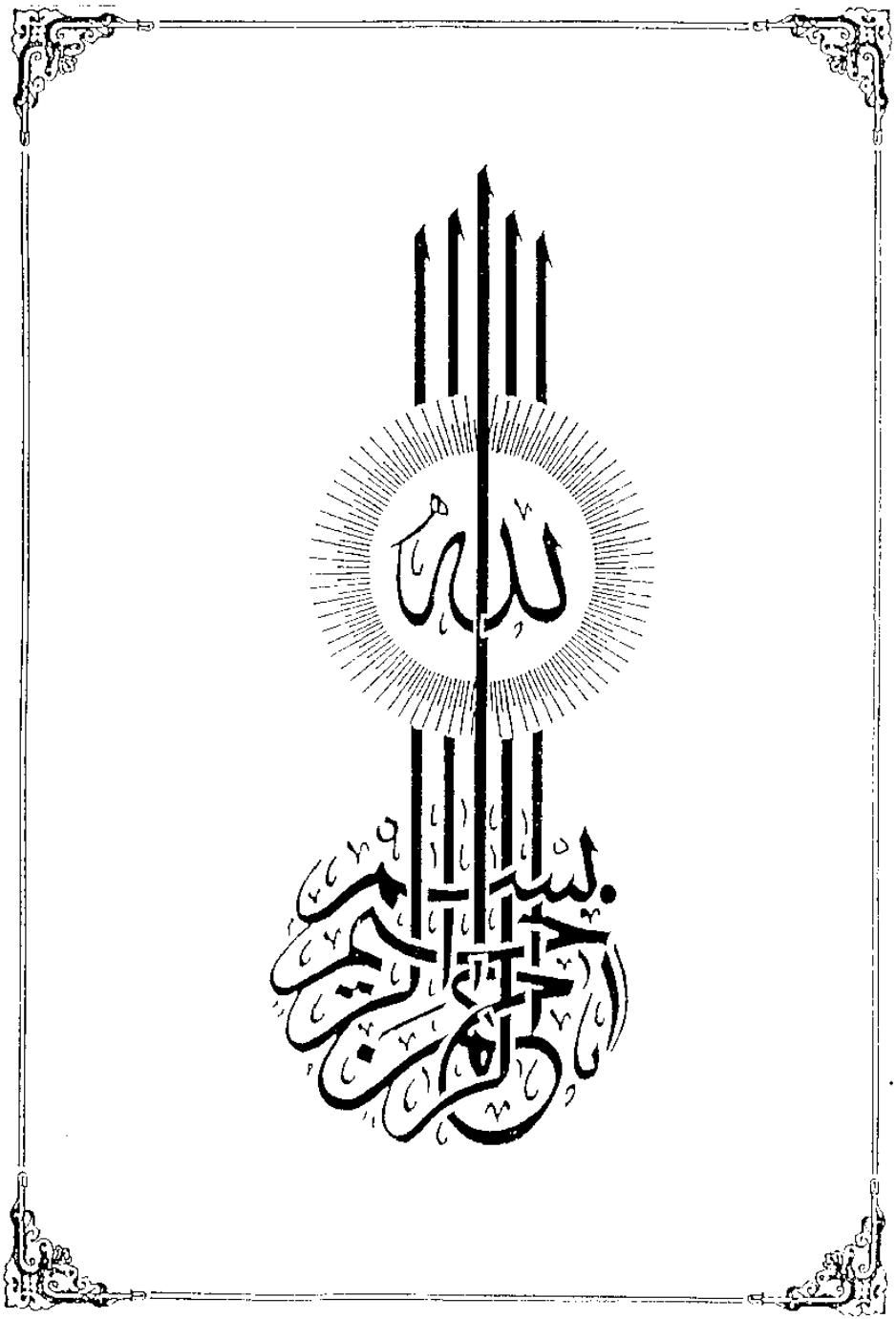

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For the past 25 years, most immunologists have considered IgA primarily as a carrier of antibody activity in external secretions protecting a large surface area of mucous membrane (**Hade and Ambrosies, 1988**).

Further diversification, has occurred with respects to molecular form, distribution in body fluids, sites of production, antibody activity and effector function. The secretory and serum IgA display a considerable degree of independence. In contrast to IgM, IgG, IgE as an antibody, IgA isotype does not utilize inflammatory pathway of antigen disposal. This is advantageous, not only for elimination of exogenous antigens but also for interaction with endogenous antigens. Thus, the serum and secretory IgA system must be viewed differently from other immunoglobulins (**Mestecky et al., 1986**).

Two subclasses of IgA namely IgA_1, and IgA_2 are identified with no difference between these except that IgA_2 is resistant to cleavage by specific IgA protease (**Bruce et al., 1990**). From the functional point of view, IgA participates in immunity of

gastrointestinal tract (**Owen et al., 1988**), male reproductive tract (**Kay et al., 1992**), female reproductive tract (**Brandtzaeg, 1989**), and pulmonary tract (**Lutsenko, 1991**). It also inhibits the streptococcal adherence to saliva (**Nikolova et al., 1992**), reduces infection of RBCs by Toxoplasma gondii (**Mc Leod et al., 1992**), and participates in the protective immune response against Schistosomiasis (**Jean et al., 1993**). Selective IgA deficiency is the most common immunodeficiency disorder and many disorders have been reported with this deficiency (**Schaffer et al., 1991**).

IgA participates in the pathogenesis of systemic lupus erythematosus (**Horest et al., 1990**), and other autoimmune disorders (**Veys et al., 1988**), liver diseases (**Kaskino et al., 1992**), nephropathy (**Layward et al., 1993**), and human immunodeficiency virus (HIV) (**Rossi et al., 1993**).

AIM OF THE WORK:

The aim of this work is to review the reassessment of IgA in health and disease.

REVIEW OF LITERATURE

IMMUNOGLOBULIN-A-CHARACTERIZATION

Immunoglobulin A was first identified in the serum in the 1950s (**Graber and Williams, 1955**), initially noted as a distinct band in an immuno-electrophoretic analysis. IgA was soon recognized to be functionally and biochemically related to the other serum immunoglobulins (**Slater et al., 1955**).

Between 1960 and 1980, the production and function of mucosal IgA were studied intensively. IgA was found to constitute a significant proportion of the total serum immunoglobulins (6-15%). It is present in the serum in relatively high concentrations of 1.0-2.0 mg/ml (**Flanagan and Rabbittis, 1986**).

Winter et al. in **1987** considered IgA as the predominant class of immunoglobulins in secretions such as saliva, nasal fluids, genitourinary secretions, seromucous secretions of the lung and intestine, tears and breast milk.

IgA normally exists in serum in both monomeric and polymeric forms. The latter is essential for binding to the mucosal transport receptor and increases the avidity for antigen (**Radl et al., 1984**). The concentration of IgA in initial breast secretion (colostrum) is

extremely high, averaging 50 mg/ml versus 2.5 mg/ml in adult serum (**Stobere et al., 1988**). It falls rapidly to serum levels after the first 4 days, owing partly to the dilutional effect of increased milk secretion volume (**Brown et al., 1988**).

The IgA of breast milk originates from IgA-B cells in breast tissues, which migrate there from gastrointestinal and respiratory follicles (**Irani and Clancy, 1988**). Migration is dependent on as yet unidentified changes in breast tissue brought about by the action of hormones. The locally synthesized IgA is then transported across the epithelium by secretory-component transport mechanism (**Mestecky et al., 1988**).

Table I: Estimation of daily production of IgA

	IgA
*Circulation	18.5-30 mg/kg/day
*Saliva	100-20 mg/kg/day
*Tears	1.25-5.5 mg/kg/day
*Bile	54-400 mg/kg/day
*Intestine- (small)	2100-5223 mg/kg/day
(large)	1170 mg/kg/day
*Urine	1-3 mg/kg/day
*Respiratory nasopharynx	45 mg/kg/day

(Ramband et al., 1987).

Carlsson et al. in **1986** reported that, the levels of IgA in the child, reach the adult level in secretions by 1 year of age but are not reached in serum until about 12 years of age.

Subclasses of IgA:

In humans, there are two subclasses of IgA, IgA_1 and IgA_2. These immunoglobulin isotypes, the products of separate genes, are represented in approximately equal amounts in secretions **(Delacroix et al., 1986),** but IgA_1 is marked in serum and constitutes 85% of serum IgA **(Conely and Koopman, 1986).** Although 95% of IgA in secretions is polymeric, only 12% of the IgA in serum is in this form with 88% being monomeric **(Elkom et al., 1986).**

No biological differences are known to exist between IgA_1 and IgA_2 except that, IgA_1 is susceptible to cleavage in its hinge region by proteases secreted by a number of different bacteria such as Neisseria gonorrhea, streptosanguis **(Mestecky et al., 1989).** This cleavage can lead to markedly reduced functional activity. Given the fact that IgA_2 is also present in the part of the mucosa where IgA protease-producing bacteria reside, such proteases probably have little effect on the host defense function of IgA system as a whole **(Hodgson et al., 1988).**

Basic structure of IgA:

IgA is a glycoprotein, composed of 82-96% polypeptide and 4-18% carbohydrate. The polypeptide component possesses almost all of the biologic properties associated with antibody molecules. The molecular weight of secretory IgA is 400.000 **(Alzari et al., 1988).**

Structural studies have revealed that IgA is composed of four polypeptide chains. One pair of the chains contains approximately twice the molecular weight of the other pair of identical polypeptide chains **(Ermak et al., 1987).** The chains of higher molecular weight are designated heavy (H) chains and those of lower molecular weight are designated light (L) chains **(Davie et al., 1989).**

Each polypeptide chain contains amino-terminal portion, the variable (V) region, and a carboxy-terminal portion, the constant (C) region **(Prince et al., 1987).** The polypeptide chains are folded by disulfide bonds into globular regions called domains. The domains of heavy (H) chains are designated V_H and C_H1, C_H2, C_H3, C_H4 and those in light (L) chains are designated V_L and C_L **(Michalek and Pierce, 1988).**

The zone where the variable and constant regions of the polypeptide chains meet is termed the switch region **(Russell et al., 1988).**

Light chain types:

All-L-chains have a molecular weight approximately 23.000 but can be classified into two types, Kappa (K) and Lambda (λ) , on the basis of multiple structural differences in the constant regions, which are reflected in antigenic differences. The two types of L-chains have been demonstrated in many mammalian species. Indeed, the amino acid sequence homologies between human and mouse (K) chains are much greater than those between the kappa and lambda chains within each species, indicating that the 2 types are separated during evolution prior to the divergence of mammalian species **(Brent et al., 1988).**

Heavy chain types:

Five classes of H-chains have been found in humans, based on structural differences in the constant regions detected by serologic and chemical methods. The different forms of H - chains, designated λ, α, μ, δ and ϵ, vary in molecular weight from 50000-70000, the μ and ϵ chains possess 5 domains (one V and four C) rather than of 4 of λ and α chains **(Capra et al., 1989).**

The source of serum IgA:

The major source of IgA in the vascular compartment in humans is probably the bone marrow. This organ represents the largest lymphoid tissue of the body (**Kutteh et al., 1987**). The IgA produced by bone marrow cells resembles serum IgA subclass distribution with its monomer and polymer distribution, and differs significantly from IgA produced at the gut lamina propria (**Allex et al., 1987**). Smaller contribution of serum IgA are probably made by the spleen and peripheral lymph nodes, including the tonsils (**Skvaril and Morell, 1986**).

The fate of serum IgA:

The serum concentrations of IgA is much lower than that of IgG because IgA is removed from the serum more rapidly. The serum half life of monomeric and polymeric IgA 3-6 days compared with 21 days of IgG (**Delacroix et al., 1988**).

The liver plays an essential role in internal catabolism. It is responsible for 90% of clearance of serum IgA. In various liver disorders, there is elevated serum IgA which is related to the failure of the liver to clear IgA through the biliary tract. However, there is

minimal elevation of total IgA and no elevation of polymeric IgA in patients with complete biliary obstruction (**Newkirk et al., 1987**).

A hepatic binding protein expressed on the cell surface of hepatocytes binds various serum asialoglycoproteins, including IgA, and has been proposed as a possible mechanism for IgA clearance by lysosomal catabolism (**Stockert et al., 1987**).

Another potential mechanism of serum IgA clearance might be by cells of the reticuloendothelial system, particularly Kupffer cells (**Kaiserlain et al., 1985**). However, because this clearance is very rapid, it is not inhibited by purified dimeric IgA, and involves only immune complexes. This route is unlikely to be the most important mechanism of IgA clearance (**Malburny et al., 1986**).

Genetic control of IgA:

Mostov et al. (1985b), demonstrated that, three gene families are employed to code for IgA molecule. Each of these families consists of large number of gene segments coding for variable region (V. genes) associated with one or several genes for constant regions (C genes). One of these families is located on