Editorial

The Central Role of the Gastrointestinal Tract in Immunological Reactions

William R. BROWN

Professor of Medicine,
University of Colorado School of Medicine,
Chief, Gastroenterology Section,
Veterans Administration Medical Center
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The gastrointestinal tract is a major immunological structure. Research during the past two decades has established that the intestine is richly populated with lymphoid tissues capable of initiating and affecting a wide variety of immunological reactions. These reactions have profound consequences not only for the gut itself but for the body in general. This review emphasizes the importance of the gut in initiating and mediating immunologic reactions that ultimately are expressed systemically or at distant mucosal sites.

The gastrointestinal lumen contains a myriad of antigenic substances—microbes, chemicals, food. Contact between these antigens and the gut's immunological apparatus initiates a diverse series of immunologic events. The best understood are those that lead either to the production of antibodies that are secreted into external body fluids or, in striking contrast, to hyporesponsiveness of certain systemic immunologic reactions.

PRODUCTION AND SECRETION OF MUCOSAL ANTIBODIES INITIATED BY ANTIGENIC ENCOUNTER IN THE GUT

Discovery of the immunological system of external-secreting organs, in which 11S secretory IgA (sIgA) is the principal immunoglobulin, clearly established the immunologic significance of the gastrointestinal tract. The intestinal mucosa was found to be densely populated by IgA-producing lymphoid cells, and intestinal fluids to contain large amounts of sIgA. Subsequent study has defined some of the complex cellular interactions that regulate the synthesis of IgA, the cellular mechanisms in assembly of sIgA molecules and their secretion into external body fluids, and the wide-spread extent of IgA secretion resulting from immunologic reactions initiated in the gut.

In Table 1 is summarized the current knowledge concerning the cellular regulation of the synthesis of sIgA antibodies. For at least certain immunologic reactions, the initial event in the gastrointestinal tract is uptake of antigen by gut-associated lymphoid tissue (GALT). A specialized epithelial...

William R. BROWN, Chief, Gastroenterology Section, Veterans Administration Medical Center. Box 111E, 1055 Clermont Street, Denver, CO 80220, U.S.A.
cell, M cell, overlying Peyer's patches might be a selective site for sampling of antigens (6). It is also known that the Peyer's patches possess some kind of macrophage-like cell(s) that is capable of presenting certain antigens to lymphoid cells for the induction of antibody synthesis. The functional relationship that must exist between M cells and antigen-presenting cells in the Peyer's patches is unclarified. Macrophage-like cells also are distributed diffusely along the intestinal mucosa; whether these cells also present antigens for the induction of immunological reactions or are simply scavengers of antigens that inadvertently cross the epithelium is unknown.

Table 1 Immunologic events leading to secretion of IgA antibodies into external body fluids

| I | Uptake, processing and presentation of antigens by gut-associated lymphoid tissues (GALT). |
| II | Activation and clonal expansion of precursor IgA cells in GALT, under T cell control. |
| III | Migration of IgA blast cells from GALT via mesenteric lymph nodes and the thoracic duct to the gut lamina propria and several other mucous membranes. |
| IV | Proliferation and maturation of IgA lymphocytes to mature plasma cells, which secrete IgA antibodies into external fluids (intestinal secretions, tears, nasal secretions, bronchial fluids, saliva, bile, breast milk, and genitourinary tract secretions). |

Ample evidence now documents that the production of IgA antibodies in response to antigenic encounter in Peyer's patches is dependent on the participation of class-specific T helper cells (3). Reportedly, T cell clones that induce IgM B cells to differentiate into IgA B cells have been extracted from murine Peyer's patches.

After activation in Peyer's patches, IgA lymphoblasts follow a most interesting course. The cells migrate to the mesenteric lymph nodes, then via the thoracic duct to the general circulation, and eventually "home" to several external-secreting organs. Some of the cells populate the intestinal mucosa; others migrate to several other sites: the bronchial mucosa, salivary glands, genital urinary tract, lacrimal glands, mammary glands, and possibly the bile ducts and gallbladder. The factors that direct and control this migration of IgA precursor cells are incompletely defined, but migration to the breast seems to be enhanced by mammotrophic hormones. Other studies have documented that IgA precursor cells from aggregated lymphoid tissue in bronchial mucosa can migrate to the gut. Consequently, it has been suggested that two-way traffic between these secretory tissues exists, and the concept of a common mucosal lymphoid system has evolved.

Figure 1 is a schema illustrating the cellular traffic in the secretory immune system. Although the schema has been constructed largely on the basis of B cell migration, gut T lymphocytes probably also originate and acquire their homing patterns in the Peyer's patches and have migration patterns similar or identical to that described for B lymphocytes.

Once "settled down" in the mucous membranes, B lymphocytes proliferate and mature, perhaps under the influence of still another kind(s) of T helper cells, into IgA-secreting plasma cells. The product of these cells consist largely of antibodies to ingested antigens. Most of the IgA antibodies
produced in the mucosal sites are dimers or larger polymers of IgA linked by the peptide J (joining) chain. Such IgA molecules have affinity for a glycoprotein, secretory component, which is synthesized by and expressed on the basolateral surfaces of secretory epithelial cells. The IgA dimers or polymers evidently can take two pathways to the exterior: either they combine with secretory component on epithelial cells immediately adjacent to the plasma cells, or enter the general circulation via lymphatics and reach secretory component-containing epithelial cells at distant sites. In either case, the IgA molecules combine with secretory component and are actively transported by endocytic vesicular transport across the epithelial cells to the exterior (4). Taking either of these routes, antibodies to antigens originally encountered in the gut lumen are secreted into several external body fluids.

![Diagram of the gastrointestinal tract and lymphatic system](image)

**Fig. 1**

An especially interesting and probably important pathway for the external secretion of IgA antibodies is that through the liver and biliary tract. The hepatic bile of man, rat and some other species contain high concentrations of sIgA (1, 5). In the rat, the biliary IgA is accounted for largely by active transport of polymeric IgA from plasma to bile. This transport occurs principally by a secretory component-mediated transport through hepatocytes (8). Consequently, a large proportion of the sIgA that enters the intestinal fluid of that species probably is derived from the liver. In man, transport of circulating dimeric IgA into bile also occurs but not to the same extent as in the rat. Indeed, studies by Dr. Nagura at Tokai University School of Medicine suggest that much of the IgA present in human hepatic bile is derived from synthesis in plasma cells located adjacent to epithelial cells of the biliary ducts.

The secretion of gut-originated sIgA antibodies at multiple distance sites has major theoretical and practical implications. Such secretion may be
a mechanism for conferring protection of several mucous membranes against a variety of microorganisms present in the external environment. It might be a major means of achieving immunologic protection of nursing infants. Ample evidence has documented that IgA antibodies to intestinal microorganisms are present in the breast milk of several species, including man, and transfer of the antibodies to suckling infants confers substantial protection against enteric infection. Since diarrhea is a leading cause of death among infants and young children in developing nations, oral immunization of mothers in order to enhance the passively acquired immune protection of their babies is of great interest. Of interest also is the work of Mestecky and colleagues (2) which indicates that oral immunization might be effective in producing salivary antibodies against cariogenic bacteria. This group demonstrated that healthy human volunteers who ingested capsules containing killed Streptococcus mutans developed strainspecific antibodies in their saliva and tears, and also that caries in rats could be prevented by oral immunization of the animals with S. mutans.

The secretion of IgA antibodies into bile may have an additional beneficial effect. In vitro and in vivo experiments have revealed that the rat liver can transfer IgA antibody-antigen complexes from plasma to bile. Hence, this might be a mechanism for the removal of potentially harmful antigens from the body. Whether such a clearance mechanism exists in man is unknown.

SYSTEMIC IMMUNOLOGIC TOLERANCE OR HYPORESPONSIVENESS

The phenomenon of immunological anergy resulting from the introduction of antigens via the gastrointestinal tract has been recognized since ancient times. Recently, the mechanisms responsible for this important immunologic response have been extensively explored. In various animals and with various antigens and assays, a general scheme has evolved: introduction of antigen into the gut, under certain circumstances, leads to inhibition of an immune response to a subsequent parenteral injection of the same antigen. However, no unifying mechanism responsible for this phenomenon has been elucidated, and it is possible that different mechanisms are responsible in different systems. In some studies, suppressor influences were transferred from fed animals to recipient animals by serum factors, which in some instances were IgG antibodies with specificity for the orally administered antigen and in other instances were suspected of being specific for antigen-binding sites, i.e., idiotypic specificity. One of the best-defined mechanisms for the induction of systemic hyporesponsiveness to enterically administered antigens is that of active T cell-mediated suppression. It has been found, for example, that a single feeding of a dietary protein antigen ovalbumin (OVA), to mice cause profound, long lasting and specific reduction in systemic IgG and IgE antibody responses to subsequent parenteral injection of the antigen. This state of hyporesponsiveness can be transferred to syngeneic mice by transfer of lymphocytes from the spleen, mesenteric lymph nodes or Peyer's patches of the tolerant animals. By treatment of the transferred cell suspension with antibodies to antigenic determinants on lymphocytes, the cells responsible for the immunologic
tolerance has been identified as T suppressor cells (7). These cells evidently are synthesized first in the Peyer's patches, then migrate to the mesenteric lymph nodes, then to the spleen.

Recently, it has been found that in addition to suppression of systemic antibody responses, the administration of certain antigens results in loss of several specific T-cell responses to these antigens, e.g., the ability to provide helper activity, proliferate in response to antigens, and mediate delayed-type hypersensitivity. At the same time, B-cell function appears to be unaffected. It has been found also that induction of the state of tolerance to antigens administered via the gastrointestinal tract is dependent upon the nature of the antigen. That is, the so-called T-dependent antigens, OVA, bovine serum albumin, and human gamma globulin are very effective in this activity, but T-independent antigens such as dinotrophenylated Ficoll, polyvinylpyrrolidone and bacterial lipopolysaccharide (LPS) are not (9).

There are undoubtedly many other constraints on the induction of systemic tolerance after oral administration of antigens. These may include the age and prior immune status of the animal, the degree of permeability of the intestinal mucosa to the antigens, and the extent of digestion and degradation of the antigens in the intestinal lumen. One or more of these factors may account for the fact that systemic immunization sometimes occurs after antigen feeding. Hence, antibodies to dietary antigens may be present in the circulation.

The contrasting ability of some enterically administered antigens to induce both the secretion of antibodies and a state of systemic tolerance has led to studies of the regulatory relationships between these two kinds of immunologic events. It has been reported that intragastric administration of OVA or S. mutans to mice induced concurrently the secretion of specific IgA salivary antibodies and suppression of systemic responses to the antigens. Furthermore, Richman et al (7) have reported that feeding OVA to mice lead to simultaneous enhancement of antigen-specific IgA antibody production and reduction of IgG antibody production by splenic B cells. Both of these responses might be mediated by two different populations of immunoglobulin-specific T cell populations (one for IgA help and another for IgG suppression) that are initially present in Peyer's patches.

Systemic IgE antibody hyporesponsiveness also has been induced experimentally in animals, and it is likely that the responsible mechanisms are analogous to those for suppression of IgG antibody synthesis. Since IgE antibodies mediate allergic reactions and may participate both in immunologic defense and immunologic injury reactions in the gut, the factors that regulate synthesis of the antibodies must be fully defined.

The capacity for developing systemic immune hyporesponsiveness might be very important in ensuring that damaging reactions to antigens that escape exclusion mechanisms at the mucosal surface do not occur. This might be a particularly appropriate response to allergens and to antigens that could crossreact with self-antigens and, therefore, induce autoimmune.

SUMMARY AND SPECULATION

The introduction of certain antigens into the gastrointestinal tract
induces on the one hand the synthesis of antibodies, principally of IgA class, that ultimately are secreted across mucous membrane surfaces throughout the body, and on the other hand suppression of systemic immunologic responses to the antigens. The functional and biological implications of these contrasting immunologic reactions are numerous and far reaching. One attractive possibility is that the secretion of sIgA comprises a "first line" of defense against invasion of the host by potentially harmful antigens. Evidence suggests that the principal function of sIgA antibodies is to form complexes with viable and non-viable antigens in mucous secretions and thereby prevent penetration of the antigens into the epithelium. On the other hand, the anergic state induced by luminal antigens might be necessary to prevent the occurrence of injurious systemic reactions to antigens that inadvertently cross the mucosal barrier. This "second line of defense" might be a particularly appropriate response to allergens and to antigens that could cross-react with self-antigens and thereby induce autoimmunity. Conceivably, yet another gut-related immunologic defense mechanism is the clearance of IgA-antigen complexes from plasma by secretion into bile or across epithelial surfaces. It is important to keep in mind the likely role of the gastrointestinal tract in modulating IgE antibody responses both systemically and in mucous membrane.

Further research on immunologic activities of the gastrointestinal tract doubtless will include efforts to manipulate mucosal antibody production and systemic hyporesponsiveness to oral immunization. Oral immunization against antigens that produce local disease, for example in the genital area or in the eye, is an appealing concept. It has even been suggested that sperm antigen packaged in capsules and given orally might produce antibodies in the cervix and vagina and thereby prevent fertilization, a reversible method of birth control. With respect to systemic hyporesponsiveness, there is conflicting evidence on the issue of whether systemic hyporesponsiveness can be induced by oral administration of antigens in animals that have been primed by the parenteral injection of the antigens. Thus currently available data suggests that reversal of established allergic or hypersensitivity states will be difficult to achieve, but the possibilities for accomplishing that much desired goal have by no means been fully exploited. The contemporary interest in gastrointestinal immunology, still only about 20 years in duration, has conclusively documented the participation of the gastrointestinal tract in a wide array of immunologic reactions. Full understanding of these reactions offers the prospect for improved understanding of the pathogenesis and treatment of several gastrointestinal and systemic diseases.

REFERENCES
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