Autacoids As Modulators of the Inflammatory and Immune Response

KENNETH L. MELMON, M.D.
Stanford, California
ROSS E. ROCKLIN, M.D.
Boston, Mass.
ROBERTO P. ROSENKRANZ, Ph.D.
Stanford, California

Once considered only mediators of inflammation, autacoids, (histamine, prostaglandins and beta-mimetic catecholamines) have been found to be generated during specific early and late phases of immunity. They need sufficient concentrations to affect immunocytes and can modulate immunity usually by inhibiting it. Receptors for the autacoids on the immunocytes are nonrandomly distributed. A small portion of T suppressor cells always appear to have receptors on them, but precursor B cells and precursors of T cells that produce lymphokines or are responsible for cytolysis do not. Instead, as these cells mature they develop their autacoid receptors. With one exception, the function of the immunocytes is inhibited by the effects of autacoids. Again, in all but one instance, that inhibitory modulating effect is mediated by and directly proportional to the intracellular concentrations of cyclic adenosine monophosphate (AMP) generated by the autacoid. The clinical implications of these observations are beginning to be appreciated. One of them is that pharmacologic antagonists of the autacoids can have predictable but hitherto unanticipated effects on immune functions. It is inconceivable that these effects will not have clinical value.

In studies on the modulation of responses to antigens, methods have been used that would illustrate the modification of early antigen processing and the cellular response to such processing or the late phase of expression of cell-mediated or humorally-mediated events (**Figure 1**). The two "periods of response to antigen" are separable by and convenient for the experimentalist but, as will be stressed herein, that separation may be artificial and responsible for little knowledge about the physiologic interdependence of the two phases. Indeed, as we understand more about the factors that can influence each phase of immunity, we recognize that mediators such as histamine, beta-mimetic catecholamines and prostaglandins (of the E and A series) are made during different phases of response to antigen and are able, directly and indirectly, to affect further response to antigen. In fact, these substances, often called autacoids (from the Greek *autos* (self) and *akos* (medicinal agent)) have been thought of only as mediators of inflammation, but they have recently been found to be substantive moderators of a number of immune functions [1–9]. It is quite possible that the concentrations of autacoids in tissues during inflammation and immune response are sufficient to allow them to modify the functions of a number of cells which control and express both humoral- and cell-mediated immunity [2]. The data are now strong enough so that we can postulate that these mediators may directly affect a number of stages of immunity and also act as feedback modifiers connecting the early and late phases of the immune response. As feedback control by autacoids can serve to modify immunity in a precise and predictable way, we should probably begin devising a

From the Department of Medicine, Stanford University School of Medicine, Stanford, California; and the Department of Medicine, Tufts University School of Medicine, Boston, Mass. This work was supported in part by HL 26340-01. Requests for reprints should be addressed to Dr. Kenneth L. Melmon, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305. Manuscript accepted March 5, 1981.

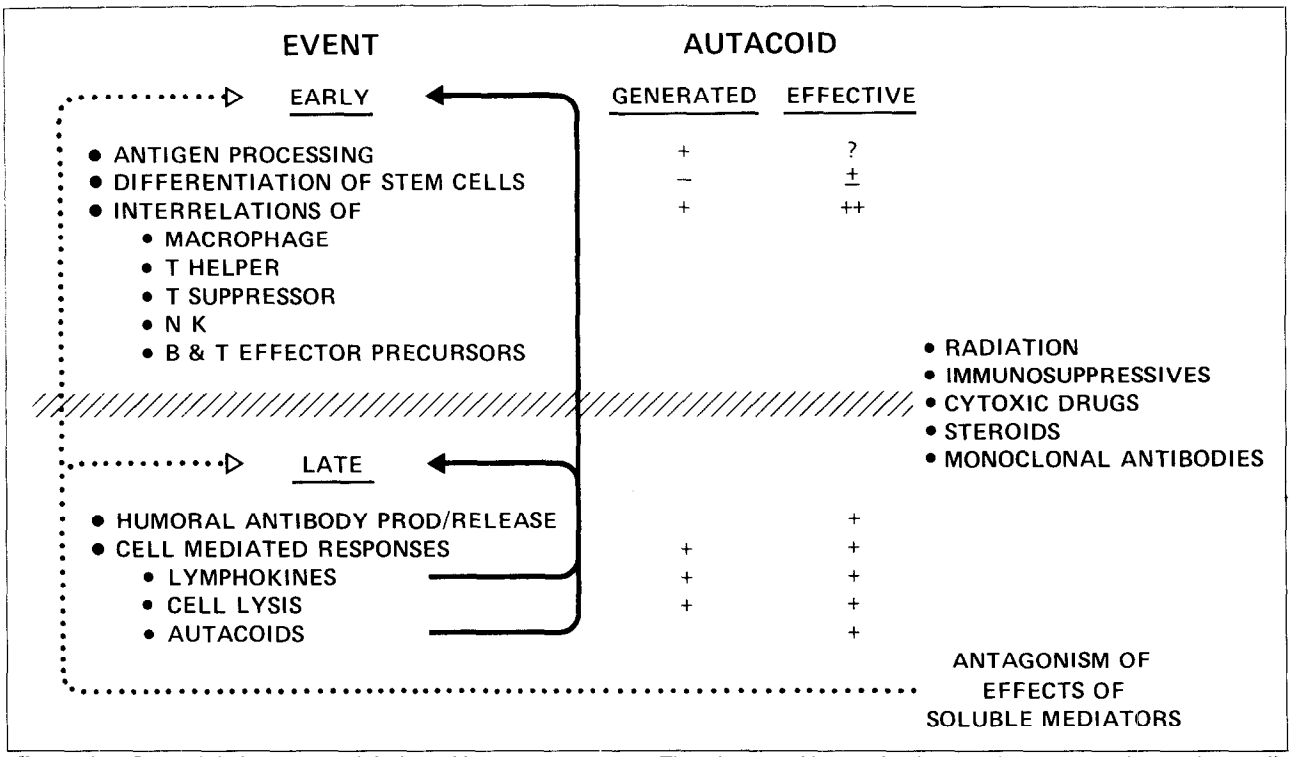

Figure 1. *Potential sites for modulation of immune response. The phases of immunity that can be separated experimentally are illustrated. The coordinated response to each exposure to antigen ultimately leads either to a cell-mediated or a humorally-mediated response, or to both. Pharmacologic modifications that have been used on early phases generally work nonspecifically on many subsets of cells involved in both the early and late process of response to antigen. Nevertheless, the roles of a number of subsets of cells have been defined. The subsets can be separated and their special potentials evaluated. The late phase of immune response has been analyzed by examining the effects of substances that can alter the function of T and B effector cells, by studying the pharmacologic modification of production or release of lymphokines (for example, macrophage migration inhibitory factor, macrophage chemotactic factor or interferon) or by isolating and testing the pharmacologic effects of lymphokines. The latter include tests of interferon on tumor cell growth and modification of host defenses in the setting of tumor or viral infections. The shaded divider between the early and late phases represents the shading of one phase into another and the drugs on the line clearly affect both phases (generally nonspecifically).*

strategy for using these "self medications" as alternatives to drugs that are less selective in their actions (Figure 1).

What possibly limits the immune response to inflammation? What better candidates than the mediators of inflammation that also are generated in different phases of immunity. A number of observations pertaining to the autacoids suggest their possible role in immunity. Logically, inflammation that must generate antigen by lowering pH, denaturing protein and disrupting cellular integrity should lead to immune responses unless some factors in inflammation modify the response to antigen. Because prominent immune response during or following inflammation is not common, we are justified in looking for factors in inflammation that modify immunity. At a minimum, such a search could be and has been based on the well known examples in biology of feedback loops where end events control a sequence of processes by interfering with early events in that sequence. Thus, it was not unrealistic to assume that autacoids are generated in inflammation and that, perhaps more importantly, during an immune response they could feed back and limit or direct the character and extent of the immune response.

Recent data have indicated that prostaglandins are generated in the process of lymphocyte activation and that histamine even at low concentrations (between 10^{-8}M and 10^{-11}M) may optimally affect, for example, the functions of both human basophils in an inflammatory site and of a T cell that is able to prevent mitogen-induced lymphocyte proliferation and the production of migratory inhibitory factor by lymphocytes. It has also become apparent that the same panoply of autacoids can modulate models of in vitro and in vivo expression of immune-related activities.

Our purpose here is to show the following: (1) Autacoids should be considered likely physiologic modula-

TABLE I Effects of Histamine on Inflammatory and Immune Processes*

	H_2 Receptor
Histamine Inhibits	
Mediator release from basophils (man)	+
Mediator release, lung and skin (monkey)	+
PCA reaction (rabbit)	+
Neutrophil chemotaxis (man)	+
Neutrophil lysosomal enzyme release (man)	+
Eosinophil chemotaxis (man)	+
T cell cytotoxicity (mouse)	+
T cell suppressor activity (mouse, man)	+
MIF production (guinea pig, man)	+
Interferon production (guinea pig, mouse, man)	+

NOTE: PCA = passive cutaneous anaphylaxis; MIF = migration inhibitory factor
* Modified from Lichtenstein [2].

tors of inflammation and of the immune response. (2) Although we have a limited knowledge of factors that lead to the expression of receptors for autacoids on immunocytes, such receptors appear to be nonrandomly distributed. It is thus reasonable to assume that the receptors have biologic importance and are employed in a purposeful physiologic or pathologic role. (3) In the early phases of an immune event, autacoids can enhance humorally-mediated responses to antigen and decrease cell-mediated responses probably by virtue of their effects on small subsets of T suppressor cells. The autacoids modulate the late phases of immunity by inhibiting the contribution to immunity of T and B effector cells. (4) The effects of the autacoids most often are mediated by and directly proportionate to the intracellular concentration of cyclic adenosine monophosphate (AMP). Use of drugs that inhibit the effects of autacoids can be expected to diminish humoral responses and enhance cell-mediated immunity. In fact, preliminary data indicate that at least the latter events are true in man. (5) If it is true that autacoids can predictably modulate the immune response, then it should follow that a therapeutic strategy could be developed to examine the effects of autacoids directed to subsets of immunocytes. This may be a feasible goal that, if achieved, would allow precise intervention in immune function. The implications of these five points will be discussed.

AUTACOIDS AS MODULATORS OF THE INFLAMMATORY AND IMMUNE RESPONSE

The release of histamine can initiate and mediate immune, infectious or traumatically-induced inflammation [1–4,7,9–13] (**Table I**). Catecholamines and prostaglandins have also been found to mediate the inflammatory process [1,2]. Antigen-immunoglobulin E (IgE) antibody-induced models of hypersensitivity and antigen-induced sensitization of host T lymphocytes which kill host cells also can release mediators of inflammation or induce the activity of B cells to produce and release antibody [9,14–17]. The autacoids not only mediate the vascular concomitants of inflammation, but can attract cells to the site of inflammation and influence their function [2,18]. They, therefore, influence the quality, extent and duration of the inflammatory response. Both histamine and its metabolite, imidazole acetic acid, as well as the metabolites of arachidonic acid released from the eosinophil, may influence the function of that cell [2,18]. Production of slow-reacting substance A (SRS-A) and eosinophilic chemotatic factor A (ECF-A) is likely to occur in both immunocytes and neutrophils and their production or release can be modified by the autacoids [2]. These findings illustrate the complex effects of the autacoids, not only on local vasculature at the site of inflammation, but also on the composition of cells and the contribution of those cells to the actual inflammatory process. The data create the apparently valid impression that autacoids play a very active role not only in revealing the inflammatory response but also in determining its course.

Although there has been extensive study of autacoids in inflammation, the role of these mediators as modifiers of the immune or inflammatory process was not understood until relatively recently. Models of immune-induced inflammation have shown that autacoids can stimulate selected migration of cells to the site [2]. In addition, each of them is able to inhibit such diverse functions as the release of lysosomal contents and production of superoxides by neutrophils that are activated either by opsonins (e.g., the C3b component of complement or the Fc portions of immunoglobulins) or by phagocytosis [14,19]. The autacoids also inhibit ragweed-induced histamine release from actively or passively sensitized mast cells [2], and they inhibit the functions of at least some antigenically naive T suppressor cells [7,8]. In a number of experimental situations they have directly or indirectly modified the turnover of T and perhaps B lymphocytes, the production or release of lymphokines, including migration inhibitory factor (MIF) and interferon, and the activity of T helper or T suppressor cells [3,6–8,10–13,20]. After B and T cells are specifically stimulated to respond to an antigen, the autacoids can inhibit the release of antibody [5]. The cell-mediated lysis produced by T effector cells is also inhibited by the autacoids discussed here [21–23].

The common biochemical mode of action of each of these events appears to be related to the production of high concentrations of intracellular cyclic AMP [1,24–28]. The effects of cyclic AMP and autacoids are often biphasic. They are dependent on the time of introduction of the autacoid during the inflammatory or immune process and the extent of accumulation of

cyclic AMP they generate [27,28]. Thus, in neutrophils, generation of cyclic AMP by calcium ionophores or antigen antibody immune complexes is not a critical component in the earliest steps of stimulus-secretion coupling of lysosomal enzymes or superoxide generation, although at higher concentrations the cyclic AMP will interfere with the release of these substances [14,19]. Cyclic AMP generated early after the introduction of antigen to B cells might interfere with precursor B cell turnover and eventually with antibody production [27], but if increased in mature B cells already producing antibody it will prevent antibody release [4]. Changes in cyclic AMP can inhibit the effects of T cell cytotoxicity to allogeneic target cells and the effects of B cell proliferation.

If receptors for autacoids were randomly distributed to all lymphocytes involved in the inflammatory or immune process, their expected effects would be chaotic and their physiologic importance minimal. But in a number of experiments it has been indicated that receptors for the autacoids are not randomly distributed. The receptors may be expressed as a function of commitment to a physiologic function, exposure to drugs, or both. For instance, Roszkowski et al. [29] have shown that thymocytes are unresponsive to histamine. However, once exposed to corticosteroid in vivo, those resistant to the killing effects of the steroid (particularly if the cells migrate to the spleen) become quite responsive to the cycle AMP generating activities of histamine. We have shown that precursor B cells are not likely to have histamine receptors, whereas those that are committed to the production of antibody become responsive to histamine [5,21]. Lichtenstein [2] has indicated that T effector cells become increasingly responsive to histamine as a function of the length of time they are exposed to allogeneic target cells.

In complementary experiments, Ballet and Merler [30] have shown that lymphocytes responsive to histamine are those that are dominantly able to respond to lectin-induced proliferation, cell-mediated cytotoxicity and secretion of their mediators. Finally, we have been able to demonstrate that T suppressor cells from antigenically naive animals can be responsive to histamine [21,27] and that only a fraction of T suppressor cells are responsive to histamine [12,13,31]. One subset of T suppressor cells produces a histamine suppressor factor (HSF) that inhibits lymphocyte proliferation to mitogens and the production of MIF. This type of cell has functional receptors only for histamine, and not other autacoids, indicating the probable selective and biologically purposeful distribution of receptors for autacoids on lymphocytes. Optimal concentrations of histamine-induced effects on migration of the human basophil or stimulation of T cell release of histamine suppressor factor ranges between 10^{-8}M and 10^{-11}M [32]. We also have information that a cell bearing the histamine receptor has a differentiation antigen on its surface that is identified by the monoclonal antibody OKT 8+. The aggregate of these data allows us to conclude that it is highly unlikely that receptors for the autacoids are randomly distributed throughout the lymphocyte population and that there is likely to be some biologic meaning to their distribution. We are also able to conclude tentatively that another mechanism of selective cell response to autacoids depends on the varying concentrations of hormone needed to produce maximal effects on different subsets of cells.

THE RELATIONSHIP OF IN VITRO MODELS OF INFLAMMATION AND IMMUNITY WITH IN VIVO EFFECTS OF AUTACOIDS ON THE INFLAMMATORY AND IMMUNE PROCESSES

Affinity chromatographic techniques have been successfully used to separate splenic leukocytes of mice with receptors for histamine from those without receptors. This led to the discovery of a number of modifications of response to an immune stimulus that can be effected by cells with histamine receptors [6,13,21–23]. Subtraction of histamine receptor-bearing cells from murine splenic cells enhances humoral antibody responses by the remaining cells. The same enhancement of humoral antibody response can also be produced in unchromatographed cells by treatment with drugs that increase splenic leukocyte cyclic AMP content when the antigen is introduced [33].

Murine T cells with receptors for histamine appear to be responsible for immune tolerance to synthetic antigens [7,8]. Experiments in man seem to indicate that histamine receptor-bearing T cells are directed to the peripheral circulation during certain types of allergic diseases and in patients with non-Hodgkin's lymphoma [31,34–36]. For instance, in human subjects with allergic rhinitis, suppressor T cells with histamine receptors appear in the peripheral blood as a function of desensitization to the ragweed antigen. Such T cells can also be used in vitro to suppress the proliferative response of mononuclear cells to ragweed antigen [31]. Observations in patients with histiocytosis X reveal that during some remissions T suppressor cells bearing receptors for histamine appeared in peripheral blood. The remission continued during their presence [34]. Whether the killer T cells found in two patients with neutropenia and recurrent infections could have been responsive to histamine stimulation is an open question [37].

THE RELATIONSHIP OF HISTAMINE RECEPTORS TO OTHER CELL SURFACE MARKERS OF IMMUNE ACTIVITY

The fact that histamine modulates the inflammatory and immune responses raises a question as to the relationship of receptors for histamine to other cell surface markers of immunocytes. Since there is a nonrandom distribution of histamine receptors on immunocytes, and since histamine has selective effects on immunity (e.g., it does not affect antigen binding to macrophages nor inhibit macrophage-lymphocyte rosette formation [12]), it is important to understand the distribution and determinants of expression of histamine receptors if we are to hypothesize and test the precise biologic functions of histamine modification of the immune response. So far, few studies have been directed to discerning these correlations. Some T suppressor cells do have receptors for histamine but anti-theta antibody destroys the majority of T suppressor cells which are attracted by insolubilized conjugates of histamine [38]. There have been no definitive studies that relate the TL, THY 1 or LY1, 2 and 3 markers on murine cells with histamine receptors, nor have there been studies to relate the HTL, T1, T4 or T5 markers of human cells with histamine receptors.

If we are to develop an economic approach towards designing drugs which might be targeted to particular lymphocytes with histamine receptors, these gaps in our knowledge must be filled. So it would be useful to consider whether the histamine receptors are on killer cells, whether the effect of radiation on subpopulations of T cells can modify the distribution or expression of histamine receptors, whether aspects of the inflammatory response may alter the complement of histamine receptors on any subpopulation of cells (e.g., in the way that inflammation alters macrophage function) and whether the presence of histamine receptors can predict susceptibility to antigenic, mitogenic or mixed lymphocytic culture (MLC) activation of T cells [39–41]. It would be of great interest to determine whether the expression of a histamine receptor on a T suppressor cell might be involved in histamine-induced modification of interrelationships between different T helper and T suppressor cells [42,43], and whether some immune diseases in man could in part be characterized by predominance of suppressor or helper T cells with an abnormal distribution of histamine receptors [44].

CONCLUSION

Autacoids have hitherto been considered primarily as mediators of the inflammatory process. Now their effects must be put into a broader perspective as both initiators and modulators of inflammatory *and* immune processes. The fact that autacoids can influence the immune process at different stages, and that they can influence different subpopulations of cells at concentrations which probably exist endogenously during physiologic and pathologic events, indicates that they can and should be seriously considered not only as ordinary modulators of the inflammatory and immune processes but also as potential drugs that can ameliorate these pathologic conditions. The hypothesis that mediators of inflammation modulate the immune process has been proved. The fact that in vitro models do apply to in vivo events and that, for example, catecholamines and histamine are able to suppress models of delayed hypersensitivity [45,46] and that antihistamines can augment these models [47,48] in mice and in man means that (1) new drugs developed from mediators of inflammation might be effective modifiers of the immune process and (2) long-term study is needed of unanticipated effects on the immune response of patients who are taking, or who have taken over long periods, anti-inflammatory agents that antagonize mediators of inflammation.

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