mediators of inflammation

edited by
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MEDIATORS OF INFLAMMATION

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PREFACE

Lewis Thomas has suggested that "Perhaps the inflammatory reaction should be regarded as a defense of an individual against all the rest of nature, symbolizing his individuality and announcing his existence as an entity."[1] Provision of these symbols and announcements is the task of various mediators of inflammation and this volume has been designed to present our current understanding of their biochemistry, cellular origins, pharmacology, and role in pathology. Unlike other volumes of collected papers, this book did not result from a specific conference or symposium at which each contributor presented his own, narrowly framed research experience. Rather, each of the chapters represents, in the form of a general review, a summary of our knowledge of the mediators and the mechanisms by which they are released to launch the inflammatory response. Much effort has been taken to insure that the often conflicting terminology in this field is defined in detail: many synonyms (e.g., of the properdin system or the alternate pathway of complement activation) have been repeatedly presented, in order to avoid confusion. Although each of the contributors is actively engaged in the field of inflammation, few text figures or tables of ongoing research have been included; the overall aim was to provide a volume readily accessible to workers in other areas as well as to the general reader.

It can now be appreciated that the study of inflammation and its mediators has passed from the purely descriptive to the soundly quantitative level of analysis, and it is hoped that this compact volume will conveniently bring the results of this effort to the attention of biologists, biochemists, immunologists, pathologists, and clinicians. Scrutiny of the chapters will indicate that they represent views of inflammation currently held in New York, Boston, Hartford, Kansas City, Baltimore, Richmond, and La Jolla; the editor would especially like to thank Drs. Charles G. Cochrane and K. Frank Austen for suggestions as to their contents.

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INTRODUCTION

Gerald Weissmann

There is probably no such thing as a general "inflammatory process" during which a variety of carefully programmed cells release, or act on, a carefully sequenced series of inflammatory mediators. Probably there are as many varieties of inflammation as there are inflammatory stimuli. Consequently, this volume will be directed toward an analysis of the *mediators* of inflammation, with the implicit assumption that one or another of these is more "important" in one or another sort of inflammation. As Lewis Thomas (1971) has pointed out, the inflammatory response may well have been devised as a means of keeping even the lowliest of organisms safe from outside invaders or fusion to its fellows in a kind of pan-syncytium. Thus when we try to understand how complex organisms handle physical injury, foreign organisms, or immune injury, we are confronted with an exercise in biological archeology. Moreover, our analysis seems destined to have become couched in military terms: "defense" and "attack," "invasion" and "retreat," "injury" and "loss."

At each step of the evolutionary ladder, organisms have added to or modified existing ways of waging this microscopic warfare. Consequently, when we begin to describe the outlines of any specific inflammatory event we are likely to encounter remnants of very primitive responses among the very latest defensive techniques. Thus chemotaxis is recognized in bacteria, unicellular organisms phagocytose and release lysosomal enzymes, complement developed before teleosts, and cyclic nucleotides and prostaglandins modulate cell functions in

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animals without backbones. But mammals use each of these means (and more) to cope with foreign material or injury.

Therefore, it is not easy to give a "general" outline of an inflammatory cycle, and to discuss a common sequence of cells and mediators which form its circumference. What can be done, however, is to look at chemically identified mediators of inflammation and to study how these appear in various discrete types of inflammation. It is this approach that has been used in this volume.

1. THE MEDIATORS OF INFLAMMATION

There are several ways of classifying these mediators of inflammation: thus histamine, serotonin, SRS-A, kinins, and prostaglandins have been called "imme-

Table I. Mediators of Inflammation

Agent	Chemical nature	Origin
1. Histamine; serotonin	Amine (stored)	Basophil, mast cell; platelets
2. Slow reacting substance of anaphylaxis (SRS-A)	Acid lipid	Leukocyte
3. Kinins	Polypeptides (split products)	Plasma substrate
4. Prostaglandins	Acid lipids (newly synthesized)	Ubiquitous intracellular precursors
5. Plasmin	Protease (split product)	Plasma substrate (liver)
6. Hageman factor (activated)	Protease	
7. Complement	Plasma proteins and split products	Reticuloendothelial cells, liver
8. Lysosomal enzymes	Intracellular proteins (stored)	PMNs, macrophages, mast cells
9. Lymphokines	Intracellular proteins (newly synthesized)	Stimulated lymphocytes

diators" by virtue of their appearance early in inflammation and in the lesions of immediate hypersensitivity. Complement and lysosomal enzymes have been called "intermediators" because they appear somewhat later, but this is the most arbitrary of divisions. In Table I, I have listed the most important mediators of inflammation, and, of course, the most noticeable aspect of this list is that it points out omissions from this volume. Thus, for example, it is clear that elements of the blood-clotting system (especially Hageman factor) and the fibrinolytic system (plasmin) have crucial roles in launching or amplifying early inflammation. However, the chapters on kinins and complement clearly indicate the possible role of these proteins of clotting and lysis in the sequences of limited proteolysis that accompany activation of the kinin and complement cascades. But perhaps the greatest omission is that of the various lymphocyte factors, or "lymphokines," which clearly mediate the later stages of immune tissue injury. Inclusion of these would probably have doubled the length of this volume. Nor has there been included a separate chapter on chemotaxis. I would classify this biological activity, not as the property of any distinct group of mediators, but as one shared by several others of the well-characterized mediators such as complement (e.g., C5a, C3a), lysosomal enzymes (neutral protease, cathepsin D), and perhaps even the prostaglandins (of the E and F series).

2. MECHANISMS COMMON TO SEVERAL MEDIATOR SYSTEMS

It is, however, possible to discern among the various trails leading to acute inflammation at least five general pathways which seem to be shared by more than one system of mediation. These are as follows:

2.1. Cellular Release

By mechanisms which bear more than a coincidental resemblance to other secretory processes, cells respond to injury, phagocytosable particles, or immune challenge by releasing previously stored or inactive substances. Examples are the release of histamine and SRS-A from lung tissue, histamine from mast cells or blood basophils, and lysosomal enzymes from polymorphonuclear leukocytes.

2.2. Fluid-Phase Activation

Surface injury to cells or supporting structures (e.g., basement membrane), as well as exposure to immune complexes, leads to activation in the fluid phase

(plasma or tissue) of coordinated, limited proteases which generate mediators by cleaving precursor substrates readily available in these fluids. Examples are the cleavage of C3 by the activation of early complement components or the properdin system, the activation of prekallikrein to kallikrein by activated Hageman factor, and the cleavage of kininogens by kallikrein to form kinins.

2.3. *Bypass Mechanisms*

Factors, usually proteases, released from cells or activated in the fluid phase can bypass earlier steps in the activation sequence of fluid-phase mediators. Examples are the cleavage by lysosomal enzymes of C3 or C5, the direct activation of kinins by leukocyte kininogenases, and the generation of separate C3 and C5 cleaving enzymes by the properdin system.

2.4. *Extracellular Control Loops*

Some mediators of inflammation inhibit or amplify steps leading to their own elaboration. Examples are the inhibition of histamine release by histamine, the enhanced release of lysosomal enzymes (some of which can cleave C5 to C5a) by C5a, the activation by plasmin of Hageman factor which may itself be used to generate more plasmin, and the requirement for C3b in the properdin-mediated activation of C3PAase (factor D).

2.5. *Intracellular Controls*

Perhaps the greatest degree of similarity is discerned among substances released from cells. It has recently been appreciated that cAMP or substances which lead to its intracellular accumulation (β-adrenergic agents, histamine, prostaglandin E_1) *inhibit* release of histamine from leukocytes or lung fragments, lysosomal enzymes from polymorphonuclear leukocytes or macrophages, and lymphokines from stimulated lymphocytes. In contrast, cGMP or substances which lead to its intracellular accumulation (cholinergic agents, prostaglandin $F_{2\alpha}$) *enhance* release of histamine from leukocytes or lung fragments, lysosomal enzymes from polymorphonuclear leukocytes, and lymphokines (Fig. 1). Moreover, good circumstantial evidence implies that the cyclic nucleotides exert their effects by virtue of their as yet undefined interaction with microtubules. Thus assembly of tubules (as in D_2O) is associated with *enhanced* release or histamine or lysosomal enzymes, and disassembly (as by colchicine or vinblastine) *diminishes* release of histamine or lysosomal enzymes. It is in this framework that one can understand the intracellular effects of the anaphylatoxin C5a, which en-

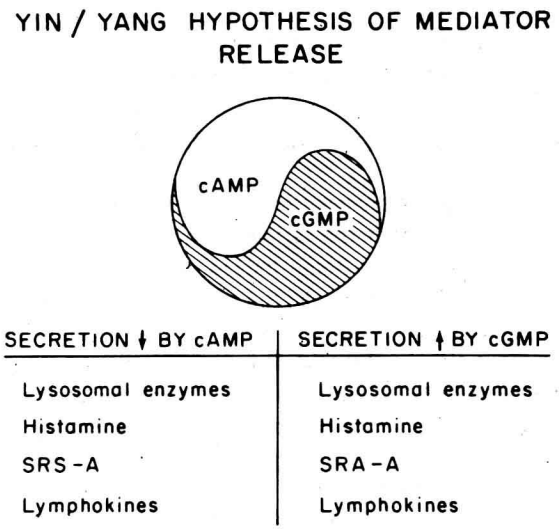

Fig. 1. Yin/yang hypothesis of mediator release.

hances lysosomal enzyme release, assembles microtubules, and provokes chemotaxis. In contrast, histamine and prostaglandins of the E series inhibit their own further elaboration by raising cAMP levels within leukocytes. Finally, it is clear that Ca^{2+} ion is required for most forms of mediator release.

3. CENTRALITY OF PHAGOCYTES

But before committing ourselves to detailed analysis of feedback loops, amplification systems, and interactions between cells and the fluid phase, let us recall some of the simplification that Metchnikoff (1905) introduced into this area in the 1800s. He correctly formulated that there is no phagocytosis without inflammation and almost as correctly proclaimed the validity of the reverse of that statement. In considering that phagocytosis is at the critical center of the inflammatory response, he was influenced by his own fight with the humoral school of Cohnheim and Ehrlich. Since Celsus, it had been clear that *rubor, calor, tumor,* and *dolor* led to *laesio functio.* But the humoral school taught that the various circulating substances which mediated redness, heat, swelling, and pain were brought to the injured site by capillaries, the function of which was at the center of inflammation. Metchnikoff, by training a zoologist, was able to show that inflammation (accumulation of phagocytes, swelling of the area, and tissue injury) took place in cold poikilotherms, so that fever was not necessary,

and proceeded to demonstrate that anesthetized limbs underwent inflammation, showing that pain was unnecessary. But even more convincing was the finding that tissues without capillaries (the sclerae) or animals without a vascular system (starfish larvae) reacted to foreign bodies with the influx of phagocytes, swelling, and tissue injury.

These observations place phagocytic cells at the center of inflammation, and suggest, to me at any rate, that the various humoral mediators are in themselves only a sort of amplification system. Indeed, the acquisition of vascular and immune systems seems to complicate the central interaction of inflammation: the release, by injured or phagocytic cells, of inflammatory materials. If we begin with this interaction as the critical point, we can go on to appreciate that tissue injury and *laesio functio* must result from the attack, by substances released from phagocytic cells, of substrates which are critical for the function of cells and connective tissue. Now for extracellular structures to be injured, we require hydrolysis of covalent bonds by enzymes; for cell membranes the problem is complicated by the fact that the lipid bilayers of biomembranes can undergo dissolution in the presence of amphipathic molecules in the absence of enzymatic attack (Sessa *et al.*, 1969).

Consequently, it seems reasonable to suggest that only those mediators which can actually cleave covalent bonds in connective tissue (lysosomal hydrolases) or which can act as amphipaths (terminal components of the complement sequence) can be held responsible for irreversible tissue injury. In contrast, the other mediators would appear to be responsible for the earlier and potentially reversible aspects of inflammation. Thus kinins, prostaglandins, histamine, and the early components of complement equip injured or invaded tissue with the responses of vasodilatation, capillary leakage, chemotaxis, and the accumulation of leukocytes. Indeed, it is the general finding that animals or humans genetically deficient in Hageman factor (i.e., chickens or Mr. Hageman) or in complement components still manage to mount adequate inflammatory responses. In contrast, absence of polymorphonuclear cells seems to diminish tissue responses to injury to a much greater degree. Therefore, and the prejudices of the editor are obvious, the response of inflammation can be viewed as resulting from the release by injured and/or phagocytic cells of substances which eventually serve a protective role, although initially provoking a nasty effect. These substances, reacting with circulating materials, activate several cascades of limited proteolysis in tissue fluids which amplify the limited capacity of individual cells. Since some of the products of inflammation (e.g., histamine or prostaglandin E_1) in turn inhibit further release of mediators, the response may be viewed as biphasic or cyclic.

If the following series of chapters serve their intended function, they should provide occasional experimental evidence in favor of the outline provided above, but, more likely, they will probably convince the reader that any such general

theory or description of "inflammation" is probably as premature as a general theory of behavior.

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