Late Phase Allergic Reactions

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THE TANGLED WEB: COOPERATION AND INTERDEPENDENCY OF MEDIATOR SYSTEMS IN INFLAMMATION

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I. INTRODUCTION: REDUNDANCY OF MEDIATOR SYSTEMS

In previous Chapters of this book, the involvement of various mediator systems in allergic inflammation has been described. This Chapter focuses on the interdependence of cell and mediator systems induced either by mechanical injury, infectious diseases, noxious agents or, last but not least, allergic reactions. In dependency on the intensity of the noxious event, a series of complex cellular and biochemical events, the so-called inflammatory response, will occur in tissues.

The inflammatory response constitutes a defense mechanism of the organism by which the stimulating agent or irritant is simultaneously eliminated and the healing process started to re-establish its integrity. The accompanying clinical symptoms of redness (rubor), swelling (tumor), heat (calor) and pain (dolor) have not lost any of their importance since their first presentation by the Roman physician Celsus (1st century A.D.).

Our perception and knowledge of the biochemical and cellular reactions underlying inflammatory processes are changing continuously as a result of ever improving techniques of investigations. The importance of known inflammatory mediators becomes relative as new factors are discovered, defined, and to date unknown interactions postulated.

An almost indefinite number of stimulators, mediators, effectors and inhibitors determines the efficiency or the failure of the inflammatory response. Taking a closer look at the pathomechanisms of inflammation, a redundancy becomes evident: Many cellular and humoral mediators cause the same or similar symptoms, and different cell types, e.g., the phagocytes, are at least partially able to replace each other in function. Obviously, the inflammatory reaction is too important a protective mechanism to be seriously impaired by the loss of a single cell type or mediator.

II. GENERAL PATHOMECHANISMS

Injuries caused by direct force or microtrauma due to muscular and skeletal strain lead to bleeding and a subsequent fibrin deposit. The primary stimulus for the activation of thrombocytes and the plasma enzyme cascade systems (coagulation, fibrinolysis, complement, kallikrein-kinin system) is the exposure of surfaces normally inaccessible to the bloodstream (e.g., subendothelial layer) to plasma constituents including cells (Figure 1) as well as the release of cellular factors including proteases. This initiates the inflammatory process.

Local inflammation can be induced by physical means (e.g., impaired tissue through straining, heat, cold, radiation, chemical substances), auto-immune processes and invasive microorganisms (bacteria, fungi, viruses). In response to the inflammatory stimuli, the defense and eliminating mechanisms are primarily cellular in nature with the phagocytes playing a major role. Vasoactive and permeability enhancing factors are released provoking the extravasation of fluid from the vasculature. This results in edema formation and thus swelling of the interstitial tissue. The impaired microcirculation leads to ischemia and hypoxia.

During both injury and inflammation the biochemical, cellular, and immunological reactions all take the same course but with different emphasis being placed on each event according to the triggering stimuli.

Attracted by chemotactic substances from the wounded or inflamed area, mobile leukocytes adhere to the endothelium of capillary vessels and migrate into the altered tissue following the concentration gradient of the attracting substances. The polymorphonuclear granulocytes, which are the first to migrate (within hours after damage), are followed by monocytes and macrophages (within 24 h) and somewhat later by eosinophils and lymphocytes (after a few days). It is the main task of these cells to eliminate degenerated and

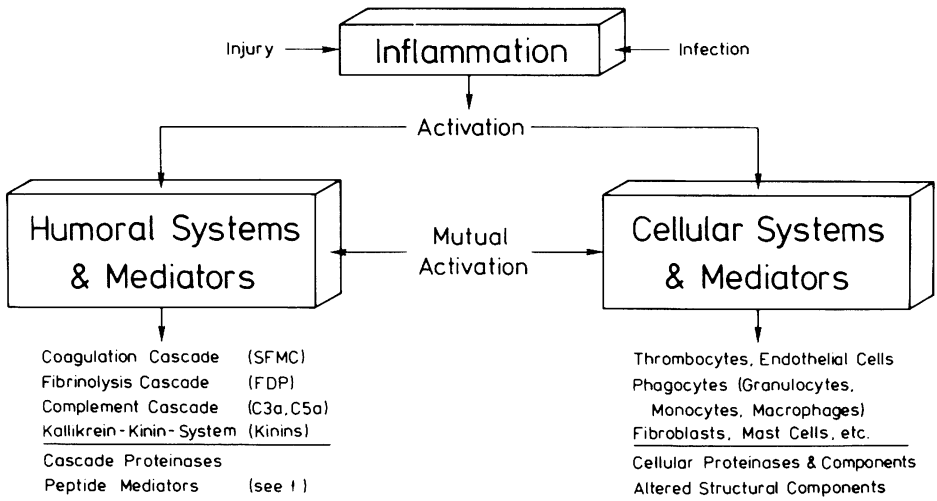

FIGURE 1. Relationships between mediator systems, the plasma protease cascades and inflammatory cells, in inflammation, cf. Figure 2 and text. SFMC: soluble fibrin monomer complexes; FDP: fibrin or fibrinogen degradation products; C3a & C5a: complement-derived anaphylatoxins; Kinins, bradykinin, etc.

impaired or destroyed tissue as well as foreign bodies and invasive microorganisms. In order to be recognized and incorporated by the phagocytes the tissue particles or microbes have to be labeled ("opsonized") as being "foreign or degenerated" by humoral factors, the so-called opsonins (e.g., fibronectin, immunoglobulins). After incorporation into phagosomes which fuse with lysosomes to digestive vacuoles, the phagolysosomes, degradation of the intracellularly deposited material by hydrolytic and oxidative processes takes place.

The immune system normally reacts more slowly than the non-specific defense mechanisms. Therefore, the specific recognition of foreign substances and invasive microorganisms via antibodies or via cytotoxic T-lymphocytes usually takes place only days after the injury. Repair mechanisms responsible for the healing process start relatively early with the proliferation of tissue-specific cells like histiocytes and fibroblasts. The stimulation of these cells by inflammatory mediators leads to the enhanced synthesis of tissue-specific substances such as collagen, elastin, and proteoglycans.

The most important aspect of the inflammatory reaction is the close cooperation between the humoral and cellular systems (Figure 1). Thereby a decisive role is played by proteolytic enzymes (proteases or proteinases) and the products of system-specific proteolysis in the humoral enzyme cascade systems on the one hand and of non-specific proteolysis caused by liberated lysosomal enzymes on the other hand. Both the proteases themselves and products of their actions, the biologically highly active polypeptides, are potent inflammatory mediators. Their pathogenetic potential becomes relevant when the extent of their production exceeds the requirement for the healing process.

The system-specific proteases of the plasma enzyme cascades are generated from their inactive precursors (proenzymes) after direct (Hageman factor) or cofactor-transmitted contact (high molecular weight kininogen for plasma prokallikrein and factor XI) with wounded surfaces as well as by cellular proteases, e.g., thrombokinases and plasminogen activators, that are released from altered or stimulated cells in the injured region. Their primary tasks are prevention of bleeding and induction of wound healing. Thrombin provokes fibrin production and aggregation of thrombocytes. Plasmin digests the fibrin during assembly of the repair tissue substances newly synthesized by fibroblasts. These cells are stimulated to produce repair tissue substances such as collagens, elastin, proteoglycans etc. by the fibrin-stabilizing factor XIII, which itself is activated by thrombin. Additionally, several system-

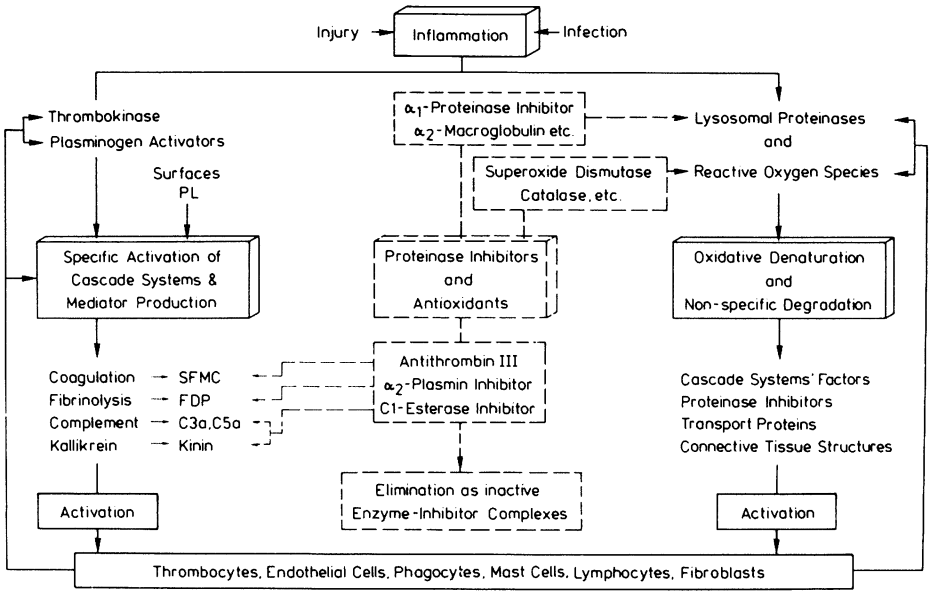

FIGURE 2. Pathomechanisms in inflammation: products of plasma proteinase cascade systems and phagocytic processes as inflammatory mediators and their natural antagonists, proteinase inhibitors and antioxidants. For abbreviations see Figure 1 and text.

specific proteases produce special inflammatory mediators (Figure 2): thrombin the soluble fibrin monomer complexes (SFMC), plasmin the fibrin and fibrinogen degradation products (FDP), the complement esterases via the classical (C1 esterases) and/or the alternative pathway (complement factor C3) the anaphylatoxins C3a, C4a, and C5a, and plasma kallikrein the kinins. These peptide mediators are pathophysiologically active in several ways, for example, by:

- Inhibition of coagulation (SFMC, FDP)
- Increase in vasoactivity and reduction of blood pressure (anaphylatoxins and kinins)
- Edema formation (FDP, anaphylatoxins and kinins)
- Chemotaxis of granulocytes and monocytes (C5a and C3a)
- Aggregation of thrombocytes and granulocytes (C5a)
- Phagocytosis of granulocytes (C5a)
- Degranulation (release of histamine) of mast cells (anaphylatoxins)

III. CELLULAR SYSTEMS AND THEIR MEDIATORS

The cellular reactions which are initiated by the peptide mediators are transmitted either directly via mediator-specific receptors on the membranes of the target cells, or indirectly by stimulation of the synthesis of cellular mediators such as prostaglandins, leukotrienes etc. (Table 1). Kinins for instance have specific receptors on certain cells. Additionally they activate the ubiquitously occurring membrane-bound phospholipase A_2 which in turn initiates the synthesis of arachidonic acid metabolites. Depending on the actual kinin concentration and cell type, antagonistic prostaglandins (e.g. PGE_2 and $PGF_{2\alpha}$) can also be produced during such a process. The diverse arachidonic acid metabolites activate particular functions of their target cells (Table 1) which may either amplify or suppress the effect of the peptide mediators. These mechanisms operate to enhance or suppress the defense mechanism.

TABLE 1
Arachidonic Acid Metabolism in Inflammation: Stimulation and Metabolites (Eicosanoids)

Stimuli	Proteinases, peptide mediators, hypoxia, toxins
↓	
Cell membrane	Phospholipase activation
↓	
Release of:	Arachidonic acid
Enzymes produce:	Cyclooxygenase or lipoxygenases etc. Prostaglandins (PG) & thromboxane (TX) or leukotrienes & HPETEs & HETEs[a]
Biological effects:	Vasoconstriction: TXA_2, $PGF_{2\alpha}$, PGD_2, PGE_2; LTC_4, LTD_6, LTE_4; HPETEs, HETEs vasodilation: PGE_2, PGI_2; HPETEs, HETEs permeability increase: LTC_4, LTD_4, LTE_4 platelet aggregation: TXA_2, PGE_2 platelet aggregation inhibition: PGI_2, PGD_2, PGE_2 neutrophil aggregation: LTB_4; HPETEs, HETEs

[a] Derivatives of hydroxyperoxy- or hydroxyeicosatetraenoic acid.

TABLE 2
Cellular Mediators in Inflammation and Their Major Sources

Mediator	Source[a]
Histamine, serotonine	Bas, Mast, Thromb
Platelet activating factor (PAF)	Bas, Mast, PMN
Cytokines	
Interleukins (IL1, 2, 3)	Lympho, Macro
GMCSF[2b]	Lympho
B-cell stimulating factor (BSF)	Lympho
Interferon-α,γ	Lympho, Macro
Tumor necrosis factor (TNF)	Macro, Mono
Arachidonic acid metabolites	
Prostaglandin E_2 (PGE_2)	Macro, Mono, PMN
Prostacyclin (PGI_2)	Eos
Thromboxane (TXA_2)	Macro, Thromb, PMN
Leukotriene B_4 (LTB_4)	Bas, Mast, PMN
Leukotriene C_4, D_4, E_4 (SRSA)[c]	Bas, Eos, PMN Macro, Mast
Lysosomal proteinases (cf. Table 4)	Fibro, Macro, Mono, PMN
Lysosomal Glycosidases (cf. Table 4)	Fibro, Macro, Mono, PMN
Oxidants (reactive oxygen metabolites)	Macro, Mono, PMN

[a] *Bas*ophils; *Lympho*cytes; *PMN* = Neutrophils; *Eos*inophils; *Macro*phages; *Mast* cells; *Fibro*blasts; *Mono*cytes; *Thrombo*cytes

[b] Granulocyte-monocyte colony stimulating factor.

[c] Slow-reacting substances of anaphylaxis.

In most cases the different defense or inflammatory cells produce several mediators. Some of the most potent ones, like the cytokines (Table 2), have been characterized in greater detail only recently. They represent polypeptides or glycoproteins which can stimulate diverse functions of different target cells: Interleukins stimulate the growth of various cell populations (IL1 and IL2 of B- and T-lymphocytes and IL3 (like GMCSF) of hemopoetic stem cells of granolocytes, monocytes and eosinophils) as well as the synthesis of acute-phase proteins (IL1). Additionally, BSF promotes the growth of mast cells. The interferons α and γ can activate monocytes and the immune defense when present in higher concentration, whereas lower amounts suppress these functions. According to recent findings the tumor necrosis factor (TNF) is especially pathogenically effective: Among other effects it induces fever and activates adipocytes to lipolysis, fibroblasts to synthesize PGE_2 and mast

cells to produce or liberate PAF, SRSA, histamine and serotonin (Table 2). Additionally, TNF can stimulate granulocytes to such an extent that they excrete their lysosomal granules into the extracellular lumen which strongly promotes the inflammatory process.

The described inflammatory mediators represent a most complex communication system whose most important function is to bring messages to cells. The messenger substances (mediators) can originate from the proteolytic cascade systems (coagulation, complement, kallikrein-kinin system etc.) and from cells. They can stimulate diverse cell populations and thus at the same time initiate different cell functions and may in some cases also activate the cells which produce them itself. On demand, they stimulate and enhance mediator production and thus an amplification of cell functions. An important characteristic of the cellular mediators is their restricted range and short lifetime: They are rapidly bound and degraded by their target cells. Generally, higher mediator concentrations are found in the inflamed area and its close surrounding as well as occasionally in the inflammatory exudates. Systemically, they can only be demonstrated (e.g., in blood) for short periods during massive injuries or inflammatory processes. With few exceptions, this also applies to the mediators originating from the proteolytic cascade systems like the kinins and anaphylatoxins.

The regeneration capability of the organism relies on the fact that different mediators can initiate the same cell function. The healing process caused by essential cell functions is thus guaranteed even though one mediator is not produced in sufficient amounts.

This communication system of the inflammatory mediators operating essentially for "impairment restriction" and rapid healing implies, therefore, the interaction of agonistic and antagonistic stimulation on a cellular level. The organism can thus appropriately respond to the manifold traumatic and inflammatory stimuli to regain the balance of the disturbed physiological homeostasis. This aim is supported by an increased production of the so-called acute-phase proteins such as fibrinogen, complement factor C3, C-reactive protein and ceruloplasmin which support the specific as well as the non-specific defense reactions.

IV. PROTEINASE INHIBITORS

Regulation of the proteinase activities of the plasma cascade systems occurs by activation of inactive proenzymes via liberated cellular proteinases (e.g., by thrombokinase and plasminogen activators) as well as by exposure of proenzymes and assembling factors to "foreign", e.g., subendothelial surfaces (intrinsic coagulation cascade). These processes which are essential for wound healing are primarily restricted to the injured area. The system-specific proteinase inhibitors, antithrombin III, α_2-plasmin inhibitor and C1-inactivator prevent excessive, i.e. systemic activation of the proteolytic cascades and thus simultaneously the formation of peptide mediators as well as non-specific proteolysis of endogenous proteins for example by plasmin (see Figure 2). In plasma these inhibitors are normally present in high excess over the maximally releasable amounts of their target enzymes. Thus they effectively restrict the activities of their primary target enzymes, thrombin (antithrombin III), plasmin (α_2-plasmin inhibitor), complement C1-esterase and plasma kallikrein (C1-inhibitor).

The outstanding characteristic of the proteinase inhibitors as protective substances against excessive proteolysis in the organism may be derived also from the fact that they represent the third largest plasma protein fraction besides albumin and the immunoglobulins. The primary target enzymes of most of these inhibitors (approximately 90% of all of them) are the cellular proteinases and in particular the lysosomal digestive enzymes from phagocytes.

It is the central task of the lysosomes containing phagocytes like granulocytes, monocytes and macrophages to limit the inflammatory process in the wound or inflamed area by phagocytosis of the inflammatory stimuli (cf. Chapter 52, Section II). During the phagocytic process various aggressive substances which arise from the intracellular oxidation/degra-

TABLE 3
Substrates of Lysosomal Proteinases from Phagocytes

Connective tissue:
elastin, collagen, proteoglycans, glycosaminoglycans, fibronectin, laminin, etc.
Muscle proteins:
myosin, tropomyosin, actin, troponin
Opsonins:
fibronectin, immunoglobulins, factors of the complement system, C-reactive protein, etc.
Transport proteins:
prealbumin, transferrin, haptoglobin, coeruloplasmin, etc.
Proteinase inhibitors:
α_1-Proteinase inhibitor (α_1-antitrypsin), α_1-antichymotrypsin, antithrombin III, α_2-plasmin inhibitor, C1-inactivator
Proteohormones:
insulin, glucagon, substance P, kinins, etc.
Receptors:
insulin receptor on cell membranes

TABLE 4
Lysosomal Digestive Enzymes

Neutral serine proteinases (elastase, cathepsin G)
Acid thiol and aspartate proteinases (cathepsins)
Neutral metallo proteinases (collagenases)
Aminopeptidases and carboxypeptidases
Carbohydrate cleaving enzymes such as α-glucosidase, α-*N*-acetylglucosaminidase, α-glucoronidase, α-galactosidase, α-mannosidase and lysozyme
Phosphatases and phosphoprotein-phosphatases
Arylsulfatases
Phospholipases, lipases, triglyceride lipases
Ribonucleases and desoxyribonucleases
Myeloperoxidase (oxidizing in the presence of hydrogen peroxide: H_2O_2)

dation machinery are released from the cell. However, they are normally rapidly inactived by specific antagonists. Those include α_1-proteinase inhibitor, which is present in high concentration in interstitial fluid, as well as antioxidants such as superoxide dismutase (SOD) and catalase being of cellular origin. After immigration of the phagocytes into the inflamed area, their overstimulation, for instance by TNF or larger amounts of C3a, can cause degranulation. In this process the lysosomal granules are excreted and their content is thus released extracellularly which may result in a local exhaustion of the endogenous protective antagonists. By this means the most important inhibitor of the lysosomal proteinase elastase from granulocytes, α_1-proteinase inhibitor, is inactivated both oxidatively by the myeloperoxidase/hydrogen peroxide system or oxygen free radicals, and proteolytically by catheptic thiol proteinases and neutral metallo proteinases from macrophages. The lysosomal elastase, which is produced in an amount of approximately 300 mg/d has its optimum proteolytic activity in the physiological pH range and can therefore unrestrictedly degrade structural elements such as basal membranes, elastin, collagen, fibronectin, and proteoglycans as well as humoral factors including the proteinase inhibitors of the plasma cascade systems (see Figure 2 and Table 3). This degradation process is strongly enhanced by various other hydrolytic enzymes derived from degranulated and disintegrated phagocytes and tissue cells in the inflamed area (see Table 4). The released lysosomal proteinases exhibit strongest pathogenetic effects (cf. Figure 2 and Table 3). Hence, the tools of the intracellular protein catabolism become extracellularly potent inflammatory mediators through the following mechanisms:

1. the destruction of vital endogenous structural and humoral substances leading among others to

2. severe alterations of tissues and thus to the exposure of normally coated structures as "foreign surfaces" which stimulate the immunological defense mechanisms; this may result in chronic inflammation or in an autoimmune disease;
3. the production of other inflammatory mediators in a direct or indirect way. For instance, lysosomal elastase can cleave off a C3a-like anaphylatoxin from complement factor C3, but can also provoke an increased production of peptide mediators of the plasma enzyme cascade systems by proteolytic inactivation of relevant proteinase inhibitors (see Figure 2 and Table 3).

In this way an initially local tissue defect or inflammatory process is spread by various transport media (interstitial fluid, lymph fluid, blood): the body temperature rises, the granulocytes are mobilised, and the synthesis of non-specific defense proteins, the acute-phase reactants, is stimulated.

Remarkably, the protective or regulatory proteinase inhibitors, α_1-proteinase inhibitor, C1-inhibitor, and α_1-antichymotrypsin, are also acute-phase reactants. The latter responds especially quickly (within a few hours) and strongly (increase in concentration up to six times of the normal level in plasma) due to an inflammatory stimulus. It seems logical that the organism reacts to an increased requirement of protective substances during the inflammatory process with an enhanced synthesis especially of α_1-antichymotrypsin and α_1-proteinase inhibitor, the inhibitors of lysosomal digestive proteinases. The importance of such a counter-regulation for the healing process is underlined by the observation that the excessive consumption of proteinase inhibitors such as antithrombin III and α_2-macroglobulin, which are not acute-phase proteins, has a very bad prognosis. α_2-Macroglobulin very effectively inhibits most of the lysosomal proteinases as well as plasmin and plasma kallikrein.

Proteolytic processes are principally irreversible and often destructive. Therefore, an increased turn-over or metabolization rate of endogenous substances (for instance after tissue injuries) has to be balanced by *de novo* synthesis of relevant substances or tissues which proceeds only slowly. This is in clear contrast to the possibility of an immediate counter-regulation with other inflammatory systems comprising for example the arachidonic acid metabolites (prostaglandins, leukotrienes etc.) and biogenic amines, whereby antagonistically effective mediators can be produced and released most rapidly.

V. DIAGNOSTIC APPROACHES TO INFLAMMATORY PROCESSES

At present, a clearcut chemical diagnosis of locally restricted inflammatory processes is not possible systemically. The quantities of inflammatory mediators present outside the inflamed area are minute as they are rapidly metabolized and eliminated. Moreover, they have only a short life-time and thus a limited range of action. However, they may be detected in inflammatory effusions, a fact, that has significantly contributed to the elucidation of locally proceeding pathomechanisms. A more favorable situation exists when characteristic metabolites accumulate and become detectable through sensitive and specific immunological methods. This is true for certain arachidonic acid metabolites and the lysosomal elastase from granulocytes. Elastase normally is present in blood as enzyme-α_1-proteinase inhibitor complex, i.e.,in an enzymatically inactive form. This complex is eliminated from the circulation via the reticulo-endothelial system (RES) with a half-life of approximately 1 h (cf. Figure 2).

Cell-specific factors of this type are gaining importance for diagnostic purposes and their release pattern during the inflammatory reaction may give valuable hints for new therapeutic approaches.

VI. MEDICINAL THERAPY CONCEPTS

Drug-related therapy concepts for the treatment of inflammatory processes should be orientated primarily on the extent of participation and the mode of action of inflammatory mediators and cells and the cascade systems as well. This especially applies to the corticosteroids which — as we know today — diversely influence the various cellular systems. For example, as membrane 1/2 protecting agents they inhibit the synthesis of prostaglandins and leukotrienes thereby diminishing protein exudation into the interstitial space and thus reducing edema formation. On the other hand, corticosteroids suppress the phagocytic potential of inflammatory cells, especially that of the granulocytes. Thereby the capability of these cells to clear damaged tissue, toxic metabolites and invasive microorganisms is significantly reduced. However, the clearance function is essential for the healing process. In addition, the corticosteroids impair the immune defense thus making the organism sensitive to bacterial and other infections. Even the plasma cascade systems are influenced by corticosteroids, e.g., by stimulation or inhibition of the synthesis of plasminogen activators and their inhibitors. This diversity of actions makes the therapeutic use of corticosteroids in inflammatory diseases rather problematic, especially if such a therapy is performed with high doses over a longer period. There is danger then that for short-term, positive effects extensive disadvantages have to be put up with regard to long-term wound healing and defense against infections.

Today's attention is directed towards the development of nonsteroidal anti-inflammatory drugs (NSAIDs). In experimental models and clinical studies, a number of such drugs are being currently tested for their compatability and therapeutic usefulness. NSAIDs are mostly substances which inhibit the synthesis of cellular mediators and certain cell functions (cf. Table 1 and 2). Inhibition of cell functions can be achieved by the blockade of mediator-specific receptors by mediator antagonists. The best results so far have been achieved by selectively acting inhibitors and antagonists. Examples are the inhibition of leukotriene synthesis or phagocyte stimulation by TNF. In the clinical application of NSAIDs one has to be aware of the fact that a close cooperation of inflammatory mediators and inflammatory cells is essential for the healing process. Drugs should control excessive production and stimulation to such a degree that physiological levels are maintained. Drug treatment should especially avoid impairment of the phagocytic process including the clearance function and the immunological defense reactions.

Compared to the application of NSAIDs, therapeutic approaches to avoid overactivation of proteolytic cascade systems on the one hand and the extracellular oxidative denaturation and proteolytic digestion on the other hand are well understood. It is possible to measure endogenous inhibitor levels of lysosomal digestive enzymes quickly and reliably. The dosage and the therapeutically effective concentration of administered proteinase inhibitors are easy to regulate *in vivo*. When unequivocal indications such as congenital or acquired massive inhibitor deficiency syndromes exist, protein-inhibitors are already applied clinically. Examples include α_1-proteinase inhibitor (as an inhibitor of granulocytic elastase) for treatment of lung emphysema, antithrombin III for treatment of life-threatening coagulation defects, and the C1-esterase inhibitor (C1-inactivator) for the treatment of angioneurotic edema (see Figure 2). Various laboratories are currently producing proteinase inhibitors by recombinant DNA techniques for therapeutic purposes. Those include the abovementioned inhibitors as well as other human proteinase inhibitors of thrombin (e.g. hirudin) and of the granulocytic elastase (e.g. variants of α_1-proteinase inhibitor and the miniprotein eglin). If the application of inhibitors in severe diseases such as sepsis, polytrauma and acute respiratory distress syndrome (ARDS) show the expected positive results, their more general therapeutic use for wound healing and local inflammatory processes should be envisaged.

The theoretical basis for the therapeutic application of antioxidants is based on the same

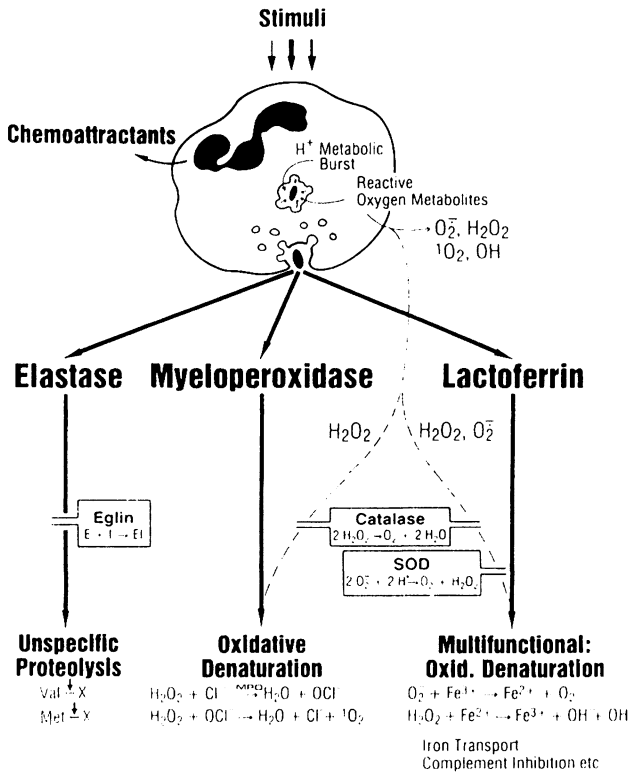

FIGURE 3. Lysosomal factors and products of phagocytic processes released extracellularly due to overstimulation of polymorphonuclear granulocytes (PMN) and suitable antagonists for their elimination.

basic principles and is similarly well defined as in the case of the proteinase inhibitors (see Figures 2 and 3). An optimal substance would be one which rapidly eliminates accumulating oxidants in the extracellular space. Superoxide dismutase (SOD), which is already applied in special clinical situations, converts the relatively short-living superoxide radicals ($O_2^{\cdot-}$) to hydrogen peroxide (H_2O_2). However hydrogen peroxide also acts — together with myeloperoxidase — as a strong oxidant and rapidly inactivates, among others, the α_1-proteinase inhibitor. Thus, the simultanous application of an agent such as catalase which eliminates H_2O_2 is necessary. On a long-term basis, a better solution is the development of low molecular mass synthetic antioxidants which have a broad scavanger spectrum and can be given orally. Intensive research in this area makes it likely that the therapy of inflammatory processes can be much improved by the application of NSAID as well as by proteinase inhibitors and antioxidants in the future.

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