Hypothesis: leukocyte endogenous mediator/ endogenous pyrogen/lymphocyte-activating factor modulates the development of nonspecific and specific immunity and affects nutritional status[1-3]

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ABSTRACT We postulate that leukocyte endogenous mediator/endogenous pyrogen/lymphocyte-activating factor (LEM/EP/LAF) integrates the host's nonspecific and specific immune responses to infection by virtue of the panoply of physiological and metabolic activities it is capable of eliciting. The alterations in systemic metabolism modulated by LEM/EP/LAF, although apparently of value to the host in the defense against infection and the repair of tissue damage, result in negative nutrient balances. Severe infections, alone or in conjunction with injury, may result in malnutrition unless the patient is adequately nourished. Preexisting nutritional deficits can compromise host resistance to infection, in part by preventing production of LEM/EP/LAF. Additional studies of the sequelae of LEM/EP/LAF action and effects of nutrition on host resistance to infection appear warranted. *Am J Clin Nutr* 1982;35:762–768.

KEY WORDS Leukocyte endogenous mediator/endogenous pyrogen/lymphocyte-activating factor, nonspecific and specific immunity, infection, metabolism, nutrition.

Introduction

Endogenous pyrogen (EP), also known as leukocyte endogenous mediator (LEM) (1, 2), has recently been demonstrated to be equivalent to lymphocyte-activating factor (LAF) (3). There are a multitude of reports that show that LEM/EP/LAF not only stimulates lymphocyte proliferation in response to antigen (4) but also induces fever and elicits neutrophilia and granulopoiesis (2, 5) and evokes profound cellular, organ, and systemic alterations in trace metal, nitrogen, and hormone distribution and metabolism (6–8). Infection induces negative nutrient balances which are related to the severity and duration of the illness (6, 9, 10). Malnutrition can compromise resistance to infection in many instances (11, 12). These findings lead us to postulate that LEM/EP/LAF acts as a broad but central mediator or modulator of the development of and interactions amongst various aspects of nonspecific and specific immunity. Moreover, we propose that this constellation of systemic metabolic and physiological events modulated by LEM/EP/LAF which lead not only to the development of immunity but also function to limit tissue injury at the site(s) of microorganism-phagocyte interaction and facilitate wound healing place metabolic demands on the host which lead to increased excretion of some nutrients, the development of negative nutrient balances and, in the absence of adequate nutrient input, eventual malnutrition.

Discussion

Nonspecific immunity involves phagocytosis, macrophage activation, localized inflammation, and certain systemic alterations

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in host physiology and metabolism which occur as part of the acute-phase response to a wide variety of circumstances usually having some degree of tissue damage as a common denominator (13–15). Specific immunity, of course, refers to the response of a lymphocyte to a single antigen which results in the development of the capability of that cell and its clone to secrete antibody or implement cell-mediated immunity.

Figure 1 summarizes the putative interactions amongst various aspects of nonspecific and specific immunity modulated by LEM/EP/LAF. A wide variety of phagocytic cell types have the ability to produce and release LEM/EP/LAF, but generally appear not to do so unless stimulated (7, 8). Activation in situ may occur after cellular ingestion of microorganisms or tissue debris or after interaction with immune complexes (13, 16–18). Perturbation of the phagocytic cell membrane appears to be a key stimulus for activation since chemicals such as colchicine (19), phorbol myristic acetate (20) and polyriboinosinic-polyribocytidylic acid complexes (21), as well as endotoxin (7) elicit LEM/EP/LAF release. Some (22, 23), but not all (24) studies of endogenous pyrogen release indicate that de novo protein synthesis may be required, while studies of lymphocyte-activating factor production suggest that variable amounts of preformed, high molecular weight precursors may exist intracellularly. Upon activation of the cells, these precursors are rapidly processed into low molecular weight (13 to 16,000 daltons) LEM/EP/LAF and released (25). Once released, LEM/EP/LAF circulates and affects or influences the activities of an amazing array of tissues and cells: lymphocytes, the reticuloendothelial system, bone marrow, hypothalamus, liver, muscle, and endocrine organs. There is evidence for a direct effect of LEM/EP/LAF on the hypothalamus, liver, granulocytes, macrophages, and lymphocytes (4, 5, 7, 8, 15, 26). LEM/EP/LAF may also act indirectly on these and other tissues and organs. Although there is evidence that LEM, EP, and LAF may be identical (1–3), there are also indications that these molecules comprise a family of closely related mediators, each member of which may have a somewhat different spectrum of activities (14, 15, 25) and perhaps even distinct physical properties (27).

LEM/EP/LAF can induce fever and hypoferremia (1, 2) which in concert appear to retard microorganism proliferation (28). LEM/EP/LAF is also able to elicit neutrophilia (1, 2) and provoke macrophages to produce colony-stimulating factor (5) which promotes granulopoiesis. Both of these actions of LEM/EP/LAF would appear to be designed to provide more granulocytic phagocytes to kill macroorganisms and clear tissue debris. LEM/EP/LAF can also stimulate neutrophil oxygen-dependent metabolism (29) which appears to be related to the microbicidal activity of these cells. LEM/EP/LAF is capable of causing granulocytes to release selectively lysozyme and lactoferrin (30). Lysozyme appears to facilitate the phagocytosis of certain microorganisms while lactoferrin restricts the availability of iron to microorganisms, thereby hindering their growth and/or toxin production. Lactoferrin may also contribute to the abrupt onset of hypoferremia by enhancing the flux of iron into the liver. Taken together these activities of LEM/EP/LAF may account, at least in part, for the observed antimicrobial activity of LEM/EP/LAF (31).

LEM/EP/LAF triggers marked alterations in amino acid, trace metal, and protein metabolism and distribution (6–8) which characterize infections and inflammatory states (6, 32). Uptake of zinc by the liver appears to correlate with the increased production of acute-phase proteins (13) which is supported by an enhanced flux of amino acids from muscle to liver (6, 33). Although the zinc seems to accumulate in the liver in the form of metallothionein (34), some of it may redistribute throughout the body in the form of α_2-macroglobulin. α_2-Macroglobulin is a protease inhibitor and as such may limit tissue damage due to proteolytic enzymes released by stimulated phagocytes or already damaged tissue. There are indications that α_2-macroglobulin may be involved in wound healing (35) and in the modulation of the specific immune response (36). LEM/EP/LAF stimulates an increase in plasma copper in the form of ceruloplasmin (37). Ceruloplasmin is capable of donating copper to various enzymes (6, 35), such as lysyl oxidase, which are involved in wound healing. Ceruloplasmin also acts as a scavenger of superoxide ions (38) generated by stimulated phagocytes,

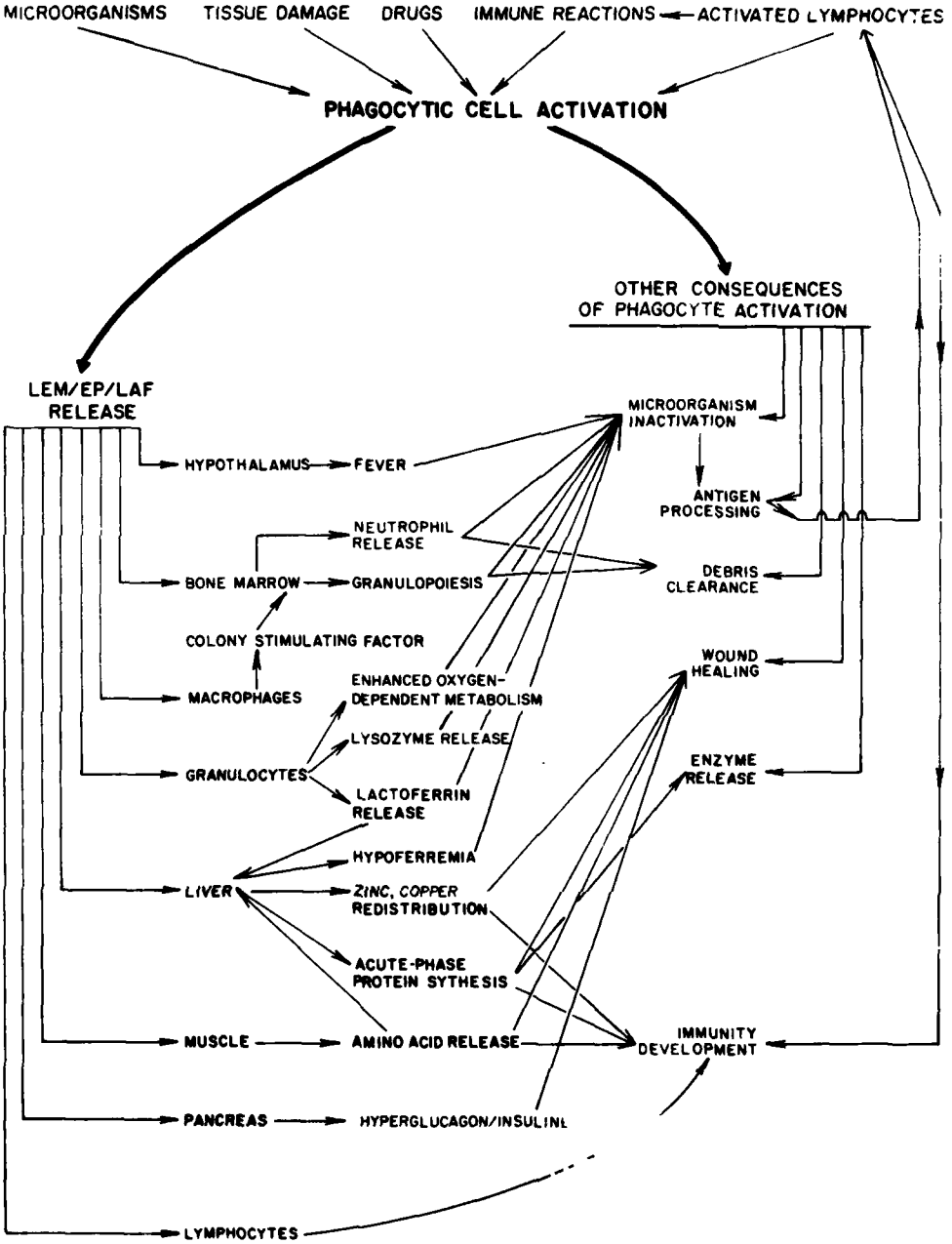

FIG. 1. Postulated interactions amongst various aspects of nonspecific and specific immunity modulated by LEM/EP/LAF.

thereby helping to limit tissue damage resulting from the phagocyte-microorganism confrontation. LEM/EP/LAF increases the plasma concentration of haptoglobin 2- to 3-fold and of C-reactive protein several 100-fold (8). These proteins accumulate at the site of injury and appear to participate in wound healing (35). There is also considerable evi-

dence that C-reactive protein modulates the development of the immune response. C-reactive protein may mute the sensitivity of the specific immune response so that it is involved only in clearing microorganisms the nonspecific immune system cannot eliminate, thereby avoiding futile antibody production (39). There are other plasma proteins such as α_1-antitrypsin and lipoproteins which appear to participate in host defense or repair (6, 14, 35, 39). It is not known whether the synthesis or concentration of these proteins is affected by LEM/EP/LAF.

The hyperglucagonemia and insulinemia that attend severe infections can also be induced by LEM/EP/LAF (40). Insulin and glucagon are needed to regulate the production and distribution of glucose during infection as in health, but the elevated concentrations of these hormones may have other functions. Insulin and glucagon facilitate liver regeneration and appear to protect the liver against hepatitis-induced damage. Insulin is said to promote wound healing, preserve leukocyte function and maintain cell-mediated immunological processes. Glucagon, in pharmacological amounts, has been reported to protect against stress-induced hemorrhagic gastritis (41).

Malnutrition as a consequence of inflammatory stress is not an uncommon finding even in hospitalized patients (12, 42) and clearly is a frequent aftermath of infection in poorly nourished populations (11). The putative relationship between the systemic metabolic and physiological sequelae induced by LEM/EP/LAF and altered nutritional status is depicted in **Figure 2**. Although the constellation of physiological and metabolic events modulated by LEM/EP/LAF appears to facilitate host defense against acute infections and repair of tissue damage (6, 35, 39, 41), there are often heavy costs to the host. It should be apparent that increased heat production, the massive shifts in trace elements and amino acids within the body and the proliferation of protein synthesis and secretory systems in the liver to allow for the greatly increased production of acute-phase proteins (43, 44) as well as the healing of wounds and the production of antibody require considerable energy. In addition to the requirement for energy, there is a need for nitrogen which may result in extensive wasting of muscle tissue.

The liver is the key organ in orchestrating the majority of metabolic alterations mediated by LEM/EP/LAF. It appears that the liver attempts to sequester nutrients for later use, e.g., zinc and iron, if there is a readily available storage form or as long as the material stored is not likely to be or become "toxic." Thus the ammonia moiety that is released when amino acids are cannibalized to generate glucose is converted into a form that can be readily excreted. The increase in tryptophan (10) and tyrosine (45) degradation during infection may be an attempt to prevent an accumulation of these precursors of potent neurotransmitters (46). Despite the attempts to store valuable nutrients for recycling, the energy demands of host defense as well as the requirement of preventing an accumulation of actual or potential "toxic" substances result in considerable inefficiency in the retention of nutrients, hence the en-

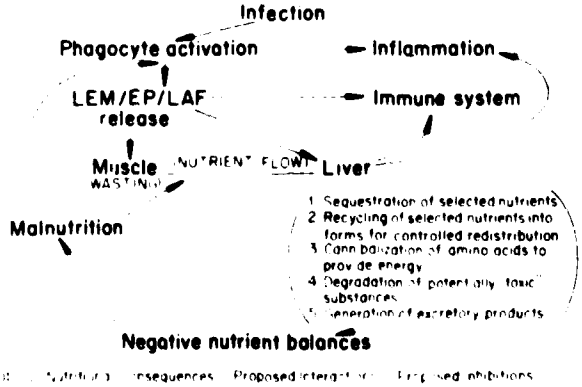

FIG. 2. The roles of LEM/EP/LAF in some aspects of the interaction between nutrition and infection

hanced excretion of many nutrients especially during the illness phase of infection. The anoretic state which often accompanies infection exacerbates this seemingly wasteful series of events. However, anorexia may also be construed as a means of preventing the introduction of exogenous nutrients which might compromise the endogenous antiinfection system (47). Of course even if anorexia is momentarily beneficial, it seems clear that prolonged periods of reduced food intake compromise the patient (12).

Malnutrition can increase susceptibility to numerous types of infection (11). Although malnutrition may simply reduce the availability of endogenous stores of critical nutrients to be mobilized in defense of the host, there is recent evidence that protein deprivation may lead to increased susceptibility to infection through reduced synthesis of LEM/EP/LAF (47).

In regard to the development of specific immunity, the metabolic and physiological sequelae modulated by LEM/EP/LAF appear designed to eliminate the infecting microorganism before it proliferates and spreads. Failing this, these LEM/EP/LAF-induced alterations would seem arranged so as to limit dissemination and growth of the microorganism until a specific immune response may be developed to aid in clearing the infection. Moreover, a number of these physiological and metabolic alterations seem to facilitate the development of specific immunity (6, 39). LEM/EP/LAF appears to modulate the development of specific immunity directly as well as indirectly. Macrophages not only process antigen for use in the development of specific immunity, but also modulate the immune response through release of various soluble factors. LAF, now recognized to be identical to LEM/EP (3), potentiates DNA synthesis in stimulated lymphocytes (48) and enhances antibody synthesis in spleen cells (49). LEM/EP/LAF induces macrophages to make colony-stimulating factor (5). Colony-stimulating factor activates macrophages to produce LAF (50). Thus there appears to be an amplification cycle that promotes the generation of granulocytes to clear infection and tissue debris and enhances antibody production as well as engendering systemic metabolic and physiological alterations that appear to facilitate host defense and repair. It would therefore seem that a more complete understanding of the roles of altered endogenous nutrient distribution and metabolism mediated by LEM/EP/LAF in, and the effects of exogenous nutrient supply on, host defense/repair processes may provide a means of shifting the balance in favor of host during a host-microorganism conflict and hastening the healing processes.

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