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Role for Interleukin-1 in the Pathogenesis of Hypersensitivity Diseases

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Interleukin-1 (IL-1), a polypeptide product of various cells, is one of the key mediators of the body's response to microbial invasion, inflammation, immunological reactions, and tissue injury. IL-1 is a prominent member of a group of polypeptide mediators now called "cytokines." Current evidence suggests that IL-1 is not produced in health but that any perturbation such as inflammation or even slight injury triggers the expression of IL-1 genes. The biological effects of IL-1 are manifested in nearly every tissue and organ. These include various proinflammatory effects such as increased production of arachidonate metabolites, synovial cell proteases, activation of basophils, eosinophils and neutrophils, endothelial cell adhesiveness, and stimulation of lymphocyte responses. Control of IL-1 synthesis in certain diseases is often appropriate. Although corticosteroids reduce both the transcription and translation of IL-1, we have recently investigated the effect of dietary supplementation with N-3 (omega-3) fatty acids in human volunteers. The results indicate that increasing the amount of N-fatty acids in the diet decreases the ability of blood mononuclear cells to synthesize IL-1 in vitro. It is suggested that the ameliorative effects of N-3 fatty acid dietary supplements in patients with hypersensitive diseases may be, in part, the result of decreased IL-1 production.

Key words: cytokines, monocytes, eicosapentaenoic acid, prostaglandins, inflammation, fever

Interleukin-1 (IL-1) is not a newly discovered molecule. In the 1940s, this material was called endogenous pyrogen for its ability to produce fever [1]. Purified endogenous pyrogen [2,3], however, did more than cause fever. It copurified with a substance called "leukocytic endogenous mediator" [4], which induced hepatic acute phase protein synthesis, decreased plasma iron and zinc levels, and produced a neutrophilia. "Lymphocyte-activating factor" was a protein described by Gery and Waksman [5] that augmented T-lymphocyte responses to mitogens and antigens but was indistinguishable from endogenous pyrogen [reviewed in 6]. The term IL-1 now includes the originally described endogenous pyrogen, leukocytic endogenous mediator, lymphocyte-activating factor, as well as mononuclear cell factor [7], catabolin [8], osteoclast-activating factor [9], and hemopoietin-1 [10].

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MOLECULAR STUDIES ON IL-1

Two biochemically IL-1 molecules have been cloned—IL-1β [11] and IL-1α [12]. These two IL-1s share only small stretches of similar amino acids (26% in the case of human IL-1) and hence, in the strict sense, are not homologous proteins. However, the two forms of IL-1 are structurally related, both being composed of beta pleated sheets and both forms being recognized by the same receptor. IL-1β and IL-1α are products of separate genes; both genes are located on chromosome 2, and each gene contains seven exons [13,14]. In human blood monocytes, mRNA coding for IL-1β predominates over that coding for IL-1α by ten- to 50-fold [11,15]. This prevalence of IL-1β has been observed in the proportion of the two IL-1 forms measured in the circulation and other body fluids, although the finding of IL-1b in body fluids may reflect the more efficient processing and extracellular transport of IL-1β over that of IL-1α.

The areas of similar amino acids found in IL-1β and IL-1α have been examined for evidence of unique common sites for receptor recognition. Of particular interest are the β/α "homologous" regions at amino acids 150–186, which are entirely coded by the VIth exon, and the carboxy-terminal amino acids (amino acids 219–240), which are encoded by the VIIth exon. Synthetic peptides have been made to these areas. A synthetic nonapeptide [17] possesses immunological activity but is devoid of proinflammatory properties. This nonapeptide does not compete with the 17,500-Da IL-1 for receptor binding. Others have made specific amino acid deletions, which suggest that the histidine (position 147) may contribute to the recognition site or affect the tertiary folding of the molecule for receptor binding [18]. IL-1β and IL-1α without this histidine compete less effectively with native structure IL-1 for receptors on T-cells. Others have used N-terminal amino acid deletions and mutants [19] to show that the N-terminal amino acids of IL-1β also contribute to receptor binding. It is interesting that some N-terminal deletions drastically reduce their ability to compete with native IL-1 binding to cells because there is no similarity between IL-1β and IL-1α in the amino terminal amino acids. Other studies report that the synthetic peptide coding for the terminal carboxyl 33 amino acids blocks the binding of native IL-1 [20]. This study is supported by the finding that antibodies produced against the synthetic peptides of the carboxyl terminal block IL-1 bioactivity, whereas antibodies to the N-terminal synthetic peptides have no effect [21].

Attention has turned to the tertiary structure of the two IL-1s to explain why both forms share the same spectrum of biological responses and recognize the same receptor. Computerized molecular modeling studies reveal that the two IL-1s comprise similar beta-strands (F. Cohen, personal communication). Recently, human IL-1β has been crystallized, and the X-ray defraction patterns of the IL-1β crystals reveal a structure with 12 beta-strands [22], which are, in fact, nearly the same as those predicted by computer-assisted modeling studies. The IL-1β core structure forms a tetrahedron whose edges are composed of two antiparallel beta-strands. The folding topology of human IL-1β is similar to that of the soybean trypsin inhibitor. Although there are no crystallographic studies on IL-1α, it is likely that the IL-1α tertiary structure is similar to that of the beta. Of interest in these studies on the tertiary structure of IL-1β is the fact that both the N and C terminals are exposed on the outside of the molecule and approximate each other. Thus, both the N and C terminals

may participate in receptor-binding events. The histidine is also exposed and may, as the experimental data suggest, contribute to receptor-ligand interaction.

Synthesis and Processing of IL-1

Both forms of IL-1 are unique in that they are initially translated as precursor polypeptides (31,000 Da), and despite the fact that IL-1 is found in the extracellular compartment, neither form contains a signal cleavage sequence. The generation of the N-terminus of the mature peptide (17,500 Da) and smaller peptides occurs by the action of serine proteases [28]. Most studies on the processing or cleavage and transport of IL-1 from an intracellular protein of 3,000 Da to an extracellular molecule of 17,500 Da have been carried out in monocytes and macrophages in vitro.

However, IL-1 is synthesized by a wide variety of cells. These include synovial fibroblasts, keratinocytes and Langerhans cells of the skin, mesangial cells of the kidney, B-lymphocytes, natural killer cells, astrocytes and microglial cells of the brain, vascular endothelial and smooth muscle cells, corneal, gingival, and thymic epithelial cells, and some T-lymphocyte cell lines. Transcription for IL-1 can be initiated in monocytes by adherence to foreign surfaces without detectable translation into the IL-1 protein, and in some mice with a genetic defect, there is a high level of transcription with low levels of translated protein [23]. Stimulating cells with agents such as endotoxin or by phagocytosis of particles increases transcription but, in addition, has a major effect on translation and processing of the IL-1 precursor. There is a period of short-lived transcription, which can be increased by suppressing the synthesis of a repressor protein [24]. Translation is reduced by prostaglandin-induced cyclic AMP production [25]. Transcription can be blocked by corticosteroids given before the cell becomes activated [26]. Post-transcriptional regulation involving the stability of mRNA has also been reported [24]. A positive signal is provided by calcium ionophores and products of arachidonate lipoxygenase (leukotrienes). The monocyte/macrophage remains an important source of IL-1 because of its strategic locations, its ability to synthesize large amounts of IL-1β (100 fg/cell/24 hours), and its ability to process the IL-1 precursor more effectively than other cells, perhaps because of its high levels of elastase and other serine proteases.

Cell-Associated IL-1

Lacking a distinct cleavage sequence, a considerable amount of IL-1 remains cell-associated, either intracellularly [27–29] or as part of the cell membrane. The 31,000-Da IL-1 precursor and a 22,000-Da form are found associated with the cell, and this latter form could comprise "membrane-bound IL-1" [30,31]. Processing of IL-1 is accomplished through the action of serine proteases, particularly elastase and plasmin [28,29], and in the cell, IL-1 is found in association with lysosomes, not the endoplasmic reticulum [32]. Membrane-bound IL-1, first described by Unanue and associates, is biologically active [30,31]; in fact, membrane-bound IL-1 may account for a significant part of the immunostimulatory effects of IL-1 in local tissues such as lymph nodes, joints, and skin. Membrane-bound IL-1 participates in antigen presentation and is also active on nonlymphoid cells such as chondrocytes and hepatocytes. Evidence suggests that most of the membrane-bound IL-1 is the alpha form [33] and that the beta form is secreted into the extracellular fluid. However, the IL-1β is also found associated with the cell, including stainable IL-1 in the activated human

monocytes [34] and in tumor cells [35]. The concept of membrane-bound IL-1 explains the ability of IL-1 to participate in autocrine and paracrine events without inducing the systemic effects, which occur when IL-1 is processed into its mature peptide, is released from cells, and gains access to the circulation.

BIOLOGIC EFFECTS OF IL-1

Because of the wide spectrum of biological responses attributed to native IL-1 [6], some effects were thought to be due to contaminating proteins. Using recombinant IL-1, however, the multiple biological properties proposed for natural IL-1 have been confirmed and are shown in Figure 1. For example, recombinant IL-1 functions as both a growth factor as well as an inflammatory mediator; IL-1 produces endogenous pyrogen fever, stimulates prostaglandin (PG) E2, and induces the proliferation of fibroblasts, smooth muscle cells, and T-lymphocytes. The effective concentration of IL-1 that induces these and other effects ranges from 1 nM to 1 pM (in some cases less); unlike interferons and bone marrow growth factors, IL-1 has little or no species specificity.

IL-1 acts on the hypothalamic thermoregulatory center to initiate fever, but there is no evidence that it crosses the blood-brain barrier and directly stimulates thermosensitive neurons. IL-1 triggers the synthesis of PGE_2 from hypothalamic vascular organs, and IL-1 induced PGE_2 elevates cAMP, which, in turn, can then act as a neurotransmitter. The ability of IL-1 to initiate PG synthesis is perhaps one of its most important biological properties, accounting for many local and systemic effects. Like the febrile response to IL-1, increased slow wave sleep can be observed within minutes following an intravenous injection. IL-1 also induces the release of several hypothalamic and pituitary peptides including endorphins, corticotropin-releasing factor, ACTH, and recently somatostatin [36]. Although IL-1 raises the level of circulating corticosterone via the release of ACTH [37], IL-1 also acts directly on the adrenal to augment steroid synthesis [38]. Increased sodium excretion and elevated insulin levels following an infusion of IL-1 are attributed to a direct effect of IL-1 on these organs. In vitro, IL-1 is a potent inducer of insulin transcription, but overstimulation results in cytotoxic changes in the insulin-producing beta cells [39].

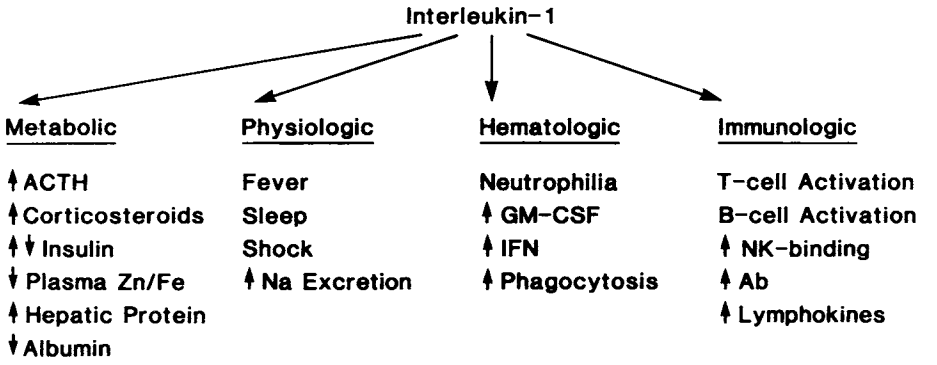

Fig. 1. Multiple biologic properties of recombinant IL-1. Effects have been reported for both IL-1β and IL-1α.

In isolated hepatocytes incubated with IL-1, the transcription of albumin decreases, transcription of factor B and metallothionen increases, transcription of serum amyloid A is initiated, but the transcription of the structural protein actin is unaffected. IL-1 stimulates the biosynthesis of complement protein C3, α-1-antichymotrypsin, α-1-acid glycoprotein, and inter-α-1-trypsin inhibitor [40]. IL-1 depresses the activity of liver cytochrome P450-dependent drug metabolism [41].

IL-1 contributes to the wasting and negative nitrogen balance observed in some diseases. For example, IL-1 inhibits lipoprotein lipase synthesis decreasing utilization of fat for energy; healthy animals given IL-1 exhibit anorexia, which seems to be mediated by the liver rather than by suppresssion of the brain satiety center [42]. Infusion of IL-1 into rats contributes increased release of amino acids into the urine, although recombinant IL-1 has no effect on muscle amino acid release in vitro [43].

Recent studies indicate that IL-1 potentiates the catabolic effects of tumor necrosis factor (TNF), also known as cachectin [44]. In fact, IL-1 and TNF share several biological properties [44,45]; moreover, the combined effects of these two distinct cytokines is often greater than either one alone. IL-1 and TNF act synergistically in the production of hemodynamic shock [46], cytotoxicity of the insulin-producing pancreatic beta cells [47], production of PGE from fibroblasts [48], and the induction of the local Shwartzman reaction [49]. IL-1 also potentiates the responses to IL-2 and the interferons on natural killer cells. Despite the synergistic activities of IL-1 and TNF, IL-1 down regulates TNF receptors [50] as well as its own receptor [51].

With the exception of hepatic albumin transcription and cytochrome P450, exposure of a wide variety of cells to IL-1 results in increased gene expression. IL-1 stimulates synthesis of insulin, collagen, collagenases, procoagulant proteins, proteoglycans, and several growth factors. Cells that themselves produce IL-1 will, in turn, respond to IL-1 and produce more IL-1 [52]. This includes IL-1-induced IL-1 from human monocytes [53]. IL-1 also stimulates the production of IL-2, gamma and beta inteferons, IL-3 and other bone marrow colony stimulating factors, and B-cell stimulating factor-2 [54], which is identical with interferon-β-2, now termed IL-6. Although IL-1 has no direct effect on marrow precursors, it acts synergistically with bone marrow growth factors during the reconstitution of hematopoiesis. This is a recently described property of IL-1 that identifies IL-1 as a previously described molecule called hemopoietin-1 [55]. It is clear that IL-1 participates in what could be described as a network of cytokine-induced cytokine. Such a network may be important for the augmentation or suppression of various biological properties during host responses to infection or inflammation. For immunological responses, IL-1-induced production of itself, IL-2, and B-lymphocyte growth factors augments the immune response to antigens, whereas IL-1-induced gamma-interferon production results in an antiproliferative and anti-inflammatory effect.

As shown in Figure 2, IL-1-induced IL-1 production involves not only macrophage activation but also T- and B-cell stimulation. IL-1 is a growth factor for B-cells, and B-cells produce IL-1. However, IL-1 is a potent stimulator for macrophages, inducing more IL-1, other cytokines such as granulocyte-macrophage colony-stimulating factors, and arachidonic acid metabolites [53]. Here, the induction of PGE_2 may play a role of downregulation of the IL-1-induced IL-1 response since PGE_2-induced cAMP suppresses IL-1 translation [25]. The ability of cyclooxygenase inhibitors to *increase* IL-1 production stimulated by a variety of agents may be

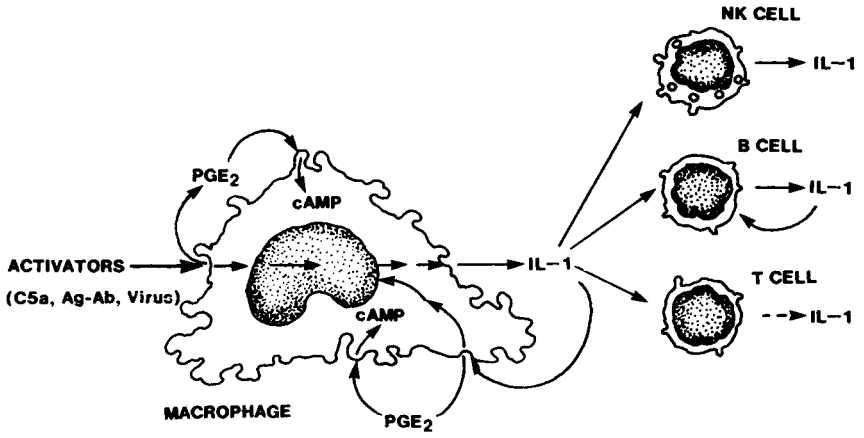

Fig. 2. IL-1 induced IL-1. Exogenous activators of macrophages induce IL-1; IL-1, in turn, induces more IL-1 from macrophages as well as other cells (B- and perhaps T and NK cells). The role of PGE_2 suppression of IL-1-induced IL-1 is shown via PGE_2-induced cAMP.

through this mechanism. One wonders if the widespread use of cyclooxygenase inhibitors in various inflammatory diseases results in the removal of this negative feedback effect.

Endothelial and smooth muscle cell responses to IL-1 can be viewed from two perspectives: 1) the systemic effects of circulating IL-1 and 2) local cellular responses. Cultured endothelial cells exposed to IL-1 synthesize PGE_2, PGI_2, and platelet-activating factor [56]—potent vasodilators. When administered intravenously, IL-1 induces a prompt but reversible fall in arterial blood pressure [46]. On a local level, however, IL-1 also orchestrates a cascade of cellular and biochemical events that lead to vascular congestion, clot formation, cellular infiltration, and endothelial leakage. IL-1 alters the endothelial surface receptors so that leukocytes adhere avidly and migrate into the extravascular tissue. The IL-1-activated endothelium expresses increased procoagulant [57] and plasminogen activator inhibitor activity. Taken together, the effects of IL-1 on the vascular endothelium promote the containment of infection and localization of injury. As with other inflammatory processes, mechanisms of repair and new growth are initiated at the same time. IL-1 is a growth factor for smooth muscle cells [58] and induces angiogenesis in the rabbit cornea. These biological properties of IL-1 have stimulated interest in a role for IL-1 in the pathogenesis of atherosclerosis, particularly since the structure of acidic fibroblast (endothelial cell) growth factor is related to IL-1.

IL-1 AS A MEDIATOR OF INFLAMMATION

IL-1 is found in the joint fluid of individuals with inflammatory and destructive arthritis where it is thought to contribute to pain, leukocyte migration, and tissue remodeling [7]. In vitro, IL-1 induces synovial cell and chondrocyte PGE_2, collagenase, and phospholipase A2 production [59]. In addition to attracting leukocytes into inflamed tissues, IL-1 also causes degranulation of basophils [60] and eosinophils

[61], stimulates thromboxane synthesis in macrophages and neutrophils, and potentiates the activation of neutrophils by chemoattractant peptides. Neutrophils express IL-1 receptors. Osteoclast activation is also a property of IL-1, and the purification of human osteoclast activating factor reveals an identical N-terminal amino acid sequence with that of human IL-1β. In contrast to its catabolic activities, IL-1 participates in the reparative process by increasing fibroblast proliferation and by the synthesis of collagens and glucosaminoglycans. IL-1 is mitogenic for mesangial cells in the kidney, glial cells in the brain, and for keratinocytes. In fibroblasts, IL-1 directly increases the transcription of type 1, type III, and type IV (basement membrane) collagen. Fibrosis and deposition of abnormal proteins in tissues appear to be, in part, mediated by IL-1, and in rheumatoid joint disease, this contributes to thickening of scar tissue, which restricts joint movement.

MODULATION OF IL-1

Altering the Production of IL-1

The production and biological activities of IL-1 are important considerations in some pathological processes. Circulating levels of IL-1 increase in a variety of diseases and during organ transplant rejection, but there are also brief elevations of IL-1 following ovulation, strenuous exercise, and exposure to ultraviolet light. In some infectious and inflammatory diseases, IL-1 production by circulating leukocytes is elevated such as sarcoidosis, rheumatoid arthritis, and tuberculosis, whereas decreased production has been observed in humans and animals with metastatic tumors and certain nutritional deficiencies. Because IL-1 is highly inflammatory and stimulates catabolic processes in bone and cartilage, attention has focused on how to reduce IL-1 production. To date, the only drugs that are used routinely to treat various diseases where IL-1 appears to be elevated are the corticosteroids. These agents, although increasing transcription of a variety of proteins, block IL-1 transcription and prevent the some translation [26]. Since IL-1 induces ACTH release and increases adrenal corticosteroid synthesis, a built-in negative feedback loop for reducing IL-1 production may exist. Because corticosteroids also block phospholipase activity and reduce PGE synthesis, they can also upregulate IL-1 translation of already formed IL-1 mRNA. In general, drugs that block PGE and PGI synthesis tend to increase IL-1 production when added in vitro [25]. Recent studies from our laboratory indicate that the blood leukocytes from human subjects taking oral cyclooxygenase inhibitors produce statistically more IL-1 and TNF in vitro than leukocytes from human subjects not taking these agents [62]. What role chronic cyclooxgenase inhibitors have in IL-1 production in vivo remains unclear.

Effect of Dietary N-3 Fatty Acid Supplementation on IL-1 Production by Human Mononuclear Cells In Vitro

We recently investigated the ability of N-3 (omega-3) fatty acid dietary supplementation in human volunteers to affect the ability of their blood leukocytes to produce IL-1. Studies concerning the beneficial effects of N-3 fatty acids have recently been reviewed [63]. In the present study, six human male volunteers supplemented their "normal American diet" with 3 g/day of eicosapentaenoic acid (as fish oil concentrates, MaxEPA). Blood mononuclear cells (MNC) were obtained on 18 occasions: three times before the dietary supplementation, three times after 6 weeks of the

diet, three times 10 weeks after stopping the diet, and three times 20 weeks after stopping the fish oil supplementation, MNC were stimulated in vitro with endotoxin and total (cell-associated plus secreted) IL-1β, IL-1α and TNF production was assessed following three freeze-thaw cycles by specific radioimmunoassays (RIA). All RIA were performed at the end of the study.

The results are depicted in Figure 3. Our findings demonstrate that N-3 fatty acid supplementation reduced the ability of IL-1β production induced by endotoxin. The effect was most pronounced 10 weeks after stopping the dietary N-3 fatty acids and suggests that the incorporation of these fatty acids into the pool of circulating MNC is delayed. The ability of the MNC from these donors to synthesize IL-1β returned to the prediet levels. Similar results were observed when we measured IL-1α and TNF (data not shown). We also observed similar reductions at the same time points when we measured the three cytokines using phytohemagglutinin as a stimulant.

We speculate from these findings that, similar to corticosteroids, agents that alleviate inflammatory and hypersensitivity diseases may be effective, in part, because they reduce the synthesis of IL-1 and TNF. The effect of N-3 fatty acid supplementation in the present study is consistent with this concept.

Altering the Effects of IL-1

Cyclooxygenase inhibitors are useful for reducing IL-1-induced PG and thromboxane synthesis. Thus, drugs with cyclooxygenase-inhibiting activity are often used to treat IL-1-mediated fever, pain, muscle aches, headaches, and similar PGE-related effects. Some biologic effects of IL-1 are, however, not affected by cyclooxygenase inhibitors. These usually include the noninflammatory effects of IL-1 such as increased hepatic protein synthesis, lymphocyte activation, and increased nonspecific resistance to infection.

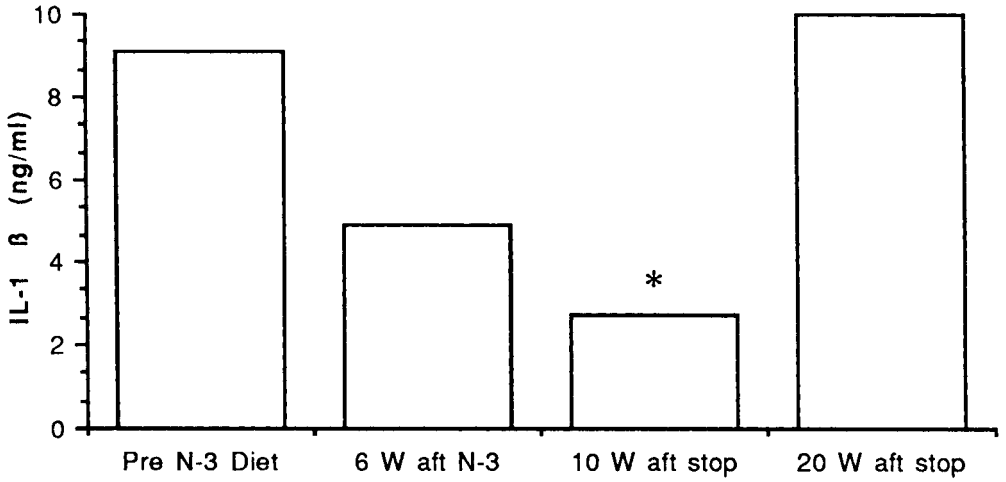

Fig. 3. Mean IL-1β (ng/ml) levels produced by the MNC of six human volunteers taking 3 g of supplemental eicosapentaenoic acid per day for 6 weeks. Each time point bar represents the mean total of IL-1β production from the MNC of six subjects stimulated with 10 ng/ml of endotoxin on 3 separate days for a total of 18 determinations. *$P < .01$.

The host also produces its own substances that inhibit the biological activity of IL-1 by either binding the molecule [64], interfering with the IL-1 receptor [65], or, as is the case with alpha-melanocyte-stimulating hormone, by suppressing the effect of IL-1 on a variety of cells. It is presently unclear whether these naturally produced inhibitors will be useful in treating clinical disease, but it is important to recognize, from a biological point of view, that these counterregulatory molecules exist and that an imbalance between IL-1 and its natural inhibitors may underlie certain disease states. Another aspect of modulating IL-1's effects is the ability of IL-1 to downregulate its own receptor [51], which may explain the protective role of pretreatment with IL-1 to a subsequent lethal challenge by radiation, hyperoxia, or infection.

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REFERENCES

1. Atkins E: Physiol Rev 40:580, 1960.
2. Murphy PA, Chesney J, Wood WB, Jr: J Lab Clin Med 83:310, 1974.
3. Dinarello CA, Renfer L, Wolff SM: Proc Natl Acad Sci USA 74:4624, 1977.
4. Merriman CR, Pulliam LA, Kampschmidt RF: Proc Soc Exp Biol Med 154:224, 1977.
5. Gery I, Waksman BH: J Exp Med 136:143, 1972.
6. Dinarello CA: Rev Infect Dis 6:51, 1984.
7. Krane SM, Dayer J-M, Simon LS, Byrne S: Coll Relat Res 5:99, 1985.
8. Saklatvala J, Sarsfield SJ, Townsend Y: J Exp Med 162:1208, 1985.
9. Dewhirst FE, Stashenko PP, Mole JE, Tsurumachi T: J Immunol 135:2562, 1985.
10. Moore MA, Warren DJ: Proc Natl Acad Sci USA 84:7134, 1987.
11. Auron PE, Webb AC, Rosenwasser LJ, Mucci SF, Rich A, Wolff SM, Dinarello CA: Proc Natl Acad Sci USA 81:7907, 1984.
12. Lomedico PT, Gubler U, Hellman CP, Dukovich M, Giri JG, Pan YE, Collier K, Semionow R, Chua AO, Mizel SB: Nature 312:458, 1984.
13. Clark BD, Collins KL, Gancy MS, Webb AC, Auron PE: Nucleic Acids Res 14:7897, 1986.
14. Furutani Y, Notake M, Yamayoshi M, Yamagishi J, Nomura H, Ohue M, Furuta R, Fukui T, Yamada M, Nakamura S: Nucleic Acids Res 13:5869, 1985.
15. Demczuk S, Baumberger D, Mach B, Dayer J-M: J Mol Cell Cardiol 3:255, 1987.
16. Auron PE, Rosenwasser LJ, Matsushima K, Copeland T, Dinarello CA, Oppenheim JJ, Webb AC: J Mol Immunol 2:169, 1985.
17. Antoni G, Presentini R, Perin F, Talgliabue A, Ghiara P, Censini S, Volpini G, Villa L, Boraschi D: J Immunol 137:3201, 1986.
18. MacDonald HR, Wingfield P, Schmeissner U, Shaw A, Clore GM, Gronenborn AM: FEBS Lett 209:295, 1986.
19. Horuk R, Huan JJ, Covington M, Newton RC: J Biol Chem 262:16275, 1987.
20. Palaszynski EW: Biochem Biophys Res Commun 147:204, 1987.
21. Riveau G, Dinarello CA, Chedid L: J Immunol, in press.
22. Priestle JP, Schaer H-P, Gruetter MG: EMBO J, in press, 1988.
23. Ikejima T, Orencole SF, Warner SJC, Dinarello CA: J Leukocyte Biol 42:561, 1987.
24. Fenton MT, Clark BD, Collins KL, Webb AC, Rich A, Auron PE: J Immunol 140:2267, 1987.
25. Knudsen PJ, Dinarello CA, Strom TB: J Immunol 137:3189, 1986.
26. Knudsen PJ, Dinarello CA, Strom TB: J Immunol 139:4129, 1987.
27. Lepe-Zuniga B, Gery I: Clin Immunol Immunopathol 31:222, 1984.
28. Auron PE, Warner SJC, Webb AC, Cannon JG, Bernheim HA, McAdam KJPW, Rosenwasser LJ, LoPreste G, Mucci SF, Dinarello CA: J Immunol 138:3403, 1987.

29. Matsushima K, Taguchi M, Kovacs EJ, Young HA, Oppenheim JJ: J Immunol 136:2883, 1987.
30. Kurt-Jones EA, Kiely JM, Unanue ER: J Immunol 135:1548, 1985.
31. Beuscher HU, Fallon RJ, Colten HR: Immunology 139:1896, 1987.
32. Bakouche O, Brown DC, Lachman LB: J Immunol 138:4249, 1987.
33. Conlon PJ, Grabstein KH, Alpert A, Prickett KS, Hopp TP, Gillis S: J Immunol 139:98, 1987.
34. Bayne EK, Rupp EA, Limjuco G, Chin J, Schmidt JA: J Exp Med 163:1267, 1986.
35. Ree HJ, Crowley JP, Dinarello CA: Cancer 59:1717, 1987.
36. Scarborough DE, Dinarello CA, Reichlin S: J Leukocyte Biol 42:560, 1987.
37. Besedovsky H, del Rey A, Sorkin E, Dinarello CA: Science 233:652, 1986.
38. Roh M, Drazenovich KA, Jeffrey BS, Barbose JJ, Dinarello CA, Cobb CF: Surgery 102:140, 1987.
39. Mandrup-Poulsen T, Bendtzen K, Nerup J, Dinarello CA, Svenson M, Nielson JH: Diabetologia 29:63, 1986.
40. Perlmutter DH, Dinarello CA, Punsal P, Colten HR: J Clin Invest 78:1349, 1986.
41. Ghezzi P, Saccardo B, Villa P, Rossi V, Bianchi M, Dinarello CA: Infect Immun 54:837, 1986.
42. McCarthy DO, Kluger MJ, Vander AJ: Am J Clin Nutr 42:1179, 1987.
43. Moldawer LL, Svaninger G, Gelin J, Lundholm KG: Am J Physiol 253:C773, 1987.
44. Beutler B, Cerami A: Nature 32:584, 1986.
45. Dinarello CA: Year Immunol 2:68, 1986.
46. Okusawa S, Gelfand JA, Ikejima T, Connoll RA, Dinarello CA: J Clin Invest 81:1162–1172, 1988.
47. Mandrup-Poulsen T, Bendtzen K, Dinarello CA, Nerup J: J Immunol 139:4077, 1987.
48. Elias JA, Gustilio K, Baeder W, Freundlich B: J Immunol 138:3812, 1987.
49. Movat HZ, Burrowes CE, Cybulsy MI, Dinarello CA: Am J Pathol 129:463, 1987.
50. Holtman H, Wallach D: J Immunol 139:1161, 1987.
51. Matsushima K, Yodoi J, Tagaya Y, Oppenheim JJ: J Immunol 137:3183, 1986.
52. Warner SJC, Auger KR, Libby P: J Exp Med 165:1316, 1987.
53. Dinarello CA, Ikejima T, Warner SJC, Orencole SF, Lonnemann G, Cannon JG, Libby P: J Immunol 139:1902, 1987.
54. Van Damme J, Billiau A: J Exp Med 165:914, 1987.
55. Stanley ER, Bartocci A, Patinkin D, Rosendall M, Bradley TR: Cell 45:667, 1986.
56. Dejana E, Brevario F, Erroi A, Bussolino F, Mussoni L, Bramse M, Fintucci G, Casali B, Dinarello CA, Van Damme J, Mantovani A: Blood 69:695, 1987.
57. Bevilacqua MP, Pober JS, Majeau GR, Cotran RS, Gimbrone MA Jr: J Exp Med 160:618, 1984.
58. Libby P, Warner SJC, Friedman GB: J Clin Invest, in press.
59. Gilman SC, Berner PR, Chang J: Agents Actions 21:347, 1987.
60. Subramanian N, Bray MA: J Immunol 138:271, 1987.
61. Pincus SH, Whitcomb EA, Dinarello CA: J Immunol 137:3509, 1986.
62. Endres S, Cannon JG, Ghorbani R, Dempsey RA, Lonnemann G, van der Meer JWM, Dinarello CA: J Immunol, in press.
63. Leaf A, Weber PC: N Engl J Med 318:549, 1988.
64. Brown K, Muchmore AV, Rosenstreich DL: Proc Natl Acad Sci USA 83:9119, 1987.
65. Balavoine JF, deRochemonteix B, Williamson K, Seckinger P, Cruchaud A, Dayer J-M: J Clin Invest 78:1120, 1987.