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Mediators of Fever and Muscle Proteolysis

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Mediators
Skeletal Muscle Proteolysis
Leukocytic Pyrogen (LP)
Endogenous Pyrogen (EP)

Leukocytic Endogenous Mediator (LEM)
Interleukin-1
Prostaglandin E₂ (PGE₂)

This is an invited editorial for The New England Journal of Medicine which discusses a new finding, i.e., that a mediator released by phagocytic cells during severe trauma or infection serves to initiate proteolysis of skeletal muscle. The mediator causes PGE₂ formation in muscle which in turn activates lysosomal proteases. The importance of this sequence is discussed in terms of host survival and defensive mechanisms. Interrelationships among the mediators are also discussed.
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an Editorial by

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The accelerated catabolism of skeletal muscle protein which accompanies severe trauma and infection can now be ascribed to the actions of endogenously produced mediators. Reports (1,2) in this issue of the Journal have identified these actions using in vitro preparations of rat skeletal muscle as a bioassay. Rates of proteolysis in these muscle preparations were quantitated by measuring free amino acid release into the media.

Clowes et al (1) isolated and partially characterized a small glycopeptide from the plasma of traumatized or septic patients. When compared to control samples of normal plasma, mediator-containing samples were found to induce significantly greater rates of bioassay muscle proteolysis. Intermediate rates of amino acid release were generated by plasma from patients who had undergone noncomplicated elective surgery. Further, the magnitude of in vivo proteolysis in the uninjured leg muscles of septic or traumatized patients was estimated by measuring arterio-venous differences in the plasma concentrations of representative free amino acids. Leg muscle proteolysis in individual patients correlates well with their plasma bioactivity in the assay system.

Although evidence for a circulating proteolytic mediator was indirect in the study of Clowes et al (1), additional support for the presumptive role of circulating mediators was found by Baracos et al (2), who studied the actions of highly purified human leukocytic pyrogen (LP) in a similar rat muscle bioassay system. LP produced a rapid increase in muscle proteolysis without affecting the synthesis of new muscle protein. Baracos et al (2) also showed that LP-induced proteolysis was mediated through the synthesis of prostaglandin E₂ (PGE₂) in muscle. Both the accumulation of PGE₂ and the
proteolytic action of LP could be blocked by incubation of assay muscle with indomethacin, a drug known to inhibit PGE$_2$ synthesis. Baracos et al (2) demonstrated further that the LP-induced acceleration of muscle proteolysis could be blocked through a different mechanism by an experimental drug, Ep-475. This agent appears specific in its ability to inactivate the lysosomal cathepsins B, H, and L in intact skeletal muscle. The findings suggested that the proteolytic actions of LP in skeletal muscle were caused by an increased production of PGE$_2$ which, in turn, activated thiol proteases in muscle cell lysosomes (2). Alternatively, naturally occurring cathepsin inhibitors in muscle (3) might be deactivated.

Endogenous peptide mediators are formed and released when mobile phagocytic cells are suitably stimulated. LP-induced fever is mediated in hypothalamic thermal regulatory centers via a localized formation of PGE$_2$ in neuronal cells (4). The action of LP on skeletal muscle would thus appear to employ the same secondary messenger. Further work will be required to determine if the glycopeptide mediator identified in plasma by Clowes et al (1) is structurally related to LP, if it is produced by activated phagocytes, and if it works by a similar molecular mechanism.

The findings (1,2) extend the concept that activated phagocytic cells can produce hormone-like mediators to signal distant tissues. Mediator activities are reflected by a variety of names (5), including LP, endogenous pyrogen (EP), leukocytic endogenous mediator (LEM), neutrophil releasing factor, lymphocyte activating factor, and most recently interleukin-1. However, the molecular structure is not known for any of these mediators and their relationships are uncertain.
Many of the generalized, but diverse, metabolic and physiologic responses which accompany severe trauma, infection, or inflammatory states have been ascribed to the action of endogenous mediators (5,6). Such responses include the experimentally demonstrated generation of fever, the production and release from bone marrow of neutrophils, the accelerated hepatic uptake of amino acids from plasma, the hepatic synthesis of intracellular enzymes and metal-binding proteins, the hepatic production of acute-phase plasma proteins, the hepatic sequestration of iron and zinc, and the stimulation of phagocyte and lymphocyte populations to greater activity (5,6). Mediator activities that can be demonstrated in vitro using cultured cell or tissue preparations would appear to be independent of intervening CNS or hormonal controls.

Acceleration of skeletal muscle proteolysis was previously included on theoretical grounds (5) within this list of mediator-induced responses. It seemed logical that mediator release might activate a mechanism for generating the free amino acids needed for host defenses. It remains possible that another consistent response to illness, i.e., anorexia, is also initiated by an endogenous mediator.

Muscle proteolysis during severe illness is of positive value for survival. In this regard, skeletal muscle provides a metabolically dynamic protein bank and potential source of free amino acids (7,8). This role of skeletal muscle protein is beneficial, because each of the different immunological and nonimmunological host defense mechanisms is based, ultimately, on the ability of body cells to synthesize new proteins. With severe trauma, infection, or inflammation, the labile source of amino acids in muscle can be tapped for high priority defensive needs of the host. On the
other hand, if the pool of labile nitrogen becomes depleted, as in cachectic
diseases or severe protein malnutrition, the patient becomes especially
vulnerable to superimposed infections, often by opportunistic microorganisms
(7).

In addition to the reutilization of amino acids for synthesis of new
proteins, branched-chain amino acids released during proteolysis can be
metabolized within muscle as direct sources of energy. Some other amino
acids, similarly released or synthesized within muscle cells, travel via
plasma to the liver where they may become substrates for gluconeogenesis
(7). The additional glucose is used, in turn, to initiate and sustain the
heightened consumption of oxygen which accompanies fever (7). The _Journal_
papers (1,2) should stimulate comparisons of muscle proteolysis due to various
cachectic illnesses, to glucocorticosteroids and other hormones (8), and to
previously identified muscle protease regulators (3). Differences or
similarities of cardiac muscle must also be ascertained in comparison to
responses of striated skeletal muscle.

Unfortunately, variously named mediator substances have not been
available in sufficient purity or quantity to allow for broad testing in all
bioassay systems by which mediator activities have previously been explored.
The possibility that a single mediator initiates all recognized host responses
seems remote in view of physicochemical and immunological differences between
partially purified species of LP (9). Further, a single mediator could not
account for disease-related differences in clinical fever patterns, WBC
responses, and acute-phase protein fluctuations. However, since laboratory
production of variously named mediators employs similar cells and methods, it
is possible that different mediator species are all members of a closely
related family (6).

Despite more than three decades of study, these endogenous mediators have
not been precisely identified or characterized. Formidable obstacles to
progress remain. The need to obtain mediators \textit{in vitro} from living phagocytic
cells limits the size of production runs. Biological characterizations still
depend upon relatively insensitive bioassay systems. Large mediator losses
occur during purification and standardization. Specific structural
characterization and workable quantities of mediators will be required to
determine individual physiologic roles.

Hopefully, these obstacles can be overcome. Recently, Flynn \textit{et al} (10)
identified mononuclear phagocytes in human placentas as sources for mediator
production. Recombinant DNA technologies offer a possible future production
method. Bioassay systems should be made more sensitive, use cultured tissue
or cells to minimize expenditures of purified mediator, or be replaced by
physiocochemical quantitation or immunoassay. The latter should improve when
well characterized mediators and specific, high affinity polyclonal or
monoclonal antibodies are produced.
REFERENCES


