Meeting report


Round Table Conference on Mediators of Sepsis – Brussels, Belgium, March 21–23, 1992

M. Lamy1, L.G. Thijs2

1Department of Anesthesiology and Intensive Care, Centre Hospitalier Universitaire de Liège, Belgium
2Department of Intensive Care, Free University Hospital, Amsterdam, The Netherlands

Received: 14 June 1993/Accepted: 13 August 1993

The clinical syndrome of sepsis has now been recognized as the result of excessive activation of host defence mechanisms rather than the direct effect of microorganisms. A large number of well-defined humoral mediator cascades and products released by various cells are involved in this exaggerated systemic response. Invasive bacterial infection is a major (albeit not the only) trigger that sets in motion an orchestra of mediators which activates cell-cell interactions and induces metabolic alterations, processes that ultimately lead to tissue damage and multiple organ failure. The major (initial) players in this orchestra are cytokines (tumor necrosis factor (TNF), interleukins), the complement system, the contact system and the extrinsic pathway of coagulation, the fibrinolytic system and cellular elements such as mononuclear cells, neutrophils, endothelial cells and platelets. Activation of these cellular and humoral elements may result in the release of other active products such as prostaglandins, leukotrienes, platelet activating factor (PAF), oxygen free radicals, and proteinases. In addition, the neuro-endocrine as well the autonomic nervous system are activated as part of the general (stress) response. As a result significant changes in hormonal levels occur and mediators such as endorphins are released. Important interactions take place between the neuro-endocrine stress response and the generalized inflammatory response: cytokines can stimulate hypothalamic centers and the release of hormones and autonomic nervous activity can increase TNF release.

In recent years our knowledge of the role of mediators in sepsis has dramatically increased based on data from various sources: experimental animal models, studies in human volunteers and observations in septic patients. Recently, also strenuous exercise has been shown to induce a generalized inflammatory response not unlike that observed in early sepsis although of a lesser magnitude.

The molecular structure, the source(s), the biological activities and the target cells of almost all known mediators have been clarified to a large extent. Also, important interactions between mediator systems and cellular systems have been documented, but in this area much needs yet to be unraveled. Both in septic animal models and in patients with severe sepsis plasma levels of (activated) products of virtually all humoral and cellular inflammatory systems are elevated and for many it has been demonstrated that the higher the levels are, the more likely organ failure or death will ensue. Although plasma levels may not precisely reflect activation in the tissues, these observations suggest an important role for these mediators in the pathophysiology of sepsis. Infusion of specific mediators such as cytokines (TNF, IL-1), PAF, C5a in the animal model induces pathophysiological changes including hemodynamic alterations and organ failure as observed in septic shock. Moreover, administration of antibodies to (e.g. anti TNF, anti PAF, anti C5a) or natural inhibitors (e.g. IL-1 receptor antagonists) of specific mediators in the animal model has been shown to prevent or significantly modify the effects of a septic insult, supporting the concept of their important pathogenetic role.

An important issue now arises: what is the hierarchy of these mediator systems in terms of sequence of activation and of their relative pathogenetic importance? This is not...
only important for our understanding of the pathophysiology of sepsis but also for the development of therapeutic strategies to interfere with the deleterious effects of the inflammatory reaction. A major impediment in unraveling the precise role of mediators in the pathophysiology of sepsis is the observation that most mediators activate other mediators or cells with subsequent release of mediators or toxic products which in turn can amplify the effects or induce additional release of the initial mediator. Also, that mediators may exert their effects directly or also (in part) by activation of others. In such a way an extensive network of positive feedback loops is created. Once the septic syndrome is established an extremely complex process of ongoing interactions and activations makes analysis of the relative importance of specific mediators extremely difficult if at all possible.

Studies in animal models and in human volunteers challenged with endotoxin have demonstrated a repeatedly confirmed sequence of activation by which a certain hierarchy of mediator systems has been disclosed. From these studies it emerged that TNF released by mononuclear cells may be considered a primary mediator. It subsequently induces other cytokines (IL-1, IL-6, IL-8), activates endothelial cells, neutrophils and the coagulation system. Simultaneously, changes occur in systemic hemodynamics, ventricular function, pulmonary and gut permeability which are qualitatively similar to those observed in sepsis. Although animal models and studies in healthy human volunteers may not exactly mirror the patient (usually with an underlying condition or disease) who attracts sepsis, it is now widely accepted that cytokines and in particular TNF play an essential role in the inflammatory response and are the most important initiating mediators.

This is in keeping with the observation that administration of anti-TNF antibodies prior to a septic insult may prevent the whole array of signs and symptoms of severe sepsis as well as the development of organ failure. However, the dominant role of TNF has been challenged as in some animal models, anti-TNF antibodies fail in this respect.

Some mediators have natural inhibitors and their plasma levels may increase during a sepsis period (e.g. C1-esterase inhibitor). Recently, high levels of soluble TNF receptors and IL-1 receptor antagonist have been identified in plasma of patients with sepsis. Apparently, their inhibitory action is insufficient to balance mediator activities in these patients but they have promise for future interventions. In addition, some inhibitors such as C1-esterase inhibitor may become proteolytically inactivated.

A central mechanism in the pathogenesis of sepsis-induced tissue damage is the interaction between neutrophils and endothelial cells. Cytokines (TNF, IL-1) can induce expression of adhesion molecules (ELAM-1, ICAM) on endothelial cells which act as ligands for activated neutrophil adhesion molecules (e.g. CD11/CD18 integrins). These molecules mediate adhesion of neutrophils to endothelial cells with subsequent release of toxic neutrophil products such as oxygen free radicals and proteinases (e.g. elastase, collagenase) which damage tissues.

This seems to be a self-perpetuating process as any plasma inhibitor gaining access to the area of close contact is antagonized by oxygen free radicals and other toxic products. In this way inhibitors of e.g. elastase are inactivated in the micro-environment of neutrophils and elastase can exert its activity for a longer period despite the presence of large amounts of inhibitors in plasma and interstitial fluid. This mechanism is likely to be a major factor responsible for increased microvascular permeability. Neutrophils can be activated by cytokines (TNF, IL-1, IL-8), complement activation products (C5a), contact activation products and bacterial products.

Increased pulmonary vascular permeability followed by the adult respiratory distress syndrome (ARDS) is a common complication of severe sepsis. This increase in permeability is mediated by the interplay between cells (neutrophils, platelets, endothelial cells), and circulating humoral factors. Among the latter are thromboxane A2, leukotriene LTB4, PAF and activated complement factors in addition to cytokines. Aggregation of activated neutrophils and platelets in the pulmonary vasculature contributes significantly to pulmonary tissue damage mediated by the release of toxic products.

Sepsis has long been recognized as the major cause of diffuse intravascular coagulation (DIC) which may contribute to multiple organ failure. Although the contact system of coagulation is activated during sepsis this system plays little role in inducing DIC. The major mechanism is activation of the extrinsic pathway of coagulation which is initiated by the interaction of TNF (and IL-1) with endothelial cells. Both cytokines can induce expression of tissue factor and down regulation of thrombomodulin on endothelial cells by which the endothelial surface becomes procoagulant and promotes the development of DIC.

Evidence of generation of thrombin are elevated levels of prothrombine F1+2 fragments and thrombin-antithrombin III complexes as observed in human volunteers challenged with endotoxin or TNF.

Also the fibrinolytic system is activated as indicated by high levels of tissue plasminogen activator (tPA) found after administration of endotoxin or TNF in humans. In this models, however, this effect is counteracted by rising levels of plasminogen activator inhibitor (PAI-1) creating a procoagulant state a few hours after the challenge. Although at present the precise role of coagulation and fibrinolysis in human sepsis is unknown it is likely that also in this state similar changes occur. And it is clear that the balance between coagulation and fibrinolysis is in favour of the former. The observation that signs of coagulation are more pronounced in non-survivors than in survivors indicates its clinical significance.

Renewed interest in the role of the intestinal tract as a source of bacteria and endotoxin has resulted in the concept of translocation due to damage of the gut barrier. Intestinal ischemia seems to be its major mechanism. The gut-liver axis has been appreciated not only as an important source of mediators but also as effector organs. This has far reaching metabolic consequences and eventually liver failure will ensue. Exocrine pancreatic damage has also been demonstrated, with release of enzymes like...