CYCLIC NUCLEOTIDES IN THE IMMUNOPHARMACOLOGY OF
LIPOPOLYSACCHARIDE ENDOOTOXINS

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INTRODUCTION

Lipopolysaccharides (LPS) are responsible for the characteristic immunopharmacologic activities of the endotoxins of gram-negative bacteria. This chapter will discuss their immunopharmacologic actions including some new observations and the evidence that their actions are mediated in part by cyclic nucleotides. The lipopolysaccharides are to be distinguished, for the purposes of this discussion, from bacterially derived protein toxins, like cholera toxin and E. coli enterotoxins, which have also been implicated as immunomodulators acting via cyclic nucleotide pathways.

E. coli protein enterotoxins have been classified into two forms, a heat labile enterotoxin acting to regulate adenylate cyclase and to increase cellular levels of cyclic 3',5' adenosine monophosphate (cyclic AMP) in several tissues (14) and a heat stable enterotoxin acting to regulate guanylate cyclase and to increase cyclic 3'5' guanosine monophosphate (cyclic GMP) levels in gastrointestinal epithelial cells (16). In both cases, these cyclic nucleotide related actions are thought to contribute to the mechanisms by which these organisms induce diarrhea and intestinal cramps. Another example is the Vibrio cholera protein toxin called cholera toxin which has been shown to activate adenylate cyclase in lymphocytes, macrophages, neutrophils and mast cells and to increase cellular levels of cyclic AMP in association with the inhibition of secretory, motile, and proliferative functions (see 6 for review). The role of these protein toxins in immune regulation in gastrointestinal disease has not been ascertained and their relative rarity in nature would indicate that they play little role in the healthy individual.

In contrast to the protein toxins, the lipopolysaccharides are ubiquitously present in nature, and have many immunomodulatory activities, to the extent that many immunologists consider them ever present nuisances bent on fouling their experiments. Clearly in the context of sepsis and endotoxemia the toxicities of endotoxins on the body's defense systems, including hyperpyrexia, intravascular coagulation, RES blockade, etc., can be considered host destructive. On the other hand, in the absence of disease, low doses of endotoxins may be considered benign or even positive immunoregulators contributing to more effective host defense. It is even possible to envision

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them as being a very part of the host defense mechanism. It may be that our nonpathogenic gastrointestinal flora provides us with a continuous low level of LPS molecules acting as hormonal signals to promote the development and enhance the function of the entire immune system. This latter comment may, for the traditionally trained immunologist, seem heretic, yet we hope in the course of this chapter to make clear several points which support the tenability of this notion. In brief, endotoxins regulate, either directly or indirectly, almost every phase of the development and function of the major natural and specific immune defense systems of the body. Their effects are positive, i.e., they generally promote growth and function of the cell populations involved. They do so at μg/ml concentrations and in some cases at ng/ml concentrations, i.e., at concentrations which may be periodically, even regularly, achieved locally and perhaps also systemically. Finally, where analyzed, they appear to act via the cyclic nucleotide pathways by which many of the body's hormones act and many of the molecules mediating immune function are also thought to act. They, therefore, qualify as specific messengers acting via receptors and hormone pathways in physiologically constructive ways. In order to allow the reader to evaluate this speculative notion in greater depth, a brief review of the immunopharmacology of endotoxins is essential.

IMMUNOPHARMACOLOGIC ACTIONS OF ENDOTOXIN

In Vivo Studies

Firstly, endotoxins by nature of their polysaccharide components are antigenic and through their diversity elicit a spectrum of antibodies capable of neutralizing their function and preventing the endotoxins, in general, from being immunotoxic and dysregulatory to the system. The lipid A moiety is generally considered to provide the basis of the immunoregulatory functions although there is not unanimity on this point for all aspects of the nonspecific action of LPS on the immune system and evidence for a role of the polysaccharide moiety exists (see Friedman and Nowotny in this volume). The many actions of LPS on the immune system have been reviewed extensively in this book and elsewhere (see 22 and 34). Endotoxins generally enhance host resistance to pathogen challenge particularly when administered just prior to challenge. They have been shown to enhance resistance to transplantable tumors and are thought to be part of tumor destructive processes initiated by bacterial immunotherapies such as BCG, C. Parvum and mixed bacterial vaccines (7). They are potent adjuvants for antibody production when administered with or just following antigen. They restore humoral immunity in aged mice, enhance the response to weak antigens, render tolerogenic doses of antigen immunogenic and prevent the induction of B-cell tolerance but not T-cell tolerance. They inhibit cellular immune responses under circumstances where they concomitantly enhance humoral immunity yet they enhance cellular immunity to unrelated antigens including delayed-type hypersensitivity, graft-versus-host reaction, and allograft rejection. They expand the hematopoietic and reticuloendothelial systems and enhance nonspecific resistance mechanism. LPS also promotes complement (C) activation via the alternate pathway which leads to the production of activated C3. B cells and macrophages bear C3 receptors and C3 activation is thought to play a role in stimulating these cells. LPS-induced production of chemotactic peptides C5A and C5A can also be envisioned to participate in granulocyte and macrophage chemotaxis and accumulation.

In Vitro Studies

The cellular targets and molecular mediators of these various LPS actions are many; the essential features are summarized in Figure 1.