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Anti-endotoxin therapeutic options for the treatment of sepsis

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The identification of lipopolysaccharide binding protein (LBP) and CD14 as key molecules in the cellular response to endotoxin has been a major advance in unravelling the pathophysiological basis of Gram-negative sepsis. Much interest has focused on developing effective anti-endotoxin treatments to abrogate the inflammatory consequences of Gram-negative infection. The therapeutic options can be divided into those aimed at neutralizing or clearing circulating endotoxin, including anti-endotoxin antibodies and endotoxin neutralizing proteins, and those that antagonize the effects of endotoxin on human cells—for example, lipid A analogues. Initial experiences with anti-lipopolysaccharide antibodies have been disappointing but a new generation of anti-endotoxin agents is about to enter clinical trials. Whether these will prove sufficiently effective to reduce the morbidity and mortality of Gram-negative sepsis remains to be seen.

Introduction

Endotoxin, or lipopolysaccharide (LPS), is a component of Gram-negative bacteria and is an extremely potent toxin.[1] Lipid A has been recognized to be the main toxic moiety of LPS and is responsible for many of the pathophysiological responses leading to multiple organ failure in Gram-negative sepsis. The past decade has seen enormous advances in our understanding of the cellular and molecular basis of human responses to LPS.[2] Characterization of these events is now leading to the design of rational therapies directed against endotoxin in an attempt to reduce the high morbidity and mortality associated with sepsis.[3] In this paper I will briefly review the basic structure of endotoxin and lipid A, the current understanding of the cellular basis for the pathophysiological response to LPS and the various therapeutic approaches under development.

Historical background

In 1892 Pfeiffer and Centanni independently described a heat-stable pyrogenic toxin intrinsic to *Vibrio cholerae* and *Salmonella typhi*.[4] Pfeiffer called this 'endotoxin' but it was not until the 1930s that Boivin was able to extract endotoxin using the trichloroacetic acid technique. Endotoxin purified in this way is a crude fraction containing many cell wall proteins and in the 1940s Westphal & Luderitz were finally able to purify the active fraction of endotoxin which was shown to be LPS.[4] The role of LPS in experimental Gram-negative sepsis was confirmed in the 1970s by the classic studies of Braude & McCabe, amongst others, who demonstrated that antisera directed against the core structures of LPS were able to protect animals against challenge with heterologous Gram-negative bacteria,[5,6] work that was to form the foundation for later attempts to alter the course of sepsis in man.

It was not until 1983 that the correct structure of Salmonella lipid A was elucidated by Takayama & Raetz in the USA and that of *Escherichia coli* lipid A by Rietschel *et al.* in Europe.[1,4] The synthesis of pure lipid A allowed experimental work to confirm that lipid A is capable of inducing the pathophysiological events seen in sepsis.[1,4] Final proof that LPS alone can induce all of the characteristic features of septic shock in man came from a laboratory worker who self-administered 1 mg of purified *Salmonella minnesota* LPS intravenously which resulted in severe shock and organ failure within 3 h.[7]

Structure of endotoxin

LPS is found in the external membrane of the outer cell wall of Gram-negative bacteria with the polysaccharide chain directed outwards (Figure 1). LPS consists of a polysaccharide domain covalently bound to the unique diglucosamine-based acylated phospholipid, lipid A (Figure 2).[1]

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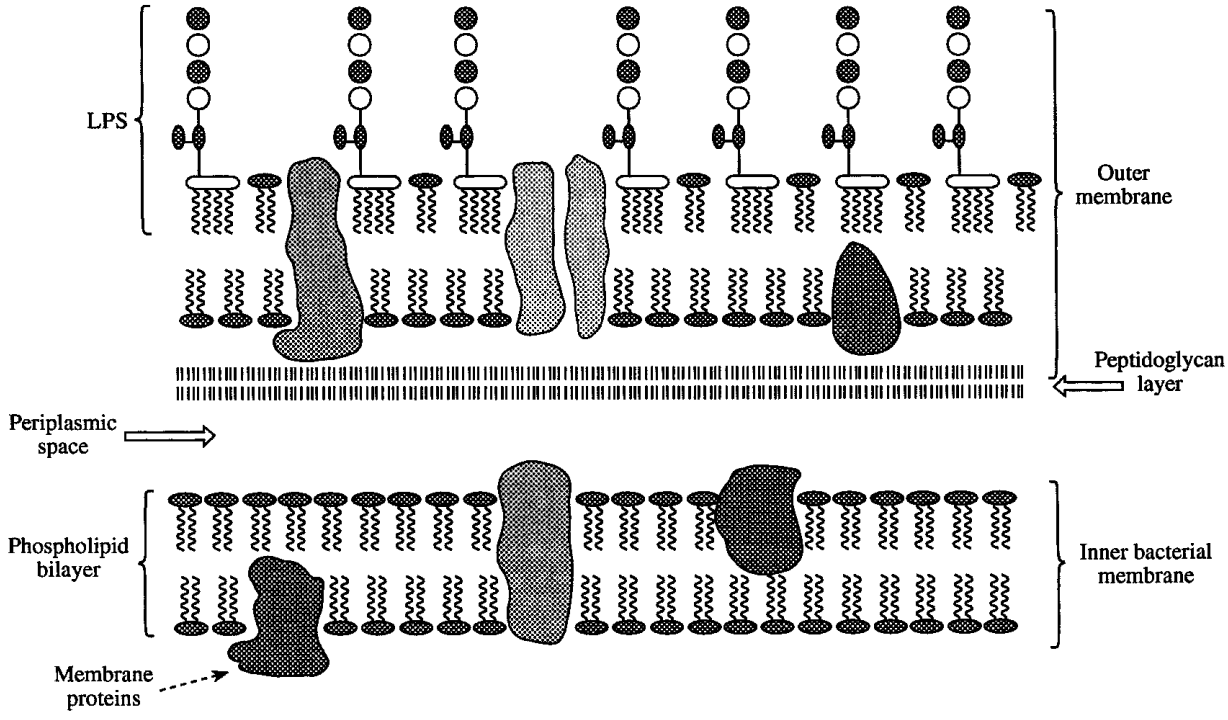


Figure 1. Structure of the Gram-negative bacterial cell wall. The lipid A portion of LPS is embedded in the outer leaflet of the cell membrane with the polysaccharide chain directed outwards. The inner leaflet is composed of glycerophospholipids and is separated by the periplasmic space from the inner cell membrane (adapted from Raetz *et al.*[1]).

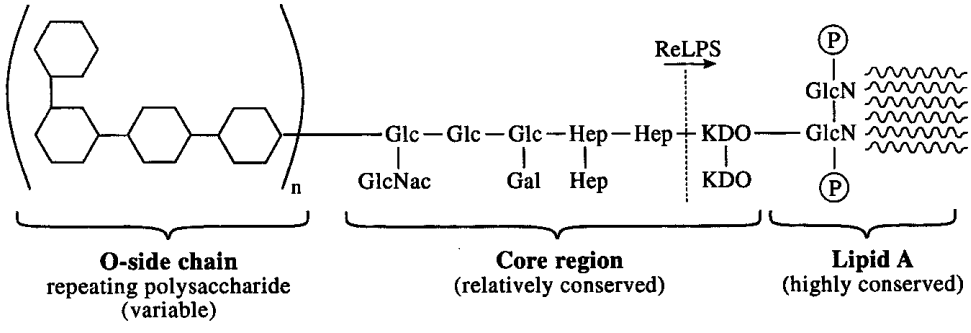


Figure 2. Structure of lipopolysaccharide. The outer variable polysaccharide O chain is separated from lipid A by a relatively conserved core region consisting of a small number of oligosaccharide subunits. Antibodies directed against this core region may cross react with a range of Gram-negative bacteria while those directed against the O side-chain are strain specific. Antibodies against the core region can be obtained by immunization of animals with mutant (rough) bacteria, such as *E. coli* J5, that lack the outer polysaccharide. The minimum structure capable of sustaining bacterial growth consists of lipid A attached to two or three KDO residues (ReLPS). KDO, 3-deoxy-D-manno-octulosonic acid; Hep, L-glycero-D-manno-heptose; Glc, D-glucose; Gal, D-galactose; GlcNac, *N*-acetyl-D-glucosamine.

Cellular responses to LPS

The response to LPS is extremely complex, involving interaction between LPS, serum components that may augment or inhibit the actions of LPS, and specific cell surface receptors. Although the lipid A portion of LPS is buried in the cell membrane, LPS is released from the cell wall of growing bacteria and also when bacteria are damaged, such as by complement or antibiotics. Free LPS rapidly forms complexes in the circulation with a variety of circulating proteins and lipids and thus the host cell may encounter LPS in free or bound forms that can dramatically alter cell responses.[8]

Neutrophils and macrophages

The observation that the presence or absence of serum had a marked effect on the macrophage response to LPS led to the discovery of LPS binding protein (LBP). LBP is present in the circulation and concentrations are increased in

response to inflammatory stimuli. LBP binds LPS and the LPS–LBP complex then interacts with CD14.[9,10] CD14 is a 55 kDa glycosphosphatidyl (GPI)-linked protein found on the surface of monocytes and macrophages.[11] CD14 lacks an intracellular signalling domain; the precise pathway by which ligation results in cell signalling has not been elucidated. The most widely held hypothesis is that CD14 acts as a carrier molecule, presenting LPS to a 'signalling' receptor (Figure 3). The identity, location (cell surface or intracellular), and binding characteristics of this receptor are unknown and the subject of an intense research effort. Following CD14 ligation by LPS, macrophages and monocytes are rapidly activated by a number of pathways involving tyrosine kinase, protein kinase C and NF-κB.

It is also apparent that monocytes and neutrophils can respond to LPS through a LBP/CD14-independent pathway but at a much higher LPS concentration.[12] This direct pathway of cell activation by LPS may occur through the unidentified LPS receptor or through other receptors. For example, it has recently been shown that the surface adhesion molecule CR3 can signal cells in response to LPS.[13] The acetylated LDL (scavenger) receptor on macrophages also directly binds LPS but in this case the LPS does not activate the cell but is internalized and detoxified.[14]

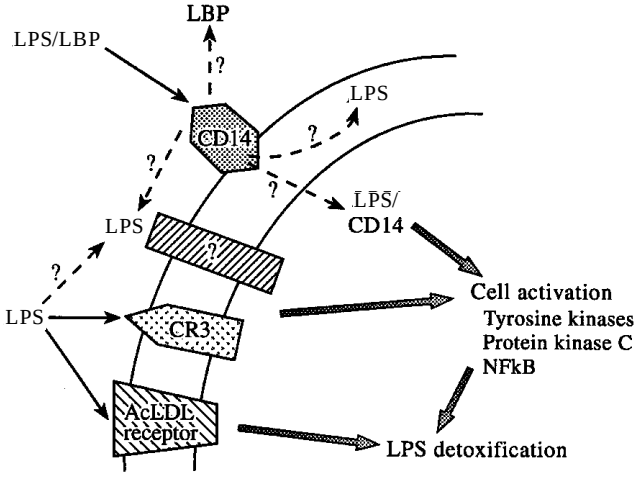


Figure 3. Schematic representation of the known and postulated pathways of macrophage and neutrophil activation by LPS. Free LPS complexes in the fluid phase with LBP and the LBP–LPS complex interacts with CD14 on the cell surface. The mechanism of cell signalling following CD14 ligation is unknown but may involve a second cell surface receptor. Alternatively CD14 may internalize LPS or mediate transfer of LPS into the cell membrane. LPS can interact with the cell surface independently of CD14 and LBP. Known interactions include LPS binding to complement receptor type 3 (CR3) and the acetylated LDL receptor (AcLDL). In addition, at high concentrations, LPS can directly activate cells independently of currently recognized surface receptors.

Endothelial cells

Endothelial cells do not express surface CD14 and so it came as a surprise to discover that the endothelial cell's response to LPS is CD14-dependent (Figure 4).[15,16] Again, the precise signalling pathway is unknown but it appears that LBP acts as a carrier molecule and presents LPS to circulating soluble CD14 (sCD14). The sCD14–LPS–LBP complex then binds to an, as yet unidentified, endothelial receptor.[17] Endothelial cells are also activated by interleukin 1 (IL-1) and tumour necrosis factor-α (TNF-α) produced in response to endotoxin.

Counter-regulatory mechanisms to limit LPS activity

LPS forms complexes with serum lipoproteins, including low density lipoproteins (LDL), high density lipoproteins (HDL) and apolipoprotein A, which result in reduced toxicity: bound LPS can subsequently be cleared from the circulation.[18] LBP sera remove LPS from the lipoprotein complexes and present LPS to bound or soluble CD14 (Figure 5). In addition all sera contain anti-LPS antibodies and these may act as a buffer to the biological effects of released LPS. Neutrophils also possess specific anti-LPS activities. LPS-neutralizing proteins are released during phagocyte activation, the best known of which is bactericidal/permeability-increasing protein (BPI), and neutrophil enzymes such as acyloxyacylhydrolase can detoxify LPS.[19,20] Thus the balance between these opposing forces may decide whether sepsis and shock develop and manipulation of this system could be beneficial.

Sites of intervention

It is apparent from above that there are a number of potential targets for the response LPS to be modified. Key sites and some examples of therapeutic agents under evaluation are given in Table I.

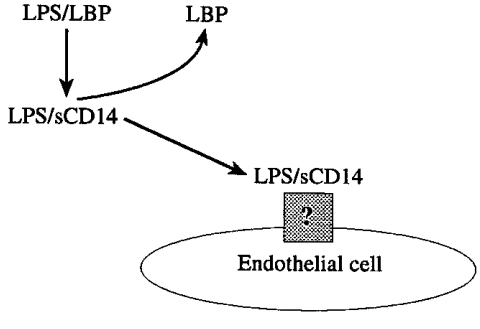


Figure 4. Schematic representation of endothelial cell activation by LPS. LPS–LBP complexes interact with soluble CD14 (sCD14) in the circulation. The LPS–sCD14 complex is then able to bind directly to endothelial cells. LBP may still be present as part of the LPS–sCD14 complex but is not necessary for LPS to bind to the endothelium. The cell surface determinant that binds LPS–sCD14 and subsequent pathways leading to endothelial cell activation have not been identified.

Specific anti-endotoxin therapies

Antibodies to endotoxin

Antibodies directed against the polysaccharide (O antigen) of LPS protect against infection and shock but are specific to the individual bacterial serotype.[21] However, antibodies directed against the inner core of LPS (Figure 2) protect against heterologous Gram-negative bacteria.[5,6] In the light of these findings polyclonal human antisera were raised containing high levels of cross-reactive anti-LPS antibodies. In clinical trials these anti-LPS antisera appeared to reduce mortality in patients with Gram-negative septicaemia.[22] However, IgG rather than IgM anti-LPS antibody failed to demonstrate a consistently protective effect.[23] These problems, together with the difficulties in establishing an adequate supply of human antisera, led to the development of anti-LPS monoclonal antibodies (mAbs), two of which, HA-1A and E5, have been the subject of major clinical trials.[24–26]

HA-1A (Centoxin, Centocar, Leiden, The Netherlands) is a humanized IgM mAb derived from the spleen of a patient vaccinated with the *E. coli* rough mutant J5.[27] *In vitro*, HA-1A does not directly neutralize LPS but *in vivo* it enhances clearance of LPS–HA-1A/complement immune complexes via complement receptor type 1 on the surface of red blood cells.[28] The results of clinical trials with HA-1A are shown in Table II. The first phase III trial showed no overall reduction in 28 day mortality but there appeared to be a significant ($P = 0.01$) survival advantage in a sub-group of 200 patients with Gram-negative bacteraemia.[26] The interpretation of this trial led to considerable controversy,[29] with HA-1A initially being granted a product licence in Europe in 1992 and subsequently being withdrawn from the market in 1993. In the second placebo-controlled study in which 2199 patients were enrolled, mortality in the 621 patients with Gram-negative bacteraemia was 33% and 32% in the HA–1A and placebo groups, respectively.[30] In all patients without Gram-negative bacteraemia, mortality was 41% in those receiving HA-1A compared with 37% in the placebo group, and further development of HA-1A for the treatment of septic shock was halted.

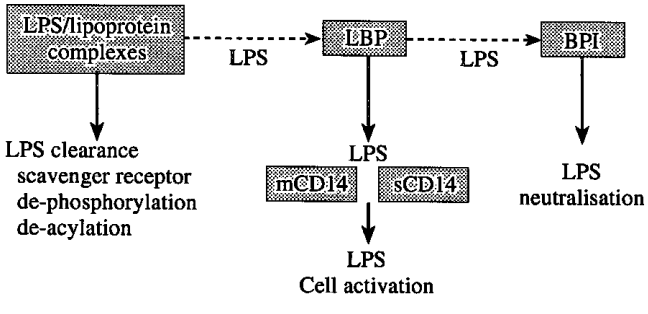


Figure 5. Fate of free LPS in the circulation. LPS can form a complex with serum lipoproteins which is then cleared from the circulation. LBP can bind free LPS or remove LPS from lipoprotein complexes and then present the LPS to soluble or membrane-bound CD14, leading to cell activation. LPS neutralizing proteins such as BPI may interrupt this by removing LPS from the LPS–LBP complex.

E5 (Xoma, Berkeley, CA, USA) is a murine anti-LPS mAb and there have been similar difficulties in establishing a role for this agent in the treatment of Gram-negative sepsis (Table II). In the first E5 trial there appeared to be an increase in survival rate of patients not in shock[24] but this finding was not confirmed in the second study which demonstrated a trend for an improvement in survival only in the subgroup of patients with major organ failure.[25] A further trial of E5 in patients with Gram-negative bacteraemia is in progress. It may be possible to develop a more effective LPS-neutralizing antibody but, in light of these previous failures, it may be difficult to raise the necessary enthusiasm to conduct large clinical studies.

The Chiron corporation (Emeryville, CA, USA) have developed an antibody (T88) to a common enterobacterial antigen that has shown promise in animal studies. A phase III trial in 826 patients with sepsis has been completed and although full data are not available there was no overall benefit.[31] Other cross-reactive anti-LPS antibodies have been described but have not reached clinical trials.[21,32] Cross-reactive anti-LPS antibodies would be most widely applicable to patients with Gram-negative sepsis, but antisera or mAbs have also been raised to specific pathogens such as *Klebsiella* sp. and *Pseudomonas* sp. and these may prove to have a therapeutic role under certain circumstances.[33,34]

Using a different approach, Bhattacharjee *et al.*[35] have employed a vaccine derived from a deacylated LPS from a J5 *E. coli* mutant complexed with an outer membrane

Table I. Potential targets and examples of therapeutic agents underevaluation

Enhanced LPS clearance
anti-LPS antibodies
haemoglobin derivatives
direct removal of LPS through filtration
Direct neutralization of circulating LPS
anti-LPS antibodies
LPS neutralizing proteins (ENP, BPI, defensins)
polymyxin B
Inhibition of LPS–LBP and/or LPS–sCD14 interactions
lipid A analogues
anti-LBP antibodies, anti-CD14 antibodies
BPI
Blocking cellular LPS receptors
lipid A analogues
anti-CD14 antibodies
Inhibition of cell signal transduction
tyrosine kinase or protein kinase C inhibitors

Table II. Anti-endotoxin antibodies

Antibody	Study	Reference	No. of patients	Outcome
HA-1A human anti-lipid A mAb (Centocor)	phase III	26	543	no overall benefit; improvement in subset with Gram-negative bacteraemia ($P = 0.01$)
	CHESS study	30	2199	no overall benefit; patients without Gram-negative bacteraemia worse had outcome ($P = 0.07$)
	French HA-1A study group 1994	77	600	no benefit in Gram-negative infection; suggestion of deterioration in patients with Gram-positive infection
	meningococcal sepsis			continuing, no data
E5 murine anti-lipid A mAb (Xoma)	phase III	24	468	no overall benefit: possible improvement in Gram-negative infection without shock
	phase III	25	830	no overall benefit, trend to improvement in organ function in shock
	phase III continuing			no data
T88 anti-enterobacterial common antigen (Chiron)	phase III	31	826	no overall benefit

protein from *Neisseria meningitidis.* Administration of this vaccine to rabbits induced cross-reactive antibodies that protected mice from a lethal challenge with a strain of *Pseudomonas aeruginosa.* However, passive immunization with this antiserum did not protect against all strains of *P. aeruginosa* and, *in vitro,* the same serum did not bind to all strains of Gram-negative bacteria. Thus, the potential role of active immunization with this vaccine awaits clarification.

Inhibition of LBP/CD14

Cellular activation by LPS involves the interaction of LPS–LBP complexes with CD14. Anti-CD14 mAbs inhibit macrophage, neutrophil and endothelial responses to LPS.[10,16,36] Excess recombinant soluble CD14 (sCD14) is protective when given in some animal models of Gram-negative sepsis.[37] However, recent human investigations suggest that sCD14 levels are raised in septic shock and are involved in the pathogenesis of organ damage.[17] Therefore, there is considerable doubt whether sCD14 will prove to be a useful therapeutic compound. It is likely that when the LPS binding domain on CD14 has been fully defined compounds will be developed that specifically inhibit these interactions.

Anti-LBP antibodies inhibit cell responses to low concentrations of LPS *in vitro* and protect mice against lethal challenge with LPS or lipid A.[38] More extensive studies of antagonists of LBP and CD14 are awaited but it is likely that one or more of these therapeutic agents will progress to clinical trials.

LPS neutralizing proteins

A number of LPS neutralizing proteins have been described of which BPI has been most extensively studied and is currently in clinical trials for patients with Gram-negative sepsis.[19] BPI is a 55–60 kDa neutrophil primary granule protein with 45% sequence homology to LBP.[2,39] BPI has a higher affinity for LPS than LBP and will therefore displace LPS from the LPS–LBP complex.[2] In addition, BPI is cytotoxic for many species of Gram-negative bacteria.[19] A recombinant N-terminal fragment of BPI retains the LPS neutralizing capacity and is protective in some Gram-negative models of infection.[40] Recombinant BPI has a short half-life and requires continuous infusion. To solve this problem a chimeric construct of the last 21 amino acids of the N-terminus of BPI fused to the Fc portion of human IgG has been produced. In human volunteers $rBPI_{23}$ abolished the physiological response to endotoxin challenge.[41] Phase II/III clinical studies of BPI_{23} are in progress including a multi-national placebo-controlled trial in meningococcaemia. Fusion chimeras of LBP and BPI have also been constructed which neutralize endotoxin but have a longer circulating half-life than BPI. One of these, consisting of residues 1–199 of LBP with amino acids 201–245 of the C-terminus of BPI, has shown protection against LPS challenge in animals.[42]

A number of other neutrophil-derived LPS binding proteins have been described, including CAP-37,[43] CAP-7 and CAP-18,[44,45] P-15 and defensins.[46,47] Other LPS neutralizing proteins have been derived from horseshoe crabs (*Limulus polyphemus* and *Tachypleus tridenta* -

tus).[48,49] These proteins inhibit LPS responses *in vitro* and an 11.8 kDa protein from *L. polyphemus* (endotoxin neutralizing protein, ENP) has been shown to protect rabbits from *E. coli* sepsis.[49,50] Human studies are in progress. Battafaraono *et al.*[51] have synthesized three 27 amino-acid peptides, based on the known sequences of BPI, LBP and a Limulus protein, that have endotoxin neutralizing activity.

Adsorption of endotoxin into complexes with serum proteins or lipoproteins reduces its toxicity[18] and may provide a degree of natural protection from endotoxaemia by sequestering LPS. LDL, HDL and apoliprotein A-1 inhibit LPS-induced cytokine release from macrophages and are protective in some animal models of sepsis.[18,52] Although Intralipid (Pharmacia & UpJohn, Milton Keynes, UK) inhibited endotoxin-induced TNF-α release in human blood *ex vivo*, Intralipid failed to modify the cytokine response to endotoxin challenge in healthy volunteers.[53]

Polymyxin B is a polycationic antibiotic that binds the lipid A portion of LPS and protects animals from endotoxaemia.[54] Clinical use of polymyxins has been limited by toxicity. A less toxic derivative of polymyxin B, polymyxin B nonapeptide, has been investigated but is not as effective at inhibiting LPS.[55] Polymyxin B has been conjugated with dextran 70 resulting in reduced toxicity whilst retaining antibacterial and anti-LPS activity.[56]

Lipid A analogues

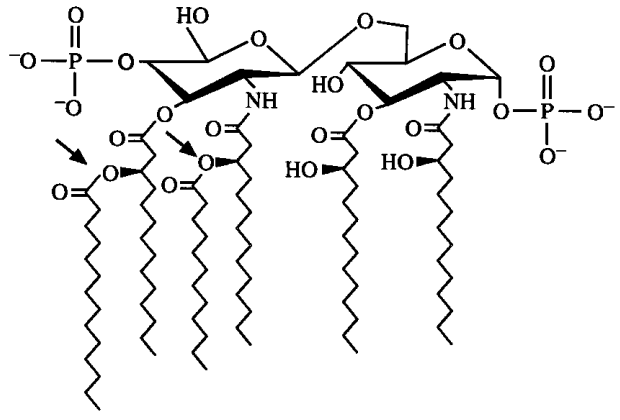
Analogues based on the structure of lipid A display reduced or absent cellular toxicity and a number of compounds are competitive antagonists of lipid A and LPS as listed in Table III.[57] The first compound described with such activity was the monosaccharide lipid A precursor, lipid X, which has limited LPS-inhibitory effects. Highly purified lipid X appears to be less inhibitory than earlier preparations and afforded no protection in a canine model of sepsis.[58] Diglucosamine-based lipid A analogues are more potent LPS antagonists and are very effective *in vitro*.[36,59,60] Approximately a five- to ten-fold excess of the antagonists (w/w) is required to completely block the effects of LPS on macrophages, neutrophils and endothelial cells.[59] The structure of lipid IVa in comparison with lipid A is shown in Figure 6. Lipid A analogues compete with LPS for LBP, depleting the serum of bioavailable LBP.[61] Lipid A analogues inhibit CD14-mediated activation of cells by LPS but also block the CD14-independent LPS binding to macrophages and neutrophils, presumably at the 'unidentified' LPS receptor site.[12,62,63]

Difficulties in purifying sufficient quantities of pure lipid for use in manufacturing processes have hampered the progress of clinical studies. More recently Esai (Andover, MA, USA) have developed a synthetic lipid A analogue, E5331, based on the proposed structure of *Rhodobacter capsulatus* LPS. E5331 is the most potent LPS antagonist yet described and has been shown to block endotoxin binding to cells, to inhibit LPS-induced TNF-α release and to protect mice from *E. coli* challenge. E5331 inhibited endotoxin-induced cytokine release in human volunteers in response to low dose endotoxin infusion and phase I/II studies are in progress.[64]

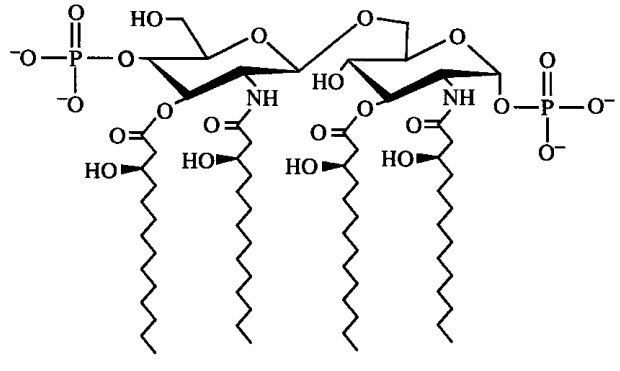
Monophosphoryl lipid A (MPL) is not an LPS antagonist but is less toxic than unmodified LPS and is capable of inducing tolerance to subsequent exposure to LPS.[66,67] It also has adjuvant properties. Thus MPL may have the unique ability to blunt the more deleterious effects of endotoxin whilst limiting the immunosuppression that accompanies sepsis, recently termed the compensatory anti-inflammatory response syndrome (CARS).[68] Pretreatment of animals with MPL reduces the mortality

Table III. Lipid A analogues

Compound	Origin	Activity	References
Lipid X	precursor of *E. coli* lipid A purified and synthetic compounds	non-toxic, weak adjuvant activity, weak LPS antagonist	78
Lipid IVa (lipid Ia, LA-14-PP)	precursor of *E. coli* lipid A purified and synthetic compounds	non-toxic, competitive LPS and lipid A antagonist; LPS-like activity in mice	60, 61
De-acylated LPS	ReLPS deacylated by a neutrophil enzyme, acyoxyacylhydrolase	non-toxic, competitive LPS/lipid A antagonist	20
Rhodobacter sphaeroides lipid A (RSLA)	purified from this photosynthetic bacterium	non-toxic, competitive LPS/lipid A antagonist. LPS-like activity in rabbits;	36, 59
E5331	synthetic compound based on the structure of *R. capsulatus*	potent LPS and lipid A antagonist	64
DT-5461	synthetic lipid A analogue	potent LPS and lipid A antagonist	65
Monophosphoryl lipid A	dephosphorylated lipid A or synthetic preparations	reduced toxicity, minimal antagonist effects, retains adjuvant and endotoxin tolerance-inducing properties of LPS	66, 67



Lipid A



Lipid IVa

Figure 6. Comparison of lipid A and lipid IVa. The top panel shows the structure of Salmonella lipid A. There is a diglucosamine backbone phosphorylated at the 1 and 4′ positions and decorated with 6- or 7-acyl side chains. Removal of the 2 ester-linked fatty acids (at the sites shown by the arrows) produces lipid IVa (lipid Ia, LA-14-PP). This change is sufficient to convert the molecule from a powerful toxin into a competitive LPS antagonist. A neutrophil enzyme, acyloxyacylhydrolase, can catalyse this reaction *in vivo*, producing a non-toxic deacylated LPS.

of subsequent bacterial challenge.[69] In humans MPL attenuates the response to endotoxin in healthy volunteers[66] and shows promise as a prophylactic agent for patients at high risk of developing Gram-negative sepsis.[70]

Direct removal of circulating endotoxin

Endotoxin and cytokines, can be removed from the circulation by plasmaphoresis or filtration. In animal models this may abrogate the response to infection and there have been a number of reports of this type of therapy in human sepsis.[71] At present there are no randomized trial data to support routine use of plasma filtration in sepsis. Extracorporeal removal of endotoxin from plasma by absorption to polymyxin B has been used in animal models.[72] In an open study of 16 septic patients, Aoki *et al.*[73] used a polymyxin B-immobilized filter to remove endotoxin from the circulation. In this study there was a fall in detectable endotoxin in the circulation and qualitative improvements in the patients' haemodynamic status. Further studies to confirm this are in progress.[73,74]

Signal transduction inhibitors

Although not true LPS antagonists, agents that inhibit the second messenger pathways activated by endotoxin would be expected to limit the physiological response to LPS. Inhibitors of protein kinase C (e.g. H-7) and tyrosine kinases (e.g. genistein) are in development and reduce murine cell responses to LPS.[75] A specific inhibitor of phosphatidic acid species, lisofylline (CT-1501R), inhibits the cell activation by LPS, IL-1 and TNF-α in human blood *ex vivo* and protects mice from endotoxin challenge.[76] Whether these compounds will be safe and effective in human disease remains to be proven.

Potential therapeutic applications

If the compounds described above are effective, where will they be used? In almost all animal models anti-LPS therapy is only effective if given before or simultaneously with the LPS challenge. Except for prophylactic use this will not be possible in human disease. Clinical sepsis is a very different entity from animal models and it is likely that continuing activation of the immune system by endotoxin is important at various stages of sepsis in man. Despite this, it is still improbable that anti-LPS treatment alone would have much impact on patients with established shock and organ failure. Therefore the most likely situations in which these agents might be useful are for patients with early Gram-negative sepsis or prophylaxis in high-risk patients, for example those undergoing major abdominal surgery. One problem that needs to be overcome is how to identify patients with Gram-negative infection rapidly, to avoid inappropriately treating patients with sepsis due to other causes. Combining anti-LPS treatment with therapy against other inflammatory mediators is attractive and in the limited experimental studies performed to date appears to be promising.[33] Finally, if antibiotic-induced endotoxin release is proven to be an important factor in the pathological consequences of Gram-negative infection then combining antibiotics with LPS antagonists may have a role in the treatment of patients with, or at risk of, Gram-negative sepsis.

Conclusion

An extensive research effort over several decades has begun to elucidate the basis of the cellular response to LPS

and the role that this plays in the pathogenesis of Gram-negative sepsis. With this has come the development of highly specific therapies aimed at neutralizing the biological effects of LPS. Initial experience with anti-LPS antibodies has been disappointing but these were not efficient LPS antagonists and the results of clinical trials with newer agents are eagerly awaited. Effective anti-LPS drugs are almost a clinical reality. The challenge for the future will be the design of suitable clinical trials to demonstrate efficacy and to define the range of conditions and patients for whom therapy is likely to be beneficial.

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