Introduction

A number of small molecules, commonly described as autacoids, are extremely important mediators of inflammation. Among the autacoids are a group of lipid mediators called eicosanoids, which are derivatives of the 20-carbon polyunsaturated fatty acid (PUFA), arachidonic acid. Platelet activating factor (PAF), another important lipid mediator of inflammation, is \(1\)-O-alkyl-2(\(R\))-acetyl-glycero-3-phosphorylcholine, its ether-linked alkyl group being either a 16- or 18-carbon straight-chain aliphatic (full saturated) residue. Two other important autacoids involved in inflammatory processes are small peptides: bradykinin is a nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), whereas kallidin is a decapeptide, Lys-bradykinin.

Eicosanoid biosynthetic pathways (Figure 1)

Biologically active subclasses within the eicosanoid group include the prostaglandins, thromboxanes, leukotrienes, lipoxins, hydroxy-eicosatetraenoic acids (HETEs) and epoxides. Eicosanoids are synthesized as needed by appropriately stimulated cells and are not stored preformed.

A arachidonic acid, the precursor of the eicosanoids, is derived from certain long-chain PUFA's (particularly linoleic acid), which are essential nutritional components. The first, rate-limiting, step in the biosynthesis of the eicosanoids is the release of arachidonic acid from phospholipid in cell membranes. This reaction can occur via three different pathways.\(^1\) The phospholipases A\(_2\) catalyse the hydrolysis of the sn-2 ester linkage of phosphoglycerides to yield arachidonic acid plus a 1-acyl-phosphoglyceride. Phospholipase C hydrolyses the glyceryl-phosphate bond of the phosphoglyceride molecule, releasing a phosphorylated base (choline, serine, ethanolamine or inositol) and diacylglycerol. The latter moiety may be a substrate for diglyceride lipase and then monoglyceride lipase to release arachidonate. Phospholipase D converts phosphatidylethanolamine (or phosphatidylcholine) to phosphatidic acid plus the free base.

Various autacoids, including the eicosanoids, platelet activating factor (PAF) and bradykinin, have been implicated in the pathogenesis of sepsis and septic shock. The precise role of these compounds as mediators of the diffuse inflammatory state characteristic of sepsis remains to be determined, but, in animal models, beneficial effects have been observed as a result of treatment with various inhibitors of eicosanoid biosynthesis or antagonists of PAF or bradykinin receptors. To date, however, it has been impossible to translate these encouraging results from animal models into convincingly positive results in the clinical setting.

**Figure 1.** Simplified scheme of arachidonic acid metabolism leading to the formation of eicosanoids. PLA\(_2\) and PLC are phospholipase A\(_2\) and phospholipase C, respectively. COX-1 and COX-2 are, respectively, the constitutive and inducible isoforms of cyclo-oxygenase. TXA\(_2\) is thromboxane A\(_2\). PGI\(_2\) is prostacyclin. LTC\(_4\), LTD\(_4\) and LTE\(_4\) are the leukotrienes C\(_4\), D\(_4\) and E\(_4\), respectively.
Phosphatidic acid is a potential substrate for diglyceride and monoglyceride lipases, releasing arachidonic acid.

The phospholipases A₂ belong to three main classes: secretory, pancreatic (type I); secretory, non-pancreatic (type II); and cytosolic. Intracellular cytosolic phospholipases A₂ are associated with the plasma membrane of cells, whereas secretory phospholipases A₂ are stored within organelles and can be discharged from cells by exocytosis of secretory granules or lysosomes. Large amounts of extracellular phospholipase A₂ (type I) are present in pancreatic secretions. A nother antigenically distinct phospholipase A₂ can be found in synovial fluid of patients with rheumatoid arthritis or plasma, lymph and peritoneal exudate fluid from animals or human volunteers challenged with lipopolysaccharide (LPS).

A rachidonic acid can be converted into biologically active metabolites through several pathways. The cyclooxygenase pathway leads to the formation of prostanoids and thromboxanes. The various lipoxygenase pathways result in the formation of leukotrienes, HETEs and lipoxins. An enzyme called prostaglandin endoperoxide H synthase (PGHS) or cyclooxygenase (COX) catalyses the formation of prostaglandin H₂, a committed step in the formation of prostaglandins and thromboxanes. The metabolic fate of prostaglandin H₂ depends on cell type; for example, endothelial cells preferentially metabolize it to prostacyclin (prostaglandin I₂), whereas platelets produce thromboxane A₂.

The two isomers of PGH are referred to as PGHS-1 and PGHS-2 (or COX-1 and COX-2, respectively). PGHS-1 is constitutively expressed in most tissues, but PGHS-2 expression is induced in endothelial cells, fibroblasts and macrophages by various pro-inflammatory substances, including LPS, tumour necrosis factor (TNF)-α and interleukin 1 (IL-1). A nti-inflammatory steroids inhibit the induction of PGHS-2. Until recently, PGHS-1 was thought to be the target of various non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and meclofenamate. Now however, accumulating data suggest that NSAIDs diminish inflammation primarily by inhibiting PGHS-2.

The leukotrienes, HETEs and lipoxins result from the action of lipoxygenases on arachidonic acid. The leukotrienes are products of the 5-lipoxygenase (5-LO) pathway. The partial oxidation of arachidonate catalysed by 5-LO depends in human myeloid cells on the presence of 5-lipoxygenase activating protein (FLAP), a unique membrane-associated protein. The first intermediate in the 5-LO pathway is an unstable epoxide, leukotriene A₄, which can be hydrolysed to leukotriene B₄ or converted by a specific glutathione transferase to leukotriene C₄. Sequential cleavage of peptide residues from leukotriene C₄ results in the formation of leukotrienes D₄ and E₄. Leukotrienes C₄, D₄ and E₄ are collectively referred to as peptidoleukotrienes or cysteinyl leukotrienes, and represent the slow-reacting substance of anaphylaxis (SR-S-A). Metabolism of arachidonic via the cyclooxygenase pathway results in the production of compounds containing two double bonds, which are called bisenoic prostanoids and are designated by a subscript 2 (e.g., prostaglandin E₂). When cyclooxygenase acts on dihomo-γ-linolenic acid rather than arachidonic acid, the resulting compounds contain only one double bond, and hence are referred to as monoenoic prostanoids and are designated by a subscript 1 (e.g., prostaglandin E₁). Trienoic prostanoids (e.g., prostaglandin E₃) are derived from eicosapentaenoic acid (EPA). Products derived from arachidonate via the 5-LO pathway are designated by a subscript 4 (e.g., leukotriene B₄), whereas products resulting from the action of 5-LO on EPA are designated by a subscript 5 (e.g., leukotriene B₅). The 1-series and 2-series prostanoids manifest similar biological activity. In contrast, the 3-series prostanoids and the 5-series leukotrienes derived from EPA are much less active than are the 2-series compounds derived from arachidonate.

PAF biosynthesis and metabolism

PAF is released by various cells, including platelets, monocytes, macrophages, neutrophils and endothelial cells. PAF biosynthesis and metabolism

Synthesis of the ether linkage in PAF is catalysed by alkylidihydroxyacetonephosphate synthase. PAF can be generated by two different pathways: (i) it is synthesized de novo in a three-step sequence of reactions from an ether lipid intermediate, and (ii) in the remodelling pathway, it is formed in a two-step process from pre-existing membrane-associated ether-linked phospholipids. The remodelling pathway (which also generates arachidonate) is thought to be the most important source of PAF in inflammatory states. PAF is metabolized by PAF acetylhydrolase (PAF-AH) to form a biologically inactive lipid, lyso-PAF. In 1994, guinea pig PAF-AH was purified and characterized by K arasawa et al. More recently, human recombinant human PAF-AH has been produced by scientists at ICOS Corporation (Bothwell, WA, USA).

Kinins

The kinins (i.e., kallidin and bradykinin) are produced by the action of specific proteolytic enzymes acting on pre-formed proteins. The enzyme plasma kallikrein acts on high molecular weight kininogen (HMWK) to form bradykinin (Figure 2). The enzyme tissue kallikrein acts on low molecular weight kininogen (LMWK) to form kallidin. Bradykinin is destroyed by either angiotensin converting enzyme (ACE) or carboxypeptidase N (CPN). A CE, which also plays a key biological role in the conversion of angiotensin I to angiotensin II, is present in endothelium, especially the pulmonary microvasculature, and inactivates more than 99% of plasma bradykinin during a single passage through the lungs.
The kinin pathways are closely involved with other key proteolytic cascades involved in tissue injury and inflammation, including the intrinsic coagulation and complement systems. HMWK circulates as a trimolecular complex with coagulation factor XI and an inactive form of kallikrein, pre-kallikrein. Factor XII (Hageman factor), the initiator of the intrinsic coagulation cascade, binds by electrostatic interaction to negatively charged substances, such as the highly sulphated polysaccharides in basement membranes, which are exposed when vascular tissue is damaged. The adherence of factor XII changes the shape of the molecule, rendering it enzymatically active. In addition to activating factor XI (and thereby initiating coagulation), activated factor XII (XIIa) converts pre-kallikrein to the enzymatically active protein kallikrein, resulting in formation of bradykinin from HMWK. The first step in the classical pathway of complement activation involves activation of C-1 esterase (C1r and C1s), which activates C4 of the complement pathway, and also liberates bradykinin from kininogens. C1-inhibitor, a plasma protein of the serine protease inhibitor superfamily (the serpins), is the only known circulating inhibitor of C1r and C1s and also is a major inhibitor of activated factor XII and kallikrein.

Cellular sources and biological actions of the eicosanoids, PAF and kinins

A full account of the myriad biological actions of the eicosanoids, PAF and kinins is beyond the scope of this essay, but a brief review is necessary to introduce the role of these autacoids in sepsis. Thromboxane A2 is synthesized primarily by platelets, neutrophils, macrophages and monocytes, and is a potent promoter of platelet aggregation, vasoconstriction, bronchoconstriction and leucocyte adhesion. After release, thromboxane A2 is rapidly hydrolysed to an inactive metabolite, thromboxane B2. Thromboxane B2 plasma concentrations have been used extensively in clinical or experimental studies to estimate changes in thromboxane A2 production, but total body synthesis of thromboxane A2 is better estimated in terms of its major urinary metabolite, 2,3-dinor-thromboxane B2. Many biological actions of prostacyclin and the E-series prostaglandins are similar. Prostacyclin, the main endothelial prostaglandin produced, tends to oppose the effects of thromboxane A2. Thus, prostacyclin is a potent platelet anti-agregant and endothelium-independent vasodilator. Although in vivo production of prostacyclin is commonly measured in terms of its stable hydrolysis product, 6-keto-prostaglandin F1α, concentrations of a major urinary metabolite (2,3-dinor-6-keto-prostaglandin F1α) more reliably indicate total body synthesis of this prostanooid.

The vasodilators, prostacyclin and the E-series prostaglandins increase delivery of humoral and cellular mediators to sites of inflammation and thus participate in the inflammatory response. Nevertheless, their predominant actions are anti-inflammatory, since they down-regulate various immune responses, including production of cytokines by T-cells, the activation and proliferation of B-cells, the expression of MHC class I on macrophages and macrophage phagocytosis. These prostanooids also inhibit a number of neutrophil functions, including enzyme release, chemotaxis and oxygen radical production.

Pro-inflammatory cytokines, including IL-1, TNF-α and IL-6, trigger the release of prostaglandins, leukotrienes and PAF from various cell types. These cytokines increase eicosanoid production by several means, including activation of phospholipase A2, up-regulation of PGHS-2 expression and post-translational stabilization of PGHS-2 mRNA. In a form of negative feedback, E-series prostaglandins down-regulate the release of TNF-α from various inflammatory cells. This regulation, which occurs at the gene level, depends on release of the counter-regulatory cytokine, IL-10. Interruption of this feedback by NSAIDs has been shown to increase release of cytokines (TNF-α, IL-6 or IL-8) by stimulated mononuclear cells in vitro and in animals challenged with LPS or human volunteers infused with small doses of LPS.

Polymorphonuclear neutrophils (PMNs), monocytes and macrophages are the major cellular sources of leukotriene B4. Leukotriene B4 up-regulates a number of functions of PMNs, including aggregation, chemotaxis, generation of reactive oxygen intermediates, degranulation and adhesion to vascular endothelium. There is also some evidence that leukotriene B4 enhances microvascular permeability through direct, PMN-independent action on endothelial cells. In contrast to the E-series prostaglandins, leukotriene B4 up-regulates components of the immune response, such as the production of IL-6 by human monocytes, IL-2 receptor expression on human lymphocytes and monocytes and TNF-α release by IL-2-stimulated mononuclear cells.

Eosinophils and monocytes are major sources of the cysteiny1-leukotrienes, whose important actions include

**Figure 2.** Simplified scheme showing the inter-relationships between the coagulation cascade and kallikrein–kinin cascade. HMWK is high molecular weight kininogen.
bronchoconstriction, increased microvascular permeability, and arteriolar constriction.\textsuperscript{62–66} The cysteinyl-leukotrienes also depress myocardium by causing coronary vasoconstriction and by a direct inotropic effect on cardiac muscle.\textsuperscript{67–69}

PAF promotes adhesion of neutrophils to microvascular endothelium increasing permeability and causing arteriolar constriction.\textsuperscript{70,71} When injected into experimental animals, PAF causes systemic arterial hypotension, pulmonary hypertension, diminished cardiac output, increased microvascular permeability and bronchoconstriction.\textsuperscript{72–74} Although PAF has direct effects on many cell types, such as platelets\textsuperscript{75} and myocardial cells,\textsuperscript{76} many PAF-induced phenomena are caused by the release of secondary mediators, including thromboxane A\textsubscript{2}, leukotriene B\textsubscript{4}, and the cysteinyl-leukotrienes.\textsuperscript{76–79}

The pro-inflammatory effects of bradykinin include vasodilation and increased microvascular permeability. The effects of kinins are mediated through at least two classes of receptors. The recently cloned B\textsubscript{1} receptor is not normally expressed, but can be induced by pro-inflammatory stimuli, including LPS.\textsuperscript{81,82} B\textsubscript{2} receptors bind to bradykinin(1-8)desArg\textsuperscript{21}, the product of action of carboxypeptidase N on bradykinin. The B\textsubscript{2} receptor, which has been sequenced and cloned,\textsuperscript{83,84} binds bradykinin and is expressed constitutively. Many of the pro-inflammatory effects of bradykinin are mediated by the secondary release of other mediators, notably nitric oxide (NO), prostanoids and PAF.\textsuperscript{21}

The role of eicosanoids, PAF and kinins in the pathogenesis of sepsis

Studies in both patients and experimental animals have implicated the eicosanoids (particularly thromboxane A\textsubscript{2}, leukotriene B\textsubscript{4}, and the cysteinyl-leukotrienes), PAF and bradykinin in the pathogenesis of endotoxaemic shock, septic shock, multiple organ system failure and the adult respiratory distress syndrome (ARDS). Elevated circulating concentrations of the following lipid mediators (or their degradation products) have been demonstrated in models of endotoxaemia, sepsis and/or ARDS: prostaglandin E\textsubscript{2}, prostaglandin F\textsubscript{2\alpha}, prostacyclin, thromboxane A\textsubscript{2}, leukotriene B\textsubscript{4}, cysteinyl-leukotrienes\textsuperscript{99–102} and PAF.\textsuperscript{95,103,104} In many experimental studies of sepsis- or endotoxin-induced acute lung injury, raised concentrations of eicosanoids (or their degradation products) have been measured in bronchoalveolar lavage (BAL) fluid or lymph.\textsuperscript{91,92,98} Because bradykinin is rapidly degraded, measurements of its circulating concentrations are not informative. Instead, involvement of bradykinin in experimental models of sepsis has been assessed by documenting consumption of its precursor proteins.\textsuperscript{105–107}

A number of studies have assessed the release of eicosanoids, PAF and/or bradykinin in patients with sepsis and/or ARDS.\textsuperscript{108} As in experimental animals, raised concentrations of 6-keto-prostaglandin F\textsubscript{1\alpha}\textsuperscript{108} and thromboxane B\textsubscript{2}\textsuperscript{108} have been measured in plasma, BAL fluid and urine of patients with acute lung injury or sepsis. Recently, Bernard et al.\textsuperscript{119} showed that the stable dinor urinary metabolites of prostacyclin and thromboxane A\textsubscript{2} are significantly increased in septic patients. The plasma half-life of PAF is inversely related to circulating PAF-AH activity, and tends to be prolonged in patients who die of sepsis.\textsuperscript{120}

Pre-kallikrein and/or HMWK are consumed in patients with sepsis.\textsuperscript{121–124} Consumption of functional pre-kallikrein also occurs in human volunteers challenged with a small dose of LPS.\textsuperscript{125} In some of these studies, circulating levels of HMWK and/or pre-kallikrein are often lower in patients with hypotension than in those with uncomplicated sepsis,\textsuperscript{121,124,126} supporting the notion that activation of factor XII-dependent pathways and increased bradykinin production contribute to septic shock. In addition, Nuijens and colleagues have shown that sepsis is associated with proteolytic cleavage of C1-inhibitor to an inactive form, (iC1-Inh), and that high circulating levels of iC1-Inh may predict death.\textsuperscript{72}

Inhibitors and receptor antagonists in experimental models and patients with sepsis

Cyclooxygenase inhibitors and thromboxane receptor antagonists

In 1962, Northover & Subramanian showed that treatment of endotoxic dogs with aspirin, a prototypical inhibitor of prostanoid biosynthesis, improved systemic haemodynamics.\textsuperscript{127} Since this early report, much experimental evidence has accrued from models of sepsis and ARDS of the effects of inhibiting key enzymes (cyclooxygenase, 5-LO, thromboxane synthase) or blocking key receptors (those for thromboxane and leukotrienes B\textsubscript{4} and D\textsubscript{4}) involved in the synthesis or actions of eicosanoids. With very few exceptions,\textsuperscript{128,129} pharmacological inhibition of cyclooxygenase has been shown to improve systemic haemodynamics, preserve pulmonary function, limit oxidant-mediated tissue damage and prevent death in animals challenged with endotoxin or viable bacteria or animals with experimentally induced peritonitis.\textsuperscript{87,88,130–141} Infusion of prostacyclin\textsuperscript{142} or prostaglandin E\textsubscript{143} has been found to protect endotoxaemic animals and so it seems probable that cyclooxygenase inhibition is beneficial because of decreased production of thromboxane A\textsubscript{2}. This is supported by studies showing that inhibitors of thromboxane synthase or thromboxane A\textsubscript{2}-receptor antagonists also are beneficial in experimental sepsis, endotoxaemia or ARDS.\textsuperscript{95,144–150} The most notable advantage of blocking
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Thromboxane A₂ synthase or thromboxane A₂ receptors is reduced pulmonary arterial hypertension, but there are also improvements in visceral perfusion, diminished gastrointestinal mucosal injury and reduced mortality. The relative importance of the anti-inflammatory prostaglandins (i.e., prostaglandin E₂ and prostacyclin) versus thromboxane A₂ in acute endotoxaemia was highlighted in an elegant study by Conary et al. They investigated transfected rabbits with a recombinant PGHS gene. When challenged with LPS, the transfected rabbits produced more prostaglandin E₂ and prostacyclin and less thromboxane A₂ than control animals. LPS-induced pulmonary injury also improved in the animals transfected with the PGHS gene, supporting the views that thromboxane A₂ is an important mediator of acute LPS-induced lung injury and that thromboxane A₂-induced damage can be partially controlled by prostaglandin E₂ and prostacyclin.

Two small clinical trials of a thromboxane A₂ synthase inhibitor (dazoxiben) in A R D S both gave disappointing results. The failure of dazoxiben to improve outcome might have occurred because the therapy was started too late. In human volunteers challenged with a low dose of LPS, treatment with ibuprofen prevented fever, but failed to limit cardiovascular damage induced by endotoxin. Ibuprofen as an adjuvant treatment of sepsis has been evaluated in two small prospective clinical trials. Beneficial effects (e.g., reduction in heart rate and body temperature, and a trend towards more rapid reversal of shock) were observed in one of these pilot studies, and adverse effects, such as deterioration in renal function, were not seen.

Extensive preclinical data suggesting benefit and pilot studies in patients recently prompted a large, multicentre trial of ibuprofen treatment of human sepsis. This study enrolled 455 patients with sepsis. Using a balanced randomization scheme, approximately half the patients were treated with intravenous ibuprofen (10 mg/kg to a maximum dose of 800 mg) every 6 h for 2 days. Control patients received placebo. There was no difference in survival between the ibuprofen- and placebo-treated groups, although treatment with ibuprofen significantly decreased blood lactate concentrations and systemic oxygen consumption. The largely negative results in this trial may be attributed to insufficient sample size, inadequate duration of treatment, and heterogeneity of the population studied.

5-L O inhibitors and leukotriene receptor antagonists

Inconsistent results from various studies have failed to clarify the importance of 5-L O products as sepsis mediators. In mice and rats, blocking production or actions of leukotriene D₄ markedly improves survival and/or haemodynamics in various models of endotoxaemia or sepsis. In these models of LPS-induced shock, the cysteinyI-leukotrienes are important in promoting splanchnic vasoconstriction and ischaemic liver damage. Leukotriene D₄ also seems to be intimately linked to TNF-α release in murine endotoxaemia. Hence, products of the 5-L O pathway are probably important in mediating endotoxic effects in murine models. However, Chen et al. obtained mice with disruption of the 5-L O gene by means of the techniques of homologous recombination, but failed to establish that genetically eliminating leukotriene production improved survival in mice challenged with LPS. Furthermore, little or no beneficial effect of blocking 5-L O activity or blocking leukotriene D₄ receptors can be shown in larger animals such as sheep and pigs. In sheep, treatment with L-651,392, a selective 5-L O inhibitor, reduced LPS-induced pulmonary hypertension and arterial hypoxaemia, possibly by blocking prostaglandin release triggered by a product or products of the 5-L O pathway. In a very similar ovine model, however, another 5-L O inhibitor (SC-45662) attenuated early changes in lung function and pulmonary arterial pressure after LPS challenge, but had little effect on the development of pulmonary capillary leakage 4-5 h after the infusion of endotoxin. A putative cysteinyI-leukotriene receptor blocker, has been shown to prevent LPS-induced derangements in pulmonary haemodynamics and lung function in an ovine endotoxaemia model, but its selectivity is uncertain. In pigs, O Lison et al. found that treatment with LY 171883, a selective leukotriene C₄/D₄ receptor antagonist, had minimal effect on the response to continuous infusion of a low dose of endotoxin. Using a septic feline model, Schutzer and colleagues found that treatment with ICI 198,615 reduced pulmonary capillary hyperpermeability. In our porcine endotoxaemia model, we have observed modest improvements (e.g., better mesenteric perfusion, attenuated pulmonary hypertension) with two different cysteinyI-leukotriene receptor antagonists (LY 171883 and LY 203647). Using a porcine bacteraemia model, Zellner et al. found that a selective leukotriene D₄ receptor antagonist (SK F 104353) transiently improved renal blood flow and arterial oxygen tension. In rats, administration of leukotriene B₄ receptor antagonists (LY 233978 or LY 255283) attenuates LPS-induced hypotension and haemococoncentration. We previously showed that treatment with LY 255283 substantially protects against pulmonary hypertension, pulmonary oedema and arterial hypoxaemia in endotoxaemic pigs. However more recently, we showed that, in addition to being an effective leukotriene B₄ receptor antagonist, LY 255283 can also act as a thromboxane A₂ receptor antagonist. Some protection was conferred by the more specific leukotriene B₄ receptor antagonist (LY 306669) on LPS-induced lung injury in pigs in our experiments, but the effects were not as favourable as with LY 255283, suggesting that dual blockade of thromboxane A₂ and leukotriene B₄ is most effective. Indeed, in a number of studies, dual blockade of the cyclo-oxygenase and
PAF antagonists

In mice, rats, rabbits and guinea pigs challenged with LPS or bacteria, drug blockade of PAF reduces hypotension and improves survival. These effects have been demonstrated even when the drug was administered after the endotoxin challenge. In larger animals (baboons, sheep, pigs and dogs), variable results have been obtained when PAF receptor antagonists have been administered before or after an endotoxic or bacterial challenge. For example, in dogs challenged with LPS, treatment with BN 52021, a well-studied PAF antagonist, fails to prevent endotoxin-induced arterial hypotension or metabolic acidosis. Nevertheless, treatment with the drug significantly improves survival. In a primate model of lethal Gram-negative bacteraemia, treatment with a PAF antagonist (Ro 24-4736) suppresses cytokine release, but has no effect on either haemodynamics or long-term survival. In pigs infused with Pseudomonas aeruginosa, a PAF antagonist (SRI-63-675) provides transient protection against hypoxaemia, but has no effect on arterial hypotension or the delayed phase of pulmonary arterial hypotension. In pigs and sheep infused with endotoxin, various PAF antagonists (e.g., SRI 63-675, WEB 2086) provide only temporary and/or partial protection against some of the cardiovascular and pulmonary derangements induced by LPS.

In a number of species, release of PAF seems to be an early event in the cascade of lipid and peptide mediators, which is initiated by the injection of LPS. Thus, in both rats and non-human primates, drug blockade of PAF receptors inhibits the LPS-induced release of thromboxane A₂, TNF-α and/or IL-6. Moreover, PAF has been shown to act synergistically with other mediators. For example, in rats pre-treated with a small (haemodynamically insignificant) 'priming' dose of PAF, extremely small doses of LPS (0.1 μg/kg or approximately 1/1000 of the standard dose in this species) cause lung injury and shock. The priming effect of PAF is mediated by an exaggerated release of TNF-α in response to the small LPS challenge dose.

In human volunteers challenged with a low dose of LPS, pretreatment with a potent and durable PAF receptor antagonist (Ro 24-4736) blunts endotoxin-induced elevation of plasma cortisol concentrations, but fails to impair the release of key cytokines (TNF-α and IL-6). In a recently reported clinical trial of a PAF antagonist (BN 52021) in patients with severe sepsis, mortality was 51% in the placebo group and 42% in the treated group (P = 0.17). In a retrospectively defined subset of 120 patients with documented Gram-negative sepsis, treatment with the PAF receptor blocker significantly reduced mortality from 57% in the placebo group to 33% (P = 0.03).

Bradykinin receptor antagonists

The synthesis and characterization of potent and specific bradykinin receptor antagonists is a relatively recent development. In general, these compounds represent selective modifications of the basic structure of bradykinin. Many such antagonists include in their structure novel amino acids, such as β-(2-thienyl)-alanine, tetrahydrossoquinoline-2-carboxylic acid and cyclopentylglycine. Most bradykinin receptor antagonists are active only against B₂ receptors, although one class of compounds, typified by CP 0127, comprises bifunctional molecules with activity against both B₁ and B₂ receptors.

Conflicting results have been obtained in studies of the therapeutic efficacy of various such antagonists in experimental models of sepsis or endotoxaemia. Whalley et al. showed that the bifunctional bradykinin antagonist, CP 0127, blocks the development of hypotension and improves survival in rats and rabbits challenged with LPS. Ueno et al. showed that HOE 140, a potent and selective B₂ antagonist, blocks hypotension in the first 15 min after the injection of LPS in rats, but does not influence the late phase of hypotension, which occurs 70-80 min after injection of endotoxin in this model. Paya & Stoclet reported that HOE 140 partially blocks vasoplegia (manifested as hyporesponsiveness to the pressor effects of norepinephrine) in endotoxic rats. Ridings et al. showed that NPC 17731 improves systemic arterial hypotension and oxygenation in a porcine model of shock and acute lung injury induced by the intravenous infusion of viable P. aeruginosa. Wilson et al. reported that another bradykinin receptor antagonist, NPC 567, reverses hypotension, reduces the release of other mediators, and improves survival in endotoxin-challenged rats.

In contrast to these generally encouraging results, Féletou et al. showed that S16118, a potent and long-acting B₂ antagonist, controls several forms of inflammation (e.g., oedema due to caerulein-induced pancreatitis in rats), but has no effect on LPS-induced hypotension in rabbits, LPS-induced mortality in mice or mortality induced by caecal ligation and puncture in mice. Earlier, Berg et al. showed that two different bradykinin antagonists failed to block LPS-induced hypotension in rats and Otterbein et al. showed that the bradykinin antagonist, NPC 17761, failed to improve survival in endotoxaemic rats.

The bifunctional bradykinin-receptor antagonist, CP 0127 (B-Bradycor; Cortech), was evaluated in two clinical trials in humans with sepsis. The first trial evaluated a 3-day infusion of CP 0127 at three different dosages in comparison with placebo in 500 patients with the systemic inflammatory response syndrome (data from press releases from Cortech, which is no longer trading). Mortality at 28 days was not reduced, although the compound showed no
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evidence of toxicity. In a second trial, 250 patients were randomized to either placebo or a 7 day infusion of CP 0127. A gain, there was no improvement in survival.

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References


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