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EDITORIAL

Pentoxifylline and tumour necrosis factor-induced

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Acute Gram-negative bacterial infections evoke characteristic pathophysiological responses, including changes in white blood cell counts, fever, haemodynamic disorders, and various coagulatory disturbances, which may result in respiratory distress syndrome, multiorgan failure and irreversible shock. It is generally accepted that endotoxins, the lipopolysaccharides (LPS) of Gram-negative bacteria, are the agents causing these pathophysiological events. Endotoxins stimulate macrophages to elaborate various biologically active mediators, which can induce phenomena typical of endotoxaemia and bacterial sepsis.

Tumour necrosis factor-alpha (TNF) has been identified as an important mediator of lethal shock and cachexia in animals [1]. Passive immunization against TNF attenuates the lethal effect of endotoxin in mice and protects against septic shock during Gram-negative bacteraemic in primates [2]. In addition, TNF increases the adherence of polymorphonuclear leucocytes to endothelial cells. Increased adherence of activated granulocytes in the microvasculature *in vivo* is one of the major causes of pulmonary vascular injury in adult respiratory distress syndrome (ARDS), which is one of the most severe consequences of Gram-negative sepsis in man [3].

Intrapulmonary activation of leucocytes and release of cellular mediators and enzymes in ARDS is reflected by high bronchoalveolar levels of TNF and its soluble inhibitors (sTNF-Rc I + II) as well as high levels of granulocyte elastase in the bronchoalveolar fluid in the early stages of severe ARDS [4]. TNF plasma levels measured in parallel in patients developing ARDS after trauma, sepsis or shock were found to be in the normal range, indicating a local release of TNF, possibly by pulmonary macrophages or other cells [4]. This is consistent with the concept that stimulated lung macrophages can produce much more TNF than peripheral blood monocytes [5]. TNF, possibly together with interleukin-1β, may favour the adherence and accumulation of granulocytes in lung capillaries and contribute to transendothelial passage of these cells, protein and fluid. TNF may stimulate granulocyte degranulation, and, thereby, release of elastase, damaging lung capillaries, interstitium and alveolar structures. Furthermore, TNF is one of the most potent inducers of oxygen radicals in neutrophils. A major role of activated neutrophils and neutrophil-derived oxidant production has been demonstrated in animal models of lung injury, including the isolated perfused lung [6]. Lung ischaemia/reperfusion in rabbits results in transient generation of TNF, which is probably responsible for the lung injury following reperfusion [7]. Recently, a direct mediation of TNF in the decrease of surfactant production by human type II pneumocytes has been demonstrated [8].

Although a great number of circulating factors, such as other cytokines, prostaglandins and free radicals, have been implicated in the aetiology of ARDS, it is generally accepted that TNF is at least one of the major pathophysiological factors. Injection of TNF alone into experimental animals can induce all typical signs of endotoxicity, including the development of acute lung injury. Furthermore, immunotherapeutic interventions with either the murine monoclonal antibody OKT3 in transplant recipients [9], or recombinant interleukin-2 in cancer patients, results in an acute cytokine release syndrome, including severe side-effects, such as capillary leakage syndrome and ARDS, which are related to the endogenous TNF formation. These data strongly suggest that the overwhelming production of TNF plays a pivotal role in ARDS. Therefore, drugs interfering with the production of TNF or the adherence and activation of granulocytes may have beneficial effects in septic shock and ARDS.

Pentoxifylline (POF; oxpentifylline, 3,7-dimethyl-1-(5-oxohexyl)-xanthine) and related xanthines are drugs of known haemorrheological activity, and are used clinically for the treatment of patients with various types of vascular insufficiency. Its effects were supposed to be based on its ability to increase erythrocyte flexibility, to reduce blood viscosity and filterability, and to increase capillary flow. Recently, new pharmacological aspects of these established drugs could be demonstrated. Evidence was produced that POF is able to inhibit the synthesis of TNF *in vitro* and *in vivo*. In studies addressing the mechanism by which POF exerts its TNF inhibitory activity, it was found that this pharmaceutical drug reduced, in macrophage cultures *in vitro* the formation of TNF-specific messenger ribonucleic acid (mRNA) [10], and *in vivo* (in mice) the production of endotoxin-induced circulating TNF [11]. It was also found that POF selectively inhibits the formation of TNF, but not interleukin-6 (IL-6), probably by inhibiting phosphodiesterase activity and, thus, causing accumulation of intracellular cyclic adenosine monophosphate (cAMP) [12]. In addition to blocking TNF production, POF also interferes with TNF

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activity. Thus, POF has been shown to induce prostacyclin (PGI_2) synthesis in endothelial cells [13]. It is, therefore, likely that POF counteracts the TNF-mediated adherence of neutrophils to vascular endothelium by inducing the production of PGI_2.

These findings suggest that POF may be beneficial in septic shock and related disorders. *In vivo*, POF gave protection from increased pulmonary vascular permeability and sequestration of neutrophils in the lung in different models of acute lung injury. POF can reduce lung injury from sepsis in guinea-pig [14], and endotoxin-induced neutrophil sequestration and lung injury in the dog [15]. Furthermore, POF reduces injury to isolated lungs perfused with phorbol myristate acetate (PMA)-activated human neutrophils in the rat [6], and this is the first report of an effective agent that does not appear to be an oxygen scavenger. Moreover, in pigs with induced faecal peritonitis, the drug improved haemodynamic variables as well as pulmonary compliance, and reduced the number of pulmonary neutrophils and lymphocytes [16]. Consequently, as a general outcome, POF was found to improve survival in different models of haemorrhagic [17], and endotoxic shock [18].

This issue of the Journal contains an article by NAURECKAS *et al*. [19] reporting that POF does not protect against hyperoxic lung injury in rats. This paper is of great interest, because it demonstrates that the protective effect of POF depends on the cause of lung injury. It is not surprising that POF has little effect, since hyperoxic lung damage is mediated mainly by oxygen free radicals produced locally by the hyperoxia, in contrast to the above mentioned LPS and TNF-mediated forms of acute lung injury, which can be counteracted by POF. The lack of protective effect of POF in hyperoxic lung injury possibly suggests that TNF and neutrophils are not major contributors in hyperoxia. The extensive production of free radicals in hyperoxia-induced lung injury argues in favour of using free radical scavengers in this particular clinical situation.

Based on the promising findings obtained in experimental animals, we sought to determine whether POF could also inhibit TNF formation in humans. A study was, therefore, designed to investigate the effects of POF in human volunteers under conditions of controlled endotoxaemia [20]. The most notable result was that, due to POF administration, there was a significant reduction of circulating TNF levels following LPS bolus injection, whereas IL-6 levels, as well as febrile response to LPS, were not influence by POF. Furthermore, the endotoxin-induced initial leucocytopenia, caused by TNF-mediated adherence of activated leucocytes in the microcirculation, was counteracted by POF. In contrast, the following IL-6 induced leucocytosis remained unaffected [21]. This study shows that the positive effects of POF determined in animal models may possibly also apply to the human situation.

Since POF is able to attenuate endogenous TNF formation in humans in experimental conditions, it is concluded that POF may also improve therapeutic strategies in various clinical situations in which TNF is identified as a pivotal pathophysiological factor. Some of these indications have already been examined, or will be investigated in further clinical studies. In allogenic bone marrow transplantation, increased serum levels of TNF precede major complications, such as graft-*versus*-host reaction, vascular leakage syndrome and pneumonitis [22]. Data from a clinical study performed in patients undergoing allogenic bone marrow transplantation showed that prophylactic administration of POF can prevent major complications and significantly decreases mortality after one year of follow-up [23]. In renal transplantation, POF treatment may improve OKT3 therapy by its ability to suppress OKT3-induced TNF formation, and, thus, prevents severe clinical side-effects [24, 25]. TNF has been implicated as a major mediator of the severe wasting seen in terminal cancer patients, from which its name cachectin is derived [26]. Recently, it was shown that POF-treated cancer patients experienced an improvement in general well-being accompanied by significant decreases in TNF mRNA levels of peripheral blood monocytes [27]. We have demonstrated that oral POF administration in severely ill patients with pulmonary tuberculosis is able to reduce elevated TNF levels in the circulation and, consequently, reverses cachexia [28]. Recently, TNF has been identified as a critical mediator in hapten-induced irritant and contact sensitivity reactions [29], thus offering new possibilities, for therapeutic intervention. Meanwhile, the suppressive effect of oral administration of POF on allergic patch test reactions was confirmed in human volunteers known to be allergic to nickel [30].

In conclusion, POF is an established drug with no severe side-effects which may improve therapeutic strategies in various diseases in which TNF and activated neutrophils play a major pathophysiological role. In most of the possible indications, particularly in acute lung injury, the precise clinical proof is still missing. Some randomized, placebo-controlled, ongoing clinical studies have been initiated in patients with septic syndrome and ARDS, which will define the precise clinical efficacy of POF in these clinical conditions in the near future.

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