Hypothesis

A possible role for antibodies to tumour necrosis factor α and to endotoxin in the treatment of Reye's syndrome

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Reye's syndrome is a severe and often fatal disease of unknown aetiology and pathogenesis that affects children after viral illness.¹⁻⁴ It is characterised by encephalopathy and acute fatty degeneration of the liver.¹⁻⁴ Epidemiological studies have suggested a close association with the development of Reye's syndrome and administration of aspirin to children infected with different types of viruses, where over 95% of children with the full blown syndrome have a history of aspirin ingestion.^{5,6}

A role for endotoxin in the development of Reye's syndrome was suggested by Cooperstock *et al.*,⁷ who found increased concentrations of endotoxin in plasma from patients with Reye's syndrome. Furthermore, several investigators have shown that administration of a sublethal dose of endotoxin to fasted Sprague-Dawley rats produces metabolic changes and histological changes similar to those reported in Reye's syndrome.^{8,9} As endotoxin may cause most of its biological effects by the release of tumour necrosis factor α (TNF),¹⁰⁻¹⁴ and as many of the metabolic effects associated with Reye's syndrome may be mediated by TNF,¹⁵ it is reasonable to assume an important role for TNF in the pathogenesis of Reye's syndrome.

Tumour necrosis factor α

TNF is a small polypeptide (also known as cachectin) released primarily by activated macrophages with pleiotropic effects on biological and immunological processes.¹⁶⁻¹⁸ Although originally described as a cytotoxic factor, which induced haemorrhagic necrosis of transplanted tumours in mice,¹⁹ subsequently an expanded role has been shown for TNF as an important mediator of many inflammatory processes.^{17,18} TNF belongs to a class of hormone like molecules termed cytokines, a group of soluble factors that includes interferons, interleukins, and haematopoietic growth factors. These cytokines form a complex network of interactive signals that regulate their own production and the growth, differentiation or function of cells involved in inflammation, immunity, and haematopoiesis. It is now well recognised that TNF is a primary mediator in the patho-

genesis of infection, tissue injury, inflammation, and lethal shock,^{10,13,20,21} and that it occupies a central position in the cytokine cascade, because this substance, more than any other, has been shown to reproduce virtually most (if not all) of the biological actions of endotoxin when injected.^{10,13,14} It is synthesised by various activated phagocytic and non-phagocytic cells, including macrophages, monocytes, lymphocytes, natural killer cells, astrocytes, microglial cells of the brain, and Kupffer cells of the liver.²¹ A wide variety of infectious or inflammatory stimuli are capable of triggering TNF biosynthesis, for example, bacterial endotoxin, enterotoxin, toxic shock syndrome toxin-1, mycobacterial cord factor, viruses, C5a, fungal or parasitic agents, interleukins, and interferons,^{13,20,21} where endotoxin is the most potent stimulator of TNF release from the monocyte/macrophage system.^{18,20} Administration of human recombinant TNF that is virtually endotoxin free produces a variety of cardiovascular, haematological, inflammatory, and metabolic disorders, which are almost identical to those found in endotoxic or septic shock syndrome.^{10,22-24} The strongest evidence implicating TNF as a principal mediator of multiple organ injury in infection is that anti-TNF antibodies prevent the sequelae of endotoxic and Gram negative septic shock and tissue injury.¹¹⁻¹³

TNF and Reye's syndrome

Larrick and Kunkel¹⁵ were the first to hypothesise that Reye's syndrome may be caused by salicylate augmented release of TNF in children who are unusually sensitive to the toxic effects of these factors. They supported their hypothesis by the evidence that addition of aspirin to isolated macrophages results in enhanced production of TNF.¹⁵ In addition, it has been found that the median lethal dose for endotoxin is lower in young than in mature animals, and young animals are more susceptible to Gram negative bacterial infections.²⁵ Although many host factors contribute to these findings, the greater susceptibility of young mice and rats to the toxic effects of TNF may be important. The fact that Reye's syndrome is

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Accepted for publication
10 January 1995

seldom found in adults is consistent with increased susceptibility to TNF in children.¹⁵

Kilpatrick *et al*²⁶ have recently demonstrated an animal model of Reye's syndrome by administration of lipopolysaccharide and aspirin to fasted rats, supporting by their findings the hypothesis of Larrick and Kunkel.¹⁵ They suggested a possible mechanism for the development of Reye's syndrome based on a rat endotoxin model. Children who develop Reye's syndrome may have a changed sensitivity or decreased capacity to clear endotoxin by the reticuloendothelial system, or both. The increased genetic or acquired sensitivity to endotoxin leads to endotoxin stimulated macrophage production and secretion of TNF. The administration of aspirin leads to enhanced macrophage production of TNF. Following the release of TNF into the circulation, this mediator binds to and interacts with target cells and produces numerous intracellular changes. The authors of the study already mentioned²⁶ have seen increased acid proteolytic activity of serum samples of children with Reye's syndrome,²⁷ suggesting the role of endogenous mediator such as TNF where in skeletal muscle this cytokine stimulates proteolysis and the release of amino acids.

The above findings are supported by the results of a recent study²⁸ that showed increased plasma concentrations of TNF in acutely ill patients with Reye's syndrome but not in control subjects or recovered patients. Furthermore, the plasma concentrations of TNF were generally highest in the patients who died. These and other results of this study show that the pathological consequences of changes in patients who develop Reye's syndrome would appear when three conditions coexist²⁸: (a) a viral illness that stimulates local TNF production by circulating monocytes or tissue fixed macrophages; (b) the addition of aspirin to amplify TNF production; and (c) a genetic or acquired loss of the protective inhibitory component of the response to high TNF values.

TNF participates in the pathogenesis of many liver diseases,^{29,30} where increased values of this cytokine may induce severe liver damage. It has also been shown to cause hepatocyte mitochondrial dysfunction,³¹ a characteristic feature of Reye's syndrome. Furthermore, this cytokine has recently been suggested to play a central part in the pathogenesis of hepatic encephalopathy,³⁰ which also characterises Reye's syndrome. Another characteristic feature of Reye's syndrome is hypoglycaemia, and overproduction of TNF may induce profound hypoglycaemia.³²⁻³⁴ The mechanisms by which TNF induces hypoglycaemia are not fully understood. In Reye's syndrome, however, it may induce hypoglycaemia, partly, by the induction of severe liver damage.

Although TNF and endotoxin are important mediators in both bacterial sepsis and Reye's syndrome, the clinical manifestations of the two diseases are quite different. This may be related to the pleiotropic nature of TNF, which may have diverse biological actions and

target cells in different diseases and different situations.

Conclusion

Taken together, the above data strongly suggest an important role for endotoxin and TNF in the pathogenesis of Reye's syndrome. This may possess an important clinical application; according to the results of the above study,²⁸ plasma concentrations of TNF may be of an important prognostic value in Reye's syndrome. Furthermore, as already mentioned, all of the deleterious actions of TNF can be prevented by administration of anti-TNF antibodies, where these antibodies can also prevent the deleterious effects of endotoxin.^{11-13,35} In addition, it has recently been shown that monoclonal antibodies against endotoxin itself can prevent its deleterious actions.³⁶⁻³⁹ Thus, treatment with anti-TNF antibodies or with antibodies directed against endotoxin in patients with Reye's syndrome, may have potentially beneficial therapeutic effects in this serious and potentially fatal disease. The efficacy of antibodies to TNF and to endotoxin in the treatment of septic shock is still controversial. Reye's syndrome differs in its aetiology and nature from septic shock, however, and as patients with Reye's syndrome seem to have lost the protective adaptation to high concentrations of TNF,²⁸ anti-TNF treatment may prove more effective in the treatment of Reye's syndrome than in septic shock.

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