Hypothesis

IS REYE'S SYNDROME CAUSED BY AUGMENTED RELEASE OF TUMOUR NECROSIS FACTOR?

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Summary   Reye's syndrome affects children with a history of viral infection treated with aspirin. Its pathogenesis is unclear. Tumour necrosis factor (TNF) is released by macrophages activated by viral infection, endotoxin, and phagocytosis, and it has been shown to be a mediator of the toxic and metabolic effects of endotoxaemia. The metabolic effects of endotoxin and TNF are similar to those found in Reye's syndrome. Raised levels of TNF are released from macrophages treated with non-steroidal anti-inflammatory drugs, and young animals are known to be more sensitive than mature animals to both TNF and endotoxin. These observations lead to the hypothesis that an increased release of TNF in selected young patients treated with aspirin contributes to the development of Reye's syndrome.

INTRODUCTION

Reye's syndrome is an important cause of morbidity and mortality in babies and children. It is characterised by encephalopathy and acute fatty degeneration of the liver.[1,2] Antecedent viral infections (notably influenza A or B, varicella, and occasionally gastrointestinal infections) are recognised in over 90% of patients. Case-control studies have shown that over 95% of children with the full-blown syndrome have a history of aspirin ingestion.[3]

We present evidence in support of the hypothesis that increased release of tumour necrosis factor (TNF) in salicylate-treated children contributes to the pathogenesis of Reye's syndrome.

ACTIVATION OF MACROPHAGES BY VIRUSES, ENDOTOXIN, AND PHAGOCYTOSIS AND RELEASE OF TNF

Macrophages release a number of mediators when they are activated by diverse stimuli.[4,5] These mediators include two forms of interleukin-1 (IL-1),[6] arachidonate metabolites,[7,8] various enzymes,[9,10] complement components,[11] interferon,[12] and TNF.[13] Viruses and bacteria provoke the release of these mediators[4,13] by means of endotoxin[14] and lymphokines such as gamma interferon[15] and by stimulation of phagocytosis.[16] The acute-phase response,[17,18] characterised by fever,[18] myolysis,[19] a fall in serum zinc and iron,[20,21] and de-novo synthesis of various hepatocyte proteins,[22] is mediated by IL-1.[18,23] TNF probably contributes to this host response.[13] Beutler et al[24] provide strong evidence that at least part of the lethal effect of endotoxin is directly mediated by its stimulation of TNF release by macrophages; a rabbit anti-TNF antiserum given to lipopolysaccharide-challenged mice reduced lethality several-fold.[25] Furthermore, TNF contributes to inflammation by stimulation of granulocytes (unpublished),[26] endothelial cells,[27] and fat cells.[28]

SIMILARITY BETWEEN TOXIC AND METABOLIC EFFECTS OF TNF AND ENDOTOXIN AND THOSE FOUND IN REYE'S SYNDROME

Laboratory rats given sub-lethal doses of *Escherichia coli* endotoxin have shown metabolic changes (increased plasma ammonia, free fatty acids, and serum lactate levels) and histological changes (microvesicular fatty changes in liver and ultrastructural evidence of hepatocyte mitochondrial damage) similar to those found in Reye's syndrome.[29] Kim et al[30] showed that the function of hepatic Kupffer cells is impaired and endotoxaemia commonly results after infection with a number of viruses. Endotoxin has been found in the plasma of patients with Reye's syndrome,[31] but how it contributes to the pathogenesis of the syndrome is not known. Concentrations of short-chain and medium-chain fatty acid are raised in the serum of patients with Reye's syndrome.[32] When these substances are injected into experimental animals many of the clinical, pathological, and biochemical features of the syndrome are reproduced.[33] Studies of mice infected with influenza B showed them to have a block in mitochondrial β-oxidation of fatty acids with subsequent elevations in serum free-fatty-acid concentrations.[34] Released TNF can stimulate a catabolic state characterised by hypertriglyceridaemia.[28] Many of the metabolic effects associated with Reye's syndrome may be mediated by monokines such as TNF or IL-1, and/or by endotoxin released by bowel flora.

INCREASED RELEASE OF TNF BY MACROPHAGES TREATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

We have shown an augmented release of TNF by macrophages stimulated with lipopolysaccharide in the presence of cyclo-oxygenase inhibitors.[12] The augmentation of TNF release by non-steroidal anti-inflammatory drugs parallels their potency—indomethacin is more potent than aspirin, which is more potent than paracetamol (see table). When a phagocytic stimulus *(Staphylococcus aureus)* was incubated with freshly adherent peripheral blood human monocytes for 14 h, a similar increase in TNF release after non-steroidal anti-inflammatory drugs was seen: cells alone, 0 units TNF;[35] phagocytic stimulus alone, 18 units; phagocytic stimulus plus indomethacin 10^{-5} mol/l, 360 units; 10^{-6} mol/l, 250 units; 10^{-7} mol/l, 50 units. Because prostaglandins and the non-steroidal anti-inflammatory inhibitors of their synthesis have been shown to modulate IL-1 release[7,36-38] it is likely that irregularities in this pathway contribute to the enhanced release of other macrophage products including TNF.

EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON TNF RELEASE FROM MACROPHAGES*

Drug	Concentration (mol/l)					Control value
	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	
Aspirin	1380†‡	972‡	510‡	486‡	324	380
Indomethacin	. .	1458‡	1800‡	750‡	420	380
Paracetamol	524	418	408	338	354	380

*Mouse peritoneal macrophages were harvested 12 days after intraperitoneal injection of 0 5 ml of a 1:1 solution of complete Freund's adjuvant and saline. Cells were stimulated overnight with lipopolysalccharide in the presence of inhibitors.[12]

†Units of TNF are defined as the reciprocal dilution that produces half-maximal cytotoxicity in a standard L929 mouse fibroblast assay.[35]

‡Values significantly different from control (p ≤ 0·05).

AGE-RELATED TOXIC EFFECTS OF TNF IN ANIMALS

The median lethal dose for lipopolysaccharide is lower in young than in mature animals. Young animals are also more susceptible to gram-negative bacterial infections[14] (unpublished). Although many host factors contribute to these findings, the greater susceptibility of young mice and rats to the toxic effects of TNF (unpublished) may be important. The fact that Reye's syndrome is seldom found in adults is consistent with increased susceptibility to TNF in children.

HYPOTHESIS

We hypothesise that the metabolic irregularities seen in Reye's syndrome may be caused by salicylate-augmented release of TNF (or a related cytotoxin such as IL-1 or lymphotoxin) in children who are unusually sensitive to the toxic effects of these factors. There is evidence of a link between the hepatic metabolic changes observed in Reye's syndrome and TNF, and other idiopathic syndromes may result from increased levels of TNF or related toxic monokines. The acute fatty liver of pregnancy is one such syndrome.[39] The placenta is a rich reservoir of macrophages[40] that may become activated by a stimulus (as yet unidentified) late in pregnancy. Despite their superficial resemblance, Reye's syndrome and the acute fatty liver of pregnancy can be differentiated by hepatic mitochondrial morphology and clinical course. Clearly, timing of events, hormonal state and age of the patient, as well as other host factors determine the outcome of an inflammatory pathway that has gone awry. The augmented release of inflammatory mediators such as IL-1 and TNF by macrophages treated with inhibitors of prostaglandin biosynthesis, as well as the sensitivity of young animals to these mediators, suggest a novel pathogenetic mechanism for Reye's syndrome.

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"Advanced cancer is a problem that requires teamwork. It involves the needs of the patient, the resources of the family, the therapeutic strategies of the doctor, the bedside and management skills of the nurse, the emotional and spiritual support from social worker and chaplain, and most important of all, the interplay and fusion of these elements to produce a strategy agreeable to the patient. The patient needs to feel actively concerned in his management rather than a helpless prisoner.

This cannot be helped by the fact that nearly a third of dying patients have little idea of their real situation. And basic teamwork is greatly prejudiced when a third of doctors are unwilling to entrust to capable and experienced nursing colleagues honest discussions with the patients about the future. Although lies are rare, evasion is common, but it is not enough to tell the patient the truth and let them get on with it. This is a recent and growing tendency that can be as damaging as uncertainty.

Prognosis should remain uncertain within limits, for that is the truth of it. Patients should be encouraged to ask for information they want, but not have it forced upon them. Someone dying may, early in the illness, feel the need for less information than is required later on. The young usually need more information than the old, but generalisations are to be mistrusted. Relatives are to be listened to courteously but the plea 'You won't tell him will you, he couldn't stand it' is often to be translated as 'You won't tell him will you? I don't think I can handle it'."—ERIK WILKES. Terminal care: how can we do better? *J R Coll Physicians Lond* 1986; **20:** 216–18.