24/3/77

MECHANISMS OF MEDIATION OF ALLERGIC GLOMERULAR INJURY

by

Napier Maurice Thomson
MB, BS (Adelaide) : FRACP

Thesis submitted for the degree
of
Doctor of Medicine
within the Faculty of Medicine
The University of Adelaide
December 1975

CONTENTS

SUMMARY

The glomerular deposition of circulating immune complexes or antibody to glomerular basement membrane (GBM) is thought to be responsible for the majority of cases of human glomerulonephritis. As a consequence of these immune reactions in the glomerulus, mediator systems are activated and these induce glomerular injury. In this thesis I have investigated the mechanisms of mediation of glomerular injury in experimental crescentic glomerulonephritis.

Crescentic glomerulonephritis due to anti-GBM antibody (nephrotoxic nephritis: NTN) was induced in rabbits by the intravenous injection of nephrotoxic serum. Within twelve days a severe crescentic glomerulonephritis would develop in which glomerular fibrin deposition was prominent. Chronic immune-complex glomerulonephritis in rabbits was induced by the daily intravenous administration of bovine serum albumen (BSA). It was found that by preimmunising the animals with BSA in Freund's complete adjuvant and by adjusting the daily dose of BSA according to the antibody response, crescentic glomerulonephritis could be induced in 80% of animals within five to seven weeks.

The role of fibrin in experimental crescentic glomerulonephritis was investigated by examining the effect of anticoagulation with heparin of defibrination with ancrod. In NTN anticoagulation with heparin resulted in a reduction in glomerular fibrin deposition, extracapillary cell proliferation (crescent formation) and renal failure only when

heparin was administered in very large doses (2000 u/Kg/day). Defibrination with ancrod in NTN and chronic immune-complex glomerulonephritis provided protection superior to that provided by very large doses of heparin. In both models of crescentic glomerulonephritis proteinuria was unaffected by anticoagulation or defibrination. These findings suggest that glomerular fibrin deposition plays no part in the primary allergic events causing capillary damage and proteinuria but that it is a consequence of capillary damage.

Defibrination with ancrod in NTN, after glomerular fibrin deposition had occurred and crescents were developing also provided some degree of protection from crescent formation and renal failure. Sequential studies showed that once further fibrin deposition was prevented by defibrination, glomerular fibrin deposits were rapidly removed.

The function of polymorphonuclear leucocytes (PMN) in experimental crescentic glomerulonephritis was examined by depleting circulating PMN with a specific antipolymorph serum. Depletion of PMN in NTN not only prevented glomerular fibrin deposition, crescent formation and renal failure but also largely prevented proteinuria. It would seem that the PMN is the principal injurious agent in this disease and that glomerular fibrin deposition is a consequence of the PMN-induced glomerular damage.

Decomplementing animals with cobra venom factor did not reduce the glomerular fibrin deposition and crescent formation of NTN. This

indicates that complement is not important in the induction of glomerular PMN accumulation and subsequent damage.

These studies have defined a system of injury in experimental crescentic glomerulonephritis due to anti-GBM antibody, which is mediated by PMN and fibrin but is independent of complement. Although only the role of fibrin was examined in the crescentic glomerulonephritis of chronic immune-complex disease it seems likely that the mechanism of injury is also mediated by PMN.

The relevance of these findings to human crescentic glomerulonephritis and the possible therapeutic implications have been discussed.