Studies on pathogenesis and treatment of experimental immune complex glomerulonephritis.
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CHAPTER IX

SUMMARY

Chapter 1. In this thesis an investigation into the pathogenetic mechanisms of epimembranous immune complex deposition in the glomeruli was described. For this study we used two related models of experimental immune complex glomerulonephritis: the heterologous and the autologous immune complex glomerulonephritis. The "natural history" of these two models was compared and the effect of some factors which influenced the deposition of immune complexes in the GBM were studied. These factors were:
1. a treatment with a combination of immunosuppressive drugs and prednisolone.
2. injections of the constituents of immune complexes, i.e. antigen or antibody.
3. an induction of increased permeability of the GBM by aminonucleoside of puromycin.

In chapter II the "natural history" of the autologous immune complex glomerulonephritis was described. Immunisation with Fx1A antigens from the kidney resulted in a granular deposition of immune complexes containing rat IgG along the GBM, 6 weeks after the start of the immunisation. The immune complexes were deposited at the epithelial side of the GBM and were growing in size and number during the course of the disease. However in no phase of the disease a transit of immune complexes through the GBM could be detected at the ultrastructural level. It was thought that probably a separate transit of antibody and antigen through the GBM took place and that the immune complexes were formed at the epithelial side of the GBM. This theory was supported by the fact that free circulating anti-Fx1A antibody seemed to have pathogenetic significance. The rise in serum titer of anti-Fx1A antibody at week 9 coincided with the start of the proteinuria.

Furthermore we were able to transfer the disease into normal rats using serum of rats with autologous immune complex glomerulonephritis containing free anti-Fx1A antibodies.

The only reaction of the glomeruli to the continuous presence of immune complexes along the GBM was a formation of basement membrane like material, resulting in "spikes". At the end of the observation period the
deposits were subject to resolution, which was associated with a disappearance of rat anti-FxlA antibodies from the serum. However the proteinuria persisted, probably because of the damage to the GBM.

In late stages of the autologous immune complex glomerulonephritis multiple tubular adenomas were found in contrast to normal animals of the same age, in which sometimes a large single tubular adenoma was seen. It was reasoned that the multiplicity of the adenomas probably was caused by the "workload" of the tubules as a result of the high protein leakage from the glomeruli.

In chapter III the "natural history" of the heterologous immune complex glomerulonephritis was described. This heterologous model was induced by a single intraperitoneal or intravenous injection of rabbit antibodies directed against FxlA antigens. Because a heterologous protein was injected the animal made antibodies to this protein, resulting in an autologous phase. In no disease stage proteinuria was found. Like in the autologous model immune complexes were present underneath the epithelial cells and in the filtration slits, but were never observed in other layers of the GBM. Only during the first 7 days it was possible to transfer the disease into normal rats, because only in this period rabbit anti-FxlA antibody was present in the circulation. Autologous (rat) antibody directed against rabbit IgG was present in the circulation from day 7 until week 24. After this moment a resolution of depositions in the GBM started. Embedding in GBM-like material gave the impression that the aggregates were moving towards the endothelial side of the GBM, although at all times the dense layer of the original GBM could be found underneath the aggregates.

Like in normal rats, animals with heterologous immune complex glomerulonephritis showed large single tubular adenomas of the kidneys in late disease stages. This finding supported the "workload" hypothesis as described in chapter II, because no proteinuria was found in the heterologous immune complex glomerulonephritis.

In chapter IV a review of the literature was given on possibilities to influence an immune complex glomerulonephritis and a general design for the experiments was presented.

- Treatment with immunosuppressive drugs and prednisolone.
  
  From the literature it may be concluded that although immunosuppressive and anti inflammatory therapy are often used in glomerulonephritis only a few cases seem to benefit from these drugs. In this study a combination of immunosuppressive drugs and anti inflammatory drugs was chosen to influence the immune complex glomerulonephritis.

- In human as well as in experimental immune complex glomerulonephritis it is reported that immune complex aggregates may disappear from the
GBM, when antigen or antibody involved disappears from the circulation. Therefore injections of antigen and antibody might influence immune complex glomerulonephritis through changing the composition of the circulating immune complexes. This immunotherapy was only used in experimental models and it was reported that in the BSA anti-BSA system in rabbits an accelerated disappearance of immune complex aggregates from the GBM was observed following injections of BSA. In our experiments we studied the influence of injections of extra antigen or antibody given either to prevent deposition of immune complexes in the GBM or to accelerate the resolution of immune complexes deposited in the GBM.

Some literature was presented on the filtration process of the GBM and the specific influence of PAN on this filtration. Because in our model the first deposition of immune complexes appeared always in the filtration slits of the GBM, PAN was used to increase the permeability either to prevent the deposition of immune complexes or to accelerate their disappearance from the GBM.

In chapter V the influence of the above mentioned factors on the heterologous immune complex glomerulonephritis was described. Although triple drug treatment did not influence the deposition of rabbit IgG in the GBM, the autologous phase was clearly influenced. Using treatment with high dose schedules, this phase could be suppressed completely. Immunotherapy using injections of extra antibody resulted in an increased deposition of immune complexes in the GBM, associated with a transient proteinuria. Injections of extra antigen prevented immune complex deposition in the GBM completely when given just before or after the induction of the disease. High doses of antigen administration resulted in a deposition of rabbit IgG in the mesangium of the kidney. Increased permeability of the GBM at the moment of the induction of the disease, prevented the deposition of immune complexes in the GBM. Some rabbit IgG was present on the brushborders of the proximal tubules. Increased permeability of the GBM after the induction of the disease seemed to have no influence on the deposits already present in the GBM.

In chapter VI the results of the studies on factors influencing the autologous immune complex glomerulonephritis were described. Triple drug treatment could prevent the deposition of immune complexes in the GBM, when this treatment was started simultaneously with the immunisation of the rats. The influence of triple drug treatment was less marked when given on a moment at which immune complexes were present in the
GBM. In later phases of the disease when proteinuria was fully developed, no beneficial effect of triple drug treatment was observed at all. Immunotherapy using injections of extra antibody resulted in an increase in deposition of immune complexes in the GBM. This increase was caused mainly by the deposition of rat IgG along the GBM. Electron microscopy revealed that in these cases the electron lucent areas around the deposits were filled again with dense material, probably through an immune reaction of the animal causing deposition of rat anti-rabbit IgG antibody. Injections of extra Fx1A antigen seemed to have no effect on the amount of deposited immune complexes in the GBM and on the resulting proteinuria. Administration of PAN at low doses during an early observation period, seemed to decrease the amount of deposits in the GBM. PAN injections in late stages of the disease when proteinuria was present, caused ascites and death of the animals. Like in the heterologous immune complex glomerulonephritis no effect was noted on depositions already present in the GBM. The effect of PAN on the deposition of immune complexes in the GBM seemed not directly related to the amount of proteinuria induced by PAN.

In chapter VII the facts from previous chapters which were of importance for a better understanding of the pathogenesis of the heterologous and autologous immune complex glomerulonephritis were discussed. In both models the deposition of immune complexes at the epithelial side of the GBM seemed to be related to the presence in the serum of antibodies participating in the formation of immune complexes. In later stages of the disease resolution of immune complex aggregates coincided with the disappearance of antibodies from the serum which participated in immune complex formation. The proteinuria, which was present in the autologous model and absent in the heterologous immune complex glomerulonephritis, seemed to be related to the amount of immune complex depositions in the GBM rather than to the binding and activation of complement. The results from previous chapters were reviewed leading to the hypothesis that not immune complex aggregates derived from the circulation were deposited in the GBM, but that immune complex deposition resulted rather from a separate transit of antibody and antigen through the GBM. Since this hypothesis was not in agreement with the results of injections of extra rabbit anti-Fx1A antibody in heterologous immune complex glomerulonephritis, the possibility was considered that Fx1A antigens were present in the GBM as an integral part of the capillary wall. Immunohistology at the light microscopic level and the ultrastructural level using heterologous anti-Fx1A antibody, indeed demonstrated the presence of these antigens within the cell coat of epithelial cells of the glomeruli, beneath the foot processes and within the filtration slits.
This led to the concept that in these models of experimental glomerulonephritis a fixed antigen is a central feature in the pathogenesis of immune complex deposition. The implications of this finding for other forms of experimental glomerulonephritis and human glomerulonephritis were discussed and it was concluded that binding of antibody to these fixed antigens might present all the morphological and immunohistological features of glomerular immune complex disease.

In chapter VIII materials and methods were presented.