HEYMANN NEPHRITIS OF RATS: IS A VASOPERMEABILITY MECHANISM REALLY NEEDED FOR IMMUNE COMPLEX DEPOSITION?

F Alonso, J Egido, M Sanchez Crespo, L Hernando

Fundación Jiménez Diaz, Madrid, Spain

Heymann nephritis occurred in rats after repeated intraperitoneal injections of a mixture of complete Freund’s adjuvant and a low speed supernate of blood free rat kidney suspension in saline. The disease developed after several injections and closely resembled human membranous glomerulonephritis. The deposition of circulating immune complexes, in situ immune complex formation, or both simultaneously are the pathogenetic hypotheses actually considered.

In acute serum sickness of rabbits an increase of vascular permeability induced by the release of vasoactive amines from platelets, triggered by IgE sensitised basophils, seems necessary for the deposition of circulating immune complexes [1]. In this model we have shown that disodium cromoglycate (DSCG) prevents the development of nephritis in some animals [2].

The aim of this work is to study the presence of a similar anaphylactic dependent mechanism in rats and its possible inhibition by DSCG and antihistamines (AH).

Material and Methods

Heymann nephritis was induced in 50 Wistar rats of 100gr weight by intraperitoneal injections of Fx 1A. The animals were divided into three groups:

Group I   Control rats (n = 20); no treatment was given.
Group II  Rats treated from the beginning of the experiment with disodium cromoglycate (n = 15).
Group III Rats treated with disodium cromoglycate and antihistamines (n = 15).

The disodium cromoglycate and antihistamines were administered subcutaneously in three injections daily. The doses employed were: DSCG, 50mg/kg/day, Azatadine; 0.375mg/kg/day, Hydroxycine; 30mg/kg/day. The experiments lasted for 20 weeks. The existence of anti-Fx 1A homocytotropic antibodies (IgE and IgGa) was sought by passive cutaneous anaphylaxis. Histamine and PAF (Platelet Activating Factor) release was studied in the buffy coat cells (BCC) challenged by
specific antigen, calcium ionophore A-23187 (Lilly) and Zymosan (Incubation at 37°C, 45 min). Total histamine in the BCC—10^7 cells (mixing washed BCC from four control rats) was determined after three minutes boiling. PAF liberation was sought in the kidney homogenates after incubation with the same releasers. Circulating anti-brush border antibodies were studied by indirect immunofluorescence. Kidney biopsies were studied by light microscopy, immunofluorescence and in some cases electron microscopy. Proteinuria was determined weekly.

Results

The production of renal anti-brush border antibodies, the frequency of nephritis and quantity of immune deposits in the glomerular basement membrane, were similar in all animal groups. No animal produced anaphylactic antibodies. No histamine and PAF release were obtained when BCC was challenged with specific antigen.

| TABLE I. Release of Vasopermeability Mediators and Lysosomal Enzymes in Control Rats |
|---------------------------------|-----------------|-------------------|
|                                 | Histamine*      | β-glucuronidase†  | PAF U/ml      |
| Ca Ionophore A-23187 5μg/ml    | 44              | 100               | 351 ± 131*    |
| Zymosan 0.32mg/ml              | 0               | 84.81             | 71.19 ± 16.77 |
| 0.65mg/ml                      | 0               | 93.32             | 83.35 ± 16.65 |
| 1.25mg/ml                      | 0               | 144               | 94.67 ± 15    |
| 1.9mg/ml                       | 0               | 151               | 76.25 ± 8.75  |

* expressed as % of total histamine obtained after three min boiling of 10^7 BCC. (Less than 20ng)
† expressed as % of enzyme activity released by Ca Ionophore
☆ Mean ± SD of three pools of washed BCC from four rats

The release of vasopermeability mediators and lysosomal enzymes in control rats is shown in Table I. The platelet aggregating activity observed in the kidney homogenates was inhibited by indomethacin, thus excluding the existence of true PAF.

Conclusions

The antihistamines and the disodium cromoglycate, contrary to what has been suggested, have no effect on the frequency and course of Heymann nephritis.

The absence of a vasopermeability anaphylactic mechanism, the low histamine content in the buffy coat cells and the inhibition of mastocyte degranulation obtained by the DSCG suggest, contrary to the acute serum sickness of rabbits,
that there is no active anaphylactic dependent mechanism in Heymann nephritis. The release of lysosomal enzymes and PAF in the BCC suggests an important role of phagocytic cells in the glomerular inflammation.

Our results indirectly confirm the new hypothesis of in situ passive immune complex formation in the glomerular basement membrane in this type of nephritis.

References