Clin. exp. Immunol. (1992) **89**, 165–169

REVIEW

Experimental autoimmune uveoretinitis (EAU) *versus* experimental allergic encephalomyelitis (EAE): a comparison of T cell-mediated mechanisms

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(Accepted for publication 16 March 1992)

SUMMARY

EAU is a model of ocular inflammatory disease. EAU resembles another T cell-mediated autoimmune disease—experimental allergic encephalomyelitis—since both have increased expression of MHC class II molecules in the target tissue, can be adoptively transferred by activated $CD4^+$ T cells and are inhibited by cyclosporin A. The immunological findings will be compared to find out if the same cellular mechanisms are involved in both diseases.

Keywords EAU EAE immune-privileged site autoreactivity

INTRODUCTION

EAU in the rat is a good experimental model for posterior uveitis in man due to the similarities both in the pathology of the disease processes and in the function of the blood–retinal barriers in rat and man [1]. In EAU, infiltrating lymphocytes (mainly $CD4^+$ T cells) appear within the retina early in the disease, resulting in the irreversible destruction of the photoreceptor cells and a loss of integrity of the retinal layers. Throughout the disease there is an increased expression of MHC class II molecules on a variety of retinal cells. At later stages of disease increased numbers of $CD8^+$ T cells can be seen within the retina and it has been proposed that these cells could down-regulate the disease process [2]. The importance of $CD4^+$ T cells in EAU was first demonstrated in the Lewis rat where disease was successfully induced in naive recipients by adoptively transferring activated antigen-specific $CD4^+$ T cell lines [3]. Both cyclosporin A (CsA) and FK506 have been shown to be effective in preventing EAU, suggesting a pathogenic role for activated T cells in this disease [4,5]. EAU has therefore been used as a model to determine the likely T cell-mediated effector mechanisms within the retina. The aim of this review is to compare the findings obtained in EAU with those from EAE, another model of T cell-mediated autoimmunity, to find out if these diseases, both occurring in so-called 'immunologically-privileged sites', have similar effector T cell mechanisms.

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INDUCTION

EAU is induced by immunization with purified retinal proteins or their peptide fragments emulsified in Freund's complete adjuvant (FCA). The most commonly used uveitogen is retinal soluble antigen (SAg), a 48-kD intracellular protein which exists in rod outer segments and the pineal gland [6]. However, two other purified proteins—interphotoreceptor retinoid binding protein (IRBP) and rhodopsin—have also been found to be uveitogenic in some species [7,8]. Synthetic peptides made from these molecules can be uveitogenic, and studies of the EAU induced by SAg peptides have allowed identification of highly pathogenic epitopes within the whole antigen [9]. More recent studies with IRBP have found epitopes of the molecule which are highly uveitogenic but not necessarily stimulatory for T cells *in vitro* [10]. It has also been found that uveitopathogenic regions of SAg share sequence homology with a variety of viral peptides [11] and EAU has been induced by immunizing with a small synthetic peptide corresponding to amino acid positions 106–121 of yeast histone H3 [12]. Thus molecular mimicry has been proposed as a mechanism for initiating and/or perpetuating EAU.

Chronic relapsing EAE was initially described in guinea pigs using spinal cord homogenate emulsified in FCA [13] but disease has subsequently been induced in a range of species with myelin basic protein (MBP) extracted from white matter. Studies using synthesised peptides from MBP have revealed encephalitogenic sites on the molecule [14]. Recently other central nervous system (CNS) antigens have also been shown to be encephalitogenic, e.g. proteolipid protein [15]. Molecular mimicry has been implicated in EAE due to the finding that many viral infections including measles and the coronavirus JHM can increase

sensitivity to MBP [16,17] and homologous sequences have been identified between viral peptides and MBP [18].

Alternative methods for inducing EAE and EAU have been demonstrated using adoptive transfer techniques, by immunizing a sufficient number of activated antigen-specific, $CD4^+$ T cells. In early studies induction of EAU by adoptive transfer utilized lymph node cells from SAg-primed rats which initiated a uveitis and associated pinealitis [19]. The induction of EAE in rats by this method was demonstrated using lymph node cells reactive to MBP which induced a chronic demyelinating disease [20]. Exactly how these $CD4^+$ T cells, when injected peripherally, induce an organ-specific disease remains unclear. Studies using radioisotope labelling to follow the migration of the T cells after adoptive transfer of EAU in Lewis rats found only very few of the labelled cells crossed the blood–retinal barrier (BRB) into the eye [21]. This technique had previously been used in EAE to examine the trafficking of lymphocytes into the CNS across the blood–brain barrier (BBB) and an increased accumulation of cells was detected within the CNS before onset of disease [22]. Thus a clonal expansion of the inoculated autoreactive T cells within the tissue has been suggested as the amplification mechanism whereby very few cells can induce EAE or EAU in syngeneic hosts [23,24]. By comparing the methods for inducing EAU and EAE, it appears that in both models similar immunological mechanisms are involved and molecular mimicry has been implicated due to the regions of homology shared between the relevant autoantigens and various peptides.

GENETIC PREDISPOSITION

Models of EAU have been developed in guinea pigs, rats, rabbits and mice although the uveitogenic responses within species are varied with some strains of rats (PVG and Lewis) being more susceptible to disease than others [24]. In mice, EAU has only recently been achieved, and its induction requires the use of IRBP as opposed to SAg which appears to be poorly uveitogenic in this species [25]. In EAE, many species are susceptible to disease with some rat (Lewis) and mouse (SJL, PL/J) strains being more susceptible than others [26]. Several studies have attempted to map these responses to the MHC class II gene and, in the mouse, have found that a genetic predisposition to EAE partly depends on the *s* and *q* haplotypes [27]. In rats, the Lewis strain is susceptible to EAE ($RT\text{-}1^l$ locus) whereas the BN strain is resistant ($RT\text{-}1^n$) suggesting that the MHC class II gene controls the T cell responses to MBP and hence disease susceptibility [28]. However, PVG rats which are relatively resistant to EAE respond to the same MBP peptide as the susceptible Lewis rats, suggesting that the MHC class II gene is not the only factor involved in disease susceptibility [29]. In conclusion, on comparing EAU with EAE, there are many species which are susceptible to disease although the requirements for genetic predisposition remain unclear and there is no evidence that these are the same in both diseases since it is clear that whilst PVG rats are highly susceptible to EAU, this is not true for EAE.

IMMUNOPATHOGENESIS

The immunopathology of EAU is similar to that of EAE. At the early stage of disease within the retina in EAU, large numbers of infiltrating $CD4^+$ T cells and an increase in local expression of class II molecules can be seen [2]. In EAE, infiltrating perivascular $CD4^+$ T cells and MHC class II-expressing cells predominate in the lesions within the white matter of the central nervous system, suggesting that the $CD4^+$ T cells are mediating the demyelination [26].

The various effector T cell mechanisms which might be occurring during EAE and EAU have been examined *in vivo* using MoAbs recognizing T cell subsets and lymphokines in an attempt to alter the course of disease. Thus EAE in mice has been prevented using either anti-CD4 or anti-class II MoAbs [30,31]. Similarly in EAU, uveitis in rats has been inhibited with anti-I-A or anti-CD4 MoAbs [32,33]. In contrast, no change was seen in the course of disease when Lewis rats were depleted of their $CD8^+$ T cells before inducing EAE although $CD8^+$ T cells have been identified at the later stages of disease [34]. This suggests that these cells do not play an important role in initiating or down-regulating EAE. Similar studies treating rats with anti-CD8 MoAb before inducing EAU failed to alter the course of disease, suggesting that $CD8^+$ T cells are not important in regulating EAU [35].

Anti-lymphokine antibodies can also prevent disease and a recent report of the successful prevention of EAU in Lewis rats with anti-interferon-gamma (IFN-γ) antibody demonstrates the importance of this lymphokine in the pathogenesis of EAU [36]. In Lewis rat EAE, it has recently been shown that IL-1α treatment exacerbates disease and suppression of disease can be obtained by treatment with soluble IL-1 receptor [37]. Another lymphokine which has been found to play an important role in down-regulating chronic relapsing EAE in mice is transforming growth factor-β [38]. Although its role in EAU is unclear, it has recently been detected in high concentrations in normal aqueous humor from several different mammalian species [39].

IMMUNOTHERAPY

Following the success of the adoptive transfer method for inducing EAE with activated $CD4^+$ T cells, it was demonstrated that the same T cells, when inoculated into rats in subencephalitogenic doses, were able to confer protection against subsequent attacks of EAE [40]. This approach has also been successful in vaccinating rats against EAU [41]. The mechanism whereby T cell vaccination prevents disease is thought to occur by initiating an immune response against endogenous clones of lymphocytes with anti-MBP receptors or by enhancing suppression. An alternative method for down-regulating disease has been described in EAU, using a $CD8^+$ 'suppressor' T cell line [42].

One effective immunotherapy in EAE has been peptide-specific prevention of disease. By neonatally tolerizing with immunodominant peptides of MBP, adult mice were subsequently made resistant to EAE [43]. It is not known if this form of immunotherapy is effective in EAU. Another successful approach has been to immunize with peptides selected on the basis of their ability to bind class II molecules and so prevent EAE by blocking class II-mediated processes [44]. Molecular studies of the DNA rearrangements of the T cell receptor variable (V) genes have indicated that encephalitogenic T cell lines share a high degree of homology [45]. This suggests that the T cell response in EAE is polyclonal and that one form of immunotherapy might be to use peptides which can bind to and block antigen recognition sites on T cell receptors and so prevent disease. Using this approach, it has been reported that rats can

be rendered resistant to the induction of EAE by vaccination with a synthetic peptide representing a hypervariable region of the T cell receptor (TCR) Vβ8 molecule [46]. Uveitogenic T cell lines have been examined for their T cell receptor V genes and it has been found that these cells are enriched for Vβ 8.2 [47]. Whether peptides synthesised from this T cell receptor V gene can protect rats from EAU has yet to be demonstrated. Interestingly, oral immunization has been shown to be effective in preventing both EAE and EAU [48,49]. Feeding rats with MBP or SAg resulted in a markedly diminished encephalitis or uveitis. The precise mechanisms involved in this immunosuppression remain unclear although the effects could be reversed by treating the rats with anti-CD8 MoAb. In conclusion, of those immunotherapeutic approaches which have been performed in both EAU and EAE, no immunological differences in the results could be found. It is therefore not surprising that both immunosuppressive drugs CsA and FK506 are effective in preventing EAE and EAU [4,5].

REVERSIBILITY OF DISEASE

In EAE, the perivascular inflammatory infiltrate leads to damage of the myelin sheath surrounding the nerve although the myelin-producing oligodendrocytes can remyelinate [50]. In contrast in EAU, the damage to the photoreceptor cells is irreversible as these cells are not regenerated. Despite this difference in the course of disease, neither photoreceptor cells nor oligodendrocytes express class II molecules *in vivo* or *in vitro*. This seems to contradict the theory of aberrant expression of class II molecules on the target cells leading to a perpetuation of chronic inflammatory disease [51]. Perhaps the oligodendrocytes and photoreceptor cells are damaged as a bystander effect during the effector T cell response. The MHC class II molecules, necessary for recognition by $CD4^+$ T cells, have been detected within the retina during EAU on retinal endothelial cells [52] and on pigment epithelial cells [53] although this finding has been disputed by others [54]. In EAE, class II expression has been seen within the lesions, particularly at the perivascular cell level [55]. Class II induction has also been demonstrated *in vitro* on brain-derived endothelial cells, microglia and both types 1 and 2 astrocytes but not on oligodendrocytes [56–59], suggesting that a lack of expression of class II molecules by the target cells themselves does not necessarily prevent them being damaged during a T cell response.

BLOOD-BRAIN BARRIER *VERSUS* BLOOD-RETINAL BARRIER

In both EAE and EAU, successful adoptive transfer of disease requires that the T cells are activated and it has been found that activated T cells produce enzymes capable of degrading extracellular matrix [60]. It has also been recently shown that any activated T cell can cross the BBB [61] and, presumably, the BRB. Exactly how the $CD4^+$ T cells cross the BBB and BRB from the blood remains unclear, but adhesion molecules are thought to be important. An upregulation of adhesion molecules has been reported within the CNS coinciding with the onset of relapsing EAE which supports a role for receptor-mediated migration of cells into the brain [62]. Cultures of cerebrovascular endothelial cells from Lewis rats have been shown to be more adhesive for activated than for resting lymphocytes and this is thought to involve the CD11a/18 complex of adhesion molecules since adhesion could be selectively inhibited by anti-LFA-1 antibody [63]. No such studies have been done with rat retinal endothelial cells but both human retinal endothelial cells and human pigment epithelial cells have been found to express high levels of ICAM-1 following incubation with IFN-γ [64].

Although the BBB and BRB appear to have similar functions in rat and man, one important difference is in the ability of CsA to down-regulate disease. In man, CsA is only poorly effective as a treatment for multiple sclerosis and does not enter the brain in detectable amounts [65]. In contrast, CsA is an effective treatment for posterior uveitis in man [66], suggesting either that it exerts its effect at the peripheral level and reduces the numbers of cells recruited to the site of inflammation, or that it crosses the BRB to locally suppress the T cell response. Evidence that low levels of CsA can cross the BRB in uveitis in man supports the latter hypothesis [67].

CONCLUSION

From the studies carried out so far, EAU and EAE seem to involve similar immunological processes for disease induction, the cytokines produced and the appropriate target molecules for immunotherapy. We were unable to identify any immunological differences either in the induction or in the expression of the disease between EAU and EAE. Some differences exist mainly as a result of anatomical differences between the brain and the eye. Since in both models the autoantigens are localized within the target organ, autoreactive T cells could be attracted to the site of inflammation although it is not clear if in either model the autoreactive T cells expand before or after crossing the relevant barrier.

These two models of T cell-mediated autoimmunity share many common immunological features although their relevance to human disease is limited. Evidence that MBP and SAg are the autoantigens in human disease is questionable since lymphocyte responses to these antigens have been detected in the blood from controls. Nevertheless, these models are clearly of great importance in allowing a further understanding of various autoreactive T cell mechanisms.

REFERENCES

1 Forrester JV, Liversidge J, Dua HS *et al.* Comparison of clinical and experimental uveitis, Curr Eye REs 1990; **9**:75–84.
2 Chan CC, Mochizuki M, Nussenblatt RB *et al.* T-lymphocyte subsets in experimental autoimmune uveitis. Clin Immunol Immunopathol 1985; **35**:103–10.
3 Caspi RR, Roberge FG, McAllister CG *et al.* T cell lines mediating experimental autoimmune uveoretinitis (EAU) in the rat. J Immunol 1986; **136**:928–33.
4 Fujino Y, Okummura A, Nussenblatt RB. Cyclosporine-induced specific unresponsiveness to retinal soluble antigen in experimental autoimmune uveoretinitis. Clin Immunol Immunopathol 1988; **46**:234–48.
5 Kawashima H, Fujino Y, Mochizuki M. Effects of a new immunosuppressive agent, FK506, on experimental autoimmune uveoretinitis in rats. Invest Ophthal Vis Sci 1988; **29**:1265–71.
6 Wacker WB, Donoso LA, Kalsow CM *et al.* Experimental allergic uveitis. Isolation, characterization, and localization of a soluble uveitopathogenic antigen from bovine retina. J Immunol 1977; **119**:1949–58.

7 Fox GM, Kuwabara T, Wiggert B *et al.* Experimental autoimmune uveoretinitis (EAU) induced by retinal interphotoreceptor retinoid-binding protein (IRBP): differences between EAU induced by IRBP and by S-antigen. Clin Immunol Immunopathol 1987; **43**:256–64.

8 Marak GE, Shichi H, Rao NA *et al.* Patterns of experimental allergic uveitis induced by rhodopsin and retinal rod outer segments. Ophthalmic Res 1980; **12**:165–76.

9 Singh VK, Nussenblatt RB, Donoso LA *et al.* Identification of a uveitopathogenic and lymphocyte proliferation site in bovine S-antigen. Cell Immunol 1988; **115**:413–9.

10 Kotake S, de Smet MD, Wiggert B *et al.* Analysis of the pivotal residues of the immunodominant and highly uveitogenic determinant of IRBP. J Immunol 1991; **146**:2995–3001.

11 Singh VK, Kalra HK, Yamaki K, *et al.* Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. J Immunol 1990; **144**:1282–7.

12 Singh VK, Yamaki K, Donoso LA *et al.* Molecular mimicry: yeast histone H3-induced experimental autoimmune uveitis. J Immunol 1989; **142**:1512–7.

13 Stone SH, Lerner EM. Chronic disseminated allergic encephalomyelitis in guinea pigs. Ann NY Acad Sci 1965; **122**:227–41.

14 Vandenbark AA, Hashim GA, Celnik B *et al.* Determinants of human myelin basic protein that induce encephalitogenic T cells in Lewis rats. J Immunol 1989; **143**:3512–6.

15 Tuohy VK, Lu Z, Sobel RA *et al.* Identification of an encephalitogenic determinant of myelin proteolipid protein for SJL mice. J Immunol 1989; **142**:1523–7.

16 Johnson RT, Griffin DE, Hirsch RL *et al.* Measles encephalomyelitis—clinical and immunologic studies. New Eng J Med 1984; **310**:137–41.

17 Watanabe R, Wege H, ter Meulen V. Adoptive transfer of EAE-like lesions from rats with corona virus-induced demyelinating encephalomyelitis. Nature 1983; **305**:150–3.

18 Fujinami RS, Oldstone MBA. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 1985; **230**:1043–5.

19 Mochizuki M, Kuwabara T, McAllister C *et al.* Adoptive transfer of experimental autoimmune uveoretinitis in rats. Invest Ophthalmol Vis Sci 1985; **26**:1–9.

20 Paterson PY. Transfer of allergic encephalomyelitis in rats by means of lymph node cells. J Exp Med 1960; **111**:119–36.

21 Lightman SL, Caspi RR, Nussenblatt RB *et al.* Antigen-directed retention of an autoimmune T-cell line. Cell Immunol 1987; **110**:28–34.

22 Naparstek Y, Ben-Nun A, Holoshitz J *et al.* T lymphocyte line producing or vaccinating against autoimmune encephalomyelitis (EAE): Functional activation induces peanut agglutinin receptors and accumulation in the brain and thymus of line cells. Eur J Immunol 1983; **13**:418–23.

23 Wekerle H, Linington C, Lassmann H *et al.* Cellular immune reactivity within the CNS. Trends Neurosci 1986; **9**:271–7.

24 Caspi RR. Basic mechanisms in immune-mediated uveitic disease. In: Lightman S, ed. Immunology of eye diseases; Immunology and Medicine Series, Vol. 13. Dordrecht: Kluwer Academic Publishers, 1989:61–87.

25 Caspi RR, Roberge FG, Chan CC *et al.* A new model of autoimmune disease: experimental autoimmune uveoretinitis induced in mice with two different retinal antigens. J Immunol 1988; **140**:1490–5.

26 Raine CS. Analysis of autoimmune demyelination: its impact upon multiple sclerosis. Lab Invest 1984; **50**:608–35.

27 Raine CS, Barnett LB, Brown A *et al.* Neuropathology of experimental allergic encephalomyelitis in inbred strains of mice. Lab Invest 1980; **43**:150–7.

28 Williams RM, Moore MJ. Linkage of susceptibility of experimental allergic encephalomyelitis to the major histocompatibility complex in the rat. J Exp Med 1973; **135**:775–83.

29 Vandenbark AA, Offner H, Reshef T *et al.* Specificity of T-lymphocyte lines for peptides of myelin basic protein. J Immunol 1985; **135**:229–33.

30 Waldor MK, Sriram S, Hardy R *et al.* Reversal of experimental allergic encephalomyelitis with monoclonal antibody to a T-cell subset marker. Science 1985; **227**:415–7.

31 Steinman L, Solomon D, Lim M *et al.* Prevention of experimental allergic encephalitis with *in vivo* administration of anti-I-A antibody. J Neuroimmunol 1983; **5**:91–97.

32 Wetzig R, Hooks JJ, Percopo CM *et al.* Anti-Ia antibody diminishes ocular inflammation in experimental autoimmune uveitis. Curr Eye Res 1988; **7**:809–18.

33 Atalla L, Linker-Israeli M, Steinman L *et al.* Inhibition of autoimmune uveitis by anti-CD4 antibody. Invest Ophthal Vis Sci 1990; **31**:1264–70.

34 Sedgwick JD. Long-term depletion of $CD8^+$ T cells *in vivo* in the rat: no observed role for $CD8^+$ (cytotoxic/suppressor) cells in the immunoregulation of experimental allergic encephalomyelitis. Eur J Immunol 1988; **18**:495–502.

35 Calder VL, Wang Y, Lightman SL. *In vitro* and *in vivo* effects of anti-CD8 monoclonal antibody on S-antigen induced uveitis in rats. Invest Ophthal Vis Sci 1991; **32**:612 (abstr.).

36 Yoser SL, Atalla L, Rao NA. Suppression of experimental autoimmune uveoretinitis with monoclonal antibody to gamma-interferon. Invest Ophthal Vis Sci 1990; **31**:292 (abstr.).

37 Jacobs CA, Baker PE, Roux ER *et al.* Experimental autoimmune encephalomyelitis is exacerbated by IL-1α and suppressed by soluble IL-1 receptor. J Immunol 1991; **146**:2983–9.

38 Racke MK, Dhib-Jalbut S, Cannella B *et al.* Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-β. J Immunol 1991; **146**:3012–7.

39 Cousins SW, McCabe MM, Danielpour D *et al.* Identification of transforming growth factor-beta as an immunosuppressive factor in aqueous humor. Invest Ophthal Vis Sci 1991; **32**:2201–11.

40 Lider O, Reshef T, Beraud E *et al.* Anti-idiotype network induced by T cell vaccination against experimental autoimmune encephalomyelitis. Science 1988; **239**:181–3.

41 Beraud E, Kotake S, Chan CC *et al.* T-cell vaccination against experimental autoimmune uveitis (EAU). Invest Ophthal Vis Sci 1991; **31**:1049 (abstr).

42 Caspi RR, Kuwabara T, Nussenblatt RB. Characterization of a suppressor cell line which downgrades EAU in the rat. J Immunol 1988; **140**:2579–84.

43 Clayton JP, Gammon GM, Ando DG *et al.* Peptide-specific prevention of experimental allergic encephalomyelitis. J Exp Med 1989; **169**:1681–91.

44 Lamont AG, Sette A, Fujinami R *et al.* Inhibition of experimental autoimmune encephalomyelitis induction in SJL/J mice by using a peptide with high affinity for IA^s molecules. J Immunol 1990; **145**:1687–93.

45 Chluba J, Steeg C, Becker A *et al.* T cell receptor β chain usage in myelin basic protein-specific rat T lymphocytes. Eur J Immunol 1989; **19**:279–84.

46 Vandenbark A, Hashim G, Offner H. Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis. Nature 1989; **341**:541–3.

47 Egwuagwu CE, Beraud E, Chow C *et al.* Analysis of T-cell receptor variable region genes of uveitogenic T-cell lines. Invest Ophthal Vis Sci 1990; **31**:291 (abstr.).

48 Lider O, Lee CSY, Higgins PJ *et al.* Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. J Immunol 1989; **142**:748–52.

49 Nussenblatt RB, Caspi RR, Mahdi R *et al.* Inhibition of S-antigen induced experimental autoimmune uveoretinitis by oral induction of tolerance with S-antigen. J Immunol 1990; **144**:1689–95.

50 Wisniewski HM, Keith AB. Chronic relapsing EAE: an experimental model of multiple sclerosis. Ann Neurol 1977; **1**:144–8.

51 Bottazzo GF, Pujol-Borrell R, Hanafusa T. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. Lancet 1983; **ii**:1115–9.

52 Fujikawa LS, Chan CC, McAllister C *et al.* Retinal vascular endothelium expresses fibronectin and class II histocompatibility complex antigens in experimental autoimmune uveitis. Cell Immunol 1987; **106**:139–50.

53 Chan CC, Hooks JJ, Nussenblatt RB *et al.* Expression of Ia antigen on retinal pigment epithelium in experimental autoimmune uveitis. Curr Eye Res 1986; **5**:325–30.

54 Liversidge J, Thompson AW, Sewell HF *et al.* EAU in the guinea pig: inhibition of cell-mediated immunity and Ia antigen expression by cyclosporin A. Clin Exp Immunol 1987; **69**:591–600.

55 Craggs RI, Webster H de F. Ia antigens in the normal rat nervous system and in lesions of experimental allergic encephalomyelitis. Acta Neuropathol (Berl) 1985; **68**:263–72.

56 Male D, Pryce G. Induction of Ia molecules on brain endothelium is related to susceptibility to experimental allergic encephalomyelitis. J Neuroimmunol 1989; **21**:87–90.

57 Woodroofe MN, Hayes GM, Cuzner ML. Fc receptor density, MHC expression and superoxide production are increased in interferon-gamma-treated microglia isolated from adult rat brain. Immunol 1989; **68**:421–6.

58 Fontana A, Fierz W, Wekerle H. Astrocytes present myelin basic protein to encephalitogenic T-cell lines. Nature 1984; **307**:273–6.

59 Calder VL, Wolswijk G, Noble M. The differentiation of O-2A progenitor cells into oligodendrocytes is associated with a loss of inducibility of Ia antigens. Eur J Immunol 1988; **18**:1195–201.

60 Naparstek Y, Cohen IR, Fuks Z *et al.* Activated T lymphocytes produce a matrix-degrading heparan sulphate endoglycosidase. Nature 1984; **310**:241–4.

61 Hickey WF. Migration of hematogenous cells through the blood-brain barrier and the initiation of CNS inflammation. Brain Pathol 1991; **1**:97–105.

62 Cannella B, Cross AH, Raine CS. Upregulation and coexpression of adhesion molecules correlate with relapsing autoimmune demyelination in the central nervous system. J Exp Med 1990; **172**:1521–4.

63 Male D, Pryce G, Hughes C *et al.* Lymphocyte migration into brain modelled *in vitro*: control by lymphocyte activation, cytokines and antigen. Cell Immunol 1990; **127**:1–11.

64 Liversidge J, Sewell HF, Forrester JV. Interaction between lymphocytes and cells of the blood-retinal barrier: mechanisms of T lymphocyte adhesion to human retinal capillary endothelial cells and retinal pigment epithelial cells *in vitro*. Immunol 1990; **71**:390–6.

65 Rudge P, Koetsier JC, Mertin J *et al.* Randomised double blind controlled trial of cyclosporin in multiple sclerosis. J Neurol Neurosurg Psych 1989; **52**:559–65.

66 Towler HM, Cliffe AM, Whiting PH *et al.* Low dose cyclosporin A therapy in chronic posterior uveitis. Eye 1989; **3**:282–7.

67 Palestine AG, Nussenblatt RB, Chan C-C. Cyclosporine penetration into the anterior chamber and cerebrospinal fluid. Amer J Ophthal 1985; **99**:210–1.