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Relapsing Experimental Allergic Encephalomyelitis An Autoimmune Model of Multiple Sclerosis

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Introduction

Experimental allergic encephalomyelitis (EAE) has been demonstrated to be a valuable animal model for studying organ-specific autoimmune mechanisms of disease. Particularly useful has been the ability to evaluate both clinical and pathologic progression of illness. During much of the 50 years that EAE has been studied, attention has been focused on the acute monophasic form of the disease. This form, which could be easily induced in several species of mammals, has the advantage of developing rapid signs of central nervous system (CNS) dysfunction and CNS inflammation. Acute EAE is a good animal model for the human demyelinating disease, acute disseminated encephalomyelitis, or post-vaccinal encephalomyelitis. As a model of multiple sclerosis (MS), acute EAE has several drawbacks. Acute EAE is almost always monophasic and thus lacks the random relapsing-remitting or chronic progressive pattern that is characteristic of the vast majority of MS cases. Further, the CNS lesion of acute EAE consists primarily of perivascular inflammation with little or no demyelination, while the pathologic lesion of MS is characterized by disseminated demyelination.

Chronic forms of EAE have been described in the past in monkeys [8] and guinea pigs [47], but relapses were uncommon. More recently, attention has focused on models of relapsing EAE (R-EAE) because of its clinical similarity to MS. R-EAE has been described in mice [5, 9, 35], guinea pigs [20, 58], hamsters [38], rats [42], rabbits [7, 57], and monkeys [10, 44]. The clinical picture of clearly demonstrable relapses with intervening periods of varying degrees of recovery is highly reminiscent of the commonest clinical form of MS. Some of the R-EAE models have an onset of disease which has a considerable delay after innoculation [7, 35, 38]. This delay may be analogous to the hypothesized latency between the sensitization for MS in childhood and disease expression in later life [16]. In addition to the clinical similarities to MS, the pathologic changes seen in the CNS in several of these R-EAE models [6, 22, 35, 58] consist of acute, subacute, and chronic demyelinated lesions similar to those of MS.

The value of an animal model that resembles MS has been stressed [58]. The reliable production of a relapsing-remitting form of EAE has several important advantages in understanding inflammatory demyelinating disorders. Of considerable pathogenic significance is the fact that the clinical and pathologic features of MS can be duplicated by R-EAE, a clearly autoimmune disorder.

Methods of Induction

R-EAE has been induced by somewhat different techniques in different species. Most induction protocols have been derived from those used for acute EAE. In the guinea pig, R-EAE is most easily produced by immunizing juvenile animals [58], although increasing the dose of CNS antigen produces R-EAE in adult guinea pigs [59]. In the mouse, R-EAE can be induced in both young [35] and adult [5, 9, 35] animals. R-EAE has also been produced in adult rats [42] and hamsters [38]. Thus, for most species, age of immunization does not appear to be a major factor in R-EAE induction.

Guinea pig R-EAE usually is induced with whole CNS antigen. R-EAE has also been induced in guinea pigs with myelin and myelin basic protein (MBP) plus myelin lipids [37]. R-EAE has been produced with MBP alone in Lewis rats, although little demyelination occurred [42]. In mice, relapsing disease identical to that seen with whole CNS has been produced with MBP alone [9, 32]. Occasional relapses have been seen during the course of chronic EAE in rabbits immunized with bovine proteolipid apoprotein [7], but the possibility of contamination of the proteolipid with MBP has been raised [55]. Thus, for mice and rats the minimal antigen for producing R-EAE is MBP alone. Addition of cerebrosides or gangliosides to MBP does not enhance either the clinical or pathologic signs of R-EAE in mice [32]. In guinea pigs, R-EAE appears to require additional myelin components in the immunization emulsion. Table 1 outlines the models of R-EAE in different species and their necessary antigens.

Most R-EAE models employ the use of complete Freund adjuvant (CFA). The amount of mycobacteria in the adjuvant has varied from relatively low doses [5] to high doses [15, 31]. Murine R-EAE has been produced both with pertussis vaccine in the immunization emulsion given subcutaneously [32, 35] and given intravenously [9]. However, murine R-EAE can be induced without pertussis vaccine as an immunoenhancer [5, 32]. R-EAE in the Syrian hamster also employs pertussis vaccine subcutaneously [38]. Therefore, pertussis vaccine immunohancement is helpful in murine and hamster R-EAE but is not essential to its production. The effect of intravenous pertussis vaccine on the development of acute EAE has been shown to be related to both vasoactive amine sensitization [29] and enhancement of T-cell responsiveness [17]. The role of subcutaneous pertussis vaccine in R-EAE is not known.

The above studies demonstrate that the minimal requirements for production of R-EAE and CNS demyelination are MBP as antigen in complete Freund adjuvant. The factors that determine whether MBP in CFA will produce acute or relapsing EAE are not altogether clear. In SJL mice, the strain most susceptible to R-EAE, the protocol used to produce delayed R-EAE [35] does not induce acute disease. Other

Table 1. Models of relapsing EAE

Species	*Antigen*	*Reference*
Mouse	CNS	5,35
	MBP	9,32
Rat	MBP	42
Guinea pig	CNS	14, 22, 58, 59
	MBP + LIPIDS	37
Hamster	CNS	38
Rabbit	PAP	57
Monkey	CNS	10,44

CNS = whole central nervous system; *MBP* = myelin basic protein; *PAP* = myelin proteolipid apoprotein

protocols using neural antigen in CFA with [9] or without [5] pertussis administered intravenously can induce both acute and relapsing forms of disease.

Clinical Signs and Course

The clinical signs seen in R-EAE consist of hind limb (and tail, when present) paresis and paralysis – both flaccid and spastic, quadriparesis(plegia), hemiparesis(plegia), ataxia, abnormal righting responses, and incontinence. Hind limb paresis is the commonest finding. Clinical signs of optic nerve involvement have been described in rhesus monkeys [10].

The usual time course of R-EAE in the guinea pig and some mouse models is for an acute attack about two to three weeks after immunization, followed by recovery and then periodic relapses [5, 21, 58]. In other mouse models and the hamster [35, 38], there is a delayed onset of clinical signs of up to several months after immunization, followed by recovery and subsequent relapses. In addition to a relapsing-remitting course, chronic progressive disease has been described in some mice and guinea pigs immunized as outlined above.

Histopathology

The pathologic lesion of R-EAE consists of perivascular mononuclear cell inflammation with extension into CNS parenchyma and meninges (Fig. 1), and acute, subacute, and chronic demyelination (Fig. 2) with some remyelination (Fig. 3). In the mouse, these lesions are most commonly seen in the white matter of the cerebellum, brain stem, and spinal cord [35]. In demyelinated areas there is loss of myelin with relative preservation of axons, astrocytic gliosis, and loss of oligodendrocytes [35]. In the murine form of EAE that employs a two injection regimen without addition of pertussis, hemorrhagic lesions with influxes of polymorphonuclear leukocytes were seen during acute episodes [6]. Demyelination followed by remyelination was also seen [6]. In the guinea pig, R-EAE follows a topographic distribution of lesions similar to MS [22]. Periventricular lesions in the centrum semiovale are the

Fig. 1. Section of brain stem with perivascular lymphocytic infiltrates extending into parenchyma and meninges (H & E, × 112)

commonest abnormality in the brain [25]. Macroscopically visable plaques of demyelination can be seen in guinea pigs with R-EAE [22]. The microscopic lesions are similar to those of the mouse with perivenous inflammation, demyelination, oligodendrocyte loss, and gliosis [22, 58]. Older lesions tended to have fewer inflammatory cells. Areas of demyelination and remyelination occurred in different areas of the same plaque [22]. The histogenesis of the demyelinating lesions in R-EAE has been described by Lassmann et al. [23, 26].

The development of pathologic changes can occur in the absence of clinical signs. In a study where SJL mice were sacrified at fixed intervals after immunization for delayed, relapsing disease regardless of clinical signs, we found that perivascular inflammation could occur as early as two weeks after immunization and in the absence of any clinical signs. However, pathologic changes were not present in all animals, and some animals had no pathologic findings as late as one year after immunization. Conversely, clinical signs rarely occurred without corresponding pathologic changes. Chronic demyelination was most prominent in animals that had more than one clinical attack. Therefore, the pathologic changes of delayed R-EAE, although present at an earlier time than clinical signs, still follow a random pattern of occurrence, much like MS.

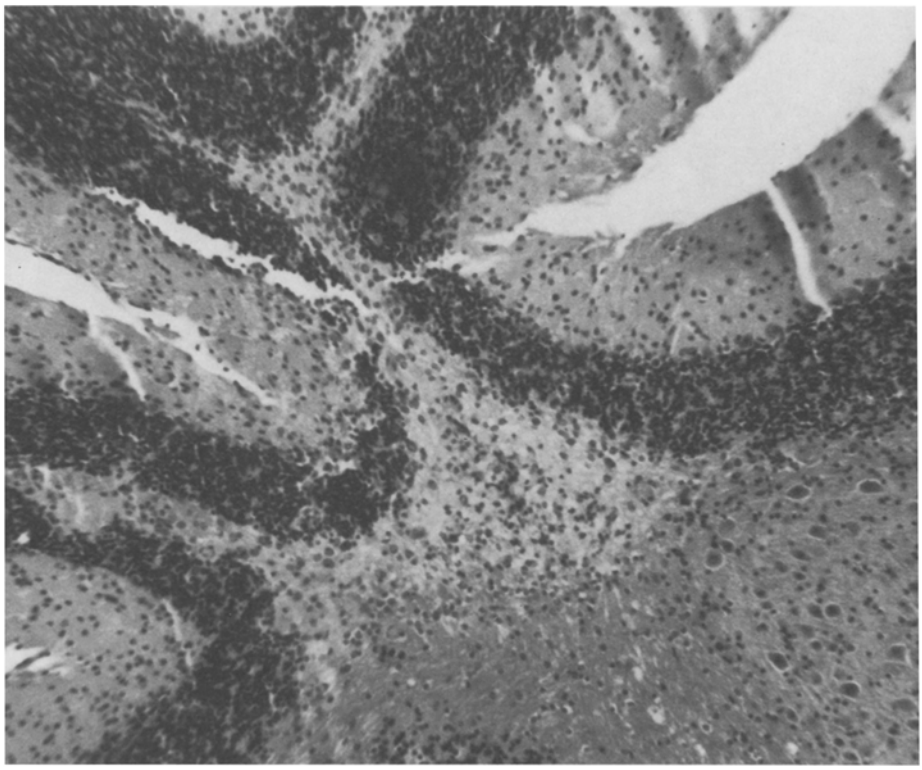

Fig. 2. Area of demyelination in cerebellar white matter (Luxul fast blue-H & E, × 56)

Immunopathogenesis

Acute monophasic EAE has been shown to be a T-cell dependent cell-mediated autoimmune disorder [1, 4]. It is reasonable to assume that R-EAE is an extension of this process. Cell-mediated immunity, as measured by a lymphocyte proliferation assay, to MBP can be found in murine R-EAE as early as two weeks after immunization, and before the onset of clinical signs. These responses are long lasting, demonstrable up to one year after immunization. The in vitro responses, however, do not seem to correlate with clinical activity (F. D. Lublin, unpublished data).

R-EAE can be adoptively transferred to naive recipients with lymphocytes as reported for R-EAE in the mouse [34, 40]. In acute EAE, the Lyt-1 subset of lymphocytes has been shown to be responsible for transfer of disease [3, 43]. The subsets needed for transfer of R-EAE have not been studied. R-EAE can be transferred with lymphocytes taken directly from immunized animals [34] or with lymphocytes cultured in vitro with MBP [34, 40] or T-cell growth factor [34]. The clinical and pathologic features of the R-EAE produced in the recipient mice are the same as those seen in actively immunized mice. Therefore, an antigen-adjuvant depot in relapsing mice does not appear to be necessary for the production of

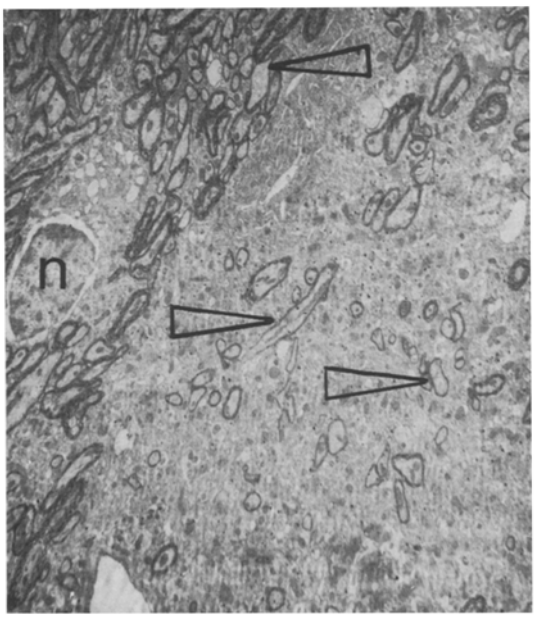

Fig. 3. Electron micrograph of brain stem. The *arrows* point to remyelinating fibers (× 2500)

episodic relapses of EAE, even though MBP can be demonstrated in these depots long after immunization [49]. Instead, specifically sensitized lymphocytes appear to be capable of periodically causing clinical signs of CNS dysfunction. It is not yet clear whether the pathological changes of R-EAE in recipients of transferred sensitized lymphocytes also fluctuate, as seen in actively immunized mice. Possibly some exogenous or endogenous factor(s) alters either the immune system or the CNS such as to precipitate attacks of R-EAE.

During exacerbations of R-EAE circulating T-cell levels are decreased [51], as also seen in attacks of acute EAE in guinea pigs [36, 50]. During remission, circulating lymphocyte levels are normal. Immunohistochemical studies of brain tissue in animals with R-EAE demonstrate that T-cells are seen predominantely in CNS white matter, while B-cells are seen primarily in meningeal and perivascular areas [52]. Similar occurrences are seen in MS where changes in both lymphocyte cell surface characteristics and functional capacities have been reported at the time of acute exacerbation [11, 54].

Increased permeability of the blood-CSF barrier and the presence of an oligoclonal IgG pattern in CSF and blood are seen in R-EAE [13, 48]. Others have shown intracerebral synthesis of IgG in R-EAE [39]. Anti-myelin antibody has been found in the sera of guinea pigs during the course of R-EAE [28, 41]. This antibody did not migrate with the oligoclonal bands founds in the same animals, suggesting that the oligoclonal bands may not be of pathogenic importance. Serum from guinea pigs with R-EAE is reported to be able to produce demyelination in central and peripheral nervous tissue in vivo [24, 27].

The evidence thus far favors a cell-mediated immune mechanism in the immunopathogenesis of R-EAE. There is, however, some evidence for a potential

role of an antibody-mediated immunopathogenesis, which could occur as either a primary reaction or, more likely, as a secondary sensitization to an initial cell-mediated attack on CNS myelin.

Much remains to be studied on the immunopathogenesis of R-EAE. The disease is undoubtably autoimmune and has similarities to acute EAE. However, the events leading to the relapses have not been clearly elucidated thus far and remain a central point for ongoing studies. There are clear analogies between the immunologic changes seen in R-EAE and those of MS.

Immunomodulation

The incidence of murine R-EAE can be reduced by treatment with mouse spinal cord (MSC) or MBP in incomplete Freund adjuvant (IFA) prior to immunization with antigen in CFA [33]. The degree of protection induced was long lasting and was similar in groups pretreated with either MSC or MBP. The degree of protection was less than that seen in similarly treated mice immunized for acute EAE [2]. Guinea pig R-EAE can also be suppressed by treatment with MBP and IFA [51]. Studies of treatment of guinea pig R-EAE after at least one relapse revealed that treatment with MBP in combination with galactocerebroside was more effective than MBP alone [53]. Amelioration of R-EAE in Rhesus monkeys has been reported after treatment with spinal cord and IFA [44].

The role of suppressor cells in the regulation of R-EAE has been a topic of considerable speculation, but little experimental data are available. In acute EAE, the prevention of disease in animals pretreated with MBP in IFA has been shown to be due to induction of suppressor cells [2]. Similar data have not been developed in R-EAE. Inhibition of suppressor cells in murine R-EAE has been attempted with low dose cyclophosphamide (CYP), using protocols reported to inhibit suppressor cells in acute EAE [18]. Low dose CYP, 20 mg/kg, when given at the time of immunization or one month after immunization had no effect on the incidence of R-EAE or the latency to onset [33]. This again differs from acute EAE where some resistant strains have become responders after pretreatment with low dose CYP [19].

Sriram and Steinman have shown that R-EAE can be effectively suppressed after the appearance of disease by treatment with antibody against immune response gene products – anti I-A antibody [46]. The mechanism of this suppression is believed to in part involve induction of a suppressor T-cell for MBP [45].

Therapy

Studies on the use of therapeutic agents in R-EAE have centered around immunomodulating agents. Treatment protocols utilizing incomplete Freund's adjuvant – CNS antigen emulsions have been outlined above. Traugott et al. [53] utilizing an MBP-galactocerebroside-IFA treatment protocol demonstrated both a decrease in clinical disease as well as evidence of remyelination and proliferation of oligodendrocytes in the CNS lesions of treated animals. Pretreatment of guinea pigs

with the synthetic polypeptide, copolymer I [15] in IFA had an effect of delaying or preventing EAE. When copolymer I was administered at the start of a clinical attack, progression of the disease was often modified.

Low dose CYP, 20 mg/kg, as detailed under "immunomodulation", was not effective in enhancing murine R-EAE. To the contrary, when give serially in five doses over eight weeks, low dose CYP reduced the incidence of clinical R-EAE to 10% in treated mice as compared to 77% in the unmodified disease. Similarly, histopathologic changes were found in only 30% of treated mice as compared to 90% of untreated mice. Higher doses of CYP, 100–200 mg/kg, were ineffective in inhibiting R-EAE [33].

Summary

R-EAE is a valuable model for human MS. Table 2 outlines the similarities between R-EAE and MS. The clinical course and pathologic changes seen in this model accurately reflect the pattern of MS. The immunologic changes seen in animals with R-EAE also are similar to those seen in MS. Therefore, the clinicopathologic features of MS can be duplicated with a purely autoimmune model. Although this is of considerable pathogenic significance in understanding MS, we do not know what the inciting event is in MS that would be the equivalent of immunizing an animal with neural antigen. Despite this, R-EAE has and should continue to provide experimental data of considerable importance to an understanding of the mechanisms involved in the evolution of inflammatory demyelination.

Other important models of MS utilize viral-induced demyelination. Although the clinical picture of most of the chronic demyelinating viral infections does not show as clear a relapsing or remitting pattern as seen in R-EAE, viral etiologies better fit the epidemiology of MS [16]. Several studies have demonstrated development of an acute EAE-like disease with sensitization to neural antigens following viral infection [12, 30, 56]. Thus, one can hypothesize an initial viral illness causing sensitization of the host to a neural antigen (?MBP) with a subsequent immunopathogenic course similar to that seen in R-EAE. Whether this will in fact be the case remains unproven as yet.

Our understanding of the immunopathogenic mechanisms underlying inflammatory demyelination has been enlarged through studies of R-EAE. It is now clear that the minimal myelin antigen necessary for production of the disease is MBP, although this may differ in some species. The relapsing nature of this disorder is mediated in part through lymphocytes, as demonstrated in transfer studies, and thus does not require persistent antigenic depots. There is a genetic susceptibility to development of the CNS autoimmune state, and we speculate that an as yet unidentified perturbation of the host immune system allows for the occurrence of relapsing disease (Table 3).

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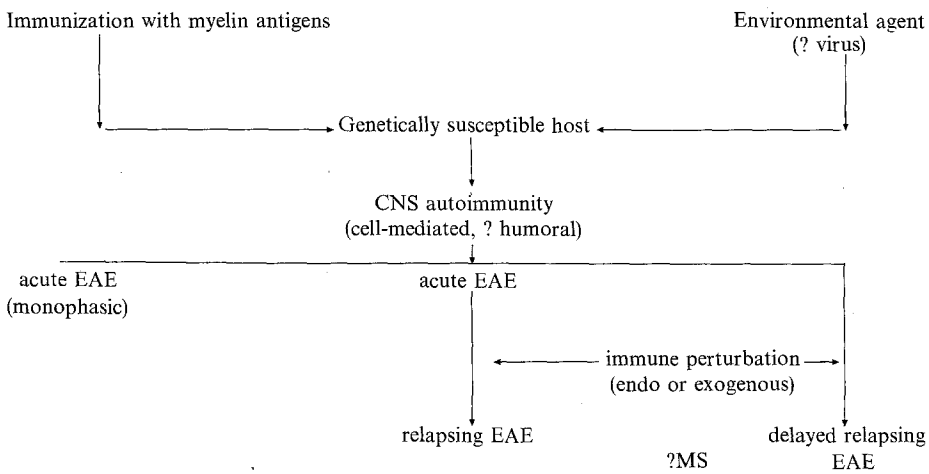
Table 2. Comparison of relapsing EAE to multiple sclerosis

	R-EAE	*MS*
Relapsing – remitting course	+	+
Chronic progressive course	+	+
Acute perivascular inflammation	+	+
Demyelination	+	+
Remyelination	+	+
Genetic predisposition	+	+
Cell-mediated immunity to MBP	+	+
Oligoclonal bands in CSF	+	+
Changes in immune function during acute attacks	+	+
Environmental factors	?	+
Known antigen	+	–

Table 3. Theoretical pathogenesis of relapsing autoimmune demyelination



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