Surges of Increased T Cell Reactivity to an Encephalitogenic Region of Myelin Proteolipid Protein Occur More Often in Patients with Multiple Sclerosis Than in Healthy Subjects

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*J Immunol 2000; 165:5322-5331;*
doi: 10.4049/jimmunol.165.9.5322
http://www.jimmunol.org/content/165/9/5322
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We have previously shown that patients with multiple sclerosis (MS) have increased T cell responses to the immunodominant region (residues 184–209) of myelin proteolipid protein (PLP). The present study investigated whether this reactivity fluctuates over time and correlates with disease activity. We performed monthly limiting dilution assays for 12–16 mo in four healthy subjects and five patients with relapsing-remitting MS to quantify the frequencies of circulating T cells proliferating in response to PLP141–58, PLP184–199, PLP190–209, myelin basic protein (MBP), MBP82–100, and tetanus toxoid. Disease activity was monitored by clinical assessment and gadolinium-enhanced magnetic resonance imaging of the brain. There were fluctuations in the frequencies of autoreactive T cells in all subjects. Compared with healthy controls, MS patients had significantly more frequent surges of T cells reactive to the 184–209 region of PLP, but infrequent surges of T cell reactivity to MBP82–100. There was temporal clustering of the surges of T cell reactivity to MBP82–100 and MBP, suggesting T cell activation by environmental stimuli. Some clinical relapses were preceded by surges of T cell reactivity to PLP184–209, and in one patient there was significant correlation between the frequency of T cells reactive to PLP184–199 and the total number of gadolinium-enhancing magnetic resonance imaging lesions. However, other relapses were not associated with surges of T cell reactivity to the Ags tested. T cells reactive to PLP184–209 may contribute to the development of some of the CNS lesions in MS. The Journal of Immunology, 2000, 165: 5322–5331.

T here is increasing evidence that multiple sclerosis (MS) is an autoimmune disease (1, 2). In a large cross-sectional study, we have previously shown that patients with relapsing-remitting MS or secondary progressive MS have increased peripheral blood T cell proliferative responses to two overlapping peptides (residues 184–199 and 190–209) in the 184–209 region of myelin proteolipid protein (PLP) (3). Epitopes within the same region of PLP (residues 178–209) are encephalitogenic in a variety of mice of different genetic backgrounds (4, 5). This region (residues 180–199) is a dominant one recognized by human T cells (control and MS) that have been stimulated several times in vitro with PLP (6). A notable feature of peptides from the 184–209 region of PLP is that they are promiscuous in their binding to a range of MHC class II molecules (5, 6). Indeed, this is why we initially chose these PLP peptides for use in our MS research. In our previous study, we also found that T cell lines stimulated with whole PLP can recognize both PLP184–199 and PLP190–209 and that T cell lines specific for these peptides can recognize the whole PLP molecule (3). These results indicated that the intact PLP molecule can be naturally processed into epitopes contained within the PLP184–199 or PLP190–209 peptides.

The aims of the present study were to determine whether the peripheral blood T cell response to the 184–209 region of PLP changes over time in healthy subjects and patients with relapsing-remitting MS and to determine whether changes in blood T cell reactivity correlate with disease activity. Limiting dilution analysis is a useful, reliable method to quantify T cell responses to Ags in individual subjects over time (7, 8). We performed monthly limiting dilution analysis to quantify the frequencies of circulating T cells capable of proliferating in response to PLP141–58, PLP184–199, PLP190–209, whole myelin basic protein (MBP), MBP82–100 (the immunodominant region of MBP (9, 10)) and to a control Ag, tetanus toxoid. Disease activity in the patients with MS was monitored by monthly clinical assessment and by gadolinium-enhanced magnetic resonance imaging (MRI) of the brain.

Materials and Methods

Patients and healthy subjects

This study was approved by the Research Ethics Committee of the Royal Brisbane Hospital and by the Medical Research Ethics Committee of the University of Queensland. All subjects gave informed consent to participate in the study. The subjects of this study consisted of five patients with clinically definite MS (11) of the relapsing-remitting type and four healthy volunteers. The sex, age, duration of MS, and HLA haplotypes of the subjects are shown in Table I. All subjects had been previously vaccinated with tetanus toxoid, but none was vaccinated during the course of the study. None of the patients with MS was receiving any immunosuppressant, immunomodulatory, or corticosteroid therapy at the time of commencement of the study, but three were commenced on IFN-β-1b (8 × 10^6 U s.c. every second day) late in
the study, and two received one course of i.v. methylprednisolone therapy (500 mg daily for 5 days) for a relapse. Once a month, at the time of blood collection, each patient with MS was assessed clinically by the same investigator (R.D.H.). A clinical relapse was defined as an episode of new or worsening neurological symptoms and new or worsening neurological signs without any other explanation (such as fever) and lasting for at least 24 h.

**HLA-DR and -DQ typing**

Genomic DNA was prepared from whole blood or from EBV-transformed lymphoblastoid cell lines from each subject. HLA-DR typing was performed using Dynal (Dynal, Carlton South, Victoria, Australia) sequence-specific primer sets according to the manufacturer’s instructions. HLA-DQ typing was conducted at the Department of Immunology, Westmead Hospital (Sydney, Australia). For HLA-DQ typing, DNA was initially amplified by PCR using generic primer pairs. HLA-DQA1 and -DQB1 alleles were determined by RFLP analysis of the PCR products.

**Antigens**

PLP<sub>41–58</sub> (GTEKLIETYFSKNYQDYE), PLP<sub>184–199</sub> (QSIAFPSKTSA SIGSL), and PLP<sub>190–209</sub> (SKTSASIGSLCADARMYGVL) were synthesized by Auspep (Melbourne, Australia) according to the human sequence (12). They were >90% pure by HPLC analysis. PLP<sub>184–199</sub> and PLP<sub>190–209</sub> are moderately hydrophobic, and were dissolved at a concentration of 5 mg/ml in 0.2 M acetic acid before dilution in tissue culture medium for limiting dilution assays. Human MBP was extracted from human brain according to the method of Deibler et al. (13). MBP<sub>82–100</sub> (DENPVH FFKNIVTPRP), numbered according to the human sequence, was synthesized by Auspep. Tetanus toxoid was a gift from CSL (Melbourne.

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**FIGURE 1.** Frequencies of circulating T cells capable of proliferating in response to specific Ags, as determined by monthly limiting dilution assays in a healthy subject (DW).
PLP\textsubscript{41-58}, Whole MBP, MBP\textsubscript{82-100}, and tetanus toxoid were dissolved in water.

**Limiting dilution assays**

Heparinized blood was collected by venepuncture from each subject at monthly intervals. PBMC were separated from the blood by centrifugation through Histopaque (Sigma, St. Louis, MO) and washed twice. For the limiting dilution assays, we used 96-well round-bottom microtiter plates (Nunc, Roskilde, Denmark) containing 200 \(\mu\)l/well RPMI 1640 supplemented with 10% heat-inactivated pooled human serum, 2 mM L-glutamine, and 10 mM HEPES buffer. The PBMC were added to the wells at four different concentrations, 100,000, 50,000, 10,000, and 5,000 cells/well. Twenty-four wells were prepared at each cell concentration for each Ag. To each of the wells, 50,000 autologous irradiated PBMC were added as APC. The Ags were added at the following concentrations: PLP\textsubscript{41-58}, PLP\textsubscript{184-199}, PLP\textsubscript{190-209} and MBP\textsubscript{82-100} at 20 \(\mu\)g/ml; whole MBP at 30 \(\mu\)g/ml; and tetanus toxoid at 10 limes flocculation U (LF)/ml. The cultures were incubated for 6 days, with 0.5 \(\mu\)Ci \([\text{H}]\)thymidine being added during the last 18 h. Cultures were harvested, and \([\text{H}]\)thymidine uptake was measured in cpm in a \(\beta\)-plate counter (LKB Instruments, Gaithersburg, MD). Wells were considered positive if the cpm exceeded twice the mean cpm for control wells (at the same concentration of responder PBMC) not containing Ag and if it exceeded the control mean cpm + 3 SD. The number of negative wells for each Ag at each cell concentration was recorded and used to determine the frequency of T cells capable of proliferating in response to the specific Ag. To calculate the frequencies and the 95% confidence intervals, we used a computer program written by Dr C. Schmidt (Queensland Institute of Medical Research, Brisbane, Australia) that used the maximum likelihood estimation method (14).

**Magnetic resonance imaging**

Four of the patients with MS had monthly MRI brain scans at the time of blood collection. The scans were performed with a 1.5 T Siemens System (Siemens, Erlangen, Germany). Scout images were taken to confirm the similar positioning of all subjects, and axial scanning was conducted parallel to the plane defined by the anterior and posterior commissures on a preliminary midline sagittal image. The slice thickness was 5 mm in the first half of the study and 3 mm in the second half. \(T_1\)-weighted imaging was performed before and 5 min after the i.v. administration of dimeglumine gadopentetate (gadolinium, 0.1 mmol/kg). All of the scans were assessed by the same investigator (P.D.M.), who was unaware of the results of the clinical assessment and the limiting dilution assays. This investigator determined the total number of gadolinium-enhancing lesions \(\geq 2\) mm in diameter and the number of new enhancing lesions since the previous scan.

**Statistical analysis**

The means of the T cell frequencies for each Ag in healthy subjects and patients with MS were compared by Student’s \(t\) test after assessing for differences between variances. A surge in T cell frequency was defined as a frequency \(\geq 2\) SD above the mean frequency for that Ag in healthy subjects (see Table II).
subjects. The percentages of time points at which surges occurred for each Ag in healthy subjects and patients with MS were compared by the χ² test with Yates’ correction. To determine whether the T cell frequencies correlated with the number of gadolinium-enhancing MRI lesions in individual patients, we used linear regression analysis.

Results

Findings in healthy subjects

The frequencies of peripheral blood T cells capable of proliferating in response to the tested specific Ags measured at monthly intervals are illustrated in detail for one of the healthy subjects in Fig. 1 and are summarized for all four healthy subjects in Fig. 2. It is clear that in each healthy subject the T cell frequencies for at least one myelin Ag fluctuated over time. From the total set of measurements in the four healthy subjects, we calculated the mean and SD of the T cell frequency for each Ag and defined a surge in the T cell frequency as a frequency $\geq 2$ SD above the mean (Table II). Surges of high frequencies of T cells for each Ag occurred in at least one of the healthy subjects and, in the case of MBP82–100, in three of these subjects (Fig. 2 and Table III). The high frequencies of T cells reactive to tetanus toxoid in two of the subjects (KC and LA in Fig. 2) were not explained by recent vaccination.

Findings in patients with MS

The frequencies of peripheral blood T cells capable of proliferating in response to the tested specific Ags measured at monthly intervals are summarized for all five MS patients in Fig. 2 and are illustrated in detail for each of the five patients in Fig. 3 and Figs. 5–8. Surges of high frequencies of T cells reactive to PLP190–209 occurred significantly more often in MS patients than in healthy subjects (Fig. 2 and Table III). These surges occurred particularly often in one MS patient (MS 48) (Figs. 2 and 5), but even when this patient was excluded the surges occurred more often in the MS patients than in the healthy subjects. Surges of high frequencies of T cells reactive to the overlapping PLP184–199 peptide also occurred more often in patients with MS but the difference was not statistically significant. When the results for the two overlapping PLP peptides were considered together, surges of high frequencies of T cells reactive to the 184–209 region of PLP were found in 32.8% of the time points analyzed in the MS patients compared with 12.0% of the time points in the healthy subjects ($p = 0.016$, Table III). Surges of high frequencies of T cells reactive to PLP184–199 and/or PLP190–209 occurred in all five patients with MS (Fig. 2). The fluctuating nature of the T cell response is emphasized by the fact that the patient (MS 35) who, of these five patients, had had the highest level of T cell reactivity to PLP190–209 (stimulation index, 8.2) in our previously published cross-sectional study (3) was the only patient who did not have one or more surges of a high frequency of T cells reactive to this peptide in the present longitudinal study (Figs. 2 and 6). Surges of high T cell frequencies for MBP, but not MBP82–100, occurred more often in patients with MS than in healthy subjects, but the difference was not significant (Fig. 2 and Table III). The above differences between MS patients and healthy subjects were not altered by excluding the measurements made after the commencement of IFN-β-1b late in the course of the study in three patients. The higher and more variable T cell reactivity to the 184–209 region of PLP in MS patients is also reflected in higher mean T cell frequencies and variances for PLP184–199 and PLP190–209 (Table II).

Correlation with disease activity

In the patients with MS the frequencies of T cells reactive to PLP184–199 or PLP190–209 partly correlated with disease activity as assessed by clinical relapses or the number of gadolinium-enhancing lesions on MRI brain scans (Figs. 3–8). In patient MS 42, there was a surge in the frequency of T cells reactive to PLP184–199 just before the first relapse shown in Fig. 3; the T cell frequencies just before the second relapse are unknown because blood was not collected in the preceding month. High frequencies of T cells

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<th>Table II. T cell frequencies in healthy subjects and patients with MS</th>
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<td>Healthy subjects</td>
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<td>$t$ test ($p$)*</td>
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* Frequency per 10⁶ PBMC.
# $Mean + 2 SD$ in healthy subjects is the level defining a surge in frequency (see Materials and Methods).

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<th>Table III. Percentages of surges of T cell reactivity</th>
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<td>Healthy subjects</td>
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<td>Patients with MS</td>
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** $\chi^2$ test on proportions.
reactive to PLP184–199, PLP190–209, or MBP also preceded or occurred concurrently with gadolinium-enhancing MRI brain lesions (Fig. 3). Furthermore, there was a significant correlation between the frequency of T cells reactive to PLP184–199 and the total number of gadolinium-enhancing MRI brain lesions in this patient (Fig. 4). In patient MS 48, a clinical relapse was preceded by a surge in the frequency of T cells reactive to PLP190–209, although other surges of this reactivity were not associated with relapses (Fig. 5). Some of the surges in the frequencies of these T cells in this patient were accompanied by increases in the frequencies of T cells reactive to other Ags, including tetanus toxoid, particularly following the i.v. administration of methylprednisolone for the relapse. This posttreatment effect may represent a rebound phenomenon following general immunosuppression by methylprednisolone. One of the surges in the frequency of T cells reactive to PLP190–209 (March 1998, Fig. 5) was accompanied by the development of gadolinium-enhancing MRI brain lesions, but there was no significant correlation between the number of gadolinium-enhancing MRI brain lesions and the frequency of T cells reactive to PLP184–199 or to PLP190–209 in patient MS 42 but not in patient MS 48. In the other three MS patients, one relapse was preceded by a surge in the frequency of T cells reactive to

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**FIGURE 3.** Numbers of total and new gadolinium-enhancing MRI brain lesions, clinical relapse profile, and frequencies of circulating T cells capable of proliferating in response to specific Ags, as determined by monthly limiting dilution assays, in patient MS 42. Bottom: , total numbers of gadolinium-enhancing lesions; , numbers of new gadolinium-enhancing lesions. IFN-β, IFN-β-1b, 8 × 10⁶ U s.c. every second day for the remainder of the study.

**FIGURE 4.** Correlation between the frequency of circulating T cells capable of proliferating in response to PLP184–199 as determined by limiting dilution analysis, and the total number of gadolinium-enhancing MRI brain lesions at the same time points in a patient with MS (MS 42; also see Fig. 3).
PLP\textsubscript{184–199} and to whole MBP (MS 35, Fig. 6), but three other relapses were not preceded by an increase in T cell reactivity to any of the Ags tested (Figs. 6 and 7). Two of these patients (MS 6 and MS 45) had no gadolinium-enhancing MRI brain lesions throughout the study despite surges in the frequencies of T cells reactive to the 184–209 region of PLP (Figs. 7 and 8). The other patient (MS 35) did not undergo MRI scanning.

**Temporal clustering of surges of high T cell reactivity to myelin Ags**

When the T cell frequencies of healthy subjects and MS patients for each Ag were plotted against time, it became evident that there was a temporal clustering of surges in the frequency of T cells reactive to MBP\textsubscript{82–100} in March–April 1998 (Fig. 9). During this period, two healthy subjects and one patient with MS had a surge in this reactivity, and in June 1998 a third healthy subject had such a surge. This temporal clustering raises the possibility of the action of an environmental factor such as infection by a virus or bacterium. No symptoms of infection were detected in these subjects at the time, but it is possible that these may have been missed. A clustering of surges of reactivity to whole MBP was observed in June–July 1997. During this time, three patients with MS had surges in this reactivity (data not shown); blood was not collected from the healthy subjects at these time points. There was no definite temporal clustering of the surges in T cell reactivity to any of the three PLP peptides.

**Discussion**

In this longitudinal study, we have shown that patients with relapsing-remitting MS have recurrent surges of high frequencies of circulating T cells capable of proliferating in response to the 184–209 region of PLP. This region of PLP is encephalitogenic in mice (4, 5) and immunodominant in humans (6). These surges occur significantly more often than in healthy subjects and partly correlate with disease activity as assessed by clinical relapses and gadolinium-enhancing MRI brain lesions. The mean frequencies of T cells reacting to the 184–209 region of PLP were also higher in the MS patients than in the healthy subjects, confirming the results of our previously published cross-sectional study, which measured stimulation indices in standard T cell proliferation assays (3). We also found that surges of T cell frequencies for the immunodominant peptide of MBP, MBP\textsubscript{82–100}, occurred no more often in...
MS patients than in healthy subjects and that surges of high T cell frequencies for whole MBP occurred more often, but the difference was not significant. The mean frequencies of T cells reactive to MBP82–100 or whole MBP in patients with MS were not significantly different from those of healthy subjects, which is consistent with the findings of our previous cross-sectional study (3), although another cross-sectional study using limiting dilution analysis found a significantly higher frequency of T cells reactive to whole MBP in eight MS patients compared with controls (16). As the PLP and MBP peptides used in the present study bind with high affinity to a broad range of HLA alleles (6, 17), we consider that the differences we observed in T cell reactivity between the MS patients and healthy subjects were not due to HLA differences.

It has been known for some time that healthy subjects possess T cells capable of reacting to self Ags, but the present study has revealed how the frequencies of circulating autoreactive T cells fluctuate over time. We found that surges of high T cell reactivity to all five myelin Ags tested occurred in healthy subjects. These surges in the frequencies of circulating autoreactive T cells indicate recent activation and expansion of these T cell populations. The temporal clustering of the surges in the frequencies of T cells reactive to MBP82–100 or MBP raises the possibility that these T cells were activated through cross-reactivity (molecular mimicry) after infection by a virus or bacterium. Recent evidence indicates that T cells are much more cross-reactive than previously thought (18) and that viral and bacterial peptides can activate myelin-reactive human T cells (19, 20). Vandenbark et al. (21) have reported temporal clustering of increases in T cell reactivity to whole MBP in patients with MS. They did not find such increases in healthy subjects but did not study the latter as often as the MS patients. It would be expected that the activated myelin-reactive T cells would enter the CNS in the healthy subjects, as activated T cells of any specificity, including autoreactive T cells, enter the normal CNS parenchyma (22, 23). The fate of myelin-reactive T cells in the CNS in healthy subjects is unknown, but it has recently been suggested that they may be eliminated by apoptosis (24), as occurs in rats recovering from experimental autoimmune encephalomyelitis (25, 26). We also observed some fluctuations in the frequencies of T cells reactive to tetanus toxoid in healthy subjects. Some variation in the frequency of T cells reactive to tetanus toxoid in healthy subjects over time has been previously observed (8) and may reflect activation through cross-reactivity or general up-regulation of the immune system after infection.

Some of the surges in T cell reactivity to myelin Ags in patients with MS may also be driven by cross-reactivity after viral or bacterial infection. Other surges may result from the activation of autoreactive T cells after the release of myelin Ags from the CNS during attacks of MS. Some previously activated myelin-reactive T cells may be reactivated nonspecifically by a general up-regulation of the immune system after infection. The latter mechanism may account for those surges of high frequencies of myelin-reactive T cells that occurred concurrently with high frequencies of T cells reactive to tetanus toxoid in the present study. As in the case of healthy subjects, it would be expected that the circulating activated...
myelin-reactive T cells would enter the CNS in MS patients. It has been hypothesized that, in contrast to the situation in healthy subjects, these T cells may fail to undergo apoptosis in the CNS and may thus be able to induce CNS demyelination with subsequent release of myelin Ags (24). The released myelin Ags may reactivate the originally aggressive autoreactive T cells and activate T cells specific for other myelin Ags, leading to the perpetuation and amplification of the autoimmune attack on the CNS.

In the present study, we found evidence that T cells reactive to PLP_{184–209} may contribute to the pathogenesis of MS. Some of the clinical relapses were preceded by surges in the frequency of circulating T cells reactive to PLP_{184–209}, and in one patient there was a significant correlation between the frequency of circulating T cells reactive to PLP_{184–199} and the total number of gadolinium-enhancing MRI brain lesions. Gadolinium enhancement indicates a breakdown of the blood-brain barrier and correlates with a marked perivascular accumulation of inflammatory cells (27). It often precedes other MRI abnormalities and clinical evidence of a new lesion (28), although a recent study suggests that some lesions may commence without a preceding phase of gadolinium enhancement (29). We suggest that some of the gadolinium-enhancing lesions and relapses in our patients developed as a consequence of the entry of T cells reactive to PLP_{184–209} into the CNS following an increase of these T cells in the circulation. However, some of the surges of T cell reactivity to PLP_{184–209} were not associated with either a clinical relapse or the development of gadolinium-enhancing MRI brain lesions. The lack of a constant association with clinical relapse is not surprising, given that clinical relapses are insensitive indicators of disease activity compared with gadolinium-enhanced MRI (30). Even with the use of gadolinium-enhanced brain MRI as in the present study, new lesions would have been missed if they occurred in the spinal cord or optic nerve, if they were small brain lesions, or if they developed without preceding gadolinium enhancement. Our study has also shown that some clinical relapses are not associated with a surge in T cell reactivity to PLP_{184–209}, PLP_{41–58}, MBP_{82–100}, or whole MBP. These relapses may have been induced by T cells reactive to other myelin Ags, such as other epitopes of PLP, epitopes of myelin/oligodendrocyte glycoprotein, or epitopes of the recently described oligodendrocyte-specific protein (31) or myelin-associated oligodendrocytic basic protein (32), but reactivity to these Ags was not determined in the present study.

Given the abundance of MBP in the CNS it is noteworthy that in contrast to the frequent surges of high T cell reactivity to

FIGURE 7. Numbers of total and new gadolinium-enhancing MRI brain lesions, clinical relapse profile, and frequencies of circulating T cells capable of proliferating in response to specific Ags, as determined by monthly limiting dilution assays, in patient MS 6. Bottom: ●, total numbers of gadolinium-enhancing lesions; ○, numbers of new gadolinium-enhancing lesions.
which contains the immunodominant PLP region, surges of high T cell reactivity to the immunodominant MBP peptide, MBP$_{82-100}$, were infrequent in MS patients. There are several possible explanations for this, including: more effective processing of PLP epitopes than MBP epitopes from the native proteins released from CNS demyelinating lesions; higher binding of PLP epitopes to MHC molecules and thus greater presentation to T cells; higher levels of Abs to PLP epitopes with resultant greater uptake of these epitopes by specific B cells and greater presentation by B cells to T cells; and apoptotic deletion of MBP-reactive T cells, but not PLP-reactive T cells, in the peripheral nervous system, which contains MBP but not PLP, although there may be a failure of apoptosis of all autoreactive T cells in the CNS (24).

We have shown that the frequencies of circulating autoreactive T cells fluctuate over time in both healthy subjects and patients with MS. We also found that surges of high T cell reactivity to the encephalitogenic 184–209 region of PLP occur more often in MS patients than in healthy subjects (25, 26).
patients than in healthy subjects. T cells reactive to this region of PLP may contribute to the development of some of the demyelinating lesions in the CNS in MS.

Acknowledgments

We thank Ray Buckley for assistance in performing the MRI scans.

References