Peroxisome Proliferator-Activated Receptor α Agonists as Therapy for Autoimmune Disease

Amy E. Lovett-Racke, Rehana Z. Hussain, Sara Northrop, Judy Choy, Anne Rocchini, Lela Matthes, Janet A. Chavis, Asim Diab, Paul D. Drew and Michael K. Racke

J Immunol 2004; 172:5790-5798; doi: 10.4049/jimmunol.172.9.5790
http://www.jimmunol.org/content/172/9/5790

Why The JI?
- Rapid Reviews! 30 days* from submission to initial decision
- No Triage! Every submission reviewed by practicing scientists
- Speedy Publication! 4 weeks from acceptance to publication

*average

References This article cites 43 articles, 20 of which you can access for free at:
http://www.jimmunol.org/content/172/9/5790.full#ref-list-1

Subscription Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscription

Permissions Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
Peroxisome proliferator-activated receptor \( \alpha \) agonists as therapy for autoimmune disease

Amy E. Lovett-Racke, Rehana Z. Hussain, Sara Northrop, Judy Choy, Anne Rocchini, Lela Matthes, Janet A. Chavis, Asim Diab, Paul D. Drew, and Michael K. Racke

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPAR\( \gamma \) ligands, which include the naturally occurring PG metabolite 15-deoxy-\( \Delta^{12,14} \)-PGJ\(_2\) (15d-PGJ\(_2\)), as well as thiazolidinediones, have been shown to have anti-inflammatory activity. The PPAR\( \alpha \) agonists, gemfibrozil, ciprofibrate, and fenofibrate, have an excellent track history as oral agents used to treat hypertriglyceridemia. In the present study, we demonstrate that these PPAR\( \alpha \) agonists can increase the production of the Th2 cytokine, IL-4, and suppress proliferation by TCR transgenic T cells specific for the myelin basic protein Ac1–11, as well as to reduce NO production by microglia. Oral administration of gemfibrozil and fenofibrate inhibited clinical signs of experimental autoimmune encephalomyelitis. More importantly, gemfibrozil was shown to shift the cytokine secretions of human T cell lines by inhibiting IFN-\( \gamma \) and promoting IL-4 secretion. These results suggest that PPAR\( \alpha \) agonists such as gemfibrozil and fenofibrate, may be attractive candidates for use in human inflammatory conditions such as multiple sclerosis. The Journal of Immunology, 2004, 172: 5790–5798.

1 Department of Neurology, and 2 Center for Immunology, University of Texas Southwestern Medical Center, Dallas, TX 75390; and 3 Department of Neurobiology and Developmental Sciences, University of Arkansas for the Medical Sciences, Little Rock, AR 72205

Received for publication December 2, 2003. Accepted for publication February 26, 2004.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 These studies were supported by the following research grants: U.S. Public Health Service Grant K24 NS044250 (to M.K.R.), U.S. Public Health Service Grant RO1 NS37513 (to M.K.R.), U.S. Public Health Service Grant RO1 NS42860 (to P.D.D.), National Multiple Sclerosis Society Grant RG 3427-A-8 (to M.K.R.), and grants from the Yellow Rose Foundation to M.K.R. and A.E.L.-R. This study was also supported by an advanced postdoctoral fellowship from the National Multiple Sclerosis Society (to A.D.).

2 Address correspondence and reprint requests to Dr. Michael K. Racke, Department of Neurology and the Center for Immunology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9036. E-mail address: Michael.Racke@utsouthwestern.edu

3 Abbreviations used in this paper: PPAR, peroxisome proliferator-activated receptor; 15d-PGJ\(_2\), 15-deoxy-\( \Delta^{12,14} \)-PGJ\(_2\); EAE, experimental autoimmune encephalomyelitis; MBP, myelin basic protein; TLR, T cell line; PLP, proteolipid protein; MS, multiple sclerosis.
when they are isolated (26). T cell clones derived during MS attacks are more likely to have a Th1 phenotype, while those derived during remission were more variable but included several T cells of a Th2 phenotype, suggesting that shifting the phenotype of T cells from Th1 to Th2 may be beneficial in MS.

In the present studies, we have examined the effects of PPARα agonists on the differentiation of autoreactive T cells and their effects on clinical signs of disease in the murine model of EAE. In addition, we have also examined the effects of gemfibrozil, a synthetic PPARα agonist with a long history of oral use in humans, on the secretion of cytokines by human myelin-reactive T cells. Our results suggest that PPARα agonists may be a useful therapeutic agent for human inflammatory diseases such as MS.

Materials and Methods

Mice

Transgenic mice bearing the rearranged Vα2.3, Vβ8.2 gene encoding the TCR specific for the myelin basic protein (MBP) Ac1–11 peptide on the B10.PL background were obtained by crossing transgenic mice bearing the individual rearranged genes (27). The Vα2.3 TCR-transgenic mice and the Vβ8.2 TCR transgenic mice were kindly provided by Dr. J. Governor (University of Washington, Seattle, WA). These mice were bred and maintained in a federally approved animal facility at the University of Texas Southwestern Medical Center (Dallas, TX) in accordance with the Institutional Animal Care and Use Committee. All mice were 7–10 wk old when experiments were performed. B10.PL mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and then bred in our animal facility.

Murine cell culture

Spleens from naive Vα2.3, Vβ8.2 TCR transgenic mice were harvested and single-cell suspensions were obtained by pressing the tissue through a wire mesh screen, as previously described (27). Proliferative responses of splenocytes (4 × 10⁵ cells/well) were determined using MBP.Ac1–11 (2 μg/ml) in the presence of various concentrations of gemfibrozil, ciprofibrate, or fenofibrate (Sigma-Aldrich, St. Louis, MO) as indicated, or equivalent volumes of solvent. Gemfibrozil, ciprofibrate, and fenofibrate were prepared as recommended by the manufacturer. Cultures were maintained in 96-well flat-bottom plates for 96 h at 37°C in humidified 5% CO₂/air. The wells were pulsed with 0.5 μCi/well [methyl-³H]thymidine for the final 16 h of culture. Cells were harvested on glass filters and incorporated [methyl-³H]thymidine was measured with a Betaplate counter (PerkinElmer Wallac, Gaithersburg, MD). Results were determined as means from quadruplicate cultures and are shown with SEM.

The NC9 microglial cell line is derived from myc-immortalized mouse microglia (28), and was graciously provided by P. Ricciardi-Castagnoli (University of Milan, Milan, Italy). Cells were cultured in MEM medium containing 10% FBS, 1.4 mM glutamine, and 20 μM 2-ME. Where indicated, cells were treated with IFN-γ (PBL Laboratories, Piscataway, NJ) plus TNF-α (R&D Systems, Minneapolis, MN) and/or the PPARα agonist, gemfibrozil, ciprofibrate, or fenofibrate (Sigma-Aldrich).

NO production assay

N9 microglial cell production of the NO derivative nitrite was assessed in culture medium by Greiss reaction as we have described previously (29). Cells were grown in 96-well plates. Where indicated, cells were pretreated for 1 h with gemfibrozil, ciprofibrate, or fenofibrate. Cells were then treated as indicated with IFN-γ (100 U/ml) plus TNF-α (500 U/ml), and nitrite levels were determined following incubation for 24 h.

Induction and clinical evaluation of EAE

EAE was induced in B10.PL mice by s.c. injection over four sites in the flank with 200 μg of MBP Ac1–11 (BioSource International, Camarillo, CA) in emulsions prepared with CFA (Difco, Detroit, MI) or pertussis toxin (200 μg/mouse) was injected i.p. at the time of immunization and 48 h later. Mice were scored on a scale of 0–6 as previously described (13): 0, no clinical disease; 1, limp/flaccid tail; 2, moderate hind limb weakness; 3, severe hind limb weakness; 4, complete hind limb paralysis; 5, quadriplegia or premoribund state; 6, death.

Administration of PPARα agonists to mice with EAE

For administration of gemfibrozil and fenofibrate to mice with EAE, stock solutions were made by dissolving these agents in ethanol (50 mg/ml).

When mice were fed by gavage, stock solution was diluted in PBS so that indicated dose of PPARα agonist was delivered in a total of 200 μl. Mouse chow was supplemented with gemfibrozil or fenofibrate by adding the stock solution to the chow (0.25% w/w), allowing the ethanol to evaporate, and then using it as the source of food. Control diet was given the same amount of ethanol without the PPARα agonist.

Pathology and immunohistochemistry

Mice were deeply anesthetized with sodium pentobarbital and transcardially perfused with sterile PBS, followed by 4% paraformaldehyde in phosphate buffer. The brain and spinal cord were removed, fixed in 4% paraformaldehyde for 6 h, and cryoprotected in 30% sucrose overnight at 4°C before being embedded in Tissue-Tek (T. Fella, Redding, CA) and quick-frozen in isopentane. Immunohistochemistry was performed on adjacent sections. After pretreatment with 0.3% hydrogen peroxide in absolute methanol, sections were blocked with 1% BSA for 2 h at room temperature and then incubated with primary Ab overnight at 4°C. Primary Abs used were MOMA-2 (1/20) mAb, for marker for macrophages (BioSource International) and KT174 (1/20), which recognizes CD4+ T cells (BioSource International).

The binding of the primary Abs was detected using a biotinylated secondary Ab and an avidin-biotin-peroxidase method under humidified conditions (ABC Elite kit; Vector Laboratories, Burlingame, CA). Peroxidase activity was visualized with 3,3’-diaminobenzidin (DAB kit; Vector Laboratories) as a substrate. Isotype IgG2c Ab served as a negative control. The tissue area was measured by a scion image analysis system (Scion, Frederick, MD). Positive cells were counted by automatic video scanning using a Leica Q500 MC (Zeiss, Oberkochen, Germany), and the numbers of stained cells per 10⁶ square pixels tissue area were calculated.

Cytokine ELISA

Mouse IFN-γ, IL-4, and IL-10 were quantified using a sandwich ELISA based on noncompeting pairs of Abs as previously described (13). Murine splenocytes from B10.PL mice with a transgenic TCR specific for MBP Ac1–11 were cultured at 8 × 10⁶ cells/well in 24-well plates with 2 μg/ml Ac1–11. Supernatants were collected at 24, 48, and 72 h and cytokine levels determined by ELISA. Human IFN-γ and IL-4 were determined similarly, using the same basic protocol with human-specific Abs. In brief, Immunulon 2 plates (Dynex Technologies, Chantilly, VA) were coated with purified monoclonal anti-IFN-γ (Code: M-700A; Endogen, Woburn, MA) or anti-IL-4 (catalog no. 554515; BD Pharmingen, San Diego, CA) at 2 μg/ml in 0.1 M NaHCO₃ at 4°C overnight. The plates were washed two times with PBS/1% Tween, blocked with 1% BSA/PBS, and 100 μl of supernatant was added to the plates in duplicate. The plates were placed at 4°C overnight and then washed four times with PBS/Tween. Biotin-labeled anti-mouse IgG (code: M-701B; Endogen, Woburn, MA) or anti-IL-4 (catalog no. 554515; BD Pharmingen) were added at 1 μg/ml and incubated at room temperature for 1.5 h. An avidin-peroxidase substrate was used to complete the assay. Concentrations of IFN-γ and IL-4 were determined using a standard curve generated using known concentrations of human recombinant IFN-γ (BD Pharmingen) and IL-4 (Calbiochem, San Diego, CA) in the assay.

Generation of human T cell lines (TCL)

Human lymphocytes were collected via leukapheresis from MS patients and healthy individuals under an Institutional Review Board approved protocol. Human TCL specific for MBP and PLP were generated as previously described (30). Bovine MBP (Sigma-Aldrich) or a mix of five PLP peptides (31–60, 91–120, 111–140, 131–160, and 177–206) were used at 10 μg/ml to generate the TCL. Lines designated with the letter M were derived from MS patients, while those designated with an H were derived from healthy individuals.

Human T cell proliferation assay

For Con A proliferation assays, 2 × 10⁵ PBMC were placed in each well of a 96-well plate. Con A was added at 1 μg/ml and various concentrations of gemfibrozil (or the same volume of ethanol which was the diluent for gemfibrozil) was added to quadruplicate wells. The wells were pulsed with 0.5 μCi/well [methyl-³H]thymidine for 18 h before harvesting at 96 h. Cells were harvested on glass filters using a Tomtec harvester (Tomtec, Hamden, CT), and incorporated [methyl-³H]thymidine was measured with a Betaplate counter (PerkinElmer Wallac).

T cell viability assay

Human PBMC or murine splenocytes were placed in 24-well plates at 5 × 10⁵ cells per well. Gemfibrozil, ciprofibrate, or fenofibrate (or an equal volume of solvent) were added to the wells at a final concentration of...
0–500 μM. At various time points, the cells were collected, resuspended in trypan blue, and the number of viable and nonviable cells were counted.

Results

PPARα agonists suppress lymphocyte proliferation in a dose-dependent manner

Because EAE is caused by CD4+ T cells specific for myelin Ags, we first examined whether various PPARα agonists have any effect on CD4+ Ag-specific proliferation. Splenocytes from naive Vaa3.2, V88.2 TCR transgenic mice were cultured with MBP Ac1–11 (2 μg/ml) in the presence of various concentrations of gemfibrozil, ciprofibrate, and fenofibrate. MBP Ac1–11-induced proliferation was inhibited by high doses of gemfibrozil (100–400 μM); however, lower doses did not affect T cell proliferation (20–50 μM) (Fig. 1A). Proliferation was decreased by 79.2% at the highest concentration tested. Similarly, lymphocyte proliferation was suppressed at higher concentrations of ciprofibrate (200–400 μM), with some minor fluctuations in proliferation at the lower doses (Fig. 1B). Fenofibrate completely inhibited lymphocyte proliferation at 50–100 μM concentrations, but had no effect at doses of 10 μM or less (Fig. 1C).

To determine whether the suppression of lymphocyte proliferation was a reflection of drug toxicity, a trypan blue exclusion assay was performed. TCR transgenic splenocytes were cultured in the presence of various concentrations of gemfibrozil, ciprofibrate, and fenofibrate. The cells were collected, washed, and counted at 1, 3, and 5 days. Both the viable and nonviable cells were counted by trypan blue exclusion. Gemfibrozil and ciprofibrate appeared to have no effect on cell viability except at 400 μM (Fig. 2, A and B). Fenofibrate appeared to have only a minimal effect on cell viability at the higher concentrations (Fig. 2C). For all three PPARα agonists, there is a suppression of proliferation at higher concentrations that is not due solely to lymphocyte death.

Stimulation of CD4+ T cells in the presence of PPARα agonists induces the expression of Th2 cytokines

Prior work had suggested that stimulation of lymphocytes with mitogen in the presence of PPARα agonists induced IL-4 production (7). We examined whether the presence of gemfibrozil, ciprofibrate, and fenofibrate affected cytokine secretion of MBP Ac1–11-specific T cells. Using ELISA, we examined the expression of IFN-γ, IL-4 and IL-10 in the supernatant of MBP Ac1–11-specific T cells stimulated in the presence of 50–400 μM gemfibrozil and ciprofibrate. A single stimulation of naive TCR transgenic splenocytes in the presence of gemfibrozil or ciprofibrate induced IL-4 expression (Fig. 3, A and C). For gemfibrozil, IL-4 levels were highest at 50 μM, a concentration that had no effect on proliferation or cell viability. For ciprofibrate, IL-4 levels were highest at 200 μM, a concentration that suppressed proliferation by 58.6%, but had no effect on lymphocyte viability. Fenofibrate did not induce IL-4 production after a single stimulation, but IL-4 production was doubled in the second stimulation in the presence of 10 μM fenofibrate (Fig. 3E). Although there was a modest decrease in the levels of IFN-γ at higher concentrations of the PPARα agonists, IFN-γ production were not signifi cantly affected by the presence of any of the three PPARα agonists (Fig. 3B, D, and F). Similarly, there was no significant affect on IL-10 production by the PPARα agonists (data not shown).

NO production by N9 microglial cells

Previously, we demonstrated that the PPARγ agonist, 15d-PGJ2, inhibited the activation of microglial cells (29), repressed microglial expression of CD40, a molecule which plays a critical role in T cell costimulation, and repressed development of EAE (13). Collectively, these studies suggest that 15d-PGJ2 may modulate EAE, at least in part, via effects on microglial cells, resident CNS cells that function in Ag presentation and phagocytosis. In the present study, we demonstrate that the PPARα agonists, gemfibrozil, ciprofibrate, and fenofibrate, inhibited NO production by microglial cells (Fig. 4). Gemfibrozil shows a dose-dependent decrease in NO production. Ciprofibrate and fenofibrate show a significant effect at doses as low as 1 μM. Fenofibrate showed a complete inhibition of NO by microglia at 50 μM which was not due to toxicity because MTT analyses indicated that these PPARα agonists did not decrease microglial cell viability (data not shown). These studies suggest that these PPARα agonists inhibit microglial cell activation, providing a second potential mechanism by which PPARα may exert its anti-inflammatory properties.

![FIGURE 1. PPARα agonists inhibit lymphocyte proliferation in a dose-dependent manner. MBP Ac1–11-specific murine TCR transgenic splenocytes were cultured with MBP Ac1–11 was added to the wells at a final concentration of 2 μg/ml. Gemfibrozil (A), ciprofibrate (B), or fenofibrate (C), were added to four replicate wells at various concentrations to wells with Ag. Equivalent volumes of solvent were used in control wells. Proliferation was determined by adding 1H]thymidine during the final 16 h of incubation. Solvent alone had no effect on lymphocyte proliferation at any of the concentrations tested.](http://www.jimmunol.org/)

Downloaded from http://www.jimmunol.org/ by guest on November 13, 2017
Effects of gemfibrozil on cytokine production by human T cells

Because gemfibrozil had important effects on altering cytokine production of murine lymphocytes, we examined whether it had similar effects on human T cell cytokine production. Because 50 μM gemfibrozil did not affect T cell proliferation or cell viability, this concentration was chosen to examine effects on cytokine production. Human PLP-specific Th1 cell lines were stimulated with...
Ag in the presence of 50 µM gemfibrozil. IFN-γ production was inhibited at both 48 and 72 h after stimulation when measuring the presence of the cytokine in the supernatant by ELISA (Fig. 9A). This phenomenon was not Ag-specific, since IFN-γ production was inhibited in both MBP- and PLP-specific human Th1-like lines (Fig. 9B). IL-4 and IL-10 were occasionally secreted by Th1 cells following gemfibrozil treatment (data not shown). Human T cells lines specific for myelin Ags were also generated in the presence of gemfibrozil (50 µM). TCLs generated from MS patients and healthy subjects in this manner secreted significant amounts of IL-4 as determined by ELISA (Fig. 9C). Thus, gemfibrozil was able to both promote IL-4 production and inhibit IFN-γ production of human myelin-specific TCLs, suggesting that this agent might be a potential therapeutic agent for MS.

Discussion
In the present study, we have shown that the PPARα agonists, gemfibrozil and fenofibrate, are able to prevent and treat the organ-specific autoimmune disorder EAE. We investigated several potential mechanisms by which this may be occurring, including altering cytokine production, inhibiting T cell proliferation, and suppressing microglia activation. We have demonstrated that gemfibrozil can induce the secretion of the prototypic Th2 cytokine,
mice were given a diet supplemented with gemfibrozil (0.25% w/w) beginning 3 days before immunization with 200 doses, thiazolidinedione activation of PPAR to induce optimal transcriptional activation. Surprisingly, at those doses required to induce programmed cell death were well above the doses required to induce apoptosis following growth factor withdrawal. Thus, at the doses used to treat patients with diabetes, the activation of PPARγ by thiazolidinediones may potentially augment the immune response.

The ability of PPARα agonists to regulate the immune response is an area of active investigation. Because of our observations and those of others that PPARα agonists such as gemfibrozil and cipriofibrate can induce IL-4 production, it is likely that transcription factors involved in T cell differentiation are affected by PPARα agonists (7). Differentiation of T cells to a Th2 phenotype involves activation of STAT-6, which is translocated to the nucleus, resulting in expression of GATA-3 (35). Although the mechanism of STAT-6 induction of GATA-3 is not entirely clear, GATA-3 is thought to be the master regulator of Th2 differentiation (36). Studies are in progress evaluating whether the production of IL-4 is responsible for the alteration of the T cell phenotype or whether this is occurring at the level of activation of PPARα. The precise mechanism of how PPAR α agonists exert their therapeutic effects remain unclear. Our work and that of others using PPARγ agonists suggested that Th1 cytokine secretion could be suppressed and that apoptosis of autoreactive T cells would be promoted (13–16). Interestingly, one study examining the effect of thiazolidinediones on T cell death suggested apoptosis was induced in a dose-dependent manner (34). The doses required to induce programmed cell death were well above the doses required to induce optimal transcriptional activation. Surprisingly, at those doses, thiazolidinedione activation of PPARγ-protected cells from apoptosis following growth factor withdrawal. Thus, at the doses

---

FIGURE 5. Oral administration of PPARα agonists has therapeutic benefit in EAE. A. B10.PL mice were fed 500 μg of gemfibrozil daily by gavage for 21 days, beginning the day before immunization with 200 μg of MBP Ac1–11/CFA. Control mice were immunized only and “PBS” mice were fed PBS by gavage daily for 21 days. Disease incidence is shown in parentheses. PBS vs gemfibrozil (GEM), p < 0.001; control vs GEM, p < 0.001. B. B10.PL mice were given a diet supplemented with gemfibrozil (0.25% w/w) beginning 3 days before immunization with 200 μg of Ac1–11/CFA. Control vs GEM, p > 0.001. C. B10.PL mice were given a diet supplemented with fenofibrate (0.25% w/w) beginning 3 days before immunization with Ac1–11/CFA. Half of the mice in the fenofibrate group died within the first 10 days, and the fenofibrate-supplemented diet was stopped. Control vs fenofibrate (FEN), p < 0.001. D. B10.PL mice were immunized with Ac1–11/CFA. At the first signs of disease, the mice were fed 500 μg of gemfibrozil, fenofibrate, or PBS by gavage for 21 days. PBS vs GEM, p < 0.001, PBS vs FEN, p < 0.001.
present in the cytoplasm of T cells was able to negatively regulate the transcription of T-bet, which indirectly influenced the amount of IFN-γ produced by the T cell. This regulation occurred independently of DNA-binding, suggesting that there may be several mechanisms of how PPARα can influence T cell activation and cytokine production.

In addition to the effects of PPARα on lymphocytes, we have investigated the effects of gemfibrozil, ciprofibrate, and fenofibrate on microglia, resident CNS cells that function in Ag presentation and phagocytosis. A variety of neuroinflammatory disorders including MS are characterized by the presence of activated microglia (39). Upon activation, microglia produce a variety of molecules including NO and TNF-α, which are important for the elimination of invading pathogens, but may also be toxic to host cells including oligodendrocytes and neurons, which are compromised in MS. In addition, fenofibrate has been shown to have protective effects in models of cerebral ischemia, suggesting that it may have neuroprotective, as well as anti-inflammatory effects (40). This suggests that agents which block microglial cell activation may also be protective in diseases such as MS.

Gemfibrozil, ciprofibrate, and fenofibrate were also capable of suppressing lymphocyte proliferation at doses that had minimal effects on cells viability. This observation was most profound at the higher concentrations of fenofibrate. Together, this data suggests that PPARα can potentially affect the activation and differentiation of autoreactive lymphocytes, as well as the activation of microglia in the CNS.

Although the ability of PPARγ agonists to regulate inflammatory processes in vivo appears to be true in a number of models (10–16), limited data is available on PPARα agonists in such situations. In a model of colitis induced by administration of dextran sodium sulfate, gastric gavage of the PPARα ligand, bezafibrate, significantly inhibited the expression of colitis, and reduced proliferation of colonic mucosa (41). Use of fenofibrate in experimental autoimmune myocarditis reduced the number of inflammatory lesions in the heart and reduced the ventricular size (42). Cardiac expression of IL-10 also appeared to be increased in the rats that received fenofibrate. Thus, this suggests that PPARα agonists may also have the potential to regulate inflammatory processes in vivo.

In summary, we have demonstrated that administration of the PPARα agonists, gemfibrozil and fenofibrate, are able to treat ongoing signs of EAE. Exposure of both murine and human T cells to these agents in vitro results in a shift in cytokine secretion pattern from a Th1-like response to that of a Th2-like response, a process known as immune deviation. In addition, PPARα agonists appear to inhibit microglial activation which may minimize CNS inflammation. Gemfibrozil has an excellent track record as a safe, beneficial, and cost-effective drug for the treatment of hyperlipidemia. Although fenofibrate has shown toxicity in mice, it has been shown to be safe and well-tolerated in humans (43). These results

**FIGURE 6.** Pathology and immunohistochemistry of the CNS of gemfibrozil-treated mice. Immunohistochemistry for macrophages (A and C) and CD4+ T cells (B and D) was performed on frozen sections (10 μm) from EAE-affected mice perfused on day 42 postimmunization. Mice receiving gemfibrozil from day -1 until day 20 are shown in C and D, while sections in A and B are from a PBS-treated control. Magnification, ×100.
raise the possibility that PPARα agonists might have benefit as a therapy in inflammatory human diseases such as MS.

References


