PPAR Activators as Antiinflammatory Mediators in Human T Lymphocytes
Implications for Atherosclerosis and Transplantation-Associated Arteriosclerosis

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Abstract—Activation of T lymphocytes and their ensuing elaboration of proinflammatory cytokines, such as interferon (IFN)-γ, represent a critical step in atherogenesis and arteriosclerosis. IFNγ pathways also appear integral to the development of transplantation-associated arteriosclerosis (Tx-AA), limiting long-term cardiac allograft survival. Although disruption of these IFNγ signaling pathways limits atherosclerosis and Tx-AA in animals, little is known about inhibitory regulation of proinflammatory cytokine production in humans. The present study investigated whether activators of peroxisome proliferator–activated receptor (PPAR)α and PPARγ, with their known antiinflammatory effects, might regulate the expression of proinflammatory cytokines in human CD4-positive T cells. Isolated human CD4-positive T cells express PPARα and PPARγ mRNA and protein. Activation of CD4-positive T cells by anti-CD3 monoclonal antibodies significantly increased IFNγ protein secretion from 0 to 504 ± 168 pg/mL as determined by ELISA. Pretreatment of cells with well-established PPARα (WY14643 or fenofibrate) or PPARγ (BRL49653; rosiglitazone or pioglitazone) activators reduced anti-CD3–induced IFNγ secretion in a concentration-dependent manner. PPAR activators also inhibited TNFα and interleukin-2 protein expression. In addition, PPAR activators markedly reduced cytokine mRNA expression in these cells. Such antiinflammatory actions were also evident in cell-cell interactions with medium conditioned by PPAR activator–treated T cells attenuating human monocyte CD64 expression and human endothelial cell major histocompatibility complex class II induction. Thus, activation of PPARα and PPARγ in human CD4-positive T cells limits the expression of proinflammatory cytokines, such as IFNγ, yielding potential therapeutic benefits in pathological processes, such as atherosclerosis and Tx-AA. (Circ Res. 2002;90:703-710.)

Key Words: atherosclerosis ■ fibrates ■ thiazolidinediones ■ peroxisome proliferator–activated receptors ■ T cells
known as BRL49653 (BRL) and pioglitazone, as well as natural ligands, such as the prostaglandin D2 derivative 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) and oxidized linoleic acid (9- or 13-HODE). In vitro experiments demonstrate that PPARα and PPARγ activators decrease inflammatory proteins, such as adhesion molecules, cytokines, and chemokines, in monocytes/macrophages, ECs, and vascular smooth muscle cells. Moreover, recent in vivo studies suggest that PPAR activators can limit experimental atherosclerosis in animal models. In human trials, preliminary clinical data in diabetic patients suggest that TZD treatment can decrease carotid intimal-medial thickness, and recent studies with PPARα-activating fibrin acids have also demonstrated decreased atherosclerosis among treated patients. Interestingly, fenofibrate treatment in patients with coronary heart disease reduced IFNγ plasma levels through an as-yet-undefined mechanism.

Given the role of T-lymphocyte inflammatory cytokine production in atherosclerosis and evidence of PPARs as antiinflammatory mediators, we hypothesized that human T lymphocytes express PPARα and PPARγ and that stimulation of these cells by PPAR activators in clinical use would limit inflammatory cytokine expression. Indeed, concurrent work suggests that PPARγ ligands may influence T-cell activation and proliferation, although those studies did not address PPARα in T-cell cytokine responses or PPAR regulation of T-cell IFNγ production.

Materials and Methods

Cell Culture
Human CD4-positive T cells were isolated from freshly drawn blood of healthy volunteers by Ficoll-Histopaque (Sigma Chemical Co) gradient centrifugation to obtain mononuclear cells and subsequent negative selection of CD4-positive T cells by magnetic bead separation (Miltenyi Biotech), as described by the manufacturer’s protocol. The purity of CD4-positive T cells was >97%, as determined by flow cytometry. Human ECs and monocytes were isolated as previously described. Human CD4-positive T cells were incubated with an equal volume of PBS containing saturating concentrations (10 mg/L) of FITC-conjugated anti-CD3 antibodies and PE-conjugated anti-CD4 antibodies for 30 minutes at room temperature. To examine the influence of PPAR activators on the proinflammatory activity of T-cell supernatants toward other vascular cells, freshly isolated human monocytes or human ECs were incubated with supernatants (50% original monocyte or EC media and 50% conditioned media from T cells) derived from T cells after CD3 activation in the absence or presence of WY14643 or BRL (Figures 5A and 6A, right panels). In some experiments, cells were first treated with conditioned media from anti-CD3–activated T cells (Figures 5B and 6B, right panels) or IFNγ (Figures 5C and 6C, right panels), and then PPAR activators at similar concentrations were directly added to monocytes or ECs. After 18 hours (in monocyte experiments) or 72 hours (in EC experiments), cells were harvested for the investigation of monocyte CD64 or endothelial major histocompatibility complex (MHC) class II (MHC II) expression on the cell surface, respectively. After washing, monocytes were stained with FITC-conjugated anti-CD64 antibodies, and ECs were stained with FITC-conjugated anti-MHC II antibodies. Finally, T cells, monocytes, or ECs were washed three times and stored in 1% paraformaldehyde (Sigma) at 4°C until flow cytometric analysis was performed within 24 hours.

Reverse Transcriptase–Polymerase Chain Reaction
Total RNA from freshly prepared CD4-positive T cells was isolated for reverse transcriptase (RT)–polymerase chain reaction (PCR) with amplification of PPARα, PPARγ, and GAPDH cDNA as described previously.

Preparation of Nuclear and Cytosolic Extracts and Western Blot Analysis
For Western blotting, nuclear and cytosolic extracts of 107 cells were prepared as previously described.

Stimulation Assays, ELISA, and Cell Viability Studies
Human CD4-positive T cells (1×106 cells/mL) were pretreated with PPARα activators (WY14643 or fenofibrate) or PPARγ activators (BRL or pioglitazone) for 2 hours before stimulation with immobilized anti-CD3 antibody (R&D Systems) for 48 hours or with phorbol 12-myristate 13-acetate (PMA, 10 ng/mL)/ionomycin (0.5 μM/mL) for 6 hours, according to previously published time courses for these stimuli. Cells were then harvested, and IFNγ, TNFα, and IL-2 ELISAs (R&D Systems) were performed on cell-free supernatants, as recommended by the manufacturer. In some experiments, cells were stimulated with PPAR activators for 24 hours, and the release of IL-4, a typical TH2-cytokine, was measured by ELISA (R&D Systems).

Cell viability was assessed by standard trypan blue exclusion, as described previously.

Northern Blot Analysis
For Northern blot experiments, cells were pretreated with PPAR activators and then stimulated with anti-CD3 antibodies for 24 hours or with PMA/ionomycin for 2 hours. Five micrograms of total RNA was used in standard Northern blot analysis by using cDNA probes against IFNγ, TNFα, or IL-2 or against the housekeeping genes B41 or GAPDH.

Flow Cytometry
Immunofluorescence staining and flow cytometry were performed as previously described. Human CD4-positive T cells were incubated with an equal volume of PBS containing saturating concentrations (10 mg/L) of FITC-conjugated anti-CD3 antibodies and PE-conjugated anti-CD4 antibodies for 30 minutes at room temperature. To examine the influence of PPAR activators on the proinflammatory activity of T-cell supernatants toward other vascular cells, freshly isolated human monocytes or human ECs were incubated with supernatants (50% original monocyte or EC media and 50% conditioned media from T cells) derived from T cells after CD3 activation in the absence or presence of WY14643 or BRL (Figures 5A and 6A, right panels). In some experiments, cells were first treated with conditioned media from anti-CD3–activated T cells (Figures 5B and 6B, right panels) or IFNγ (Figures 5C and 6C, right panels), and then PPAR activators at similar concentrations were directly added to monocytes or ECs. After 18 hours (in monocyte experiments) or 72 hours (in EC experiments), cells were harvested for the investigation of monocyte CD64 or endothelial major histocompatibility complex (MHC) class II (MHC II) expression on the cell surface, respectively. After washing, monocytes were stained with FITC-conjugated anti-CD64 antibodies, and ECs were stained with FITC-conjugated anti-MHC II antibodies. Finally, T cells, monocytes, or ECs were washed three times and stored in 1% paraformaldehyde (Sigma) at 4°C until flow cytometric analysis was performed within 24 hours.

Statistical Analysis
Results of the experimental studies are reported as mean±SEM. Differences were analyzed by one-way ANOVA, followed by the appropriate post hoc test. A value of P<0.05 was regarded as significant.

Results

Human CD4-Positive T Cells Express PPARα and PPARγ mRNA and Protein
Isolated human CD4-positive T cells express PPARα and PPARγ mRNA as determined by RT-PCR (Figure 1A). Western blot analysis revealed PPARα as well as PPARγ protein expression in the nuclear fraction but not in the cytosol of isolated CD4-positive human T cells (Figure 1B). Induction of IFNγ expression by stimulation with anti-CD3 antibodies and/or treatment with PPAR activators did not affect PPAR expression in these cells (data not shown).

PPAR Activators Inhibit IFNγ Expression in Human CD4-Positive T Cells
Unstimulated human CD4-positive T cells did not secrete IFNγ, as determined by ELISA of cell-free supernatants. As expected, incubation of cells with immobilized anti-CD3 antibodies significantly increased IFNγ protein secretion from 0 to 504±168 pg/mL (P<0.01, n=6). Two-hour pretreatment with PPARα activators, either WY14643 or...
fenofibrate, inhibited this increase in a concentration-dependent manner. IFNγ production was not detected at WY14643 (250 μmol/L) and was reduced by fenofibrate to 13±5% of the level elaborated by untreated control cells (P<0.01 for both compared with CD3-activated cells, n=4) (Figure 2A). Similarly, pretreatment of CD4-positive T cells with two different PPARγ-activating TZDs also reduced anti-CD3-induced IFNγ release in a concentration-dependent manner, with a maximal reduction to 28±8% at 10 μmol/L pioglitazone (P<0.01 for both compared with anti-CD3-activated cells, n=6) (Figure 2B). None of the PPAR activators that were used affected cell viability (by trypan blue exclusion) or cell surface CD3 expression, as determined by flow cytometry (Table).

PPAR Activators Reduce the Expression of Other Proinflammatory Cytokines in CD4-Positive Human T Cells

To examine whether the effects of PPAR activators extended beyond IFNγ to other inflammatory cytokines, we performed similar experiments measuring TNFα and IL-2 protein expression of human CD4-positive T cells. Pretreatment of cells with PPARα-activating WY14643 reduced anti-CD3–induced TNFα and IL-2 secretion in a concentration-dependent manner, with maximal inhibition to 7±4% of TNFα production at 250 μmol/L WY14643, and abrogated IL-2 expression under similar conditions (P<0.01 for both compared with CD3-activated cells, n=3) (Figure 3A). PPARγ-activating BRL had similar concentration-dependent, albeit less complete, effects; anti-CD3–induced TNFα and IL-2 protein expression decreased to 64±7% and 34±7%, respectively, at 10 μmol/L BRL (P<0.01 for both compared with CD3-activated cells, n=3) (Figure 3B). To exclude the possibility that these results stemmed from a shift of T cells toward a TH2 response, we measured IL-4 in supernatants on stimulation with PMA/ionomycin or PPAR activators. PMA/ionomycin treatment induced IL-4 protein secretion from 5±4 to 205±42 pg/mL (P<0.01, n=3), whereas none of the PPARα or PPARγ activators had a similar effect (Figure 3C).

Figure 1. CD4-positive human T cells express PPARα and PPARγ. A, RT-PCR reaction of PPARα and PPARγ RNA in freshly isolated human CD4-positive T cells (T4) reveals a cDNA fragment of the expected size. Also shown are a DNA ladder (MW), RT-PCR product from macrophage RNA as a positive control (MØ), and a negative control consisting of RT-PCR reactions lacking RT (Co). B, Western blot analysis on nuclear (Nucl) and cytosolic (Cyto) fractions of human CD4-positive T cells with use of an anti-human PPARα antibody or an anti-human PPARγ antibody.
Effects of PPAR Activators

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*As determined by flow cytometry.

PPAR Activators Inhibit PMA/Ionomycin-Induced Proinflammatory Cytokine Expression in Human CD4-Positive T Cells

To investigate whether the effects of PPAR activators on T4 cell–derived IFNγ expression depended on the stimulus used, we used PMA/iomycin to induce IFNγ release. PMA/iomycin treatment of human CD4-positive T cells stimulated more IFNγ protein expression than did CD3 activation, increasing IFNγ protein content in the supernatant to 4971 ± 1596 pg/mL. Pretreatment of the cells with the PPARα activator WY14643 (250 μmol/L) reduced IFNγ release to 36 ± 10% (P<0.01 compared with PMA/iomycin-stimulated cells, n=3), whereas pretreatment with the PPARγ activator BRL decreased IFNγ-protein secretion to 71 ± 3% (P<0.05 compared with PMA/iomycin-stimulated cells, n=3) (Figure 3D).

Figure 3. PPAR activators reduce TNFα and IL-2 protein secretion from CD4- positive human T cells. A and B, Isolated CD4-positive T cells were pretreated with PPARα-activating WY14643 (A) or PPARγ-activating BRL 2 hours before stimulation with anti-CD3 antibodies (B). After 48 hours, cytokine protein content in cell-free supernatants was measured by ELISA. Results are expressed as percentage of CD3-activated cells (% control). Bars represent mean±SEM (n=3). **P<0.05; ***P<0.01. C, PPAR activators do not induce expression of IL-4 in CD4-positive human T cells. Isolated CD4-positive T cells were treated with PPARα activators (250 μmol/L WY14643 or 100 μmol/L fenofibrate) or PPARγ activators (10 μmol/L BRL or 10 μmol/L pioglitazone) for 24 hours before IL-4 protein content in cell-free supernatant was measured by ELISA. PMA/iomycin (100 ng/mL/1 μmol/L)–treated cells served as a positive control. Results are expressed as percentage of PMA/iomycin-activated cells (% control). Bars represent mean±SEM (n=3). **P<0.01 compared with unstimulated cells. D, PPAR activators inhibit PMA/iomycin-induced IFNγ expression. Isolated CD4-positive T cells were stimulated and treated with PMA/ iomycin (10 ng/mL/0.5 μmol/L) in the absence or presence of the PPARα activator WY14643 or the PPARγ activator BRL. After 6 hours, cytokine protein contents in cell-free supernatants were measured by ELISA. Results are expressed as percentage of PMA/iomycin-treated cells (% control). Bars represent mean±SEM (n=3). *P<0.05; **P<0.01.
PPAR Activators Reduce Proinflammatory Function of T Lymphocytes on Human Monocytes and ECs

To examine the potential functional effects of PPAR-mediated reduced T-cell cytokine expression, we incubated supernatants from stimulated CD4-positive T cells with human monocytes or ECs and measured monocyte CD64 or endothelial MHC II surface expression by flow cytometry. CD64, the high-affinity receptor for IgG involved in phagocytosis and antigen capture, an IFNγ-regulated gene in human monocytes, indicates IFNγ activity on monocytes in vitro and in vivo. In addition, IFNγ potently stimulates MHC II expression on ECs and acts synergistically with TNFα. Incubation of freshly isolated human monocytes with supernatants from CD3-activated T cells significantly increased monocyte CD64 cell surface expression by ≈2-fold. Supernatants taken from activated CD4-positive T cells after WY14643 or BRL treatment reduced this increase significantly to 61±8% or 72±4%, respectively (P<0.01 or P<0.05, respectively, compared with monocytes incubated with supernatant from CD3-activated T cells; n=4) (Figure 5A), consistent with reduced cytokine content in the media (data not shown). To exclude the possibility that the results observed resulted from direct effects of residual PPAR agonist in T-cell supernatants, we stimulated human monocytes with conditioned media from CD4-positive cells to induce CD64 expression and then added WY14643 or BRL directly to the cells. None of the PPAR activators used had direct significant effects on monocyte CD64 expression (Figure 5B). Consistent with this finding, PPAR activators did not affect IFNγ-induced CD64 expression in human monocytes (Figure 5C).

Mean fluorescence intensity of MHC II expression in human ECs incubated with supernatants from unstimulated CD4-positive T cells was 10±4 (arbitrary units). Incubation of ECs with supernatants taken from CD3-activated T cells significantly increased MHC II cell surface expression to 51±13 (P<0.05, n=5). Medium conditioned by activated CD4-positive T cells after WY14643 or BRL treatment showed significantly reduced MHC II expression (64±17% or 53±14%, respectively; P<0.05 compared with ECs incubated with supernatant from CD3-activated T cells; n=5) (Figure 6A). Neither WY14643 nor BRL directly affected T-cell media– or IFNγ-induced endothelial MHC II expression (Figures 6B and 6C).

Discussion

The present study reports PPARα and PPARγ expression in human CD4-positive T cells with evidence of inhibition of inflammatory cytokine production by PPARα-activating fibric acid derivatives or PPARγ-activating TZDs in these cells. These results have potential physiological significance, given our finding that monocytes and ECs demonstrate...
expression was measured by flow cytometry (right). Results are expressed as percentage of control (monocytes incubated with supernatants from activated T cells). Bars represent mean ± SEM (n = 4). **P < 0.01. C, Human monocytes were incubated with IFN-γ (200 U/L) in the presence or absence of PPAR activators. After 18 hours, CD64 expression was measured by flow cytometry (right). Results are expressed as percentage of control (monocytes incubated with IFN-γ). Bars represent mean ± SEM (n = 5). No significant difference was seen, except for comparison with unstimulated cells. *P < 0.01.

Figure 5. PPAR activators reduce proinflammatory activity of T-cell supernatants on human monocytes in the absence of any direct effects on monocyte CD64 response. A, Freshly isolated human monocytes were incubated for 18 hours with conditioned media from CD4-positive T cells stimulated with anti-CD3 monoclonal antibodies in the presence or absence of PPAR agonists, and mean fluorescence intensity of monocyte CD64 expression was measured by flow cytometry (right). Results are expressed as percentage of control (monocytes incubated with supernatants from activated T cells). Bars represent mean ± SEM (n = 4). **P < 0.05; ***P < 0.01. B, Human monocytes were incubated with conditioned media from CD3-activated T cells to induce CD64 expression and then directly stimulated with PPAR activators for 18 hours before CD64 expression was assessed by flow cytometry (right). Results are expressed as percentage of control (monocytes incubated with supernatants from activated T cells). Bars represent mean ± SEM (n = 4). No significant difference was seen, except for comparison with unstimulated cells. **P < 0.01. 

Reduced responses toward the proinflammatory effects of activated T cells treated with these same PPAR activators.

Although PPAR expression was initially considered to be restricted to tissues like liver and fat, recent work has demonstrated PPARα and PPARγ expression in vascular cells, such as monocytes/macrophages, ECs, and smooth muscle cells. Recent studies also documented PPARγ expression in murine and human T lymphocytes. Previous work has not addressed PPARα expression by lymphocytes. The decrease in IFN-γ expression described in the present study likely occurred through the activation of PPARα and PPARγ by their respective agonists, given that such concentrations are similar to those found in the plasma of patients treated with these agonists. However, the results shown in the present study do not conclusively establish that the effects were due to specific receptor activation. Interestingly, recent work has revealed that some effects of TZDs could occur independent of the presence of PPARγ, at least in cells of the monocytic lineage. Although monocyte/macrophage responses differ in substantive ways from T-cell responses, particularly in terms of cytokine induction, the intriguing possibility that some of the effects observed in the present study might be PPARγ independent cannot be excluded. Regardless, these data reveal novel effects of antidiabetic TZDs on T lymphocytes and their interaction with vascular...
cells, with potential clinical relevance for patients. Interestingly, pioglitazone, despite a lower binding affinity to PPARγ, was more potent than BRL in inhibiting IFNγ protein production. Our results with PPARα agonists suggest that this might be due to a combined PPARα and PPARγ effect of pioglitazone, given that this agent (in contrast to BRL) can also activate PPARα. The lack of a difference between pioglitazone and BRL on mRNA expression and the mild suppression of cytokine mRNA compared with protein levels suggest that posttranscriptional modification may also play a role. In this regard, recent work has shown that TZDs inhibit the initiation of translation independent of PPARγ, and similar mechanisms may be at work in our findings.

The effects of PPARα and PPARγ activators on human T cells extend to inhibition of other proinflammatory cytokines, including TNFα and IL-2, implicating PPARs as a potential nodal point for the regulation of T-cell–modulated inflammatory responses. In addition, the results obtained do not derive from a shift of T cells toward a TH2 response, because none of the PPAR activators used increased the levels of IL-4, a classic TH2 cytokine, in CD4-positive T cells.

Prior reports demonstrating the effects of PPARγ agonists on lymphocytes varied from ours in design and results in important ways. These studies used PPAR agonists at higher concentrations (TZDs at 20 to 40 μmol/L), which are thought unlikely to prevail in vivo, or the studies used T-cell lines rather than primary isolates. Clark et al found reduced IL-2 secretion from murine T-cell clones after treatment with the PPARγ activator ciglitazone (20 to 40 μmol/L) and the putative PPARγ agonist, but they did not examine the effect on IFNγ and TNFα. These higher concentrations raise the potential for pleiotropic effects, toxicity, and increased cross-reaction with other nuclear receptors. Yang et al showed that the PPARγ activators troglitazone and 15d-PGJ2 decrease IL-2 production in human T cells, whereas the PPARα activator WY14643 had no effects on phytohemagglutinin-PMA-induced IL-2 release. Beyond issues specific to each agonist, eg, the potential antioxidant properties of troglitazone or the low concentrations used for WY14643, relevant experimental differences include the use of mixed T-lymphocyte populations as opposed to selected CD4-positive cells, the nature of the stimuli used to induce IL-2 expression, and the differing protocols for the addition of agonists (concurrent addition versus pretreatment). Harris and Phipps recently found PPARγ expression in a transgenic lymphocyte mouse cell line (D011.10) and induction of apoptosis by troglitazone and 15d-PGJ2 at high concentrations (10 to 100 μmol/L).

We find that stimulation of isolated CD4-positive human T cells, when stimulated with canonical PPARα and PPARγ agonists at clinically relevant concentrations, demonstrates decreased IFNγ, TNFα, and IL-2 production, with no effect on viability. Such findings likely have relevance to the function of T lymphocytes in atherosclerosis and Tx-AA. In human atheroma, activated CD4-positive T cells release inflammatory cytokines such as IFNγ, TNFα, and IL-2, presumably promoting lesion progression through the activation of other vascular cells in a paracrine fashion. In ECs, these T-cell–derived cytokines induce the expression of leukocyte-recruiting chemokines, such as monocyte chemoattractant protein-1 or interferon-inducible protein of 10 kDa, and the expression of adhesion molecules. Such actions may contribute to an ongoing cycle of inflammatory cell recruitment, attachment, and migration into the vessel wall, along with further cellular activation. Similar inflammatory effects contribute to Tx-AA, a condition in which IFNγ-induced MHC class II expression on the surface of donor ECs triggers host T-cell activation. A reduction of IFNγ release with inhibition of endothelial MHC class II expression, as shown in the present study, raises the possibility that PPAR agonists might modulate allograft vasculopathy.

In monocytes/macrophages, IFNγ stimulates the secretion of cytokines, whereas in smooth muscle cells, IFNγ inhibits proliferation and extracellular matrix synthesis. This mechanism might destabilize the protective fibrous cap of the lesion and, thus, contribute to plaque rupture with its sequelae, such as unstable angina or acute myocardial infarction. Interestingly, patients with unstable angina show increased IFNγ production by CD4-positive cells, bolstering the hypothesis that T-cell activation contributes to the acute coronary syndromes. In contrast, Tx-AA is characterized by smooth muscle cell proliferation, which is thought to be driven in part by cytokine and cytokine-induced growth factors, but also in the development of diabetes itself, the results reported in the present study suggest that PPAR modulation of inflammatory pathways not only in atherosclerosis but also in the development of diabetes itself, the results reported in the present study suggest that PPAR modulation of inflammatory pathways in T cells may offer clinical benefits in pathological processes, such as atherosclerosis and Tx-AA, and is certainly worthy of study in future clinical trials with PPAR agonists.

Acknowledgments

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References


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