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Induction of IκBα Expression as a Mechanism Contributing to the Anti-inflammatory Activities of Peroxisome Proliferator-activated Receptor-α Activators*

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Chronic inflammation is a hallmark of degenerative diseases such as atherosclerosis. Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily, which are expressed in the cells of the atherosclerosic lesion. PPARα ligands have been reported to exert anti-inflammatory activities in different cell types by antagonizing the transcriptional activity of NF-κB. In the present study, the influence of PPARα activators on the NF-κB signaling pathway was investigated. Our results show that fibrates, synthetic PPARα activators, induced the expression of the inhibitory protein IκBα in human aortic smooth muscle cells as well as in primary human hepatocytes, whereas neither IκB-kinase activity nor the degradation rate of IκBα were affected. Using PPARα-null mice, we demonstrated that fibrates induced IκBα in liver *in vivo* and that this action required PPARα. Furthermore, fibrate treatment induced IκBα protein expression in the cytoplasm and also enhanced IL-1β-induced accumulation of IκBα protein in the nucleus. These actions of fibrates on IκBα expression were accompanied by a decrease in NF-κB DNA binding activity as demonstrated by electrophoretic mobility shift assays. Taken together, these data provide an additional molecular mechanism for the anti-inflammatory activity of PPARα agonists and reinforce their potential use in the treatment of inflammatory diseases.

The NF-κB family of transcription factors plays a major role in the regulation of the expression of a number of genes implicated in cell growth, inflammation, and apoptosis (1, 2). This NF-κB/Rel family consists of five members, c-Rel, p65, Rel B, p50, and p52, which form heterodimeric complexes that are most frequently composed of p50 and p65 proteins. In most non-activated cells, NF-κB remains in a cytoplasmic inactive complex through its association with the inhibitory proteins IκBs (3). Inducers of NF-κB, which include inflammatory cytokines, reactive oxygen species, and viral products, activate a dimeric IκB kinase (IKK)[1] complex (4–6), which phosphorylates IκBα on Ser-32 and Ser-36 leading to subsequent ubiquitination and degradation of IκBα and release of NF-κB proteins (1, 2). Free NF-κB dimers translocate to the nucleus where they regulate target gene transcription. NF-κB has been suggested to play a crucial role in the pathogenesis of atherosclerosis (7). NF-κB was reported to be essential for the proliferation of vascular smooth muscle cells (SMC) (8), and activated NF-κB heterodimers are detected in human atherosclerotic lesions (9).

Peroxisome proliferator-activated receptors (PPARs), transcription factors belonging to the nuclear receptor superfamily, have also been reported to be expressed in vascular cells *in vitro* and *in vivo* (10–19). To date, three different PPAR subtypes have been identified: PPARα, PPARβ/δ, and PPARγ. PPARs regulate gene expression by binding with the retinoid receptor RXR as a heterodimeric partner to specific DNA sequence elements termed PPAR response elements (PPRE) (20). In addition to regulating gene transcription via PPREs, PPARs have recently been shown to modulate gene transcription also by negatively interfering with other transcription factor pathways in a DNA binding-independent manner (18, 21). Among the three different PPARs, PPARα activation has been shown to repress cytokine-induced activation of a number of inflammatory genes such as *VCAM-1*, *COX-2*, and *IL-6* by negatively interfering with NF-κB transcriptional activity (14, 22).

However, the influence of PPARα activators on the different components of the NF-κB signaling cascade have not yet been explored. In the present study, we show that fibrates, synthetic PPARα ligands, induce IκBα expression in a PPARα-dependent manner. By contrast, PPARα agonists do not influence IκBα degradation nor IKK activity. This induction results in an inhibition of NF-κB DNA binding leading to a sharp reduction of the p65-mediated gene activation. These actions may contribute to the anti-inflammatory activities of PPARα ligands.

EXPERIMENTAL PROCEDURES

Cell Culture and Chemical Reagents—Human aortic SMC (Cascade Biologics, Portland, OR) were cultured in SMC basal medium containing 5% SMC growth supplement (Cascade Biologics). Cells from passages 5–8 were used for the experiments. Human primary hepatocytes were prepared as described previously (23). Wy-14643 was from Chemsyn, Lenexa, KS; fenofibric acid from Laboratoires Fournier, Dijon, France, IL-1β from Genzyme, Cambridge, MD; and ciprofibrate from Sigma, Saint Quentin, France.

IKK Assays—IKK assays were performed as described previously (24). Briefly, total protein extracts were subjected to immunoprecipitation with anti-NEMO antibody (a kind gift of Dr Israël, Institut Pasteur, France) in TNT buffer (200 mM NaCl, Tris 20 mM, pH 7.5, 1% Triton X-100) and collected on protein A-Sepharose beads. The beads

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[1] The abbreviations used are: IKK, IκB kinase; SMC, smooth muscle cells; PPAR, peroxisome proliferator-activated receptors; PPRE, PPAR response element; IL, interleukin; GST, glutathione *S*-transferase; EMSA, electrophoretic mobility shift assay; HASMC, human aortic SMC; STAT, signal transducers and activators of transcription; PAGE, polyacrylamide gel electrophoresis.

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were then washed three times with TNT buffer and three times with kinase buffer (20 mM HEPES, 10 mM $MgCl_2$, 100 μM Na_3VO_4, 20 mM β-glycerophosphate, 2 mM dithiothreitol, 50 mM NaCl, pH 7.5). Kinase reactions were performed for 30 min at 30 °C using 5 μCi of [γ-^{32}P]ATP and GST·IκBα-(1–72) as substrate. The reaction products were analyzed on 10% SDS-polyacrylamide gels and detected by autoradiography.

RNA Analysis—RNA preparation and Northern blot hybridizations were performed as described previously (25). Human IL-6, IκBα (26), and 36B4 cDNA fragments were used as probes.

Western Blot Analysis—Protein extracts were fractionated on 10% polyacrylamide gels under reducing conditions (sample buffer containing 10 mM dithiothreitol, transferred onto nitrocellulose membranes, and probed with various antibodies as stated in figure legends). After incubation with a secondary peroxidase-conjugated antibody, signals were visualized by chemiluminescence (Amersham Pharmacia Biotech).

Nuclear Extracts and Electrophoretic Mobility Shift Assay (EMSA)—SMC cells (3×10^6) were cultured for 2 or 24 h in SMC medium with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) and were subsequently treated with IL-1β (10 ng/ml) for 1 h. Cells were then harvested, and nuclear extracts were obtained as described previously (27). Nuclear proteins were quantified using the bicinchonic acid assay and stored at −80 °C. For EMSA, an NF-κB and an OCT1 double-stranded oligonucleotide (Promega) were end-labeled with [γ-^{32}P]ATP using T4 polynucleotide kinase according to standard protocols. 5 μg of nuclear extracts from SMC cells were incubated with 50,000 cpm of labeled probes for 20 min at room temperature in 20 μl of buffer containing 10 mM Tris pH 7.5, 50 mM NaCl, 1 mM dithiothreitol, 1 mM EDTA, 5% glycerol, 0.3 μg bovine serum albumin, and 2 μg of poly(dIdC). The reactions were analyzed by electrophoresis in a non-denaturing 5% polyacrylamide gel in 0.5× Tris-borate-EDTA buffer. The gels were then dried and exposed at −80 °C for autoradiography.

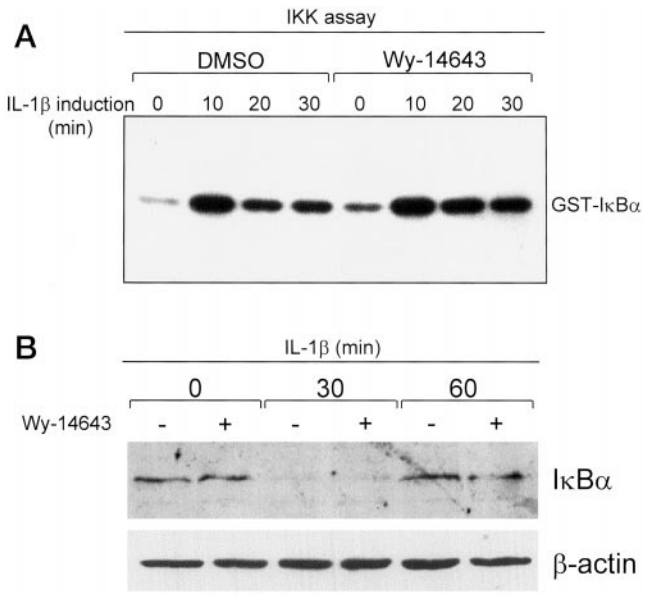

FIG. 1. **PPARα activators do not influence IκBα degradation.** *A,* human aortic SMC (80% confluence) were incubated for 2 h in standard medium with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) and were subsequently stimulated with IL-1β (10 ng/ml) for different time periods (min). Cytoplasmic extracts were prepared and subjected to IKK assay as described previously (46). *B,* human aortic SMC (80% confluence) were incubated for 2 h in standard medium with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) and were subsequently stimulated with IL-1β (10 ng/ml) for different time periods (min). Total protein extracts were prepared and proteins (50 μg) were separated by SDS-PAGE, transferred to a Hybond membrane, and probed with antibodies to IκBα and β-actin (Santa Cruz Biotechnology).

RESULTS AND DISCUSSION

Recently, it was demonstrated that PPARα activators inhibit IL-1β-induced IL-6 secretion by human aortic SMC (HASMC) in a dose-dependent manner (14). Furthermore, PPARα activators negatively regulate IL-1β-induced-IL-6 production at the gene expression level by inhibiting NF-κB transcriptional activity (21). Activation of the transcription factor NF-κB is controlled by a cytokine-activated protein kinase complex, which phosphorylates IκBα, triggering its polyubiquitination (5). Because PPARα agonists negatively interfere with IL-1β-induced NF-κB transcriptional activity in HASMC, we investigated whether PPARα activators influence IL-1β-induced IKK activity in these cells. IKK activity was very low in non-stimulated HASMC treated with or without the PPARα ligand Wy-14643 (Fig. 1*A*). Treatment with IL-1β for 10 min resulted in a strong induction of IKK activity. This induction was not affected by preincubation with the PPARα activator Wy-14643 for 2 h, the time period previously reported to inhibit IL-1β-induced *COX-2* gene expression (14). This result indicates that PPARα activators do not regulate NF-κB transcriptional activity by modulating IKK function. Furthermore, we investigated the influence of Wy-14643 on IL-1β-induced-IκBα degradation. Western blot analysis showed that IκBα protein was degraded within 30 min after IL-1β stimulation, followed by reappearance of the protein at 1 h as previously reported (28) (Fig. 1*B*). Fibrate treatment did not affect IκBα protein degradation, consistent with the absence of any effect on IKK. Taken together, these data indicate that fibrates do not impair NF-κB transcriptional activation by modulating IKK activity or IκBα degradation.

Next, it was investigated whether PPARα agonists influence IκBα expression. Incubation of HASMC with IL-1β resulted in the induction of both IL-6 and IκBα mRNA (Fig. 2*A*), which is consistent with the previous demonstration that NF-κB controls the expression of IκBα by an inducible autoregulatory loop (28). Wy-14643 alone induced IκBα mRNA (Fig. 2*A*), and this effect was further enhanced by IL-1β suggesting that PPARα and IL-1β regulate *IκBα* gene expression by different mechanisms. By contrast, Wy-14643 treatment inhibited the induction of IL-6 mRNA levels by IL-1β as described previously (21). Similarly, when incubations were done with fenofibric acid, another PPARα ligand, IκBα mRNA was significantly induced (Fig. 1*B*). This induction occurred rapidly with a maximum reached after 1 h. IκBα mRNA levels declined thereafter but remained elevated to increase again at 24 h (Fig. 2*B*). Moreover, Wy-14643 increased IκBα mRNA levels in a dose-dependent manner (Fig. 2*C*). Results from actinomycin D transcription inhibition experiments demonstrated that fibrates induce IκBα expression at the transcriptional level (data not shown). In HASMC, Wy-14643 also increased IκBα protein with a maximum of induction reached after 24 h of treatment (2.25 ± 0.19-fold; $p < 0.05$), demonstrating that the induction of *IκBα* gene expression results in increased protein levels (Fig. 2*D*).

To determine whether this induction of *IκBα* expression by fibrates occurs in other PPARα- expressing cell types, IκBα regulation was next studied in the liver, where PPARα is highly expressed (29, 30). In line with previous studies (31), human primary hepatocytes express IκBα mRNA under basal conditions (Fig. 3*A*). Interestingly, treatment with Wy-14643 increased IκBα mRNA (approximately 3-fold)(Fig. 3*A*), indicating that PPARα ligands regulate IκBα expression also in human primary hepatocytes. Western blot analysis confirmed that Wy-14643 treatment led to IκBα protein induction in human primary hepatocytes (Fig. 3*C*). To determine whether IκBα mRNA induction by fibrates in liver is mediated by PPARα, further studies were performed in PPARα-null mice (32). In livers of PPARα wild-type mice, treatment with the PPARα agonist ciprofibrate resulted in a significant increase (>4-fold) of IκBα mRNA, whereas in PPARα−null mice no induction was observed (Fig. 3*B*). This result indicates that fibrates regulate IκBα in liver in a PPARα-dependent manner. Because the liver constitutes a major organ implicated in the synthesis of numerous acute phase proteins such as cytokines

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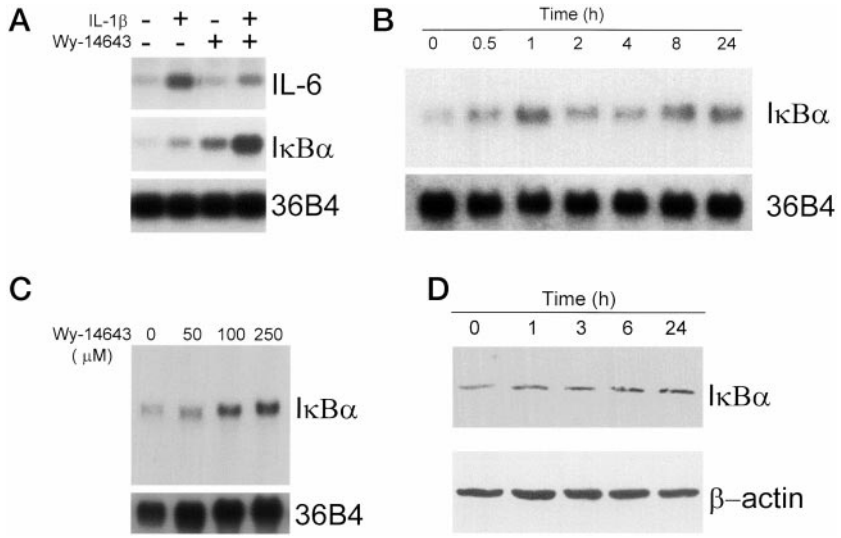

FIG. 2. **PPARα activators induce IκBα mRNA and protein levels in human aortic SMC.** *A,* human aortic SMC (80% confluence) were incubated for 2 h in standard medium with Wy-14643 (250 μM) or vehicle (Me_2SO, 0.1%) and were subsequently stimulated with IL-1β (10 ng/ml) for 3 h. IL-6, IκBα, and 36B4 mRNA were measured by Northern blot analysis. *B,* SMC were cultured in standard medium with fenofibric acid (100 μM) for different times as indicated. RNA (10 μg) was extracted, separated on a 1% agarose-formaldehyde gel, transferred to a nylon membrane, and analyzed by hybridization to IκBα and 36B4 cDNA probes. *C,* SMC were cultured in standard medium with increasing concentrations of Wy-14643 for 1 h. RNA (10 μg) was extracted, separated on a 1% agarose-formaldehyde gel, transferred to a nylon membrane, and analyzed by hybridization to IκBα and 36B4 cDNA probes. *D,* human aortic SMC were cultured in standard medium with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) for different lengths of time (h). Protein extracts were prepared, and 30 μg of each extract were separated by SDS-PAGE, transferred to Hybond membrane, and probed with antibodies to IκBα and β-actin.

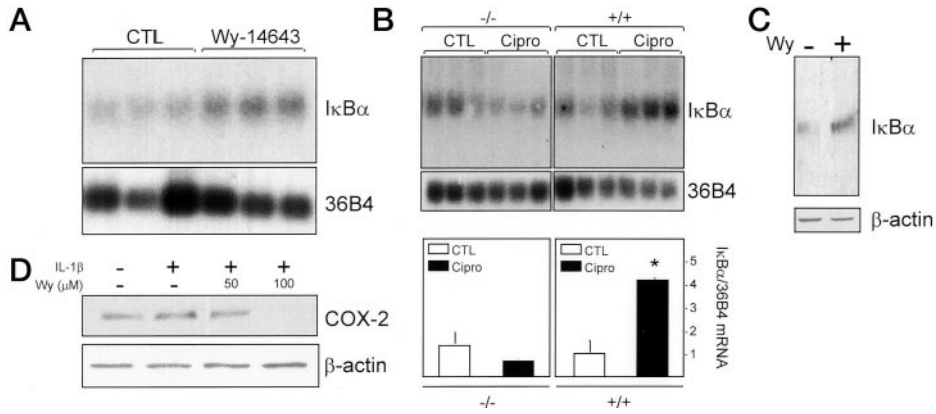

FIG. 3. **Fibrates induce IκBα mRNA and protein expression in human primary hepatocytes and in livers of PPARα +/+ but not of PPARα −/− mice.** *A*, human primary hepatocytes were cultured with standard medium supplemented with Wy-14643 (50 μM) or vehicle (Me_2SO, 0.1%) for 24 h. RNA (10 μg) was extracted, separated on a 1% agarose-formaldehyde gel, transferred to a nylon membrane, and analyzed by hybridization to IκBα and 36B4 cDNA probes. *B,* male PPARα −/− and +/+ mice (n = 3/group) were fed with rodent chow or rodent chow supplemented with 0.05% ciprofibrate for 2 weeks. At the end of the treatment period, livers were isolated and total RNA was extracted. RNA (10 μg) was separated on 1% agarose, transferred to a nylon membrane, and analyzed by hybridization to IκBα and 36B4 cDNA probes. Statistical analysis was assessed by analysis of variance ($p < 0.05$). Statistical significant differences between groups were then evaluated by the Student's t test. *C,* human primary hepatocytes were cultured with standard medium supplemented with Wy-14643 (50 μM) or vehicle (Me_2SO, 0.1%) for 24 h. Protein extracts were prepared and 50 μg of each extract were separated by SDS-PAGE, transferred to Hybond membrane, and probed with antibodies to IκBα and β-actin. *D,* human primary hepatocytes were cultured with standard medium supplemented with Wy-14643 (50 μM or 100 μM) or vehicle (Me_2SO, 0.1%) for 24 h and subsequently stimulated with IL-1β (10 ng/ml) for 16 h. Protein extracts were then prepared, and 50 μg of each extract were separated by SDS-PAGE, transferred to Hybond membrane, and probed with antibodies to COX-2 (a kind gift from Dr Habib, Paris, France) and β-actin.

and hemostatic factors, whose transcription is under the control of NF-κB transcription factors (33, 34), we next studied NF-κB target gene regulation by fibrates in human primary hepatocytes. Primary human hepatocytes express basal COX-2 protein levels, which were modestly induced by IL-1β (Fig. 3*D*). Fibrate treatment dose-dependently inhibited COX-2 expression similarly as described previously in human aortic SMC (14), suggesting a similar role for PPARα in the control of the hepatic inflammatory response.

After IκBα degradation, p50/p65 dimers translocate to the nucleus and activate gene transcription. To explore the functional consequences of IκBα up-regulation, EMSAs, using a NF-κB consensus site probe, were performed. Extracts from non-activated SMC contained a basal NF-κB binding activity, which was inhibited by fibrate treatment (Fig. 4*A*). The presence of NF-κB proteins in the complex was verified by shifting the complex using an anti-p65 antibody (data not shown). Treatment with IL-1β resulted in a drastic increase of NF-κB binding, which was reduced by Wy-14643 treatment for 2 h and completely abolished after 24-h fibrate pretreatment, whereas binding of OCT1 proteins to their respective consensus site was unaffected (Fig. 4*A*). As a control, Western blot analysis demonstrated that PPARα activators do not affect either p50 or p65 protein levels (Fig. 4*B* and data not shown). Poynter and

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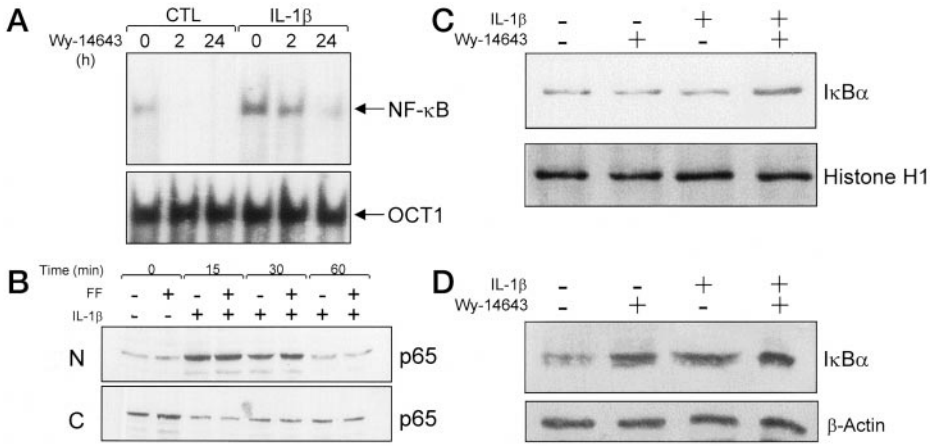

FIG. 4. **Wy-14643 reduces IL-1β-induced NF-κB DNA binding activities in cultured HASMC and increases nuclear IκBα protein.** *A,* human aortic SMC were cultured for 2 or 24 h with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) and were subsequently treated with IL-1β (10 ng/ml) for 1 h. Nuclear proteins were extracted and 5 μg of each sample were subjected to EMSAs using NF-κB consensus site or consensus OCT1 site radiolabeled probes (Promega). Complexes were visualized by autoradiography. *B,* SMC were cultured in standard medium with fenofibric acid (100 μM) or vehicle (Me_2SO, 0.1%) for 24 h and subsequently treated with IL-1β (10 ng/ml) for different time intervals (min). Nuclear and cytoplasmic protein extracts were prepared and proteins (20 μg) were separated by SDS-PAGE, transferred to a Hybond membrane, and probed with antibodies to p65. *C* and *D,* SMC were cultured in standard medium with Wy-14643 (100 μM) or vehicle (Me_2SO, 0.1%) for 24 h and were subsequently treated with or without IL-1β for 1 h. Nuclear (*C*) and cytoplasmic protein extracts (*D*) were prepared and proteins (50 μg) were separated by SDS-PAGE, transferred to a Hybond membrane, and probed with antibodies to IκBα, histone H1, and β-actin.

Daynes (35) and Marx *et al.* (22) showed that PPARα activators significantly reduced NF-κB DNA binding activities in aged murine splenocytes and in TNFα-stimulated endothelial cells, respectively. Therefore, our data are in line with the findings of these studies and suggest that the inhibition of NF-κB DNA binding activities depends on the time of PPARα agonist exposure.

In resting cells, IκBα sequesters p50/p65 heterodimers in a cytoplasmic inactive complex. To determine whether IκBα induction modulates NF-κB protein translocation, nuclear and cytoplasmic extracts from cultured SMC were isolated. IL-1β induced a rapid but transient p65 translocation to the nucleus (Fig. 4*B*). Surprisingly, fenofibric acid treatment did not inhibit IL-1β-induced p65 translocation suggesting that IκBα up-regulation by fibrates does not result in an increased sequestration of NF-κB in the cytoplasm (Fig. 4*B*). This result constitutes a major difference between fibrates and glucocorticoids, which were reported to induce IκBα in T cells and to block p65 translocation (36, 37). Because newly synthesized IκBα protein accumulates not only in the cytoplasm but also in the nucleus reducing thereby NF-κB binding (38, 39), IκBα protein localization was analyzed in cytoplasmic and nuclear extracts from human aortic SMC after fibrate treatment by Western blot analysis using a monoclonal anti-IκBα antibody. As a control, fibrate treatment resulted in an increase of the IκBα cytoplasmic content (Fig. 4*D*), which is consistent with our findings in Fig. 2*D*. Surprisingly, in non-stimulated cells, IκBα protein was also present in the nucleus but its levels were not affected by fibrate treatment (Fig. 4*C*). IL-1β treatment for 1 h did not result in an increased nuclear content of IκBα. This finding is in line with a previous study demonstrating that newly synthesized IκBα protein is only detectable in the nucleus after 2 h of IL-1β or TNFα exposure in HeLa S3 cells (39). Interestingly, fibrate treatment in the presence of IL-1β for 1 h led to an increase of nuclear IκBα protein content (Fig. 4*C*), which occurs concomitantly with the loss of NF-κB DNA binding activity observed in IL-1β treated cells (Fig. 4*A*).

Several concurring mechanisms may explain the overall anti-inflammatory activities of PPARα ligands. First, PPARs have been shown to down-regulate inflammatory response genes by negatively interfering with the STAT, AP-1, and NF-κB transcriptional pathways (14, 18, 21, 40). Direct protein-protein interactions between PPARα and AP-1 and NF-κB proteins have been invoked as mechanisms of transrepression (21). Second, by regulating anti-oxidant enzyme activities such as catalase (41), PPARα activators reduce the oxidative stress, and, as such, may inhibit NF-κB activation. Finally, the results of the present study provide an additional mechanism through which PPARα activators may antagonize NF-κB activation (Fig. 5). Induction of IκBα mRNA by fibrates may contribute to the inhibition of inflammatory gene activation such as *COX-2* or *IL-6*. The induction of IκBα by fibrates in cytokine-activated cells should result in an acceleration of NF-κB nuclear desactivation. This is consistent with a previous report in which PPARα ligands were shown to affect the duration of the inflammatory response in a PPARα-dependent manner (42). Consistent with this observation, the increase of IκBα protein after treatment with PPARα activators would lead to a halt in p65-

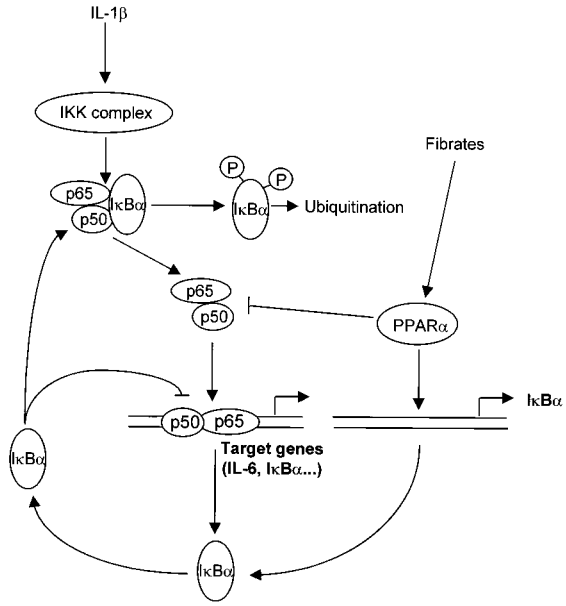

FIG. 5. **Model of NF-κB signaling pathway inhibition by PPARα activators.**

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mediated gene activation thereby reducing the duration of the inflammatory response.

The IκBα promoter contains several regulatory regions among which are sites for NF-κB (43, 44). The results using the PPARα-deficient mice indicate that IκBα activation by fibrates occurs in a PPARα-dependent manner. Our EMSA experiments indicate that PPARα activators do not activate IκBα transcription in a NF-κB-dependent manner because basal NF-κB binding activity present in SMC was not increased by Wy-14643 but was conversely lowered. Furthermore, IκBα mRNA appeared to be synergistically induced by fibrates in the presence of IL-1β (Fig. 2*A*) suggesting that PPARα activators regulate *IκBα* gene expression via a distinct signaling pathway. In addition, PPARα was reported to play a major role in the control of the cellular redox status (35). Klucis *et al.* (41) reported that administration of PPARα activators results in a drastic increase in the activity of catalase, an anti-oxidant enzyme. This induction occurs in the absence of oxidative stress as demonstrated by the absence of increase of F2-isoprostanes after Wy-14643 treatment (45). Taken together, these observations allow us to exclude that PPARα activators induce an oxidative stress resulting in NF-κB activation and induction of IκBα.

In conclusion, the demonstration that PPARα activators modulate NF-κB activation by inducing IκBα provides an additional, complementary action mechanism contributing to the overall anti-inflammatory properties of PPARα agonists.

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