Adiponectin Inhibits Endothelial Synthesis of Interleukin-8

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Abstract—Adiponectin is an antiatherogenic adipokine that inhibits inflammation by mechanisms that are not completely understood. We explored the effect of adiponectin on endothelial synthesis of interleukin-8 (IL-8), a pro-inflammatory chemokine that plays a role in atherogenesis. Adiponectin decreased the secretion of IL-8 from human aortic endothelial cells (HAEC) stimulated with tumor necrosis factor-α (TNF-α). Adiponectin also inhibited IL-8 mRNA expression induced by TNF-α. Phosphorylation of IkB-α was decreased by adiponectin, but phosphorylation of ERK, SAPK/JNK, and p38MAPK were unaffected. Adiponectin increased intra-cellular cAMP levels in HAEC in a dose-dependent manner; PKA activity was also increased. The inhibitory effect of adiponectin on TNF-α-induced IL-8 synthesis was inhibited by pretreatment with Rp-cAMP, a PKA inhibitor. These observations suggest that adiponectin inhibits IL-8 synthesis through inhibition of a PKA dependent NF-κB signaling pathway. We also showed that adiponectin enhances Akt phosphorylation. The inhibitory effect of adiponectin on TNF-α-induced IL-8 synthesis was abrogated in part by pretreatment with the PI3 kinase inhibitor LY294002 or by Akt siRNA transfection, suggesting that Akt activation might inhibit IL-8 synthesis induced by TNF-α. We conclude that inhibition of NF-κB and activation of Akt phosphorylation may mediate adiponectin inhibition of atherosclerosis. (Circ Res. 2005;97:1245-1252.)

Key Words: adiponectin ■ Akt ■ endothelial cells ■ IL-8 ■ PKA

Atherosclerotic complications are the leading cause of high cardiovascular mortality rates among patients with diabetes mellitus. The pathogenesis of atherosclerosis is based on several mechanisms. In recent years, theories about the role of chronic inflammation in the pathogenesis of both atherosclerosis1 and type 2 diabetes mellitus2 have been developed. Inflammatory processes are associated not only with initiation and progression of atherosclerosis but also are responsible for acute thrombotic complications.

Interleukin-8 (IL-8) is a pro-inflammatory cytokine that might have atherogenic properties through its multiple actions. Those actions include recruitment of neutrophils and T lymphocytes into the subendothelial space, monocyte adhesion to endothelium,3,4 and migration of vascular smooth muscle cells.5,6 Macrophage-derived human foam cells contain high amounts of IL-8,7,8 which can also increase the instability of atherosclerotic plaque through inhibition of tissue inhibitor of metalloproteinase expression.9

Adipose tissue is now recognized as an endocrine organ. Adipocytes secrete various biologically active molecules, termed adipocytokines, which might influence the function and structural integrity of the cardiovascular system.10 Adiponectin (Adp), an adipocytokine, is a recently discovered protein that circulates in high concentrations in plasma (≈0.01% of total plasma protein).11,12 In vascular injury experimental models, Adp seems to play a protective role.13,14 Hypo-adiponectinemia was observed in patients with obesity, type 2 diabetes mellitus, and coronary artery disease.15–16 Basic research has shown that physiological concentrations of human recombinant Adp suppressed tumor necrosis factor-α (TNF-α)–induced endothelial adhesion molecule expression, transformation from macrophage to foam cell, and TNF-α expression in macrophages.17–19 These data suggest that Adp has antiinflammatory properties and that Adp might regulate inflammatory responses at atherosclerotic lesions. However, no data elucidate the effects of Adp on synthesis of IL-8 in human endothelial cells.

This study was designed to examine the effects of Adp on the TNF-α–induced IL-8 synthesis and on signal transduction pathways in TNF-α–stimulated human aortic endothelial cells.

Materials and Methods

Cell Culture
Human aortic endothelial cells (HAECs) (Sanko Junyaku Co, Japan) at passages 8 to 12 were cultured in 10-cm or 6-cm culture dishes.
coated with type I collagen (Iwaki Glass Co, Japan) in MCDB 131 (Sigma Chemical Co) as described in a previous study. For experiments, HAECs were cultured with media in the presence or absence of 10 to 30 μg/mL human recombinant Adp (BioVendor Laboratory Medicine, Inc) for 24 hours. The HAECs were pretreated with 10 μmol/L of a protein kinase A (PKA) inhibitor, Rp-cAMPs, TEA (Rp-cAMP; Calbiochem-Novabiochem AG), 40 μmol/L of a PI3 kinase inhibitor, LY294002 hydrochloride (LY294002; Sigma), or vehicle for 1 hour.

**Measurement of IL-8 in the Media**

HAECs were cultured with media in the presence or absence of 10 to 30 μg/mL Adp in 24-well or 48-well culture plates coated with type-I collagen for 24 hours and then pre-treated with Rp-cAMP, LY294002, or vehicle for 1 hour. For measurement of IL-8 release from the HAEC in the medium, the media were collected after stimulation with TNF-α (Cosmobio Co Ltd, Japan) for 8 hours. The concentrations of IL-8 in the media were measured using enzyme-linked immunosorbent assay (ELISA).

**Northern Blot Analysis**

Northern blot analysis was performed according to the previously described method. Briefly, HAECs were cultured with media in the presence or absence of 30 μg/mL Adp in 10 cm culture dishes for 24 hours. Then cells were serum-starved with media containing 1% fetal calf serum (FCS) for 1 hour. After stimulation with 10 ng/mL TNF-α for 3 hours, RNA from the HAEC was extracted using ISOGEN (Nippon Gene Co Ltd, Japan). A digoxigenin-labeled probe for human IL-8 cDNA with dUTP by the random priming method (Roche Diagnostic Systems Inc) was used for hybridization. The band intensity was analyzed with NIH image.

**Western Blot Analysis**

Phosphorylation of MAP kinases, IκB-α, Akt (Thr308), and AMPK analyses were performed using a nonradioactive method with a commercial kit (New England Biolabs Inc, Cell Signaling Technologies). HAECs were cultured with or without 30 μg/mL Adp for 24 hours. They were then stimulated with 10 ng/mL TNF-α for 15 minutes. After that, cell lysates were prepared using lysis buffer. The cell lysates were then loaded on sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE), and transferred onto a membrane (Millipore Corp). The following antibodies were used: phospho-specific p44/42 MAP kinase (Thr202 and Tyr204) antibody (New England Biolabs Inc), phospho-p38 MAP kinase (Thr180 and Tyr182) antibody, phospho-SAPK/JNK antibody, phospho-specific IκB-α (Ser32) antibody, IκB-α antibody, phospho-AMPK-α (Thr172) antibody, AMPK-α antibody, phospho-specific Akt (Thr308) antibody, Akt antibody (Cell Signaling Technologies), and an anti-rabbit secondary antibody conjugated to horseradish peroxidase (Amersham Pharmacia Biotech Inc). The band intensity was analyzed using NIH image.

**cAMP Measurement**

The HAECs (2×10^4 cells per well in 24-well plates) were cultured with the indicated amount of Adp in the medium containing 1% FCS for 24 hours. Plates were placed on ice, and media were changed to ice-cold phosphate-buffered saline to terminate the reaction. Intra-cellular cAMP was measured using an enzyme immunoassay kit (Amersham Pharmacia Biotech Inc) according to the manufacturer’s instructions.

**PKA Activity Assay**

HAECs were cultured in 6-cm dishes and treated with 30 μg/mL Adp for 24 hours. At the end of the incubation period, cells were washed twice with phosphate-buffered saline and proteins were extracted using an extraction buffer. After centrifugation at 14 000g for 15 minutes, the supernatants were retained for cAMP-dependent protein kinase (PKA) activity assay. The PKA activity was measured using the PepTag Assay for nonradioactive detection of PKA (Promega Corp) based on the phosphorylation of fluorescent-tagged PKA-specific peptides, according to the manufacturer’s instructions. The fluorescence intensity of phosphorylated peptides, which reflected the PKA activity, was quantified.

**NF-κB Binding Activity Assay**

Activation of nuclear factor-κB (NF-κB) was determined using TransAM assay (Active Motif) according to the manufacturer’s instructions. Briefly, HAEC were cultured with media in the presence or absence of 30 μg/mL Adp in 6-cm dishes coated with type-I collagen for 24 hour. They were subsequently pretreated with Rp-cAMP or vehicle for 1 hour. After stimulation with 10 ng/mL TNF-α for 1 hour, the cells were washed, centrifuged, and lysed (Nuclear Extract Kit; Active Motif). Nuclear extracts were suspended in TransAm lysis buffer (Active Motif); suspensions were then microcentrifuged at 14 000g for 10 minutes at 4°C. Nuclear proteins (5 μg total proteins) or Raji nuclear extracts for positive control (2.5 μg/well) were incubated in 96-well plates with immobilized oligonucleotides containing the NF-κB consensus DNA-binding site (5’-GGGACTTTCC-3’) for 1 hour at room temperature. Wells were then washed three times. To each well, 100 μL of p50 and p65 subunits monoclonal antibody (1:1000 dilutions) were added; they were left for 1 hour at room temperature. Wells were washed three times. Then 100 μL of horseradish-peroxidase–conjugated secondary antibody (1:1000 dilutions) were added to each well for 1 hour at room temperature. The absorbance at 450 nm was determined using a spectrophotometer.

**Transfection of Cells With siRNA**

Small interfering (siRNA) oligonucleotides against Akt and control nonspecific siRNA oligonucleotides were purchased from Santa Cruz Biotechnology Inc. HAECs were transfected transiently with Akt siRNA using a synthetic amphilic delivery system (Synvolux Therapeutics B.V.) according to the manufacturer’s instructions. Cell lysates were analyzed by immunoblotting with anti-Akt antibody to confirm the knock-down effect of siRNA. The ERK was detected by reprobing the same blots with anti-ERK antibodies.

**Data Analyses**

Data are presented as the mean±SD. Statistical analyses were performed by ANOVA with subsequent Scheffe’s t test. A value of P<0.05 was inferred as significant.

**Results**

**Effect of Adp on IL-8 Production Induced by TNF-α in HAECs**

Changes in the TNF-α–induced IL-8 release and mRNA expression by Adp are shown, respectively, in Figure 1A and 1B. The Adp alone exhibited no effect on IL-8 synthesis, and inhibited the IL-8 release induced by TNF-α in a dose-dependent manner. Northern blot analysis was performed to examine whether Adp regulates IL-8 mRNA expression. Figure 1B shows that TNF-α extremely enhanced the expression of IL-8 mRNA; Adp markedly reduced the TNF-α–induced IL-8 mRNA expression (P<0.05). We measured the concentration of IL-10 to determine whether this inhibitory effect of Adp was caused by the antiinflammatory cytokine in HAECs. No significant difference was observed in the concentration of IL-10 between Adp-treated and nontreated HAECs (data not shown).

**Effect of Adp on Signal Transduction Pathways Activated by TNF-α in HAECs**

We examined the effect of Adp on several signal transduction pathways in TNF-α–stimulated HAEC to examine the mechanism by which Adp inhibits IL-8 synthesis.
First, we measured the content of cAMP and the PKA activity in HAEC after incubation with Adp. The cAMP content in HAEC was increased after incubation with Adp in a dose-dependent manner (Figure 2A). The PKA activity was also activated by incubation with Adp (Figure 2B). These findings, which are consistent with the previous report that Adp activates PKA activity, suggested that Adp might inhibit TNF-alpha-induced IL-8 synthesis through the cAMP-PKA dependent pathway.

Then, we examined whether the PKA inhibitor abrogated the effect of Adp. Figure 3 shows that, by treatment with an inhibitor of PKA, Rp-cAMP, the inhibitory effect of Adp on the IL-8 release was abrogated by ~50%, suggesting that the action of Adp is performed at least partly through the cAMP-PKA dependent pathway.

Next, we examined the respective effects of Adp on TNF-alpha–induced phosphorylation of ERK, p38 MAPK, and SAPK/JNK. Figure 4 shows that Adp alone did not phosphor-ylate these kinases. None of three kinase activities induced by TNF-alpha was antagonized by Adp.

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siRNA. Transfection of HAEC with human Akt siRNA remarkably reduced endogenous Akt expression (Figure 6B), whereas control siRNA had no effect. The inhibitory effect of Adp on TNF-α–induced IL-8 synthesis in HAECs was also abrogated by reduction of endogenous Akt expression by the siRNA transfection (Figure 6B). The combination of Rp-cAMP and LY-294002 abrogated the effect of Adp by 95% (Figure 6A), suggesting that the action of Adp is performed through both PKA-dependent and Akt-dependent pathways.

Figure 4. Effect of Adp on phosphorylation of ERK, p38MAPK, and SAPK/JNK induced by TNF-α in HAECs. After treatment with or without Adp for 24 hours, HAECs were stimulated with TNF-α (10 ng/mL) for 15 minutes. Phosphorylation of p44/42 MAPK, p38 MAPK, and SAPK/JNK induced by TNF-α was analyzed using Western blot analysis. Data are representative of three different experiments (means ± SD).

Figure 5. Effect of Adp on phosphorylation of Akt (A) and AMPK (B) in HAECs. After treatment with or without Adp for 24 hours, HAECs were stimulated with insulin (100 nM) for 15 minutes. Phosphorylation of Akt and AMPK induced by adiponectin and/or insulin was analyzed by Western blot analysis. Data are representative of three experiments (means ± SD). *P < 0.01.

Figure 6. A, Rp-cAMP and/or LY-294002 abrogate the inhibitory effect of Adp on the TNF-α–induced IL-8 release in HAECs. After treatment with or without Adp for 24 hours, HAECs were stimulated using TNF-α (10 ng/mL) for 8 hours. The LY-294002 and Rp-cAMP were added, respectively, 1 hour before stimulation with TNF-α. Concentration of IL-8 in the medium was measured using ELISA. Data are representative of three different experiments (means ± SD). P < 0.01, **P < 0.05. B, Akt knockdown by siRNA abrogates the inhibitory effect of Adp on the IL-8 synthesis in HAECs. HAECs were transfected with scrambled siRNA (control) or human Akt siRNA for 48 hours; then, they were cultured with or without Adp. After stimulation with TNF-α, the concentration of IL-8 in the medium was measured using ELISA. Data are representative of three experiments (means ± SD). *P < 0.01, **P < 0.05. Representative immunoblots are also shown.

Effect of Adp on NF-κB Activation Induced by TNF-α in HAECs

The NF-κB transcription factor is a major regulator of pro-inflammatory cytokine expression in TNF-α–stimulated endothelial cells. Therefore, we focused the effect of Adp on the NF-κB dependent pathway as a downstream of PKA-dependent and Akt-dependent pathways. We examined the effect of Adp on the phosphorylation of IκB-α induced by TNF-α. The increase of the phosphorylation of IκB-α indicates the increase of the NF-κB translocation from cytosol into the nucleus. Figure 7 shows that Adp alone had no effect on the IκB-α phosphorylation, but it inhibited the TNF-α–induced IκB-α phosphorylation by 60%, which is consistent with results of a previous report.17

Next, we examined the effect of Adp on the binding activity of the NF-κB subunit (p50 and p65) induced by...
TNF-α in HAECs. Results showed that Adp inhibited the TNF-α–induced binding activity of the p65 subunit (Figure 8); that of the p50 subunit was also inhibited by Adp (data not shown). The inhibitory effect of Adp on the TNF-α–induced NF-κB p65 subunit binding activity was abrogated in part by incubation with either Rp-cAMP or LY-294002. The combination of Rp-cAMP and LY-294002 abrogated the inhibitory effect of Adp by $\approx 95\%$, suggesting that NF-κB exists downstream of both PKA-dependent and Akt-dependent pathways.

Discussion

In this study, we demonstrated for the first time that Adp inhibits TNF-α–induced IL-8 production in HAECs at both the protein and mRNA levels, suggesting that Adp has an antiinflammatory effect on endothelial cells. We also provide novel evidence that the mechanism of the inhibitory effect of Adp on the TNF-α–induced IL-8 production is mediated by the NF-κB–dependent pathway, and that Adp also separately affects the cAMP-PKA pathway and the PI3 kinase-Akt pathway. Interestingly, Adp affected no phosphorylation of ERK, p38 MAPK, and SAPK/JNK, induced by TNF-α in HAEC.

It is well-known that key pathogenic events in atherosclerosis can be described as inflammatory processes, and insulin resistance and type 2 diabetes could be caused by chronic inflammation. Considering that insulin resistance is an independent risk factor for cardiovascular disease, sustained low-grade inflammation might be a factor that explains why type 2 diabetes and cardiovascular disease often develop simultaneously.

IL-8, a member of the CXC chemokine family, has been shown to be expressed by plaque macrophages in humans and to play an important role in the pathogenesis of atherosclerosis. IL-8 can induce vascular smooth muscle cell proliferation and migration; it has also been shown to be critical for chemotaxis and firm adhesion of monocytes to endothelial cells, a pivotal step in early stages of atherosclerosis. The IL-8 expression level was elevated in atherosclerotic lesions in carotid arteries. Those data suggest that IL-8 has an important role in progression of atherosclerotic lesions. Therefore, the inhibitory effect of adiponectin on the TNF-α–induced IL-8 production in HAECs might be an important effect of antiatherogenesis.

Adp is a 29-kDa protein, expressed exclusively in adipocytes, that was initially called adipocyte complement-related protein of 30 kDa (ACRP30) because of its homology to complement factor C1q. In vitro, Adp inhibits monocyte adhesion to endothelial cells, macrophage transformation to foam cells, and vascular smooth muscle cell proliferation. These data suggest that Adp has antiatherogenic effects in patients with diabetes and/or metabolic syndrome. Yokota et al reported that treatment of cultured macrophages with Adp significantly inhibited their phagocytic activity and their lipopolysaccharide (LPS)-induced production of TNF-α. We also observed that Adp inhibited LPS-induced inflammatory cytokines (TNF-α and IL-8) in THP-1 cells (our unpublished data). These antiinflammatory effects of Adp seem to be extremely important for prevention of coronary artery disease and macroangiopathy in diabetic patients.

TNF-α is a potent cytokine that is predominantly produced in macrophages, and elicits a broad spectrum of responses in various cells and organisms. Furthermore, TNF-α is overexpressed in adipose tissue; it affects intracellular insulin signaling in fat, skeletal muscle, endothelial cells, and other insulin-responsive tissues by inhibiting kinase activities in the insulin-signaling pathway. In addition, TNF-α is putatively an important regulator of atherogenesis and thrombogenesis in vascular endothelial cells. It is also known that TNF-α can induce IL-8 production strongly in endothelial cells. Taken together, we hypothesized that antiatherogenic effects of Adp are involved in IL-8 production induced by TNF-α. As shown in this study, Adp inhibits TNF-α–induced IL-8 production in HAEC at both protein and mRNA levels.
Reportedly, Adp neither affects the binding of TNF-α to its receptor on HAECS, nor the cell surface expression of TNF-α receptors on HAECS: Adp affects the TNF-α-induced signaling pathway at the post-receptor level.17

In the intracellular signal transduction pathways inducing IL-8 production by TNF-α, it is as yet unclear. TNF-α binds to surface receptors and activates several signal transduction pathways such as ERK1/2, SAPK/JNK, and p38 MAP kinase.29 The role of those kinases in the TNF-α-induced IL-8 synthesis in endothelial cells is already reported.30 We also observed that each inhibitor of ERK1/2, p38 MAPK, and SAPK/JNK respectively inhibited the TNF-α-induced IL-8 synthesis in HAECS (data not shown). However, as shown in Figure 4, Adp did not affect phosphorylation of ERK1/2, p38 MAPK, and SAPK/JNK induced by TNF-α, suggesting that none of those kinase dependent pathways is involved in the inhibitory effect of Adp. Our data are inconsistent with a previous report that Adp suppresses activation of p42/p44 MAP kinase induced by PDGF-BB in human aortic smooth muscle cells (HASMC).23 This discrepancy in results might arise from the different cell types (HASMCs versus HAECS) and stimulants (PDGF-BB versus TNF-α) that were used in the respective studies.

TNF-α-induced IL-8 production in human endothelial cells is associated with activation of transcription factors including NF-κB.30 Therefore, a potential mechanism whereby Adp can modulate inflammatory responses to TNF-α is blocking of the activation of those signal transduction pathways. NF-κB, a critical signaling molecule in TNF-α-induced inflammation, is a transcription factor composed of the Rel family of DNA-binding proteins that recognize a common sequence motif.31 In its inactive form, NF-κB is normally sequestered in the cytoplasm of nonstimulated cells, bound by members of the IκB family of inhibitor proteins. Consequently, it must be translocated into the nucleus to function. Exposure of cells to various extracellular stimuli including TNF-α engenders rapid phosphorylation, ubiquitination, and ultimately proteolytic degradation of IκB, which frees NF-κB to translocate to the nucleus, where it binds with consensus sequences of various genes and regulates gene transcription. Phosphorylation of IκB by an IκB kinase complex exposes nuclear localization signals on the NF-κB subunits and induces translocation of the molecule to the nucleus. Our observation, that Adp inhibited the TNF-α–induced IκB-α phosphorylation and NF-κB activation, suggests a mechanism of the antiinflammatory effects of Adp.

NF-κB inducing kinase (NIK) phosphorylates the IκB kinase (IKK) complex, leading to IκB phosphorylation and subsequent NF-κB activation.31 It has been reported that the activation of cAMP-PKA signaling pathway attenuated NF-κB activity through stabilization of IκB-α, but its precise mechanism has not been clarified.32,33 In the present study, we observed that Adp increased the level of intracellular cAMP and activated PKA. It is already reported that Adp inhibits the endothelial NF-κB signaling pathway through the cAMP-PKA–dependent pathway.17 It has been suggested that the inhibition of IL-8 production is also caused by the same mechanism from this result. We postulated that the cAMP-PKA pathway involves the inhibitory effect of Adp on IL-8 production induced by TNF-α because Adp is known to activate the cAMP-PKA pathway. As shown in Figure 3, we found that the inhibitory effect of Adp on TNF-α–induced IL-8 production was abrogated by an inhibitor of PKA, Rp-cAMP.

Notwithstanding, other mechanisms might participate in Adp-induced inhibition of NF-κB signaling because the Adp-induced inhibition of IL-8 synthesis was not relieved completely by pretreatment of Rp-cAMP alone. For that reason, we examined whether the PI3K-Akt pathway and AMPK are involved in the inhibitory effect of Adp, which is known to activate those pathways in endothelial cells.34 As shown in Figure 5, we also observed that Adp enhanced the phosphorylation of Akt and AMPK.

The serine-threonine protein kinase Akt is a downstream effector of phosphatidylinositol 3-kinase (PI3K), a lipid kinase controlled by membrane phospholipid inositol 1,4,5-trisphosphate.35 Activation of PI3K increases the intracellular amount of phosphatidylinositol-4,5-bisphosphate and phosphatidylinositol-3,4,5-trisphosphate, which positively regulate Akt. At present, conflicting reports exist as to the role of PI3K in NF-κB activation. The NF-κB activation is distinctly regulated in response to specific cytokines in different cell types. Several studies have demonstrated that the PI3K-Akt pathway plays a positive role in NF-κB activation in response to certain stimuli,36,37 whereas other studies have proposed conflicting results.38,39 The regulatory role of the PI3K-Akt signal cascade in NF-κB activity appears to be cell-specific and ligand-specific.

Kim et al40 reported that insulin, an activator of PI3K, decreased basal and VEGF-induced ICAM-1, VCAM-1, and E-selectin expression, suggesting that PI3K could be an intra-cellular suppressor for expression of ICAM-1, VCAM-1, and E-selectin through as yet unidentified signaling pathways. Another study has found that the inhibition of PI3K with wortmannin enhanced tissue factor expression induced by VEGF and TNF-α.41 Therefore, the activation of PI3K-Akt pathway might suppress the TNF-α–induced transcriptional activation of NF-κB in endothelial cells, and the activation of PI3K by Adp might be considered as a role for reducing TNF-α–induced inflammation in endothelial cells. We report here that the inhibitory effect of Adp is almost completely abrogated by inhibition of both the cAMP-PKA pathway and PI3K-Akt pathway (Figures 6 and 8). Nevertheless, the detailed pathway through which the Adp-induced PI3K-Akt activation suppresses the NF-κB activation in endothelial cells remains to be determined. Further work will be necessary to fully define the mechanism of Adp-induced suppression of TNF-α–induced IL-8 release from endothelial cells.

Because cardiovascular disease is the major cause of mortality in patients with obesity and insulin resistance,42 who typically have reduced levels of circulating Adp, a better understanding of the pathogenesis of atherosclerosis in this setting will facilitate development of more effective treatments to control these adverse outcomes. Targeting the Adp signaling pathway might ultimately engender novel approaches to the management of cardiovascular risk in those...
individuals. Taken together, results of this study suggest that Adp exerts atheroprotective effects on endothelial cells by attenuating IL-8 expression; these results also provide insight into some mechanisms in endothelial cells that underlie the vascular protective properties of Adp, highlighting its effects on IL-8 production.

Conclusions

In conclusion, we showed for the first time that Adp attenuates the TNF-α–induced IL-8 synthesis in HAEC. This inhibitory effect of Adp is accomplished through PKA-dependent and Akt-dependent pathways; it is achieved by inhibition of NF-κB activation. Our results suggest that the inhibition of IL-8 synthesis might be involved as a part of antiatherosclerotic effects of Adp and provide potential therapeutic benefits of Adp for prevention of atherosclerosis through inhibition of IL-8 synthesis from endothelial cells.

References


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