Cross-talk between \( \alpha_{1B} \)-Adrenergic Receptor (\( \alpha_{1B} \)AR) and Interleukin-6 (IL-6) Signaling Pathways

ACTIVATION OF \( \alpha_{1B} \)AR INHIBITS IL-6-ACTIVATED STAT3 IN HEPATIC CELLS BY A p42/44 MITOGEN-ACTIVATED PROTEIN KINASE-DEPENDENT MECHANISM*

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Treatment of primary rat hepatocytes or transfected HepG2 cells with the \( \alpha_{1B} \)-adrenergic receptor (\( \alpha_{1B} \)AR) agonist phenylephrine (PE) significantly inhibited interleukin 6 (IL-6)-induced STAT3 binding, tyrosine phosphorylation, and IL-6-induced serum amyloid A mRNA expression. Western analyses and in vitro kinase assays indicate that this inhibition is not due to either down-regulation of STAT3 protein expression or inactivation of upstream-located JAK1 and JAK2. Blocking the new RNA and protein syntheses antagonized the inhibitory effect of PE on IL-6-activated STAT3, suggesting synthesis of an inhibitory factor(s) is involved. The inhibitory effect of PE on IL-6 activation of STAT3 was also abolished by the tyrosine phosphatase inhibitor sodium vanadate, indicating involvement of protein tyrosine phosphatases. Furthermore, precubation of the cells with the specific MEK1 inhibitor PD98059 or a dominant negative MEK1 reversed the inhibitory effect of PE, and expression of constitutively activated MEK1 alone abolished IL-6-activated STAT3. Taken together, these data indicate that PE inhibits IL-6 activation of STAT3 in hepatic cells by a p42/44 mitogen-activated protein kinase-dependent mechanism, and tyrosine phosphatases are involved. This inhibitory cross-talk between the \( \alpha_{1B} \)AR and IL-6 signaling pathways implicates the \( \alpha_{1B} \)AR involvement in regulating the IL-6-mediated inflammatory responses.

The \( \alpha_{1B} \)-adrenergic receptor (\( \alpha_{1B} \)AR) is a G-protein-coupled receptor that is primarily coupled to a polyphosphoinositide-specific phospholipase C through G\(_i\), which catalyzes the breakdown of polyphosphatidylinositol 4,5-bisphosphate to inositol 1, 4,5-trisphosphate, which subsequently releases intracellular calcium (1–3). Recent evidence showed that the \( \alpha_{1B} \)AR is also linked to several downstream signaling cascades such as p42/44 mitogen-activated protein (p42/44 MAP) kinase, p38 MAP kinase, c-Jun NH\(_2\)-terminal kinase, and PI3-kinase (1, 5–7). \( \alpha \)1ARs play an important role in key components of the sympathoadrenal response to stress including the acute effects of catecholamines on liver carbohydrate and lipid and amino acid metabolism (1–3). In addition to such short term metabolic effects, stimulation of \( \alpha \)1ARs can influence hepatocyte growth and differentiation; it results in increased DNA synthesis (8) and has a co-mitogenic role in the early phases of the regenerative response after hepatic injury or partial hepaectomy (9). \( \alpha \)1ARs also play important roles in cardiac and smooth muscle contractility, cardiac hypertrophy, contraction of the spleen, and melatonin secretion in the pineal gland (1–3).

Interleukin-6 (IL-6) is a multifunctional cytokine that has been implicated in a variety of cellular functions in the hematopoietic, immune, neuronal, and hepatic systems (10–15). In the liver, IL-6 stimulates hepatocytes to produce a variety of acute-phase proteins, including serum amyloid A, C-reactive protein, complement C3, fibrinogen, and macroglobulin. Recent evidence from knock-out mice suggests that IL-6-induced STAT3 activation is a critical component of the regenerative response (15). Mice with targeted disruption of the IL-6 gene have impaired liver regeneration characterized by liver necrosis and failure. Treatment of the IL-6-deficient mice with a single dose of IL-6 before partial hepatectomy returned STAT3 binding, gene expression, and hepatocyte proliferation to levels seen in control animals following partial hepatectomy as well as prevented liver damage in these mice. The role of IL-6 in the liver inflammatory response and regeneration is believed to be linked through the gp130 protein. The interaction of IL-6 with the IL-6R\(_\alpha\) induces homodimerization of gp130, which is followed by activation of the receptor-associated Janus kinases, known as JAK1, JAK2, and Tyk2. This receptor-kinase complex interacts with and activates the SH2-containing cytoplasmic STAT3 transcription factor, which then translocates to the nucleus to activate the transcription of many target genes such as c-jun, c-myc, JunB, cyclin D1, C/EBP, p21waf1/cip1, and acute-phase genes (10–15).

Stress has been implicated as a modulator of gastrointestinal inflammation in both animal and human studies (16, 17). We wondered whether activation of \( \alpha_{1B} \)AR, an important component mediating the sympathoadrenal response to acute metabolic stress, modulates the major inflammatory cytokine IL-6 signaling pathway in the liver. Our data showed that activation of \( \alpha_{1B} \)AR markedly attenuated IL-6-activated STAT3 and IL-6-induced serum amyloid A mRNA expression in normal hepa-
toocytes and transfected HepG2 cells. Further studies suggest that this inhibition is p42/44 MAP kinase-dependent, and tyrosine phosphatases may be involved.

**EXPERIMENTAL PROCEDURES**

**Materials**—STAT3, JAK1, JAK2, and Tyk2 antibodies were obtained from Upstate Biotechnology, Inc. (Lake Placid, NY). Phospho-STAT3 (Tyr705) was obtained from New England Biolabs. PD98059, SB203580, SB202190, wortmannin, actinomycin D, puromycin, MG132, lactacystin, and bisindolylmaleimide I (GF109203X) were purchased from Calbiochem. Radiolabeled [γ-32P]ATP was obtained from NEN Life Science Products. HepG2 human hepatocellular cells were supplied by ATCC (Rockville, MD) and cultured as directed. HepG2 cells were stably transfected with α1B AR to generate TFG2 cells, as described previously (18).

**Western Blot Analysis**—Western blot analysis was described previously (19). TFG2 cells were resuspended in lysis buffer (30 mM Tris, pH 7.5, 150 mM NaCl, 1 mM phenylmethylsulfonyl fluoride, 1 mM Na3VO4, 1% Nonidet P-40, 10% glycerol) and then centrifuged for 10 min at 4 °C. Protein concentration of the supernatant (protein fraction) was calculated using the Bio-Rad protein assay. An aliquot of 40 μg of protein was mixed with an equivalent volume of 2× protein loading buffer containing β-mercaptoethanol and boiled for 5 min before loading onto an 8% SDS-polyacrylamide gel. Protein bands were detected using an enhanced chemiluminescence kit.

**Isolation of Hepatocytes**—Male Harlan Sprague-Dawley rats weighing 200–250 g were anesthetized with sodium pentobarbital, 50 mg/kg intraperitoneally, and the portal vein was cannulated under aseptic conditions. Liver cells were isolated by a collagenase perfusion protocol as described earlier (19). The isolated cells were washed twice and resuspended with Ca2+/-plus Krebs-Henseleit solution (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 2.5 mM CaCl2, 1.2 mM KH2PO4, NaHCO3, and 10 mM glucose) containing 1.5% gelatin and further treated with PE and/or IL-6. For cell cultures, the isolated cells were washed twice with hepatocyte medium (Dulbecco’s modified Eagle’s medium containing 0.5 ml of lysis buffer (30 mM Tris, pH 7.4, 150 mM NaCl, 1 mM phenylmethylsulfonyl fluoride, 1 mM Na3VO4, 1% Nonidet P-40, 10% glycerol). The isolated cells were washed twice with hepatocyte medium (Dulbecco’s modified Eagle’s medium containing 1×10^6 st dexamethasone, 2.5 μg/ml fungizone, 50 μg/ml gentamycin, 67 μg/ml penicillin, 100 μg/ml streptomycin) and plated onto rat tail collagen-coated culture dishes in hepatocyte medium containing 5% fetal bovine serum. After 2 h, the medium was changed to hepatocyte medium containing 0.5% serum and then treated with stimulated concentrations of PE and/or IL-6.

**DNA Gel Mobility Shift Assay (DMSA)**—DNA mobility gel shift assay was described previously (20). STAT3 activation was determined by DMSA. Preincubation with 10 μg/ml of 32P-labeled DNA containing a high affinity serum-induced element m67 (5’ GTG CAT TTC CCG TAA ATC TTG TCT ACA 3’), was described previously (21). The constitutively activated MEK1 plasmid DNA was transfected into the cells by adenovirus lysis-mediated protocol as described previously (22). Adenovirus-DNA complexes were prepared by incubating lysine-modified adenovirus with a constitutively activated MEK1 (S218D/S222D double mutant) expression vector (Upstate Biotechnology, Inc.) for 30 min at 22 °C in the dark, followed by a 30-min incubation with polyethylene at a molar concentration equivalent to 125 times the molar plasmid DNA concentrations. Adenovirus-DNA-lysine complex was then added to the cells and incubated for 8 h at 37 °C. The cells were washed with media to remove the virus and cultured for a further 48 h in DME containing 10% fetal calf serum.

**RESULTS**

**Activation of α1B AR by PE Significantly Inhibits IL-6-induced STAT3 Activation in Normal Adult Rat Hepatocytes**—As shown in Fig. 1A, IL-6 (20 ng/ml) treatment for 30 min caused significant STAT3 activation in primary cultured hepatocytes (2nd lane). The identity of STAT3 was proved by supershift assay as described previously (21). Preincubation with 10 μM PE for 1 h did not significantly inhibit this activation, while treatment with PE for 2–4 h markedly attenuated the IL-6-induced STAT3 activation. This result indicates that PE is able to inhibit IL-6-induced STAT3 activation in cultured hepatocytes. Fig. 1B demonstrated that the inhibitory effect of PE on IL-6-induced STAT3 activation was also observed in suspension of freshly isolated hepatocytes. PE alone did not activate STAT3 in hepatocytes (data not shown).

**PE Significantly Inhibits IL-6-induced STAT3 Activation in TFG2 cells**—The effect of PE on IL-6-induced STAT3 activation was also examined in the transfected HepG2 cells (TFG2 cells). As shown in Fig. 2A, stimulation of TFG2 cells with IL-6 (20 ng/ml) for 30 min significantly attenuated STAT3 activation (2nd lane). The identity of STAT3 was proved by supershift assay (data not shown). The pretreatment of TFG2 cells with PE within 1.5 h did not significantly affect IL-6-induced STAT3 activation, while pretreatment 2–4 h markedly attenuated this activation. PE alone did not activate STAT3 in TFG2 cells (data not shown).

To confirm further the inhibitory effect of PE, the effect of PE on the kinetics of IL-6-induced STAT3 activation was studied. TFG2 cells were treated with 10^−5 M PE for 2 or 3 h and then...
stimulated with 20 ng/ml IL-6 for various times. As shown in Fig. 2B, IL-6 treatment caused a rapid activation of STAT3 that peaked at 30 min (1st to 4th lanes). Preincubation with 10⁻⁵ M PE for 2 and 3 h almost completely abolished this activation (5th to 8th and 9th to 12th lanes). Fig. 2C showed that PE inhibition of IL-6-activated STAT3 was completely prevented by preincubation with prazosin (10⁻⁵ or 10⁻⁶ M), a specific α₁AR antagonist, suggesting that the effect of PE is α₁AR-mediated.

Next, we examined whether PE was able to inhibit IL-6-induced acute-phase protein (e.g. serum amyloid A) expression. TFG2 cells were treated with 10⁻⁵ M PE for 3 h and then stimulated with IL-6 for 2 h. The total RNA was isolated and used for RT-PCR. As shown in Fig. 2D, IL-6 significantly stimulated serum amyloid A mRNA expression (2nd lane), and these effects were inhibited by pretreatment with PE for 3 h (3rd lane). Fig. 3D also showed that PE treatment alone did not affect basal serum amyloid A mRNA expression (4th lane).

Inhibition of STAT3 Tyrosine Phosphorylation but Not STAT3 Protein Degradation Is Involved in PE Inhibition of IL-6 Activation of STAT3—To check whether PE inhibition of IL-6-induced STAT activation is due to down-regulation of STAT3 protein expression or due to inhibition of STAT3 tyrosine phosphorylation, Western blot analyses were conducted by using anti-STAT3 or anti-phospho-STAT3 (Tyr705) antibodies. TFG2 cells were stimulated with 10⁻⁵ M PE for various times, and then cell extracts were isolated and subjected to DMSA or Western analyses. As shown in Fig. 3, PE treatment for 2–4 h markedly inhibited IL-6-activated STAT binding to m67 probe, as demonstrated by DMSA in the top panel. The same treatment significantly attenuated IL-6-induced STAT3 tyrosine phosphorylation (middle panel) but did not inhibit rather than enhanced STAT3 protein expression. These data suggest that PE inhibition of IL-6 activation of STAT3 is due to inhibition of STAT3 tyrosine phosphorylation and is not due to STAT3 protein degradation.

PE Does Not Significantly Inhibit IL-6 Activation of JAKs in TFG2 cells—To examine whether PE inhibition of IL-6-induced STAT activation is due to blocking the upstream-located JAK1, JAK2, and Tyk2 activation, autophosphorylation assays were performed. As shown in Fig. 4, a 5-min IL-6 treatment rapidly induced JAK1 or JAK2 activation (2nd lane in A and B), and preincubation with PE for 3 h did not significantly affect this activation (3rd lane in A and B). On the contrary, preincubation of TFG2 cells with PMA for 10 min significantly inhibited IL-6-induced JAK2 activation. These results indicate that PE does not inhibit IL-6 activation of JAKs.

PE Inhibition of IL-6-induced STAT3 Activation Requires New RNA and Protein Syntheses—PE inhibition of IL-6-induced STAT activation only occurred after preincubation of cells for 2 h, suggesting that this inhibition may require synthesis of a new negative regulator. To test this hypothesis, actinomycin D, a RNA synthesis inhibitor, and puromycin, a protein synthesis inhibitor, were used. As shown in Fig. 5, preincubation with actinomycin D or puromycin alone did not affect IL-6-activated STAT3 (4th and 6th lanes) but significantly antagonized PE-mediated inhibition of IL-6-induced STAT3 activation (5th and 7th lanes). These results suggest that PE inhibition of IL-6-induced STAT3 activation requires a newly synthesized factor(s) that contributes to the inhibition.

Evidence for Tyrosine Phosphatases but Not Proteasomes Involvement in PE-mediated Inhibition of IL-6 Activation of STAT3.
STAT3—PE inhibition of STAT3 tyrosine phosphorylation could be due to inactivation of kinases responsible for tyrosine phosphorylation of STAT3 or, alternatively, to activation of a protein tyrosine phosphatase that dephosphorylates STAT3 (10–14). To examine the latter possibility, TFG2 cells were pretreated with sodium orthovanadate, a non-selective tyrosine phosphatase inhibitor, for 30 min, followed by a 30-min stimulation with IL-6. Cell lysates were then subjected to DMSA and Western analyses to quantify STAT3 binding and tyrosine phosphorylation. As shown in Fig. 6A, 1 mM sodium vanadate alone did not stimulate STAT3 binding (2nd lane, top panel) nor tyrosine phosphorylation (2nd lane, middle panel) but instead significantly enhanced IL-6-induced STAT3 protein binding (3rd lane, top panel) and phosphorylation (3rd lane, middle panel). Sodium vanadate also significantly prevented the PE inhibition of IL-6-induced STAT3 binding (6th lane, top panel) and tyrosine phosphorylation (6th lane, middle panel). The bottom panel indicated that these treatments did not significantly affect STAT3 protein expression. These data suggest that tyrosine phosphatases may be involved in PE inhibition of IL-6 activation of STAT3.

The ubiquitin-proteasome pathway has been implicated in down-regulation of activated STATs (23–25). We wondered whether this pathway was also involved in PE-mediated inhibition of IL-6 activation of STAT3. As shown in Fig. 6B, pretreatment of TFG2 cells with the proteasome inhibitors, MG132 or lactacystin, did not significantly antagonize PE-mediated inhibition of IL-6 activation of STAT3, suggesting that the ubiquitin-proteasome pathway is not involved.

**PE Inhibition of IL-6-induced STAT3 Activation Is Mediated through a p42/44 MAP Kinase-dependent Mechanism**—It has been shown that PE can activate many signaling pathways, such as the p42/44 MAP kinase, p38 MAP kinase, c-Jun NH2-terminal kinase, and PKC-kinase (4–7). To check whether these signaling pathways are involved in PE inhibition of IL-6-induced STAT3 activation, TFG2 cells were incubated with the protein kinase C inhibitor GF109203X, the p42/44 MAP kinase inhibitor PD98059, the p38 MAP kinase inhibitors SB202190 and SB203580, or the PKC-kinase inhibitor wortmannin for 30 min and were then incubated with 10−8 M PE for 3 h, followed by a 30-min stimulation with IL-6. The cell extracts were then isolated and subjected to DMSA for detection of STAT3 activation. As shown in Fig. 7A, IL-6 treatment caused a rapid

**STAT3 activation (2nd lane), whereas preincubation with PE for 3 h significantly inhibited this activation (3rd lane).** Pretreatment with PD98059 significantly reversed the PE inhibition of IL-6-induced STAT3 activation. Pretreatment with SB202190 or SB203580 also slightly reversed this inhibitory effect of PE, whereas pretreatment with GF109203X or wortmannin did not affect PE inhibition of IL-6-induced STAT activation. These results suggest that activation of p42/44 MAP kinase is involved in PE inhibition of IL-6 activation of STAT3.

To confirm further the role of p42/44 MAP kinase in the inhibitory effect of PE, TFG2 cells were infected with a dominant negative MEK1 recombinant adenovirus to block the activation of p42/44 MAP kinase. As shown in Fig. 7B, infection with MEK1 dominant negative adenovirus but not with control virus almost completely reversed PE inhibition of IL-6 activation of STAT3, which further suggests that p42/44 MAP kinase is involved.
MAP Kinase Activation Profile of PE and IL-6—Because the above data suggest that p42/44 MAP kinase is involved in PE inhibition of IL-6-activated STAT3, we wondered whether EGF and insulin, the major activators of p42/44 MAP kinase, inhibited IL-6-induced STAT3 activation. As shown in Fig. 8A, pre-incubation of TFG2 cells with EGF or insulin for 2 h did not significantly affect IL-6-induced STAT3 activation, whereas PE completely abolished this STAT3 activation.

To explain why EGF and insulin do not have the same inhibitory effect as PE, we compared the p42/44 MAP kinase activation profile of PE, EGF, insulin, and IL-6. Treatment of TFG2 cells with EGF or insulin caused a transient p42/44 MAP kinase activation profile of PE, EGF, insulin, and IL-6. Treatment of TFG2 cells with EGF or insulin for 2 h did not significantly affect IL-6-induced STAT3 activation, whereas PE completely abolished this STAT3 activation.

In the present study, we demonstrated that IL-6-activated STAT3 was partially antagonized by pretreatment with vanadate, a nonselective protein tyrosine phosphatase inhibitor, suggesting that a tyrosine phosphatase(s) may be involved in the inhibitory effect of PE. Since vanadate significantly enhanced IL-6-activated STAT3, we cannot rule out that partial reversal of IL-6 inhibition of IL-6-activated STAT3 by vanadate is due to stabilization of STAT3 tyrosine phosphorylation. Further experiments are required to clarify the role of tyrosine phosphatases in PE-mediated inhibition of IL-6-activated STAT3.

Proteolytic degradation of phosphorylated STAT has been shown to be another mechanism for down-regulating the JAK-STAT signaling pathway. Several tyrosine phosphatases, including SHP1 and SHP2 (12, 36), have been implicated in down-regulation of the JAK-STAT signaling pathway. Evidence suggests that tyrosine phosphatases are involved in UV light (37) and phorbol ester (35)-mediated inhibition of the JAK-STAT signaling pathway. In the present study, we demonstrated that PE-mediated inhibition of IL-6-activated STAT3 was partially antagonized by pretreatment with vanadate, a nonselective protein tyrosine phosphatase inhibitor, suggesting that a tyrosine phosphatase(s) may be involved in the inhibitory effect of PE. Since vanadate significantly enhanced IL-6-activated STAT3, we cannot rule out that partial reversal of IL-6 inhibition of IL-6-activated STAT3 by vanadate is due to stabilization of STAT3 tyrosine phosphorylation. Further experiments are required to clarify the role of tyrosine phosphatases in PE-mediated inhibition of IL-6-activated STAT3.

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Blocking RNA synthesis and protein synthesis abolished PE-mediated inhibition of IL-6-activated STAT3 activation, suggesting that PE induced an inhibitory protein(s) that inhibits IL-6 signaling pathway. The identity of this inhibitory protein(s) remains unclear. Two different families of inhibitory regulators of JAK-STAT signaling pathway have recently been identified. The first family of proteins, named JAB, SOCS, or CIS, is induced by cytokines (29–31). The second family of protein is protein inhibitor of activated STAT (PIAS) that can bind to activated STAT and down-regulate the JAK-STAT signaling pathway (32, 33). Our data show that PE inhibits IL-6-induced STAT3 tyrosine phosphorylation but does not affect JAK phos-

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phorylation. This suggests that JAB/ SOCS/SSI proteins were probably not involved in PE inhibition of IL-6-activated STAT3, because JAB/ SOCS/SSI proteins exert their function by preventing phosphorylation of JakS (38). Treatment of TG2 cells with PE for 3 h completely abolished IL-6-induced STAT3 tyrosine phosphorylation. This indicates that PIAS is probably not involved in PE inhibition of IL-6-activated STAT3, because PIAS does not inhibit STAT tyrosine phosphorylation (13, 32).

Several protein kinases, including p42/44 MAP kinase (34), protein kinase A (27), and protein kinase C (35), have been implicated in down-regulation of the JAK-STAT signaling pathway. PE was able to activate p42/44 MAP kinase, p38 MAP kinase, c-Jun NH2-terminal kinase, and PI3-kinase (4–7) but did not activate protein kinase C or protein kinase A2 in TG2 cells. Blocking p42/44 MAP kinase but not p38 MAP kinase or PI3-kinase significantly antagonized PE inhibition of IL-6-activated STAT3, suggesting that p42/44 MAP kinase is involved. Inhibition of IL-6-activated STAT3 by PE-activated p42/44 MAP kinase is slow (only occurring after 2 h of addition of PE in hepatocytes and TG2 cells) and requires new protein synthesis, which is similar to granulocyte-macrophage colony-stimulating factor-mediated inhibition of IL-6 signaling pathway (39). However, this is different from PMA- or ionomycin-activated p42/44 MAP kinase inhibition of IL-6-activated STAT3, which is rapid (occurring within 5 min of addition of PMA or ionomycin). The mechanism for p42/44 MAP kinase-mediated rapid and slow inhibition of IL-6 activation STAT3 remains unclear. Although EGF and insulin also significantly activate p42/44 MAP kinase in TG2 cells, they do not have the same inhibitory effect as PE. Comparison of p42/44 MAP kinase activation profile showed that PE induced a sustained p42/44 MAP kinase activation, whereas EGF or insulin induced transient p42/44 MAP kinase activation. It has been reported that the sustained activation and transient activation of p42/44 MAP kinase caused different end responses (40). Therefore, we believed that PE inhibition of IL-6-activated STAT3 is mediated by a sustained activation of p42/44 MAP kinase. This was further confirmed by that constitutive activation of p42/44 MAP kinase by transfection of constitutively activated MEK1 can inhibit IL-6-activated STAT3 in the absence of PE in Fig. 8C.

Pretreatment of TG2 cells with 5 μM p38 MAP kinase inhibitors SB202190 or SB203580 also slightly reversed PE-mediated inhibition of IL-6 activation STAT3, suggesting that p38 MAP kinase may also be involved. Five μM SB202190 or SB203580 significantly inhibited (by 90%) the activation of p38 MAP kinase but also partially blocked (by 20%) p42/44 MAP kinase,2 so we cannot rule out that the effects of SB202190 and SB203580 are due to inhibition of p42/44 MAP kinase further experiments are required to clarify the role of p38 MAP kinase in PE-mediated inhibition of IL-6 activation of STAT3.

In summary, our data described here demonstrated that stimulation of α1AR attenuated IL-6-induced STAT3 activation in hepatocytes and TG2 cells by a p42/44 MAP kinase-dependent mechanism and a protein tyrosine phosphatase(s) may be involved. Interestingly, we also found that activation of β2AR also rapidly inhibited IL-6-induced STAT3 activation in the liver.2 This suggests that catecholamines can inhibit IL-6 signaling pathway in the liver by activation of both α1AR and β2AR. The inhibitory cross-talk between the catecholamines and IL-6 signaling pathway may play an important role in the maintenance of homeostasis in the liver. The serum levels of IL-6 and catecholamines are both dramatically elevated in many severe clinical situations such as burns, endotoxemia, meningitis, and sepsis (41–43). Although IL-6-induced acute phase response is the defense reaction, long stimulation by IL-6 has been implicated in the pathogenesis of a wide variety of inflammatory, infectious, and malignant disorders including hepatitis, cirrhosis in liver (44). Therefore, it is tempting to speculate that the role of inhibition of IL-6-induced signal transduction by catecholamines through activation of α1AR and β2AR in stress reaction is to maintain the autocrine and paracrine balance of positive and negative factors to prevent its potential progress to liver diseases. Indeed, there is evidence that interaction between many stress mediators including epinephrine and IL-6 play an important role in inducing the hypermetabolic stress state in the liver after major injuries (45).

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α-Adrenergic Agonist Inhibits IL-6 Signaling Pathway

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