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Fenoterol inhibits LPS-induced AMPK activation and inflammatory cytokine production through β-arrestin-2 in THP-1 cell line

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ABSTRACT

The AMP-activated protein kinase (AMPK) pathway is involved in regulating inflammation in several cell lines. We reported that fenoterol, a β_2-adrenergic receptor (β_2-AR) agonist, had anti-inflammatory effects in THP-1 cells, a monocytic cell line. Whether the fenoterol anti-inflammatory effect involves the AMPK pathway is unknown. In this study, we explored the mechanism of β_2-AR stimulation with fenoterol in a lipopolysaccharide (LPS)-induced inflammatory cytokine secretion in THP-1 cells. We studied whether fenoterol and β-arrestin-2 or AMPKα1 subunit knockdown could affect LPS-induced AMPK activation, nuclear factor-kappa B (NF-κB) activation and inflammatory cytokine secretion. LPS-induced AMPK activation and interleukin 1β (IL-1β) release were reduced with fenoterol pretreatment of THP-1 cells. SiRNA knockdown of β-arrestin-2 abolished the fenoterol inhibition of LPS-induced AMPK activation and interleukin 1β (IL-1β) release, thus β-arrestin-2 mediated the anti-inflammatory effects of fenoterol on LPS-treated THP-1 cells. In addition, siRNA knockdown of AMPKα1 significantly attenuated the LPS-induced NF-κB activation and IL-1β release, so AMPKα1 was a key signaling molecule involved in LPS-induced inflammatory cytokine production. These results suggested the β_2-AR agonist fenoterol inhibited LPS-induced AMPK activation and IL-1β release via β-arrestin-2 in THP-1 cells. The exploration of these mechanisms may help optimize therapeutic agents targeting these pathways in inflammatory diseases.
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1. Introduction

Stimulation of monocytes and macrophages by bacterial lipopolysaccharide (LPS) increases the production several inflammatory cytokines contributing to the innate immune response [1]. Activated macrophages secrete various pro-inflammatory cytokines, including tumour necrosis factor α (TNF-α), interleukin 1β (IL-1β) and IL-6 [2]. Toll-like receptor (TLR) and nuclear factor-kappa B (NF-κB) signaling is a classical pathway in the LPS-induced inflammatory response [3,4]. However, the intermediate signaling molecules in TLR and NF-κB signaling are still not clear. β_2-adrenergic receptor (β_2-AR) agonists have been used in several respiratory diseases because of their bronchodilating effects [5–7]. In recent years, the effect of β_2-AR agonists on regulating inflammatory cytokine secretion was investigated [8–10]. We previously reported that fenoterol, a β_2-AR agonist, inhibited inflammatory cytokine secretion in THP-1 cells [11], but the exact target of β_2-AR signaling during the anti-inflammation effect is unclear.

AMP-activated protein kinase (AMPK) is a ubiquitous Ser/Thr kinase that exists as a heterotrimer with a catalytic α subunit and regulatory β and γ subunits [12]. As a sensor of energy balance, AMPK monitors the AMP/ATP ratio to regulate cellular metabolism by restoring ATP levels [13]. Moreover, AMPK has anti-inflammatory responses and can activate a variety of transcriptional factors and signal transduction proteins such as p38 mitogen-activated protein kinase (MAPK) [14,15]. Therefore, in addition to being a key regulator of physiological energy dynamics, AMPK might also have an important role in regulating inflammatory signal transduction. However, whether AMPK plays a role in LPS-induced inflammation and whether it is the exact target of the anti-inflammatory effects of β_2-AR stimulation in monocytes still need to be elucidated.

In the present study, we aimed to explore the mechanism and target of the anti-inflammatory effects of β_2-AR agonism in LPS-

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induced IL-1β secretion in THP-1 cells. We first determined whether fenoterol inhibited LPS-induced AMPK phosphorylation and increased IL-1β level, then whether the fenoterol-inhibitory effects on AMPK activation and IL-1β release involved β-arrestin-2 by siRNA knockdown. Furthermore, siRNA-mediated knockdown of AMPKα1 subunit significantly attenuated LPS-induced NF-κB activation and IL-1β release, so AMPK may play an important role in LPS-induced IL-1β production and be a target in the anti-inflammatory effects of β_2-AR agonism.

2. Materials and methods

2.1. Reagents

5-aminoimidazole-4-carboxamide 1-β-D-ribofuranosid (AICAR) was from Toronto Research Chemicals (Toronto, Canada). Fenoterol, *Escherichia coli* 0111:B4 LPS and Compound C were from Sigma–Aldrich (St. Louis, MO, USA). Antibodies against phosphor-AMPK (Thr172) and AMPKα were from Cell Signaling Technology (Beverly, MA, USA), AMPKα1 and AMPKα2 antibodies were from Abcam (Cambridge, MA, USA), GAPDH and β-arrestin-2 antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA, USA), and horseradish peroxidase-conjugated secondary antibody was from Zhong Shan Jin Qiao Co. (Beijing).

2.2. Cell culture

The THP-1 cell line, a human monocytic cell line, was obtained from the Cell Resource Center (IBMS/CAMS/PUMC, China). Cells were cultured in RPMI 1640 medium (Sigma Chemical Co., St. Louis, MO) supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 100 g/mL streptomycin at 37 °C in 5% CO_2 in a humidified incubator. Cells were distributed on sterile microtiter plates at 10^6/mL in RPMI 1640 medium containing 2% FBS and stimulated with 0.1 μg/mL LPS for 1 or 24 h at 37 °C with or without fenoterol (10^{-6} M). In other experiments, cells were stimulated with AICAR (10^{-4} M) for 1 or 24 h with or without Compound C (10^{-5} M).

2.3. SiRNA knockdown of β-arrestin-2 and AMPKα1

We designed several short-hairpin RNA fragments that might bind to the mRNA coding sequence of β-arrestin-2 and AMPKα1 and chose the one that most effectively inhibited β-arrestin-2 and AMPKα1 expression. The sense siRNA sequence targeting β-arrestin-2 was 5′ AAGGACCGCAAAGUGUUUGUG 3′ and that targeting AMPKα1 was 5′GGUUGGCAAACAUGAAUUGtt3′ (Shanghai GeneChem Co.). The inhibitory efficiency of siRNA probes was assessed by western blot analysis of β-arrestin-2 and AMPKα1 protein levels. Cells were cultured for 24 h before transfection with β-arrestin-2 siRNA or scramble siRNA (and AMPKα1 siRNA or scramble siRNA) by use of Oligofectamine transfection reagent (Invitrogen Life Technologies, Carlsbad, CA) according to the manufacturer's protocol [16]. All assays were performed 72 h after transfection of siRNA.

2.4. ELISA assay

IL-1β level in cell supernatants was determined by use of an ELISA kit (R&D Systems, Minneapolis, MN). The detection limit for IL-1β was 10 pg/mL.

2.5. Western blot

Western blot was performed as described [17]. After cell samples were lysed in 150 μl lysis buffer, the protein concentration was estimated by use of a BCA protein assay kit (Pierce Biotechnology, Rockford, IL, USA). Protein (30 μg) was loaded onto 10% SDS–polyacrylamide gel and electrophoretically transferred to nitrocellulose membranes (Pall, NY, US), which were incubated with primary and secondary antibodies according to the supplier's protocol and visualized with peroxidase and an enhanced chemiluminescence kit (ECL kit, Pierce Biotechnology, Rockford, IL, USA). Band intensities were determined by use of Image-J.

2.6. Electrophoretic mobility shift assay (EMSA)

Stimulated cells were rapidly chilled on ice and washed twice with ice-cold phosphate buffered saline (PBS), pH 7.4. Nuclear extracts were prepared with NE-PER Nuclear and Cytoplasmic Extraction Reagents (Pierce Biotechnology, IL, USA). Then 10 μg protein was examined by use of NF-κB biotin-labeled double-strand oligonucleotide probes (5′-AGTTGAGGGGACTTTCCCAGGC-3′). The reaction mixture was analyzed by electrophoresis in a non-denaturing 5% acrylamide gel with cold 0.5 Tris-borate-EDTA running buffer. Bands were detected by chemiluminescence with use of the Light Shift Chemiluminescent EMSA kit (Pierce Biotechnology, IL, USA).

2.7. Statistical analysis

Data are presented as mean ± SEM. Data for western blot analysis are presented as fold change over the respective control that was arbitrarily defined. Analysis of 2 groups involved unpaired two-tailed Student's *t* test and more than 2 groups one-way ANOVA followed by Bonferroni *post-hoc* test. PRISM 4.0 (GRAPHPAD software, San Diego, CA, USA) was used for all statistical tests. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Fenoterol inhibits LPS-stimulated IL-1β release in THP-1 cells

The level of IL-1β was significantly increased in THP-1 cells stimulated with LPS (0.1 μg/mL), and pre-incubation with 10^{-6} M fenoterol inhibited the elevated IL-1β level (Fig. 1).

3.2. Fenoterol inhibits LPS-induced AMPK activation

Phosphorylation of Thr-172 is used as a biomarker of AMPK activation. Stimulation with LPS (0.1 μg/mL) for 1 h significantly

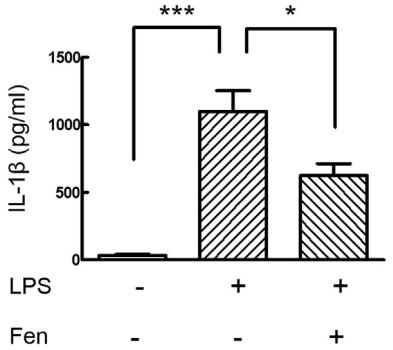

Fig. 1. Lipopolysaccharide (LPS)-stimulated interleukin 1β (IL-1β) with or without fenoterol. THP-1 cells were pre-incubated with fenoterol (10^{-6} M) for 30 min before LPS (0.1 μg/mL) for 24 h. ELISA of the IL-1β concentration in cell supernatants (n = 3). Data are mean ± SEM. *, $P < 0.05$; ***, $P < 0.001$.

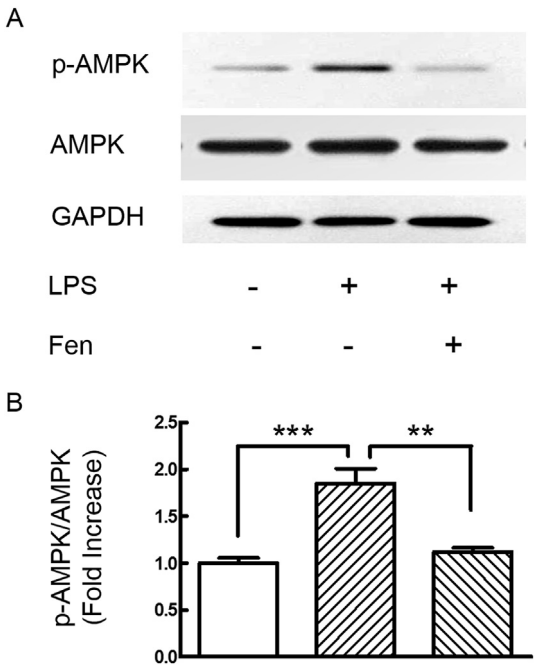

Fig. 2. Phosphorylation of AMP-activated protein kinase (AMPK) with LPS stimulation with and without fenoterol. THP-1 cells were pre-incubated with fenoterol (10^{-6} M) for 30 min or not, then stimulated with LPS (0.1 μg/mL) for 1 h. Western blot analysis (A) and quantification (B) of AMPK levels (n = 3). **, $P < 0.01$; ***, $P < 0.001$.

increased the phosphorylation of AMPK in THP-1 cells, and pre-incubation with 10^{-6} M fenoterol inhibited the increased phosphorylation of AMPK (Fig. 2).

3.3. β-arrestin-2 knockdown abolished fenoterol-inhibited IL-1β release and AMPK activation induced by LPS

To determine the effect of β-arrestin-2 knockdown on AMPK phosphorylation and the anti-inflammatory effects with fenoterol, THP-1 cells were transfected with β-arrestin-2 or scramble siRNA, then stimulated with LPS (0.1 μg/mL) with or without 10^{-6} M fenoterol pretreatment. β-arrestin-2 siRNA significantly inhibited β-arrestin-2 expression (Fig. 3A). β-arrestin-2 siRNA abolished the fenoterol-inhibited IL-1β release and AMPK phosphorylation (Fig. 3B, C and D).

3.4. SiRNA knockdown of AMPKα1 attenuates LPS-induced NF-κB activation and IL-1β release

THP-1 cells were transfected with scramble or AMPKα1 siRNA, then stimulated with LPS (0.1 μg/mL) with or without 10^{-6} M fenoterol pretreatment. AMPKα1 siRNA significantly decreased AMPKα1 expression (Fig. 4A). LPS-induced NF-κB activation was abolished by siRNA knockdown of AMPKα1 (Fig. 4B). Moreover, siRNA knockdown of AMPKα1 significantly attenuated LPS-induced IL-1β release (Fig. 4C).

4. Discussion

AMPK is a key regulator of physiological energy dynamics and has an important role regulating inflammation signal transduction [18]. In this study, we found that siRNA knockdown of AMPKα1 attenuated LPS-induced NF-κB activation and IL-1β release, which suggests the critical role of AMPK in LPS-induced inflammation in THP-1 cells. Fenoterol, a β_2-AR agonist, inhibited LPS-induced AMPK activation and IL-1β release though β-arrestin-2, so the anti-inflammatory effect of fenoterol depended on β-arrestin-2.

Activation of AMPK in different cell types may have opposite biological effects on cytokine release. In glial cells, vascular endothelial cells or BV-2 microglia cells, AMPK activation suppressed the LPS-induced expression of pro-inflammatory cytokines including TNF-α, IL-1, IL-6 and monocyte chemoattractant protein [19–21]. However, in cardiac fibroblasts of adult mice or human synovial fibroblast cells, AMPK activation had pro-inflammatory effects [22,23]. To verify the role of AMPK in monocytes, we used AICAR to stimulate AMPK in THP-1 cells (Fig. S1B) and observed the activation of IL-1β. AMPK activation by AICAR had pro-inflammatory

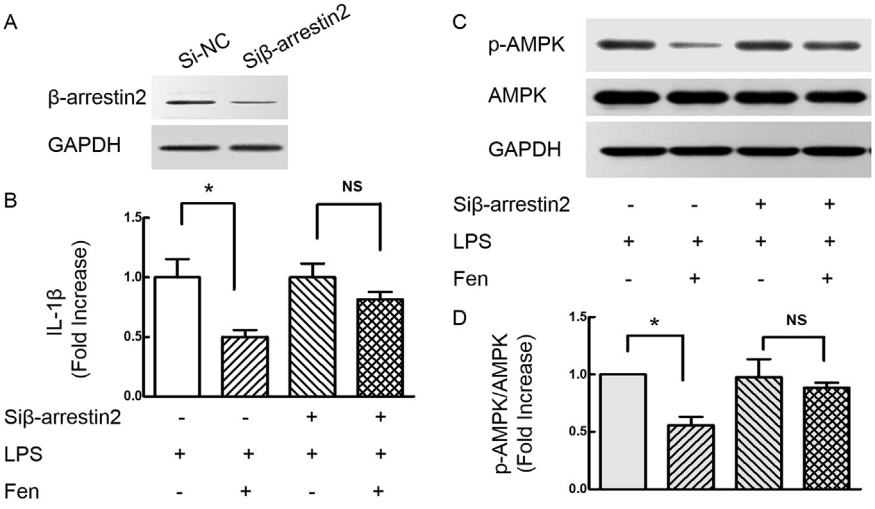

Fig. 3. Effect of siRNA knockdown of β-arrestin-2 on IL-1β production and AMPK phosphorylation. (A) Western blot analysis of β-arrestin-2 protein level with scramble or β-arrestin-2 siRNA knockdown. (B) ELISA of IL-1β secretion in THP-1 cells transfected with scramble or β-arrestin-2 siRNA, then stimulated with LPS (0.1 μg/mL) for 24 h with or without fenoterol (10^{-6} M) (n = 3). (C,D) Western blot analysis and quantification, respectively, of phosphorylation of AMPK in THP-1 cells transfected with scramble or β-arrestin-2 siRNA, then stimulated with LPS for 1 h with or without fenoterol (10^{-6} M) pretreatment (n = 3). Data are mean ± SEM. Si-NC: scramble siRNA. Siβ-arrestin2: β-arrestin2 siRNA. *, $P < 0.05$. NS, not significant.

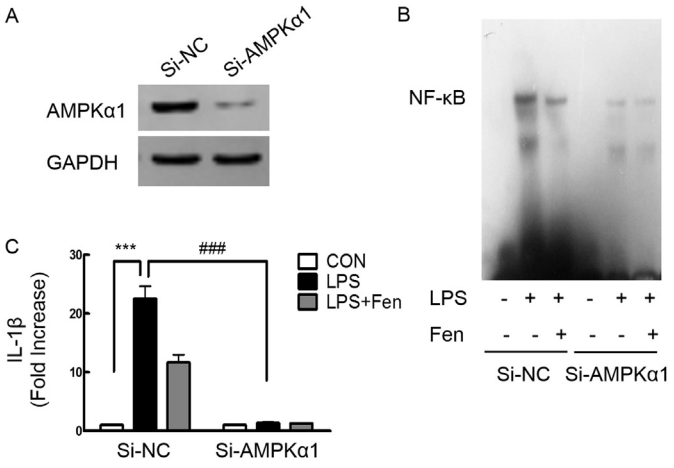

Fig. 4. Effect of siRNA knockdown of AMPKα1 on LPS-induced NF-κB activation and IL-1β production. (A) THP-1 cells were transfected with scramble or AMPKα1 siRNA for 72 h, then stimulated with LPS (0.1 μg/mL) with or without 10^{-6} M fenoterol pretreatment. Electrophoretic mobility shift assay of NF-κB activation (n = 3). (B) Western blot analysis of AMPKα1 protein level with and without AMPKα1 siRNA knockdown (n = 3). (C) ELISA of IL-1β level in THP-1 cells transfected with scramble or AMPKα1 siRNA, then stimulated with LPS (0.1 μg/mL) with or without 10^{-6} M fenoterol pretreatment (n = 3). Data are mean ± SEM. Si-NC: scramble siRNA. Si-AMPKα1: AMPKα1 siRNA. ***, $P < 0.001$. $^{###}$, $P < 0.001$.

effects on THP-1 cells by increasing IL-1β level (Fig. S1A). Most cells express both AMPKα1 and AMPKα2 isoforms, whereas THP-1 cells mainly expressed the AMPKα1 isoform (Fig. S2). In addition, siRNA knockdown of AMPKα1 attenuated LPS-induced NF-κB activation and IL-1β release in THP-1 cells (Fig. 3). This evidence suggests that the AMPKα1 subunit contributed to LPS-induced release of pro-inflammatory cytokines in THP-1 cells.

Elevated phosphorylation of AMPK in THP-1 cells promoted inflammation (Fig. S1B). The LPS-induced phosphorylation of AMPK and levels of inflammatory cytokines were significantly down-regulated with fenoterol, a β_2-AR agonist (Figs. 1 and 2). Many signaling molecules, such as NF-κB, cAMP response element-binding protein (CREB) and AP-1, are associated with inflammatory mediator release [24–27].

In human aortic endothelial cells, AMPK blocked p300-HAT–dependent NF-κB acetylation [28]. Since NF-κB has an important role in regulating the expression of inflammatory cytokines, we tested whether change in AMPK activation was associated with NF-κB activation during LPS-induced inflammatory cytokine release. SiRNA-mediated knockdown of AMPKα1 attenuated LPS-induced NF-κB activation (Fig. 4), which suggests that NF-κB is involved in AMPK-mediated release of pro-inflammatory cytokines. Although the anti-inflammatory effect of β_2-AR was associated with a change in content of IκB/NF-κB, extracellular signal-regulated kinase 1/2 (ERK1/2) or p38 MAPK [29,30], siRNA-mediated knockdown of AMPKα1 attenuated LPS-induced NF-κB activation, so AMPK may be the exact target of the fenoterol anti-inflammation process in THP-1 cells.

Activation of β_2-AR in the presence or absence of pro-inflammatory stimuli (e.g. LPS) produces pleotropic effects in inflammatory cytokine production [31]. The exact effect of β_2-AR activation on inflammatory cytokine production is determined by different inflammatory stimuli, β_2-AR agonists and cells, which is complicated. β_2-AR inhibiting LPS-mediated TNF-α or IL-8 production involves the Gs-dependent pathway, activating cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), thus resulting in phosphorylation of CREB and inhibition of the transcriptional activition of NF-κB [32,33]. In another report, β_2-AR activation promoted IL-1β and IL-6 production via PKA-independent and ERK1/2- and p38-dependent activation of transcription factors ATF-1 and ATF-2 in RAW264.7 murine macrophages [34]. In our study, fenoterol-activated β_2-AR inhibited LPS-mediated IL-1β release, which involved inhibiting AMPK and NF-κB.

G-protein– and β-arrestin-1/2–dependent pathway are the two main downstream signaling paths of β_2-AR activation [35]. β-arrestin-1/2 are ubiquitously expressed and negative regulators of G-protein–coupled receptor signaling. β-arrestin-2 plays an important role as a signaling adaptor and scaffold in regulating cellular inflammatory responses. It negatively modulates the activation of NF-κB and expression of NF-κB target genes by directly binding to IκBα, the inhibitor of NF-κB [36,37]. In mouse embryonic fibroblasts, expression of β-arrestin-2 inhibited AMPK activation stimulated by proteinase-activated-receptor-2 [38]. Our study indicated that siRNA knockdown of β-arrestin-2 abolished the anti-inflammatory effect of β_2-AR (Fig. 3B), which agrees with previous reports. Meanwhile, β-arrestin-2 knockdown abolished the down-regulated phosphorylation of AMPK mediated by fenoterol (Fig. 3C and D), which suggests that AMPK may be the downstream target of the anti-inflammatory effect of fenoterol in THP-1 cells.

Taken together, we provide evidence that phosphorylation of AMPK is involved in the inflammatory course in LPS-stimulated THP-1 cells and that β_2-AR signaling exerts anti-inflammatory effects by downregulating the phosphorylation of AMPK though β-arrestin-2. This finding will promote our understanding of the molecular mechanism of the regulation of inflammation in monocytes and provide a new target for the development of therapeutic agents for inflammatory diseases.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.04.097.

Transparency document

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