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Role of insulin-like growth factor-1 (IGF-1) in regulating cell cycle progression ☆

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ABSTRACT

Aims: Insulin-like growth factor-1 (IGF-1) is a polypeptide protein hormone, similar in molecular structure to insulin, which plays an important role in cell migration, cell cycle progression, cell survival and proliferation. In this study, we investigated the possible mechanisms of IGF-1 mediated cell cycle redistribution and apoptosis of vascular endothelial cells.

Method: Human umbilical vein endothelial cells (HUVECs) were pretreated with 0.1, 0.5, or 2.5 μg/mL of IGF-1 for 30 min before the addition of Ang II. Cell cycle redistribution and apoptosis were examined by flow cytometry. Expression of Ang II type 1 (AT_1) mRNA and cyclin E protein were determined by RT-PCR and Western blot, respectively.

Results: Ang II (1 μmol/L) induced HUVECs arrested at G_0/G_1, enhanced the expression level of AT_1 mRNA in a time-dependent manner, reduced the enzymatic activity of nitric oxide synthase (NOS) and nitric oxide (NO) content as well as the expression level of cyclin E protein. However, IGF-1 enhanced NOS activity, NO content, and the expression level of cyclin E protein, and reduced the expression level of AT_1 mRNA. L-NAME significantly counteracted these effects of IGF-1.

Conclusions: Our data suggests that IGF-1 can reverse vascular endothelial cells arrested at G_0/G_1 and apoptosis induced by Ang II, which might be mediated via a NOS–NO signaling pathway and is likely associated with the expression levels of AT1 mRNA and cyclin E proteins.

Introduction

Endothelial cells located in the vasculature serve as a barrier between the intravascular compartment and underlying tissues. They are usually exposed to various physical and biochemical stimuli, some of which may be detrimental to cell function. In order for endothelial cells to maintain functional integrity and hemostasis between the intravascular compartment and underlying tissues, mechanisms exist for purposes of adaptation or resistance to various stimuli. Regeneration of endothelium after vascular damage is an important factor that limits the development of atherogenesis [1]. Angiotensin II (Ang II) plays a central role in early atherogenesis and formation of atherosclerotic plaque. Previous studies showed that Ang II is a true cytokine at all stages of atherogenesis [2] and promotes the execution of programmed cell death [3].

Insulin-like growth factor-1 (IGF-1) is produced primarily by the liver as an endocrine hormone. The production of IGF-1 is stimulated by growth hormone and can be retarded by undernutrition, growth hormone insensitivity, and lack of growth hormone receptors among others. The primary action of IGF-1 is mediated by binding to specific IGF receptors present on many cell types in various tissues. IGF-1 is one of the most potent natural activators of the AKT signaling pathway, a stimulator of cell growth and multiplication and a potent inhibitor of programmed cell death. The over-expression of IGF-1 in myocytes protects them from apoptosis and interferes with myocyte hypertrophy by decreasing the expression levels of Ang II mRNA and AT1 mRNA in myocytes, further attenuating the response of myocytes to Ang II [4]. It is well known that inhibition of the renin–angiotensin system increases endothelial nitric oxide (NO) production [5]. Endothelial cells possess high affinity binding sites for IGF-1. The vasodilator effect of IGF-1 in the isolated perfused rat

Abbreviations: IGF-1, insulin-like growth factor-1; HUVECs, human umbilical vein endothelial cells; Ang II, angiotensin II; AT1, Ang II type 1; NOS, nitric oxide synthase; NO, nitric oxide; L-NAME, nomega-nitro-L-arginine methyl ester; PVDF, polyvinylidene difluoride; NO_x, NO metabolites; SD, standard deviation; VSMCs, vascular smooth muscle cells.

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kidney is abrogated by the NO synthase inhibitor nomega-nitro-L-arginine methyl ester (L-NAME). IGF-1 induces forearm vasodilation upon intra-arterial infusion into the brachial artery in healthy humans, which is completely reversed by addition of L-NAME [5]. However, whether IGF-1 plays a role in the cell cycle redistribution and apoptosis of vascular endothelial cells induced by Ang II is still unknown. In this study, we investigated the effects of IGF-1 on the enzymatic activity of NOS and resulting modifications in NO content, and the changes in expression levels of AT_1 mRNA and cyclin E protein in the vascular endothelial cells pretreated with 1 μmol/L Ang II.

Materials and methods

Cell culture and cell treatment. Human umbilical vein endothelial cells (HUVEC-12, ATCC, Manassas, VA, USA) were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (DMEM, Hyclone, Logan, UT, USA), benzyl penicillin (l00 U/mL), and streptomycin (l00 μg/mL) in a humidified atmosphere containing 5% CO_2 at 37 °C. Cells (1×10^5/mL) were seeded in 6-well dishes and were starved for 24 h in DMEM with 1% FCS until the cells had reached subconfluence. Then cells were treated with 1 μmol/L Ang II (Sigma Chemical Co, St. Louis, MO, USA) for 24 h in the presence or absence of IGF-1 (Sigma Chemical Co, St. Louis, MO, USA).

To explore the effects of IGF-1 on cell cycle progression and apoptosis, human umbilical vein endothelial cells were pretreated with 0.1, 0.5, and 2.5 μg/mL of IGF-1 or 10^{-4} mol/L L-NAME (Sigma Chemical Co, St. Louis, MO, USA) for 30 min before addition of Ang II. Cell viability, NOS activity, NO content, AT_1 mRNA, and cyclin E protein were determined after treatment with 1 μg/mL Ang II for 24 h.

Analysis of cell cycle distribution and apoptosis. Cells were harvested and washed twice with phosphate-buffered saline followed by fixation in 80% ethanol for 30 min at room temperature. The cells were then collected by centrifugation and stained with 50 μg/μL propidium iodide. The cells were then treated with 100 μg/μL RNase for 15 min at 37 °C followed by analysis using a FACScan flow cytometer (American Coulter EPICS XL flow cytometer, system II software). The fluorescence intensity of 1×10^5 cells for each sample was quantified.

Semi-quantitative RT-PCR analysis of AT_1 mRNA. Total RNA in endothelial cells (8×10^6 cells) was isolated using the TRIZOL reagent. Reverse transcription-polymerase chain reaction (RT-PCR) was performed using a TaKaRa one step RT-PCR kit based on the manufacturer's instructions. A total of 1 μg of total RNA served as a template for each reaction. For amplification, a primer pair for human AT_1 was as follows: sense primer, 5′-ATGCCATCCCA GAAAGTCG-3′, antisense primer, 5′-ATTCCCACCAC AAAGATGA TACTG-3′. Reverse transcription was performed at 50 °C for 15 min. For PCR, 35 cycles were used at 94 °C for 2 min, 94 °C for 30 s, 56 °C for 36 s and 72 °C for 40 s. β-Actin was amplified as a reference for quantification of AT_1 mRNA. Densitometric scanning to quantify amounts of RT-PCR product was performed using an Eagle Eye II Imageware system. The signal intensity of each AT_1 band was normalized to that of β-actin.

Western blot analysis of cyclin E protein. Sample preparation and Western blot analyses were performed as described below. Briefly, cell lysates were separated on 8% SDS–PAGE and transferred to a polyvinylidene difluoride (PVDF) membrane followed by a 12 h incubation in blocking solution at 4 °C (Tris-buffered saline containing 5% nonfat dried milk and 0.05% Tween 20). Rabbit anti-human cyclin E antibody (BD Pharmingen, USA) at a dilution of 1:500 was reacted with the blots overnight at 4 °C. After washing, the blots were incubated with goat anti-rabbit IgG1 horseradish peroxidase-conjugated antibody (BD Pharmingen, USA) as the secondary antibody at 1:1000 dilution for 2 h at room temperature. The membranes were visualized using the ECL kit (enhanced chemiluminescence, Santa Cruz). Densitometric measurements were performed using an Eagle Eye II Imageware system. β-Actin was used as the internal control.

Determinations of NO content and NOS activity. The amount of NO released in HUVECs was assessed by evaluating the concentrations of NO metabolites (NO*x*), i.e., nitrite plus nitrate. Briefly, NO*x* concentrations were evaluated by colorimetric detection of nitrite after conversion of sample nitrate to nitrite. NOS activity was also measured by colorimetric detection according to manufacturer's instructions.

Statistical analysis. All data were expressed as mean ± standard deviation (SD). Data analyses were done with SPSS software (Version 13.0; SPSS, Chicago, IL). Data among different groups were compared using one-way ANOVA or a Newman–Keuls–Student test. *P* values less than 0.05 was considered statistically significant.

Results

Effect of IGF-1 on cell cycles and apoptosis

As shown in Tables 1 and 2, it was determined that the IGF-1 + Ang II treatment group significantly reduced the apoptotic ($P < 0.01$) and G_0/G_1 phase ($P < 0.01$) cells, enhanced the cell numbers at the S phase ($P < 0.01$) and G_2/M phase ($P < 0.01$) compared with the Ang II treatment group, and reached the maximal effects when HUVECs were incubated for 24 h. However, after the HUVECs were pretreated with 100 μmol/L L-NAME for 30 min, our data showed that the Ang II + IGF-1 + L-NAME treatment group significantly enhanced the apoptotic ($P < 0.05$) and G_0/G_1 phase cells ($P < 0.05$), and reduced the cell numbers at the S phase ($P < 0.05$) and G_2/M phase ($P < 0.05$) compared with the IGF-1 + Ang II treatment group (Fig. 1).

Effect of IGF-1 on the expression of AT_1 mRNA

To further understand the role of IGF-1 on endothelial cell cycle and apoptosis regulation, we investigated the effect of IGF-1 (0.5 μg/mL) on the expression of AT_1 mRNA in HUVECs.

Table 1
Effects of IGF-1 and L-NAME on cell cycle progression and apoptosis of endothelial cells.

Group	Apoptosis (%)	G_1/G_0 (%)	S (%)	G_2/M (%)
Control	0.96 ± 0.29	74.7 ± 0.28	18.07 ± 0.09	7.20 ± 0.17
Ang II	2.55 ± 0.042*	88.13 ± 0.38*	7.43 ± 0.15*	4.43 ± 0.24*
Ang II + IGF-1	0.28 ± 0.015##	48.27 ± 0.49##	38.07 ± 0.23##	13.67 ± 0.26##
Ang II + IGF-1+L-NAME	1.21 ± 0.015+	65.57 ± 0.49+	27.30 ± 0.35+	7.10 ± 0.23+

Data are presented as mean ± SD ($n = 6$).
# $P < 0.05$.
$P < 0.01$ compared with Ang.
* $P < 0.05$ compared with control.
+ $P < 0.05$ compared with Ang II + IGF-1.

Table 2
Effect of IGF-1 on cell cycle progression and apoptosis of endothelial cells treated with Ang II for 12 h, 24 h, and 48 h, respectively.

Group	Apoptosis (%)	G_1/G_0 (%)	S (%)	G_2/M (%)
12 h				
Control	0.62 ± 0.017	67.30 ± 0.60	20.47 ± 0.43	12.17 ± 0.18
Ang II	1.18 ± 0.02*	82.80 ± 0.53*	9.27 ± 0.20*	7.93 ± 0.33*
Ang II + IGF-1	0.49 ± 0.03#	66.13 ± 0.77#	21.30 ± 0.61#	12.57 ± 0.18#
24 h				
Control	1.06 ± 0.03	74.70 ± 0.29	18.30 ± 0.31	7.20 ± 0.17
Ang II	2.55 ± 0.04*	88.13 ± 0.38*	7.43 ± 0.15*	4.43 ± 0.24*
Ang II + IGF-1	0.28 ± 0.01##	48.27 ± 0.49##	38.07 ± 0.23##	13.67 ± 0.26##
48 h				
Control	1.19 ± 0.01	84.53 ± 0.35	8.13 ± 0.15	7.33 ± 0.20
Ang II	3.06 ± 0.04*	94.37 ± 0.30*	3.37 ± 0.17*	2.27 ± 0.12*
Ang II + IGF-1	0.11 ± 0.003##	87.90 ± 0.49#	7.67 ± 0.26#	4.43 ± 0.24#

Data are presented as mean ± SD ($n = 6$).
* $P < 0.05$.
** $P < 0.01$ compared with control.
# $P < 0.05$.
$P < 0.01$ compared with Ang II treatment group.

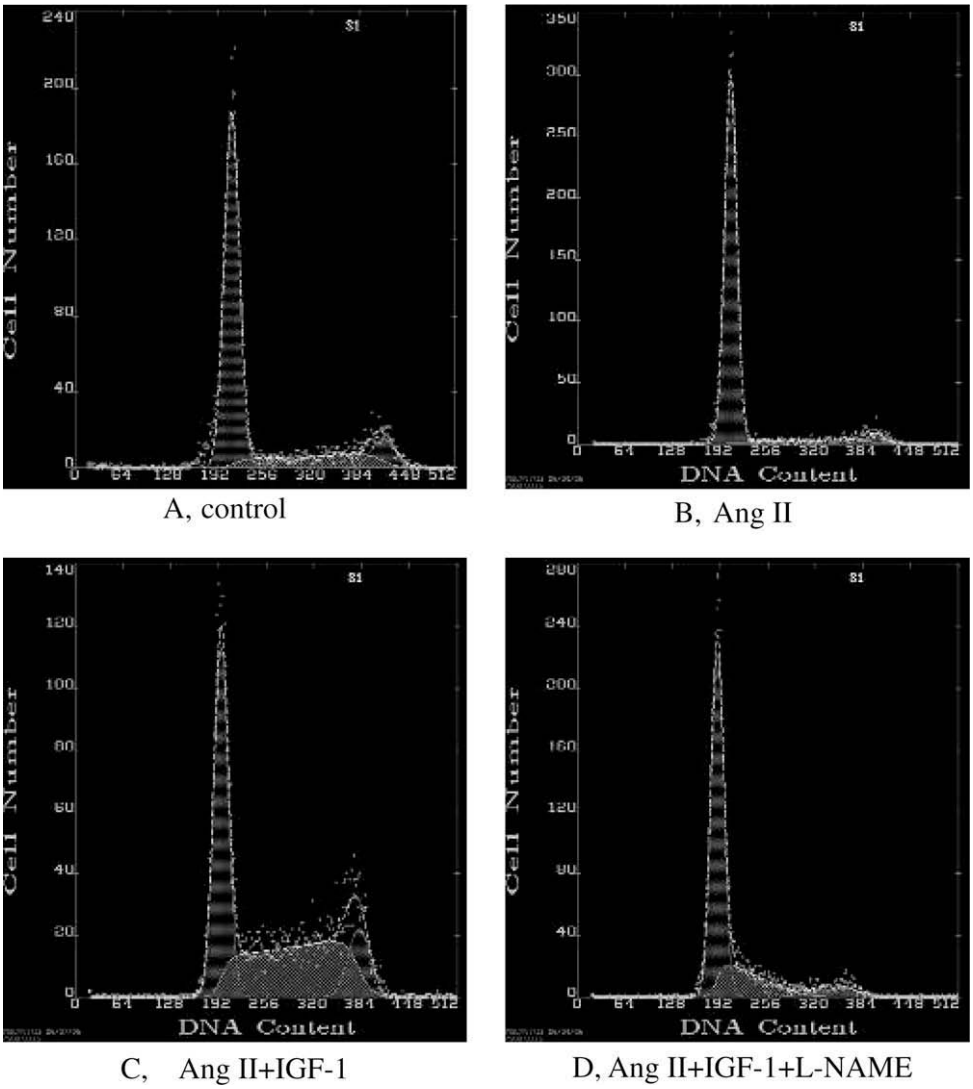

Fig. 1. The effects of IGF-1 on cell cycle distribution and apoptosis of endothelial cells incubated for 24 h. The incubated concentrations of Ang II, IGF-1 and L-NAME were 1 μmol/L, 0.5 μg/L and 100 μmol/L, respectively. Cells were treated with 0 μmol/L DMSO (A), 1 μmol/L Ang II (B), 1 μmol/L Ang II + 0.5 μg/L IGF-1 (C), and 1 μmol/L Ang II + 0.5 μg/l IGF-1 + 100 μmol/L L-NAME (D).

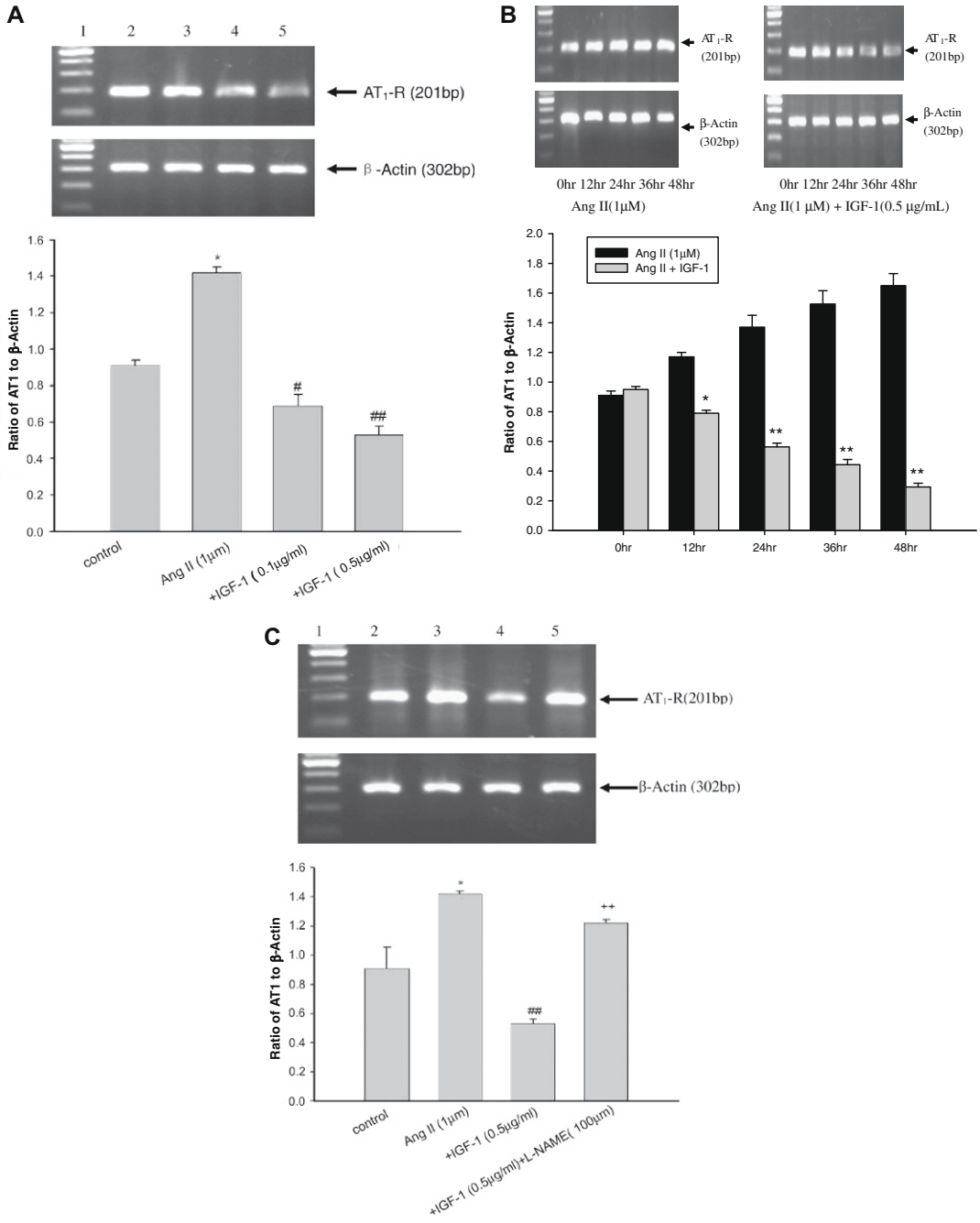

Fig. 2. (A) The effect of IGF-1 on the expression of AT_1 mRNA in endothelial cells. Panel A represents the dose-dependent effect of IGF-1 on the expression of AT_1 mRNA. Lane 1 was molecular weight marker, L2 to L5 shows cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.1 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1. Panel B shows the AT_1/β-actin mRNA ratio in endothelial cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.1 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1. The data (mean ± SD) were from six independent experiments. $^{*}P < 0.05$ compared with control, $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with the Ang II treatment group. (B) The time-dependent effect of IGF-1 at the concentration of 0.5 μg/L on the expression of AT_1 mRNA in endothelial cells. Panel A and panel B represents the time-dependent effect of 1 μmol/L Ang II (A) and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 (B) on the expression of AT_1 mRNA. Lane 1 was molecular weight marker, L2 to L6 shows cells incubated for 0 h, 12 h, 24 h, 36 h, and 48 h, respectively. Panel C shows the AT_1/β-actin mRNA ratio in endothelial cells treated for 0 h, 12 h, 24 h, 36 h, and 48 h, respectively. The data (mean ± SD) were from six independent experiments. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the Ang II treatment group. (C) The effect of L-NAME on the expression of AT_1 mRNA in endothelial cells. Panel A represents the effects of Ang II, Ang II + IGF-1, and Ang II + IGF-1 + L-NAME on the expression of AT_1 mRNA in endothelial cells. Lane 1 was molecular weight marker, L2 to L5 shows the cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.5 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 + 100 μmol/L L-NAME, respectively. Panel B shows the AT_1/β-actin mRNA ratio in endothelial cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.5 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 + 100 μmol/L L-NAME, respectively. The data (mean ± SD) were from six independent experiments. $^{*}P < 0.05$ compared with control, $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with the Ang II treatment group, $^{+}P < 0.05$ and $^{++}P < 0.01$ compared with the Ang II + IGF-1 treatment group.

As shown in Fig. 2A and B, our results showed that Ang II significantly upregulated the expression level of AT_1 mRNA in a time-dependent manner in HUVECs compared with the control group ($P < 0.05$). However, IGF-1 markedly decreased the upregulational effect of Ang II on the expression of AT_1 mRNA ($P < 0.01$). Moreover, the addition of L-NAME counteracted the effect of IGF-1 and significantly enhanced the expression level of AT_1 mRNA (Fig. 2C).

Effect of IGF-1 on the expression of cyclin E protein

In the present study, we found that Ang II significantly downregulated the protein expression level of cyclin E compared with the control ($P < 0.05$), and IGF-1 significantly enhanced the expression level of cyclin E protein ($P < 0.05$). However, the addition of L-NAME cancelled the upregulational effect of IGF-1 and markedly decreased the expression level of cyclin E protein ($P < 0.05$) (Fig. 3).

Effect of IGF-1 on NO content and NOS activity

As shown in Fig. 4, Ang II significantly decreased the NO content and enzymatic activity of NOS in HUVECs compared with the control ($P < 0.05$). However, addition of IGF-1 markedly enhanced the amount of NO and enzymatic activity of NOS in HUVECs compared with the Ang II treatment group ($P < 0.01$). Finally, we found that L-NAME counteracted the upregulational effect of IGF-1 and markedly reduced the expression level of cyclin E protein ($P < 0.05$).

Discussion

In this study we showed that Ang II induced HUVECs arrested at G_0/G_1, increased the percentage of apoptotic cells and the expression level of AT_1 mRNA, reduced the enzymatic activity of nitric oxide synthase and nitric oxide content as well as downregulated the expression level of cyclin E protein. However, IGF-1 significantly increased NOS activity and the NO level, upregulated the expression level of cyclin E protein and downregulated the expression level of AT_1 mRNA.

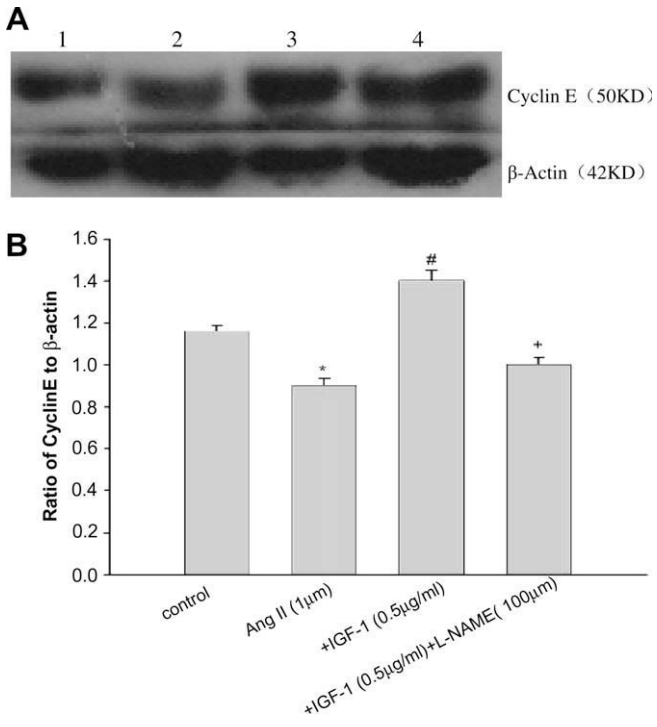

Fig. 3. The effect of IGF-1 on the expression of cyclin E protein. Panel A represents the effects of Ang II, Ang II + IGF-1, and Ang II + IGF-1 + L-NAME on the expression of cyclin E protein in endothelial cells. Lane 1 to L4 shows the cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.5 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 + 100 μmol/L L-NAME, respectively. Panel B shows the cyclin E/β-actin protein ratio in endothelial cells treated with 0 μmol/L DMSO, 1 μmol/L Ang II, 1 μmol/L Ang II + 0.5 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 + 100 μmol/L L-NAME, respectively. The data (mean ± SD) were from six independent experiments. $^{*}P < 0.05$ compared with control, $^{\#}P < 0.05$ compared with the Ang II treatment group. $^{+}P < 0.05$ compared with the Ang II + IGF-1 treatment group.

Ang II is an important stimulus of NADPH oxidase and its combination with the AT_1 receptor results in an increase of NADPH oxidase activity due to inactivation of NO, which leads to impaired endothelium-dependent vasorelaxation [6,7]. Recently, some studies reported that Ang II might induce the apoptosis of endothelial cells and negatively regulate the signaling pathway of nitric oxide, resulting in the endothelial dysfunction of endothelial cells [8,9]. One of the most important mechanisms related to Ang II and vascular endothelial toxicity may be the AT_1-dependent oxidant sensitive decrement of nitric oxide availability [10]. Angiotensin I is converted to angiotensin II through removal of two terminal residues by the enzyme angiotensin converting enzyme, which is found predominantly in the capillaries of the lung. Angiotensin I appears to have no biological activity and exists solely as a precursor to angiotensin II. Angiotensin II acts as an endocrine, autocrine/paracrine, and intracrine hormone and plays an important role in the renin–angiotensin system via binding to the AT_1 receptor [11]. In this study, our results showed that Ang II induced the arrest of the endothelial cell cycle at the G_0/G_1 phases, apoptosis, decreased NOS activity and NO content, upregulated the expression level of AT_1 mRNA, and downregulated the expression level of cyclin E protein.

IGF-1 plays an important role in cell migration, cell cycle progression, and cell survival and proliferation [12,13]. IGF-1 has been

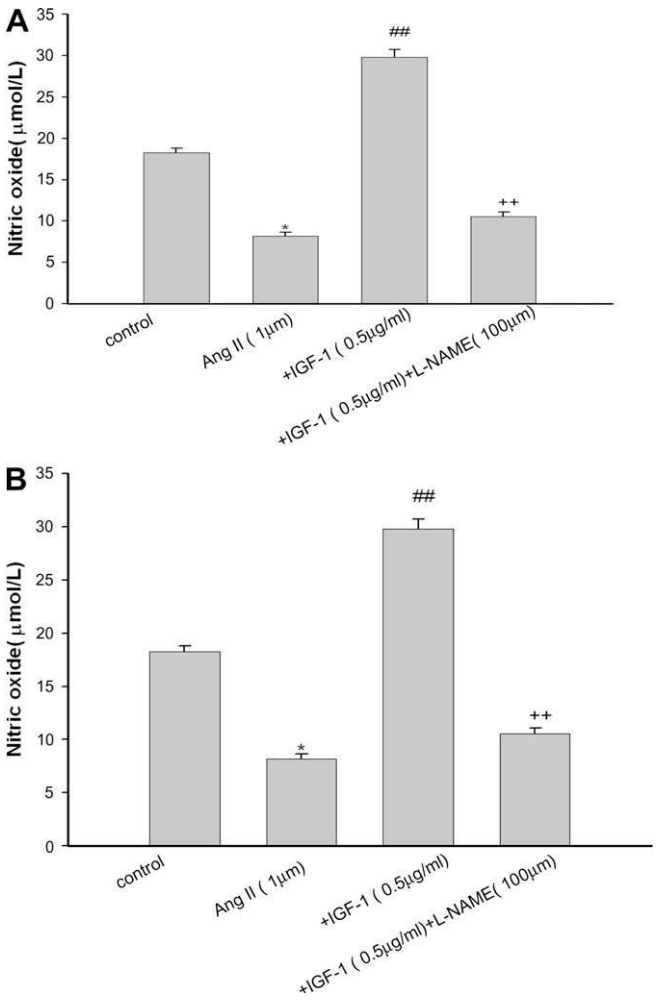

Fig. 4. The effect of IGF-1 on NO content (A) and NOS activity in endothelial cells treated with 0 μmol/L DMSO (control), 1 μmol/L Ang II, 1 μmol/L Ang II + 0.5 μg/mL IGF-1, and 1 μmol/L Ang II + 0.5 μg/mL IGF-1 + 100 μmol/L L-NAME, respectively. The data (mean ± SD) were from six independent experiments. $^{*}P < 0.05$ compared with control, $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with the Ang II treatment group, $^{+}P < 0.05$ and $^{++}P < 0.01$compared with the Ang II + IGF-1 treatment group.

shown to induce the survival and proliferation of vascular smooth muscle cells (VSMCs) and accelerate VSMCs into S-phase by significantly inducing the expression of cyclin E protein and inhibiting the expression of $P^{27(kip)}$ and $P^{21(cip)}$ protein, as well as preventing atherosclerotic plaques from destabilization [14]. Recently, Saetrum et al. reported that IGF-1 plays an important role in protecting cardiac muscle against injuries and has a well documented anti-apoptosis effect and action on cardiac muscle regeneration [15]. In addition, IGF-1 has beneficial effects on endothelial function and increases NOS activity by interacting with a tyrosine kinase membrane receptor linked to the insulin receptor substrate 1 and 2, which produce a slow and sustained release of NO [16–18].

NO production from L-arginine has been considered to be the most important mediator for vascular function and endothelium integrity. NO is an endothelial survival factor and it can inhibit apoptosis and enhance endothelial cell proliferation [19]. In the present study, we found that IGF-1 increased NOS activity and NO production, recovered cell cycle progression, inhibited apoptosis, downregulated the expression of AT_1 mRNA and upregulated the expression of cyclin E protein. However, these biological effects of IGF-1 could be counteracted by the NOS inhibitor L-NAME. NO inhibits apoptosis induced by various apoptotic stimuli [20] and is essential for angiogenesis [2]. The downregulation of the AT_1 receptor may be one of the important mechanisms for the anti-atherogenic property of NO [21]. Taken together, the maintenance of an intact endothelial monolayer and function is necessary to protect against the initiation of atherogenesis.

In conclusion, this study suggests that IGF-1 plays an important role in the cell cycle progression and apoptosis of endothelial cells. These biological effects of IGF-1 appear to be mediated via the NOS–NO signaling pathway resulting in the downregulation of AT_1 mRNA and upregulation of cyclin E protein. These findings support the idea that IGF-1 is an important molecular target for the treatment of cardiovascular diseases.

Conflict of interest

None declared.

Acknowledgments

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