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Angiotensin-(1–7) regulates Angiotensin II-induced VCAM-1 expression on vascular endothelial cells

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ABSTRACT

Angiotensin II (Ang II) and Angiotensin-(1–7) (Ang-(1–7)) are key effector peptides in the renin–angiotensin system. Increased circulatory Ang II level is associated with the development of hypertension and atherosclerosis, whereas Ang-(1–7) is a counter-regulatory mediator of Ang II which appears to be protective against cardiovascular disease. However, whether Ang-(1–7) regulates the action of Ang II on vascular endothelial cells (EC) remains unclear. We investigated the effects of Ang II and Ang-(1–7) in the context of atherogenesis, specifically endothelial cell VCAM-1 expression that is implicated in early plaque formation. The results show that Ang II increased VCAM-1 mRNA expression and protein displayed on EC surface, while Ang-(1–7) alone exerted no effects. However, Ang-(1–7) significantly suppressed Ang II-induced VCAM-1 expression. Ang-(1–7) also inhibited the Ang II-induced VCAM-1 promoter activity driven by transcription factor NF-KappaB. Furthermore, immunofluorescence assay and ELISA showed that Ang II facilitated the nuclear translocation of NF-kappaB in ECs, and this was attenuated by the presence of Ang-(1–7). The inhibitory effects of Ang-(1–7) on Ang II-induced VCAM-1 promoter activity and NF-kappaB nuclear translocation were all reversed by the competitive antagonist of Ang-(1–7) at the Mas receptor. Our results suggest that Ang-(1–7) mediates its affects on ECs through the Mas receptor, and negatively regulates Ang II-induced VCAM-1 expression by attenuating nuclear translocation of NF-kappaB.

1. Introduction

During the early stage of atherosclerosis, pro-inflammatory insults stimulate the expression of adhesion molecules on the activated endothelial cells (EC) [1]. Vascular cell adhesion molecule-1 (VCAM-1) plays a pivotal role in mediating firm adhesion of circulating inflammatory cells, including monocytes, lymphocytes and eosinophil [2]. This subsequently leads to infiltration of inflammatory cells in the vascular wall, and hence facilitates the accumulation of fatty streaks and formation of atherosclerotic plaque [2].

The renin–angiotensin system (RAS) is well recognized to control cardiovascular physiological responses including blood pressure and fluid balance, and its dysregulation is often associated with cardiovascular diseases such as atherosclerosis and hypertension [3]. Most of the pathological effects of the RAS are attributed to overproduction of Angiotensin II (Ang II). Activation of the Angiotensin II AT1 receptor, a G protein-coupled, seven transmembrane protein, results in vasoconstriction, proliferation, pro-inflammatory and pro-fibrotic activities [4]. Previous studies have suggested that Ang II, acting via AT1 receptor, also induces EC activation and increases VCAM-1 expression, and is likely to involve NF-kappaB signaling pathway [5,6].

The heptapeptide Angiotensin-(1–7) (Ang-(1–7)) can be endogenously derived from the octapeptide Ang II by angiotensin-converting enzyme 2 (ACE2), and has been shown to counteract many actions of Ang II [7]. Unlike Ang II, Ang-(1–7) is protective against cardiovascular disease, including a reduction in atherosclerotic lesion progression [8,9]. It mainly acts through Mas receptor, another G protein-coupled, seven transmembrane protein, and mediates vasodilator and anti-proliferation activities [10,11]. Hence, Ang-(1–7) attenuates myocyte hypertrophy and myocardial interstitial fibrosis [12], as well as antagonizing vasoconstriction evoked by Ang II [13]. Moreover, with diabetic nephropathy mice model, Moon et al. showed that Ang II-induced NF-kappaB and MAPK signaling pathways are negatively modulated by Ang-(1–7) in mesangial cells [14].

Hence, we aim to elucidate the role of Ang-(1–7) in atherosclerosis by investigating whether Ang-(1–7): (1) regulates Ang II-induced VCAM-1 expression on vascular endothelial cells; and (2) influences VCAM-1 expression via modulating the NF-kappaB signaling pathway.

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2. Material and methods

2.1. Cell culture and treatment conditions

EA.hy926 cell line was purchased from American Type Culture Collection and maintained in DMEM supplemented with 10% FBS, penicillin and streptomycin at 37 °C in a humidified atmosphere of 5% CO_2. Cell treatments in all experiments were carried out in the following concentrations: Ang II (10^{-7} M), Ang-(1–7) (10^{-7} M), losartan (10^{-6} M) and A-779 (10^{-6} M). For conditions requiring both Ang-(1–7) and Ang II, the two agents were added in sequence with 10 min apart. To study the inhibition of receptors for Ang II and Ang-(1–7), cells were pre-incubated with AT1 receptor antagonist (losartan, 10^{-6} M) or Mas receptor antagonist (A-779, 10^{-6} M) for 5 min before treatment with Ang II or Ang-(1–7), respectively. Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), penicillin and streptomycin were obtained from Invitrogen. A-779 was purchased from Genscrpit. Ang II, Ang-(1–7) and losartan were obtained from Sigma Aldrich.

2.2. Real- time reverse-transcriptase PCR (real-time RT-PCR)

ECs were stimulated by incubating with Ang-(1–7) (10^{-7} M) or Ang II (10^{-7} M) or both, (±losartan or A-779 blockage). After 6 h, RNA was isolated from the cells and reversely transcribed to cDNA (Fermentas). Real-time PCR of VCAM-1 was performed in duplicate in RT-PCR detection system (Bio-RadMiniOpticon) using SYBR Green I method (Takara). The sequences of PCR primers for VCAM-1 were 5′-CATGGAATTCGAACCCAAACA-3′ (sense) and 5′-GGCTGACCAAGACGGTTGTATC-3′ (anti-sense) as described elsewhere [15]. The PCR primer sequences for GAPDH were 5′-TG ACGTGCCGCCTGGAGAAAC-3′ (sense) and 5′-CCGGCATCGAAGGT GGAAGAGT-3′ (anti-sense) [16]. Real-time RT-PCR data of VCAM-1 were analyzed using the delta–delta C_T method, standardized against GAPDH reference house-keeping gene values.

2.3. Flow cytometry

Ang-(1–7) (10^{-7} M) was added to the ECs followed by Ang II (10^{-7} M) after 10 min and was further incubated for 16 h. Losartan and A-799 were used for conditions studying inhibition of receptors for Ang II and Ang-(1–7) as described above. The cells were harvested, washed and resuspended in PBS containing 0.2% BSA at 10^6 cells/mL, followed by incubation for 40 min on ice with mouse anti-human VCAM-1 monoclonal antibody (5 μg/mL) (Bio-Legend) or PE isotype-matched control antibody (5 μg/mL) (Bio-Legend). The cells were then washed and analyzed by flow cytometry.

2.4. Subcellular fractionation and enzyme-linked immuno-sorbent assay (ELISA)

ECs were incubated with or without A-779 (10^{-6} M) for 5 min, then with Ang-(1–7) (10^{-7} M) for 5 min. Ang II (10^{-7} M) was then added and incubation was continued for an additional 10 min. EC nuclear extracts were then prepared using commercially available Kit (Abcam). The concentrations of nuclear lysates were determined using Bio-Rad DC Protein Assay Kit. The level of NF-kappaB in 0.5 mg/mL of each nuclear extract was then measured using ELISA kits (Cell Signaling) according to manufacturer's instructions.

2.5. Immunofluorescence assay

ECs in chamber slides (Lab-Tek) were grown to 80% confluence. Cells were then stimulated for 15 min with Ang II (10^{-7} M) or Ang-(1–7) (10^{-7} M), or both (Ang-(1–7) was added 5 min before the addition of Ang II). Cells were washed with PBS, fixed with 4% paraformaldehyde, and permeabilized with 1% Triton-100. Cells were incubated with 10% normal goat serum for 30 min and then with a rabbit anti-human NF-kappaB monoclonal antibody in PBS (1:100) (Cell Signaling) for 1 h. ECs were then washed and incubated with PE conjugated goat anti-rabbit monoclonal antibody in PBS (1:200) (Santa Cruz) for 30 min, and visualized using fluorescence microscope (Olympus).

2.6. Transient transfection and reporter assays

Transient transfection and reporter assays were used to analyze VCAM-1 promoter activity. Genomic fragment of the VCAM-1 promoter (from position −356 bp to +22 bp containing two NF-kappaB binding sites) was cloned into the pGL3-Basic Vector (Promega) containing Firefly luciferase reporter gene. The construct was sequenced to verify that the cloned VCAM-1 promoter was in the desired orientation. The resultant construct was co-transfected with the pRL-TK Vector (Promega) containing Renilla luciferase reporter gene into the cultured ECs using lipofection method with FuGENE 6 transfection reagent. The transfected cells were first treated with or without the addition of A-779 (10^{-6} M) for 5 min, then further incubated under various conditions (± Ang II (10^{-7} M), or Ang-(1–7) (10^{-7} M), or both) for16 h. The cells were lysed 24 h post-transfection, and the Firefly-to-Renilla luciferase activity ratios in the lysates were measured with dual-luciferase assay kit (Promega) to evaluate VCAM-1 gene promoter activity. Three independent experiments in duplicates were performed.

2.7. Statistical analyses

All results are expressed as mean ± SEM. The data were evaluated by paired *t*-test and conformed by Wilcoxon test. A value of $P < 0.05$ was considered significant.

3. Results

3.1. Ang-(1–7) inhibits Ang II-induced VCAM-1 expression

Results from real-time RT-PCR showed the differential effects of Ang-(1–7) and Ang II on the expression of VCAM-1. The expression level was increased by 1.65-fold after treatment with Ang II, while Ang-(1–7) had little or no effect on VCAM-1 expression (Fig. 1A). However, Ang-(1–7) suppressed the Ang II-induced expression level to 1.35-fold. This is entirely consistent with the results from flow cytometry, which showed that Ang II significantly augmented the expressed level of VCAM-1 on ECs, and the effect was reduced by the addition of Ang-(1–7) (Fig. 1B). These results suggest an inhibitory role of Ang-(1–7) on Ang II-induced VCAM-1 expression on ECs.

3.2. Mas receptor antagonist inhibits the effects of Ang-(1–7) on VCAM-1 expression

We then examined whether the effect of Ang II and Ang-(1–7) on VCAM-1 expression was both mediated through the cell surface receptors. After addition of losartan, which is an antagonist of Ang II at the AT1 receptor, the change in VCAM-1 expression due to Ang II was rendered to almost baseline level (Fig. 2A). As expected, there were no effects on VCAM-1 expression whether the ECs were treated with Ang-(1–7) in the presence or absence of A-779, an antagonist of Ang-(1–7) at the Mas receptor. Interestingly, after addition of A-779 to cells treated with both Ang II and Ang-(1–7), the effect of Ang-(1–7) in controlling the Ang II-induced

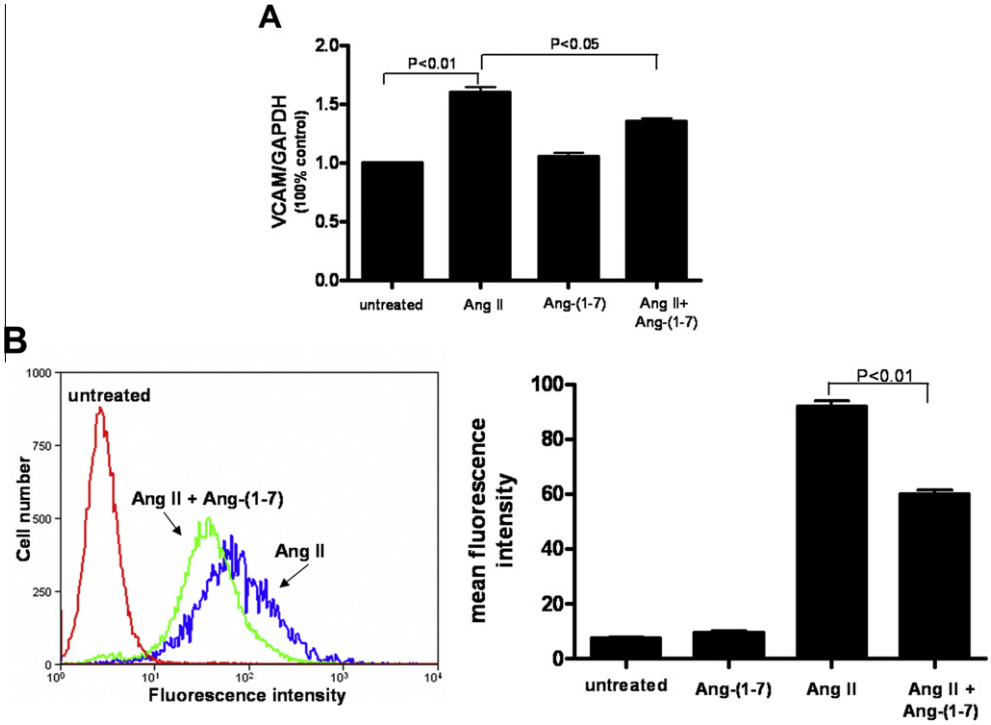

Fig. 1. Ang-(1–7) inhibits Ang II-induced VCAM-1 expression. (A) Endothelial cell VCAM-1 mRNA expression in the presence of Ang II, Ang-(1–7), and both. Data are expressed as fold differences of VCAM-1 expression compared to control sample (untreated). (B) Left: flow cytometry histogram plot showing the expressed level of VCAM-1 in the presence of Ang II (blue), and both of Ang II and Ang-(1–7) (green). Right: the corresponding mean fluorescence intensity of VCAM-1. Error bars represent standard error of mean from triplicates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

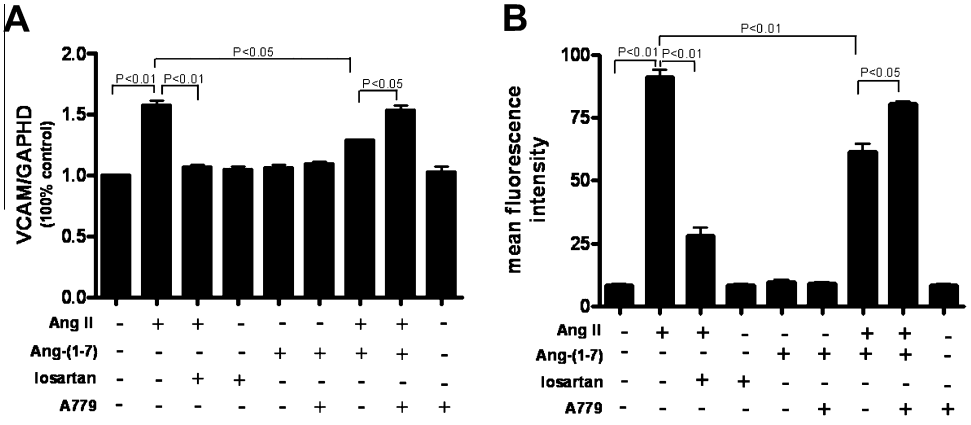

Fig. 2. Antagonists abrogate the effects of Ang II and Ang-(1–7) on VCAM-1 expression. (A) Endothelial cell VCAM-1 mRNA expression under different treatment conditions involving Ang II, Ang-(1–7), and their antagonists losartan and A-779. Data are expressed as fold differences of VCAM-1 expression compared to control sample (untreated). (B) Column chart in panel showing mean fluorescence intensity of VCAM-1 under the corresponding treatment conditions. Error bars represent standard error of mean from triplicates.

VCAM-1 expression appears to have diminished (Fig. 2A). The same pattern was also demonstrated by cell cytometry, where A-779 inhibited the effect of Ang-(1–7) on Ang II, and the ECs showed increased level of expressed VCAM-1 (Fig. 2B).

3.3. Ang-(1–7) modulates Ang II-induced VCAM-1 promoter activity

To further investigate the molecular mechanism of Ang-(1–7) on inhibiting Ang II-induced VCAM-1 expression, we evaluated the VCAM-1 promoter activity in the presence of Ang II, Ang-(1–7), or both. Transient transfection and reporter assay showed an increase in VCAM-1 promoter activity when ECs were stimulated with Ang II, and this was negatively modulated by the addition of Ang-(1–7) (Fig. 3). Again, we observed that the inhibitory effect of Ang-(1–7) was blocked by A-779. As the VCAM-1 promoter construct was designed to include the two transcription factor binding sites for NF-kappaB, these results suggests that Ang II influences transcription of VCAM-1 in ECs in a NF-kappaB dependent pathway, and Ang-(1–7) exerts its inhibitory effect through regulating the transcriptional activities.

3.4. Ang-(1–7) inhibits Ang II induced-translocation of NF-kappaB

NF-kappaB usually resides in the cytoplasm of ECs, and is translocated into nucleus after cellular activation, resulting in increased expression of the target genes, including VCAM-1 [17,18]. To inves-

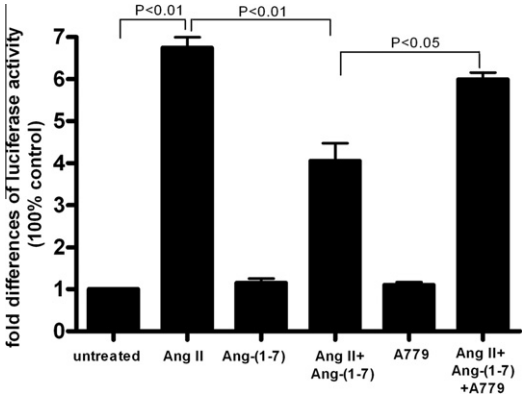

Fig. 3. Ang-(1–7) modulated Ang II-induced VCAM-1 promoter activity. Luciferase activity in endothelial cells transfected with a modified pGL3 vector containing VCAM-1 promoter. The data are fold differences of luciferase activity compared to control samples (untreated). Luciferase activity is calculated by normalization with pRL-TK vector and after subtraction by luciferase of pGL3-Basic vector. Error bars represent standard error of mean from triplicates.

tigate whether Ang-(1–7) and Ang II have any effects on the translocation of NF-kappaB in ECs, immunofluorescence assay was performed to visualize the location of NF-kappaB after stimulation with Ang II or Ang-(1–7), or both. As shown in Fig. 4A, NF-kappaB was translocated from cytoplasm into the nucleus after treatment with Ang II. However, in the presence of Ang-(1–7), Ang II-induced NF-kappaB translocation was diminished (Fig. 4A).

To quantify the degree of NF-kappaB nuclear translocation stimulated by Ang II, ELISA was used to measure the level of NF-kappaB from the purified ECs nuclear extracts. The results showed significantly higher nuclear NF-kappaB levels, whereas treatment with Ang-(1–7) alone had little or no effects. However, pre-treatment with Ang-(1–7) significantly inhibited Ang II-induced nuclear NF-kappaB translocation (Fig. 4B). These results confirm the impressions from immunofluorescence assay.

4. Discussion

Our results showed that Ang-(1–7), a peptide endogenously derived from Ang II by angiotensin converting enzyme 2 (ACE2), attenuates Ang II-mediated endothelial VCAM-1 expression. In addition, Ang-(1–7) exerts this effect on ECs via the activation of the Mas receptor, as evidenced by the reduction in its inhibitory effect in the presence of Mas receptor antagonist A-779. Moreover, we found that Ang-(1–7) inhibits Ang II-induced NF-kappaB translocation and VCAM-1 promoter activity. This gives a plausible explanation for the molecular mechanism underlying the inhibitory effects of the ACE2/Ang-(1–7)/Mas axis on Ang II-stimulated endothelial VCAM-1 expression (Fig. S1).

The inhibitory relationship between Ang-(1–7) and Ang II was first suggested by the observations in relation to vascular smooth muscles functions, where Ang-(1–7) analogue Sar-Ang-(1–7) suppress the contractile effect of Ang II in the rabbit aorta [19]. Further studies showed that Ang-(1–7) attenuates Ang II-induced vasoconstriction, including human forearm resistant vessels and internal mammary arteries, by restoring the NOS activity and hence the release of nitric oxide [13,20]. In addition, we have also previously shown that Ang-(1–7) antagonizes Ang II-induced vascular smooth muscle cell proliferation and migration via the inhibition of ERK1/2 activity [21]. The findings of this study on endothelial VCAM-1 expression suggested that the interactions between the ACE2/Ang-(1–7)/Mas axis and Ang II are not only implicated in vascular contractility/remodeling, but also in the early atherogenic events by affecting endothelial adhesion molecules.

Furthermore, we showed that Ang II-induced NF-kappaB activation is negatively modulated by Ang-(1–7). Ang II is well known to stimulate VCAM-1 expression and activate ECs via NF-kappaB signaling pathway during the development of atherosclerosis [5,6,22,23]. Our results provide direct evidence that this is achieved by facilitating nuclear translocation of NF-kappaB. The inhibitory effect of Ang-(1–7) in this event could explain the protective role of Ang-(1–7) against the development of atherosclerotic lesion [8]. This is supported by the favorable effect of Ang-(1–7) in a variety of pathological phenotypes which are associated with NF-KappaB signaling pathway. For example, Ang-(1–7) reduces ischemia/reperfusion-induced cardiac dysfunction by inhibiting cardiac NF-kappaB activity [24]. Ang-(1–7) also reduces proteinuria and structural damage in renal tissue of hypertensive rats [25]. Ang-(1–7) prevents infarct volume and improved neurological deficits in rat with permanent cerebral ischemia by suppressing NF-kappaB dependent pathway [26].These could all be explained, at least in part, by the effect of Ang-(1–7) ameliorating the detrimental inflammatory and proliferative effects of Ang II through negative modulation of the NF-kappaB signaling pathway.

Hence, novel therapy of atherosclerosis could explore the potentials of ACE2/Ang-(1–7)/Mas axis in restoring the balance of Ang II. Ang-(1–7) treatment has been shown to inhibit the progression of atherosclerotic lesion in apolipoprotein E-deficient mice [8], which is supported by our previous study that Ang-(1–7)

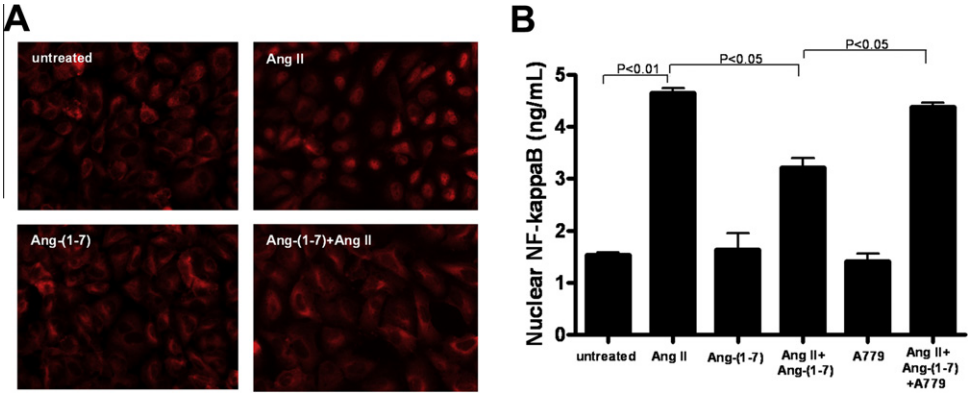

Fig. 4. Ang-(1–7) inhibited Ang II-stimulated NF-kappaB translocation. (A) Representative images of immunofluorescence showing NF-kappaB (Red) in the presence of Ang II, Ang-(1–7), and both Ang II and Ang-(1–7). (B) Chart showing nuclear NF-kappaB levels in nuclei. Data shown are mean ± SEM from 3 experiments, each with duplicate wells per condition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

suppresses smooth muscle cell proliferation and migration [21]. In addition, Ang-(1–7) inhibits endothelial cell tube formation, preventing the formation of new vessels in atherosclerotic lesions [27]. Ang-(1–7) also mediates endothelial nitric oxide synthase activation and improves endothelial dependent vascular relaxation [28]. Our study adds that the atheroprotective effect of Ang-(1–7) could also be attributed to the inhibitory effect on AngII-induced VCAM-1 expression.

Taken together, our findings show that Ang-(1–7), a key peptide of the renin–angiotensin system, mediates its effects on ECs through Mas receptors, and negatively regulates Ang II-induced VCAM-1 expression by attenuating nuclear translocation of NF-kappaB. This provides a further rationale for ACE2/Ang-(1–7)/Mas axis as a therapeutic target for atherosclerosis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.11.098.

References

[1] E. Galkina, K. Ley, Vascular adhesion molecules in atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 2292–2301.
[2] J.M. Cook-Mills, M.E. Marchese, H. Abdala-Valencia, Vascular cell adhesion molecule-1 expression and signaling during disease: regulation by reactive oxygen species and antioxidants, Antioxid. Redox. Signal. 15 (2011) 1607–1638.
[3] D. Weiss, D. Sorescu, W.R. Taylor, Angiotensin II and atherosclerosis, Am. J. Cardiol. 87 (2001) 25C–32C.
[4] A. Benigni, P. Cassis, G. Remuzzi, Angiotensin II revisited: new roles in inflammation, immunology and aging, EMBO Mol. Med. 2 (2010) 247–257.
[5] A. Costanzo, F. Moretti, V.L. Burgio, C. Bravi, F. Guido, M. Levrero, P.L. Puri, Endothelial activation by angiotensin II through NFkappaB and p38 pathways: involvement of NFkappaB-inducible kinase (NIK), free oxygen radicals, and selective inhibition by aspirin, J. Cell. Physiol. 195 (2003) 402–410.
[6] P.E. Tummala, X.L. Chen, C.L. Sundell, J.B. Laursen, C.P. Hammes, R.W. Alexander, D.G. Harrison, R.M. Medford, Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: a potential link between the renin–angiotensin system and atherosclerosis, Circulation 100 (1999) 1223–1229.
[7] S. Keidar, M. Kaplan, A. Gamliel-Lazarovich, ACE2 of the heart: from angiotensin I to angiotensin (1–7), Cardiovasc. Res. 73 (2007) 463–469.
[8] S. Tesanovic, A. Vinh, T.A. Gaspari, D. Casley, R.E. Widdop, Vasoprotective and atheroprotective effects of angiotensin (1–7) in apolipoprotein E-deficient mice, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1606–1613.
[9] J. Toton-Zuranska, M. Gajda, G. Pyka-Fosciak, K. Kus, M. Pawlowska, A. Niepsuj, P. Wolkow, R. Olszanecki, J. Jawien, R. Korbut, AVE 0991-angiotensin-(1–7) receptor agonist, inhibits atherogenesis in apoE-knockout mice, J. Physiol. Pharmacol. 61 (2010) 181–183.
[10] A.J. Ferreira, T.M. Murca, R.A. Fraga-Silva, C.H. Castro, M.K. Raizada, R.A. Santos, New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1–7)/mas receptor axis, Int. J. Hypertens. 2012 (2012) 147825.
[11] L.A. Rabelo, N. Alenina, M. Bader, ACE2-angiotensin-(1–7)-Mas axis and oxidative stress in cardiovascular disease, Hypertens. Res. 34 (2011) 154–160.
[12] C. Mercure, A. Yogi, G.E. Callera, A.B. Aranha, M. Bader, A.J. Ferreira, R.A. Santos, T. Walther, R.M. Touyz, T.L. Reudelhuber, Angiotensin(1–7) blunts hypertensive cardiac remodeling by a direct effect on the heart, Circ. Res. 103 (2008) 1319–1326.
[13] S. Ueda, S. Masumori-Maemoto, K. Ashino, T. Nagahara, E. Gotoh, S. Umemura, M. Ishii, Angiotensin-(1–7) attenuates vasoconstriction evoked by angiotensin II but not by noradrenaline in man, Hypertension 35 (2000) 998–1001.
[14] J.Y. Moon, M. Tanimoto, T. Gohda, S. Hagiwara, T. Yamazaki, I. Ohara, M. Murakoshi, T. Aoki, Y. Ishikawa, S.H. Lee, K.H. Jeong, T.W. Lee, C.G. Ihm, S.J. Lim, Y. Tomino, Attenuating effect of angiotensin-(1–7) on angiotensin II-mediated NAD(P)H oxidase activation in type 2 diabetic nephropathy of KK-A(y)/Ta mice, Am. J. Physiol. Renal. Physiol. 300 (2011) F1271–1282.
[15] P. Dhawan, Y. Su, Y.M. Thu, Y. Yu, P. Baugher, D.L. Ellis, T. Sobolik-Delmaire, M. Kelley, T.C. Cheung, C.F. Ware, A. Richmond, The lymphotoxin-beta receptor is an upstream activator of NF-kappaB-mediated transcription in melanoma cells, J. Biol. Chem. 283 (2008) 15399–15408.
[16] R.C. Laxton, Y. Hu, J. Duchene, F. Zhang, Z. Zhang, K.Y. Leung, Q. Xiao, R.S. Scotland, C.P. Hodgkinson, K. Smith, J. Willeit, C. Lopez-Otin, I.A. Simpson, S. Kiechl, A. Ahluwalia, Q. Xu, S. Ye, A role of matrix metalloproteinase-8 in atherosclerosis, Circ. Res. 105 (2009) 921–929.
[17] M. Zerfaoui, Y. Suzuki, A.S. Naura, C.P. Hans, C. Nichols, A.H. Boulares, Nuclear translocation of p65 NF-kappaB is sufficient for VCAM-1, but not ICAM-1, expression in TNF-stimulated smooth muscle cells: differential requirement for PARP-1 expression and interaction, Cell. Signal. 20 (2008) 186–194.
[18] C.D. Collard, A. Agah, W. Reenstra, J. Buras, G.L. Stahl, Endothelial nuclear factor-kappaB translocation and vascular cell adhesion molecule-1 induction by complement: inhibition with anti-human C5 therapy or cGMP analogues, Arterioscler. Thromb. Vasc. Biol. 19 (1999) 2623–2629.
[19] P.R. Bovy, A.J. Trapani, E.G. McMahon, M. Palomo, A carboxy-terminus truncated analogue of angiotensin II, [Sar1]angiotensin II-(1–7)-amide, provides an entry to a new class of angiotensin II antagonists, J. Med. Chem. 32 (1989) 520–522.
[20] A.J. Roks, P.P. van Geel, Y.M. Pinto, H. Buikema, R.H. Henning, D. de Zeeuw, W.H. van Gilst, Angiotensin-(1–7) is a modulator of the human renin-angiotensin system, Hypertension 34 (1999) 296–301.
[21] F. Zhang, Y. Hu, Q. Xu, S. Ye, Different effects of angiotensin II and angiotensin-(1–7) on vascular smooth muscle cell proliferation and migration, PLoS ONE 5 (2010) e12323.
[22] M.E. Pueyo, W. Gonzalez, A. Nicoletti, F. Savoie, J.F. Arnal, J.B. Michel, Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kappaB activation induced by intracellular oxidative stress, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 645–651.
[23] D.M. Tham, B. Martin-McNulty, Y.X. Wang, D.W. Wilson, R. Vergona, M.E. Sullivan, W. Dole, J.C. Rutledge, Angiotensin II is associated with activation of NF-kappaB-mediated genes and downregulation of PPARs, Physiol. Genomics 11 (2002) 21–30.
[24] M. Al-Maghrebi, I.F. Benter, D.I. Diz, Endogenous angiotensin-(1–7) reduces cardiac ischemia-induced dysfunction in diabetic hypertensive rats, Pharmacol. Res. 59 (2009) 263–268.
[25] J.F. Giani, M.C. Munoz, R.A. Pons, G. Cao, J.E. Toblli, D. Turyn, F.P. Dominici, Angiotensin-(1–7) reduces proteinuria and diminishes structural damage in renal tissue of stroke-prone spontaneously hypertensive rats, Am. J. Physiol. Renal Physiol. 300 (2010) F272–282.
[26] T. Jiang, L. Gao, J. Guo, J. Lu, Y. Wang, Y. Zhang, Suppressing inflammation by inhibiting NF-kappaB pathway contributes to the neuroprotection ofik Angiotensin-(1–7) in rats with permanent cerebral ischemia, Br. J. Pharmacol. (2012).
[27] L. Anton, D.C. Merrill, L.A. Neves, K.B. Brosnihan, Angiotensin-(1–7) inhibits in vitro endothelial cell tube formation in human umbilical vein endothelial cells through the AT(1–7) receptor, Endocrine 32 (2007) 212–218.
[28] J. Stegbauer, S.A. Potthoff, I. Quack, E. Mergia, T. Clasen, S. Friedrich, O. Vonend, M. Woznowski, E. Konigshausen, L. Sellin, L.C. Rump, Chronic treatment with angiotensin-(1–7) improves renal endothelial dysfunction in apolipoprotein E-deficient mice, Br. J. Pharmacol. 163 (2011) 974–983.