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Angiotensin type 2-receptor (AT$_2$R) activation induces hypotension in apolipoprotein E-deficient mice by activating peroxisome proliferator-activated receptor-γ

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Abstract: Angiotensin II (Ang II) modulates blood pressure and atherosclerosis development through its vascular type-1 (AT$_1$R) and type-2 (AT$_2$R) receptors, which have opposing effects. AT$_2$R activation produces hypotension, and is anti-atherogenic. Targeted overexpression of AT$_2$Rs in vascular smooth muscle cells (VSMCs) indicates that these effects are due to increased nitric oxide (NO) generation. However, the role of endogenous VSMC AT$_2$Rs in these events is unknown. Effect of 7-day low-dose Ang II-infusion (12 µg/kg/hr) on blood pressure was tested in 9-week-old apoE(-/-) mice fed a low or high cholesterol diet (LCD or HCD, respectively). Cardiac output was measured by echo-cardiography. Immunohistochemistry was performed to localize and quantify AT$_2$Rs and p-Ser$^{1177}$-endothelial nitric oxide synthase (eNOS) levels in the aortic arch. PD123319 and GW-9662 were used to selectively block the AT$_2$R and peroxisome proliferator-activated receptor-γ (PPAR-γ), respectively. Ang II infusion decreased blood pressure by 12 mmHg (P < 0.001) in LCD/apoE(-/-) mice without altering cardiac output; a response blocked by PD123319. Although, AT$_2$R stimulation neither activated eNOS (p-Ser$^{1177}$-eNOS) nor changed plasma NO metabolites, it caused an ~6-fold increase in VSMC PPAR-γ levels (P < 0.001) and the AT$_2$R-mediated hypotension was abolished by GW-9662. AT$_2$R-mediated hypotension was also inhibited by HCD, which selectively decreased VSMC AT$_2$R expression by ~6-fold (P < 0.01). These findings suggest a novel pathway for the Ang II/AT$_2$R-mediated hypotensive response that involves PPAR-γ, and is down regulated by a HCD.

Keywords: AT$_2$R, apoE(-/-), angiotensin II, blood pressure, eNOS, PPAR-γ

Introduction

Inhibition of the renin-angiotensin system is extensively used to lower blood pressure in hypertensive patients [1]. The main effector of this system is the peptide hormone angiotensin II (Ang II). Ang II exerts its effects on the vasculature through two distinct receptor subtypes: the Ang II type 1 (AT$_1$R) and type 2 (AT$_2$R) receptor [2]. Using subtype specific antagonists it has been established that the potent vasoconstrictor response produced by Ang II is mediated via AT$_1$R activation in vascular smooth muscle cells (VSMCs) [2].

AT$_2$Rs are abundantly expressed in fetal and newborn rat tissues, but in adults its expression is restricted to a few organs including the ovary, brain, and adrenal gland [3-5]. In blood vessels from adult rats, AT$_2$R is expressed in the thoracic aorta, mesenteric arteries, and coronary arteries [6]. The pressor response to low-dose, but not high-dose, Ang II is enhanced in AT$_2$R(-/-) mice [7] and Ang II produces a small vasodilator response in AT$_1$R antagonist-treated mice [8]. But, the expression of the AT$_2$R relative to the AT$_1$R in the vasculature of wild type mice is not sufficiently high for Ang II to produce a vasodilator response at any Ang II dose [7].

In the aortic arch of the apoE(-/-) mouse, AT$_2$R expression is prominently observed on macrophages and VSMCs in intimal lesions [9] and atherosclerotic lesion area and macrophage...
ApoE-deficiency, per se, increases the expression of aortic arch AT₉R mRNA levels before the onset of lesion development [9]; and [2] Takata et al. [10] recently showed that, in apoE(-/-)/α-smooth muscle actin (α-SMA): AT₉R transgenic mice, low-dose Ang II elicits an anti-atherogenic response after just 8-weeks of a HCD. The beneficial effect of AT₉R activation in transgenic mice was proposed to be due to activation of the endothelial kinin/NO axis in the aortic arch. Specifically, it was proposed that AT₉R activates kininogenase in VSMCs, which by increasing bradykinin production activates endothelial cell (EC) NO-dependent vasodilation and attenuates VCAM-1 expression and monocyte/macrophage accumulation; both of these events are important at the earliest stages of atherosclerosis development. While these findings show the early beneficial effects of forced AT₉R expression in VSMCs it does not explain why endogenous AT₉R expression in apoE(-/-) aortae does not slow disease progression. We hypothesized that either the AT₉R is not normally expressed in aortic arch VSMCs of young preatherosclerotic apoE(-/-) mice or that a HCD, which is normally used to accelerate lesion development, down regulates aortic arch VSMC AT₉Rs and consequently its modulation of NO generation. We tested this hypothesis in young preatherosclerotic apoE(-/-) mice given either a low cholesterol diet (LCD) or a HCD for 1 week.

Materials and methods

Ethics statement

Animals were handled according to University of Alabama (Animal Project Number: 07090-7642) or Emory University (DAR-2000436-010514-1) Institutional Animal Care and Use Committee guidelines.

Animals and treatment

Nine-week-old male C57BL/6 and apoE(-/-) mice (Jackson Laboratory) were used. C57BL/6 mice were maintained on a standard chow diet. ApoE(-/-) mice were given a LCD (low fat rodent diet with 0% cholesterol, D12102C, Research Diet Inc.) or a HCD (high fat rodent diet with 11.25% cholesterol, D12108C, Research Diet Inc.) ad libitum for 1 week. ApoE(-/-) mouse weights were 26.1 ± 0.5 g (n = 11) and 25.7 ± 0.54 g (n = 11) after 1 week of a LCD or a HCD, respectively. Vehicle, Ang II (12 µg/kg/hr), Ang II + PD123319 (10 mg/kg/day), GWS9662 (2 mg/kg/day) or Ang II + GW-9662 were delivered via an osmotic minipump (Alzet, model 2002) placed in the peritoneal cavity for 7 days. These drugs were purchased from Sigma-Aldrich.

Blood pressure measurements, echocardiography and tissue collection

After induction of anesthesia with isoflurane (~1-2%) a 1.0 F high fidelity pressure transducer (Millar Instruments, Houston, TX) was passed via the right carotid artery into the left ventricle (LV) of the heart. Electrodes were attached to allow ECG and heart rate recordings. LV pressure, ECG and heart rate were monitored until stable recordings were obtained. The pressure transducer was then slowly withdrawn into the aorta for measurement of central arterial pressure as described [11]. Echocardiography was performed to measure cardiac output using a Vevo 2100 ultrasound system (VisualSonics) under ~1-2% isoflurane as described [12]. Blood (0.5-1 ml) was collected by heart puncture, under isoflurane anesthesia (3%), for lipid profiling. Subsequently, aortic arches were dissected and rinsed with ice-cold saline and then snap-frozen in OCT (OCT compound, Tissue-Tek).

Blood pressure in conscious mice

At 10 weeks of age a telemetry transmitter (PA-C10, Data Sciences International) was implanted into a carotid artery and 24-hr average MAP recorded. After baseline recordings, Ang II (12 µg/kg/hr) was delivered via an osmotic minipump (Alzet, model 2002) placed subcutaneously and 24-hr average MAP recorded daily over the following 7 days.

Immunohistochemistry

Mouse ascending aorta cryosections (5 µm) were used for quantitative immunohistochem-
AT₂R activation induces hypotension through PPARγ

Figure 1. Determination of a subpressor dose of AII in C57BL/6 mice. Several doses of AII were studied to identify one that was just below the threshold for influencing blood pressure in conscious mice. 12 μg/kg/hr AII given over a 1-week period did not significantly alter 24-hr MAP in conscious mice. This subpressor dose was used in subsequent experiments to activate AT₂Rs in vivo.

Nitric oxide metabolite measurements

Nitrite and nitrate concentrations were quantified by ion chromatography (ENO20 Analyzer, Eicom). Nitrosothiol compounds (RXNO) were quantified using group specific reductive denitrosation by iodine-iodide with subsequent detection of the NO liberated by gas-phase chemiluminescence. All NO analysis procedures have been previously described in detail [15].

Data analysis

Values are mean ± S.E.M. Differences were assessed by ANOVA followed by Tukey’s test for multiple comparisons, or by unpaired 2-tailed Student’s t test. P values < 0.05 were considered significant.

Results

Comparative studies between wild type and AT₂R deficient mice have revealed that as compared to wild type mice an enhanced pressor effect was observed in AT₂R deficient mice.
AT$_2$R activation induces hypotension through PPARγ

A

B

C

D

E

Serum levels, mg/dL

Aortic arch AT$_2$R, mean fluorescence intensity arbitrary units/mm$^2$

Aortic arch AT$_2$R/GAPDH mRNA transcript ratio

Am J Cardiovasc Dis 2016;6(3):118-128
AT$_2$R activation induces hypotension through PPAR$\gamma$

Figure 2. Effect of high cholesterol diet (HCD) on the vasodilator response to low-dose Ang II infusion and AT$_2$R expression in young apoE$^{-/-}$ mice. (A) A 7-day low-dose (12 µg/kg/day) Ang II infusion in 9-week-old low cholesterol (LCD)/apoE$^{-/-}$ mice decreased MAP. The AT$_2$R antagonist PD123319 blocked this low-dose Ang II effect. In HCD/ apoE$^{-/-}$ mice, low-dose Ang II was unable to produce a vasodilator effect. (B) We also measured total peripheral resistance (tpR) using the formula: Total peripheral resistance (tpR) = (80 x MAP)/Cardiac Output. This study revealed that low dose Ang II infusion significantly reduced tpR in 9-week-old apoE$^{-/-}$ mice, fed a LCD for 1 week (A). Apressor response (that is, a subpressor dose) in C56BL/6 mice (their genetic controls). This dose was empirically determined to be 12 µg/kg/day (low-dose Ang II) (Figure 1). We compared effects of the vehicle or an AT2R antagonist (PD123319) on responses produced by 7-day Ang II infusion (12 µg/kg/hr) in apoE$^{-/-}$ mice. This duration/dose of Ang II was not sufficient to influence MAP in conscious mice (Figure 1). Effect of a 1-week HCD or LCD in 9-week-old LCD/apoE$^{-/-}$ mice on serum total cholesterol, LDL cholesterol, and triglyceride levels. Relative to the LCD, HCD increased serum total cholesterol, LDL cholesterol without significantly increasing triglyceride levels. In these mice, HCD also significantly decreased aortic arch AT2R protein expression (C) and mRNA expression (D). This effect of the HCD on AT2R expression was consistent with the loss of vasodilator response to low-dose Ang II seen in (A). Values are mean ± S.E.M. Numbers in parenthesis represent the number of independent replications. Statistical analyses performed by ANOVA (Tukey) or by Student’s t test. *P < 0.05; ***P < 0.001; n.s., not significant.

Figure 3. HCD down regulates VSMC AT$_2$R expression in the aortic arch of apoE$^{-/-}$ mice. A. In the left panel is a representative section stained with anti-aSMA (red) and anti-CD31 (green) to demarcate the VSMC and EC layers, respectively. The dotted lines (red or yellow) identify the border between the EC and VSMC layers. The middle and right panels show AT$_2$R immunoreactivity (ir) (green) and nuclei labeled with DAPI (blue) in representative sections from apoE$^{-/-}$ aortae fed LCD or HCD, respectively. B. Quantification of AT$_2$R-ir in the aortic arch showing that HCD markedly down regulates VSMC, but not EC, AT$_2$R-ir in aortae of apoE$^{-/-}$ mice. Bars denote 20 μm. Values are mean ± S.E.M. Numbers in parenthesis represent the number of independent replications. Statistical differences of continuous variables were determined by Student’s t test. **P < 0.01.

response to Ang II in AT$_2$R-deficient mice is observed only at very low doses of the hormone [7]. Because the Kd of the interaction between Ang II and these receptor subtypes is similar [3], these blood pressure findings may be interpreted to suggest that the maximal AT$_2$R-mediated effect is obtained without full receptor occupancy. We reasoned, therefore, that potential AT$_2$R-mediated vascular responses may become manifest in apoE$^{-/-}$ mice at a dose of Ang II that just fails to elicit a pressor response (that is, a subpressor dose) in C56BL/6 mice (their genetic controls). This dose was empirically determined to be 12 µg/kg/day (low-dose Ang II) (Figure 1). We compared effects of the vehicle or an AT$_2$R antagonist (PD123319) on responses produced by 7-day Ang II infusion (12 µg/kg/hr) in apoE$^{-/-}$ mice. This duration/dose of Ang II was not sufficient to influence MAP in conscious mice (Figure 1). In 9-week-old apoE$^{-/-}$ mice, fed a LCD for 1 week, a 7-day low-dose Ang II infusion produced a 12 mmHg decrease in MAP (P < 0.001) that was abolished by the selective AT$_2$R antagonist, PD123319 (Figure 2A). Echocardiographic and hemodynamic analyses in these mice indicated that this vasodepressor response was not associated with significant changes in heart rate (553 ± 21 beats/min in vehicle-infused mice, n = 7 versus 545 ± 15 beats/min in low-dose Ang II-infused mice, n = 8; P = 0.753) or cardiac output (15.5 ± 1.4 ml/min in vehicle-
AT$_2$R activation induces hypotension through PPARγ

Infused mice, n = 7 versus 16.7 ± 1.0 ml/min in low-dose Ang II-infused mice, n = 8; P = 0.501), suggesting that Ang II/AT$_2$R activation decreases total peripheral resistance (tpr) in LCD/apoE(-/-) mice. Thus we measured tpr using the formula: Total peripheral resistance (tpr) = (80 x MAP)/Cardiac Output. This study revealed that low dose Ang II infusion significantly reduced tpr in 9-week-old apoE(-/-) mice, fed a LCD for 1 week (Figure 2B).
Next we examined the effect of a 1-week HCD in 9-week-old apoE\(^{-/-}\) mice on aortic arch \(\mathrm{AT}_{2}\)R mRNA and \(\mathrm{AT}_{2}\)R expression. We selected a commercial \(\mathrm{AT}_{2}\)R antibody that specifically recognizes a single band by Western blot analysis and selectively identifies (by immunohistochemistry) \(\mathrm{AT}_{2}\)R expression in cell layers that are known to expresses this receptor subtype [16]. A 1-week HCD in apoE\(^{-/-}\) mice increased serum total cholesterol by 2.3-fold (\(P < 0.001\)) and LDL cholesterol by 2.2-fold (\(P < 0.001\)), without significantly changing triglycer-
AT$_2$R activation induces hypotension through PPARγ

ide levels (Figure 2C). Quantitative immunohistochemistry indicated that a HCD produced a 72% decrease in aortic arch AT$_2$R expression (P < 0.001) (Figure 2D), which was associated with a 65% decrease in aortic arch agtr2 gene expression (P < 0.05) (Figure 2E). In these HCD/apoE$^{(-/-)}$ mice, MAPs were not different between vehicle- and low-dose Ang II-infused mouse groups (Figure 2A). These findings indicate that short-term increases in total serum cholesterol and LDL cholesterol are sufficient to decrease the AT$_2$R-mediated blood pressure effects in apoE$^{(-/-)}$ mice, which are likely due to decreased vascular AT$_2$R expression. (Figures 3A and 3B), show that VSMC AT$_2$Rs, but not EC AT$_2$Rs, were selectively down regulated (by ~6-fold; P < 0.01) by the HCD indicating a cell layer specific effect in the aortic arch of apoE$^{(-/-)}$ mice.

To evaluate an Ang II/AT$_2$R-mediated activation of NO, we examined PD213319-inhibitable eNOS activation in the aortic arch in response to low-dose Ang II. The activity of eNOS is regulated by phosphorylation at multiple sites. The two most thoroughly studied sites are the activation site Ser$^{1177}$ and the inhibitory site Thr$^{495}$ [17]. Low-dose Ang II did not significantly change total eNOS or p-Ser$^{1177}$-eNOS in the aortic arch (Figure 4A). To determine if these Western blot analyses mask a selective increase in p-Ser$^{1177}$-eNOS in the EC layer we performed quantitative immunohistochemistry. This also failed to show an effect of low-dose Ang II on EC p-Ser$^{1177}$-eNOS levels (Figure 4B, 4C). NO generation, secondary to Ang II/AT$_2$R activation has been reported to decrease monocyte attachment in the aortic arch of apoE$^{(-/-)}$ mice [21]. We evaluated this by immunohistochemistry using an antibody to CD68, a marker for the various cells of the macrophage lineage, including monocytes. In 10-week-old apoE$^{(-/-)}$ mice, monocyte/macrophages begin to adhere to aortic arch ECs. We found that low-dose Ang II did not significantly influence this attachment in LCD/apoE$^{(-/-)}$ mice (Figure 4D). These findings do not support a role for Ang II/AT$_2$R-mediated NO production in the aortic arch of LCD/apoE$^{(-/-)}$ mice.

We next considered the possibility that the vasodilator effect of low-dose Ang II may be due to local NO production in resistance vessels that is not reflected by Ang II/AT$_2$R activation in the aortic arch. To test this we evaluated NO metabolites nitrate, nitrite and nitroso (RXNO)-species in plasma. We found that plasma nitrate, nitrite and RXNO levels were not significantly changed by low-dose Ang II or by an infusion of low-dose Ang II + PD123319 (Figure 4E). Furthermore, the expression of nNOS or iNOS was no significantly influenced by low-dose Ang II or by an infusion of low-dose Ang II + PD123319 (Figure 4F). Thus, our findings failed to support a role for Ang II/AT$_2$R in activating eNOS in the aortic arch, despite a prominent Ang II/AT$_2$R-mediated vasodilator response in 10-week-old LCD/apoE$^{(-/-)}$ mice (Figure 2A).

Ang II/AT$_2$R increases peroxisome proliferator-activated receptor γ (PPARγ) in PC12W rat pheochromocytoma cells [18]. Because PPARγ suppression in VSMCs causes hypertension [19], we investigated the possibility that low-dose Ang II causes a hypotensive response in LCD/apoE$^{(-/-)}$ mice by increasing PPARγ levels. Figures 2A and 5A show that GW9662, a PPARγ antagonist, inhibited the hypotensive response to low-dose Ang II in LCD/apoE$^{(-/-)}$ mice. Moreover, low-dose Ang II selectively increased PPARγ expression in the VSMC layer by ~6-fold (P < 0.001); an effect that was blocked by PD123319 (Figure 5B, 5C). Together, these findings suggest a role for Ang II/AT$_2$R-mediated increase in vascular PPARγ in mediating a hypotensive response.

Discussion

Monocyte adhesion to the endothelium is an early inflammatory response that characterizes the initiation of atherosclerosis development in apoE$^{(-/-)}$ mice. This process, which begins at 8-10 week of age in apoE$^{(-/-)}$ mice, is accelerated by diets that are rich in cholesterol [20]. Endothelium-derived NO inhibits adhesion molecule expression [21]. Transgenic overexpression of AT$_2$Rs in VSMCs activates kinin-dependent NO generation in apoE$^{(-/-)}$ ECs and reduces monocyte adhesion to vascular ECs [10]. Thus, apoE deficiency, which tonically increases AT$_2$R mRNA expression in the aortic arch [9], is expected to increase AT$_2$R-dependent NO generation and suppress monocyte adhesion. Detrimental effects of AT$_2$R deficiency, however, are not apparent in the aortic arch of 14-week-old HCD/apoE$^{(-/-)}$ mice where foam cell lesions are abundant [9]. Here we show that
short-term (7-day) administration of a HCD to 9-week-old apoE(-/-) mice markedly decreases AT,R mRNA and protein levels in the aortic arch; this expression was selectively decreased in VSMCs. The cholesterol rich diet also suppressed the Ang II/AT,R-dependent vasodilator effect. This down regulation of VSMC AT,Rs could explain why beneficial effects of AT,R-activation are not observed early in the apoE(-/-) mouse model of atherosclerosis that requires a HCD to accelerate the disease process [9]. However, a beneficial effect of vascular AT,R is possible when its expression is artificially driven in VSMCs by an α-SMA promoter [10].

It is believed that a prominent effect of VSMC AT,R activation is kinin production and its paracrine activation of EC eNOS, NO generation, and vasodilatation [8]. We also show a prominent AT,R-dependent vasodilator response to low-dose Ang II infusion in LCD/apoE(-/-) mice. This response was observed in the absence of an AT,R antagonist, which normally is required to unmask the AT,R effect in wild type and HCD/apoE(-/-) mice [8]. However, by contrast to the findings of Tsutsumi et al. [8], levels of total eNOS and active eNOS (p-Ser1177-eNOS) were not significantly changed during low-dose Ang II infusion. This despite abundant AT,R expression in the aortic arch VSMC layer of these LCD/apoE(-/-) mice. We considered the possibility that the vasodilator effect of low-dose Ang II might be due to local NO production in resistance vessels. We previously showed that NO synthesized within a specified location (cardiomyocytes) is transported in the blood as a bioactive NO species (nitrate, nitrite and nitroso (RXNO)-species) [22]. We evaluated NO metabolites in plasma to test whether Ang II/AT,R-activation increases NO generation in other tissues of LCD/apoE(-/-) mice. However, low-dose Ang II was unable to significantly increase plasma nitrate, nitrite and RXNO levels. These findings are not consistent with Ang II/AT,R-dependent eNOS activation as a mechanism for the vasodilator effect of low-dose Ang II in LCD/apoE(-/-) mice. By contrast, we found that a PPARγ antagonist inhibits the Ang II/AT,R-dependent vasodilator response. A finding supported by a prominent increase in aortic arch VSMC PPARγ levels that are inhibited by an AT,R antagonist. This novel effect of the AT,R in VSMCs is also supported by the report that transgenic overexpression of a dominant negative-PPARγ mutant in VSMCs produces hypertension [19]. While our studies do not negate the extensive data that supports a role for AT,R-dependent eNOS activation in the vasculature via increased kinin production, it does suggest a novel mechanism, involving PPARγ, for the Ang II/AT,R-dependent vasodilator effect. The prominent down regulation of aortic arch AT,R by a HCD would suggest that the beneficial effects of vascular AT,R may not become apparent at an early stage of atherosclerosis development in experimental models that combine apoE deficiency with a HCD. This, as well as the substantial protective effects of VSMC PPARγ in lesion development [23] leads us to speculate that VSMC AT,R activation may substantially delay the onset of atherosclerosis development in apoE(-/-) mice maintained on a LCD. If substantiated, AT,R agonist therapy may reduce atherosclerotic lesion development and, thus, augment the clinically efficacious effects of dietary fat restriction. However, effective translation of this potentially beneficial effect of AT,R activation may best be achieved by initiating AT,R therapy after an initial period of fat restriction, since a high fat diet suppresses AT,R expression, which would mask beneficial effects of AT,R agonist therapy on atherosclerotic lesion development.

Conclusions

Activation of PPARγ decreases blood pressure and attenuates the development of atherosclerotic lesions. Here we show that the vascular AT,R regulates PPARγ in the artherosclerosis-prone vasculature of the apoE(-/-) mouse and that dyslipidemia suppresses VSMC AT,R expression, a vascular protective mechanism.

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AT_{2}R activation induces hypotension through PPARγ

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Disclosure of conflict of interest

None.

Authors’ contribution


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AT$_2$R activation induces hypotension through PPAR$\gamma$


