Adiponectin is a novel humoral vasodilator

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Abstract

Objectives: Perivascular adipose tissue secretes an adipocyte-derived relaxing factor(s) (ADRF) that opens Kᵥ channels in rat arteries. Visceral fat accumulation causes adipocyte dysfunction, including hyposecretion of adiponectin. We tested the hypothesis that ADRF might be adiponectin and that adiponectin plays a role in the paracrine control of vascular tone by perivascular adipose tissue.

Methods and results: We studied Sprague–Dawley rats, wild-type and adiponectin gene-deficient (Apn 1⁻⁻) mice, and New Zealand obese (NZO) mice. In rat aortas, recombinant adiponectin at serum levels (2–5 μg/ml) inhibited serotonin-induced contractions. The effects were abolished by Kᵥ channel inhibition with 4-aminopyridine (4-AP, 2 mM). Similar effects were observed in NZO mouse mesenteric arteries. To study vascular function in Apn 1⁻⁻ mice, the mesenteric vascular bed was isolated, cannulated, and perfused at a constant 4–5-ml/min flow in the absence and presence of serotonin. 4-AP (2 mM) induced a similar increase in perfusion pressure in the Apn 1⁻⁻ perfused isolated mesenteric vascular bed, compared to wild-type mice. Removal of perivascular fat increased the vasoconstrictor responses, but abolished the 4-AP effects. The anti-contractile effects of perivascular fat were similar in mesenteric artery and aortic rings from Apn 1⁻⁻ and wild-type mice. Despite high adiponectin levels, the anti-contractile effects of perivascular fat were diminished in mesenteric arteries of NZO mice with age.

Conclusion: Adiponectin is a novel humoral vasodilator that relaxes aortic and mesenteric rings by opening Kᵥ channels. Similar to the rat, perivascular adipose tissue of the mouse harbors an ADRF, which is malfunctional in NZO mice and is not adiponectin.

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Keywords: Adipocyte-derived relaxing factor; Adiponectin; Obesity; Vascular dysfunction; Hypertension; Kᵥ channels

1. Introduction

Perivascular fat is routinely removed for isometric vessel contraction studies. Soltis and Cassis showed that perivascular fat significantly attenuates vascular responsiveness of rat isolated aortic ring preparations to norepinephrine [1]. We confirmed the inhibitory action of perivascular fat on vascular contraction in response to several hormonal agonists [2–5]. We also found that this effect is mediated by a transferable “adipocyte-derived relaxing factor” (ADRF) [2] that acts through delayed rectifier Kᵥ⁺ (Kᵥ) channel activation in vascular smooth muscle cells [4,5]. The ADRF action is not dependent on the endothelium, the cyclooxygenase or P450 pathway, activation of adenosine receptors, or presence of functional leptin receptors [2]. ADRF release is a Ca²⁺-dependent process and does not involve neuronal N-type Ca²⁺ and Na⁺ channels or vanilloid/cannabinoid and calcitonin gene related peptide receptors, suggesting that ADRF is released from perivascular adipocytes without involvement of perivascular nerves in rats [3]. The molecular identity of ADRF is unknown; however, protein bands with relative masses of
74.0, 59.8, 54.4, 28.7, and 13.8 kDa have been identified that represent candidates [6]. Whether or not perivascular adipose tissue of the mouse also harbors an ADRF is unknown. Adipose tissue produces various biologically active substances including adiponectin. Adiponectin is a 30-kDa protein, which inhibits angiogenesis [7], reduces atherosclerosis in apolipoprotein E-deficient mice [8], and prevents vascular restenosis after angioplasty [9]. Adiponectin serum levels are decreased under conditions of obesity, insulin resistance, type 2 diabetes, and essential hypertension [10–13]. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation [14,15]. Hypoadiponectinemia is also found in spontaneously hypertensive rats (SHR), which show reduced anti-contractile effects of perivascular fat in mesenteric artery rings compared to Wistar Kyoto rats (WKY) [16,17]. However, whether or not adiponectin is produced by perivascular adipose tissue and modulates vascular function directly is unknown.

2. Methods

2.1. Adiponectin determinations and detection of adiponectin receptors by RT-PCR

Adiponectin was measured in plasma and homogenates of subcutaneous fat, visceral abdominal epididymal fat, perivascular fat of the superior branch of the mesenteric artery, and perivascular fat of the aorta, by using a specific ELISA kit for rats (B-Bridge International, Inc, Sunnyvale, CA, USA). Adipose tissue was homogenized in RIPA buffer containing sodium fluoride (100 mM), peptatin (5 μg/ml), leupeptin (5 μg/ml), aprotinin (5 μg/ml), sodium orthovanadate (5 mM), phenylmethylsulphonyl fluoride (2 mM). Homogenates were centrifuged (10 min, 10,000 g, 4 °C) and aqueous phases were used for measuring adiponectin (1 μg total protein per well). Adiponectin...
concentrations were expressed as ng per microgram of protein.

Gene expression of adiponectin receptors was determined by Real Time RT-PCR in fat-removed mouse mesenteric arteries. Snap frozen tissue was homogenized by ultrasonic disruption (Sonopulse HD 70, Bandelin Electronic, Germany). Total RNA was isolated using mirVana miRNA Isolation Kit (Ambion, Austin, TX, USA) followed by determination of quality and quantity with the Agilent 2100 bioanalyzer (Agilent Technologies, Walbronn, Germany) and reverse transcription (1 μg) into cDNA (Superscript Reverse Transcriptase, Invitrogen, Karlsruhe, Germany). Relative quantitation of gene expression was performed with the 7500 Fast Real Time PCR System (Applied Biosystems, Darmstadt, Germany) using the standard curve method. Rodent glyceraldehyde-3-phosphate dehydrogenase (GAPDH, # 4308313) was chosen as the endogenous control. Ready-to-use TaqMan Gene Expression Assays for mouse adiponectin receptor 1 (AdipoR1, # Mm01291331_m1) and mouse adiponectin receptor 2 (AdipoR2, # Mm01184028_m1) were purchased from Applera Deutschland GmbH (Darmstadt, Germany).

2.2. Isometric contractions

Local authorities approved the studies according to established guidelines. Male Sprague–Dawley rats (200–300 g, 6–8 weeks) were killed under ether. The thoracic aortas were removed, quickly transferred to cold (4 °C) oxygenated (95% O2/5% CO2) physiological salt solution (PSS), and dissected into 5-mm rings. Perivascular fat and connective tissue were either removed ((−) fat) or left intact ((+) fat). After 1-h equilibration, aortic ring contractile force was measured isometrically using standard bath procedures as described. The basal tone was continuously monitored and adjusted to 1 g [2]. The composition of PSS (in mM) was 119 NaCl, 4.7 KCl, 1.2 KH2PO4, 2.5 NaHCO3, 1.2 MgSO4, 11.1 glucose, 1.6 CaCl2. The bath solution was continuously oxygenated with a gas mixture of 95% O2 plus 5% CO2, and kept at 37 °C (pH, 7.4). The bath solution volume was 20 ml.

Male and female wild-type or Apn 1−/− mice (20–25 g, 8–12 weeks) were killed under ether [15]. Male NZO mice were age-matched with male C57BL/6 mice and killed under ether [18,19]. The thoracic aorta and superior branch of the mesenteric artery were excised. The arteries were removed, quickly transferred to cold (4 °C) oxygenated (95% O2/5% CO2) PSS, and dissected into 2-mm rings whereby perivascular fat and connective tissue were either removed or left intact. The perivascular fat was removed with scissors being careful not to damage the adventitia [2,5]. Each ring was positioned between two stainless steel wires (diameter 0.0394 mm) in a 5-ml organ bath of a Small Vessel Myograph (DMT 610M, Danish Myo Technology, Aarhus, Denmark) [5]. The organ bath was filled with PSS. The rings were placed under a tension equivalent to that generated at 0.9 times the diameter of the vessel at 100 mm Hg. This normalization procedure was performed to obtain the passive diameter of the

Fig. 2. Serotonin-dependent vasocontractions are reduced in the presence of adiponectin in mouse mesenteric arteries. Perivascular fat was removed. Panel A. Original recordings of wild-type arteries. Horizontal bars show the presence of the drugs. Panel B. Summary of the results for wild-type arteries. *, p < 0.05. Panel C: Summary of the results for arteries of 25-week-old NZO mice. * , p < 0.05.

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vessel at 100 mm Hg. The software Myodaq 2.01 M610+ was used for data acquisition and display. The rings were precontracted and equilibrated for 60 min until a stable resting tension was acquired. Tension is expressed as a percentage of the steady-state tension (100%) obtained with isotonic external 60 mM KCl. In some arterial rings the endothelial layer was mechanically disrupted by gently rubbing the luminal surface of a ring back and forth several times with scissors. Endothelium integrity or functional removal was confirmed by the presence or absence, respectively, of the relaxant response to 1 μM acetylcholine. Each experiment was carried out on rings prepared from different rats.

2.3. Vascular reactivity in mesenteric vascular beds

The mesenteric vascular bed was perfused [20]. Briefly, the superior mesenteric artery was cannulated at its junction with the abdominal aorta, put on a plastic grid in an organ chamber, and perfused using a peristaltic pump (WPI, Germany) at constant flow (4–5 ml/min) with oxygenated (95% O₂–5% CO₂) PSS. Perfusion pressure was continuously determined by a pressure transducer (Living Systems Instrumentation, Burlington, VT, USA) and recorded on a polygraph. Since flow was maintained at a constant rate, changes in perfusion pressure were used as an index of changes in the resistance of

Fig. 3. Perivascular fat limits vascular reactivity to serotonin in mouse mesenteric vascular beds. Panel A. Shown are original recordings of perfusion pressure for perfused isolated mesenteric vascular beds in the absence (fat –) and presence (fat +) of perivascular fat. Dashed lines represent 30 mm Hg. Horizontal bars show the presence of the drugs. The perivascular fat was carefully removed in fat – beds. The left panels show fat – and fat + mesenteric vascular beds. Panel B. Increase in perfusion pressure by application of KCl (60 mM). Panel C. Increase in perfusion pressure by external application of serotonin. All values are normalized to 60 mM KCl responses (100%). WT, wild-type mice; Apn 1 −/−, adiponectin deficient mice. *, p < 0.05; n.s., p ≥ 0.05.
4-Aminopyridine and tetraethylammonium chloride (TEA+) were from Merck Biosciences (Taufkirchen, Germany). 4-Aminopyridine and tetraethylammonium chloride were obtained from Sigma BioVendor GmbH (Heidelberg, Germany). Glibenclamide, and unpaired Student’s t tests or ANOVA were used as appropriate. A value of \( p < 0.05 \) was considered statistically significant; \( n \) represents the number of arteries or samples tested. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health and the ethics policies of our university and the Land Berlin.

3. Results

3.1. Adiponectin levels in serum and in perivascular adipose tissue

Serum adiponectin levels were 2.5±0.74 \( \mu \text{g/ml} \) in rats. Adiponectin levels were also measured in various rat adipose tissues. In subcutaneous fat of rats, the concentration of adiponectin was 0.223±0.109 ng/\( \mu \text{g} \) total protein. Similar adiponectin levels were detected in abdominal visceral and perivascular fat. The adiponectin concentrations were 0.255±0.069 ng/\( \mu \text{g} \) total protein, 0.220±0.053 ng/\( \mu \text{g} \) total protein, and 0.249±0.026 ng/\( \mu \text{g} \) total protein in abdominal visceral fat, in perivascular fat of the superior branch of the mesenteric artery, and in periaortic adipose tissue, respectively (\( p > 0.05 \) for each comparison, \( n=4–6 \) each). These data suggest that subcutaneous adipose tissue is probably not the only source for adiponectin in the body. Instead, the substance may also be produced by abdominal visceral and perivascular adipose tissue.

3.2. Adiponectin is a novel humoral vasodilator

Serotonin produced stable contractions of aortic rings in the absence of perivascular fat with half-maximal effects at 2 \( \mu \text{M} \) [2]. The contractions were stable within 45 min (Fig. 1A) and reversible after serotonin washout [2]. Recombinant human adiponectin at serum levels (3 \( \mu \text{g/ml} \)) inhibited serotonin-dependent contractions of rat aortas (Fig. 1B, \( n=10 \)). Half-maximal effects were observed at 7.9±2.2 \( \mu \text{g/ml} \) (IC\(_{50}\), \( n=6 \), Fig. 1E). Removal of endothelium did not affect the effects of adiponectin (IC\(_{50}\), 6.9±0.5 \( \mu \text{g/ml} \), \( n=6 \), Fig. 1E). Adiponectin effects (3 \( \mu \text{g/ml} \)) were abolished by \( K_{a} \) channel inhibition with 4-AP. Fig. 1B shows that 4-AP (2 \( \mu \text{M} \)) reversed the vasorelaxant effects of adiponectin with an overshoot. 4-AP increased force to ~250% of precontracted values by serotonin (100%) (\( n=6 \)). However, similar increases in force by 4-AP were observed in the absence of adiponectin (\( n=6 \), \( p > 0.05 \)). Pretreatment of aortic rings with 4-AP (2 \( \mu \text{M} \)) prevented the vasorelaxant effects of adiponectin (Fig. 1C); adiponectin (3 \( \mu \text{g/ml} \)) produced vasorelaxation by 67.7±5.0% (\( n=6 \) and \( n=10 \)) in the absence and presence of 4-AP, respectively (\( p < 0.05 \)). Inhibition of ATP-dependent \( K_{a} \text{ ATP} \) channels with glibenclamide (3 \( \mu \text{M} \)) did not affect the vasorelaxant effects of adiponectin (Fig. 1D, \( n=4 \)). Similar effects were observed in mesenteric arteries and aortas of mice. Fig. 2A and B shows that recombinant mouse adiponectin at serum levels (5 \( \mu \text{g/ml} \)) inhibited serotonin-dependent

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**Fig. 4.** No change in vascular reactivity to serotonin in mesenteric vascular beds of Apn 1−/− mice. Panel A. Shown are original recordings of perfusion pressure for perfused isolated mesenteric vascular beds. Dashed lines represent 30 mm Hg. Horizontal bars show the presence of the drugs. Panel B. Effects of 4-aminopyridine (4-AP) on perfusion pressure in the presence of serotonin (5-HT). WT, wild-type; Apn 1−/−, adiponectin deficient mice. *\( p < 0.05 \); n.s., \( p \geq 0.05 \).
contractions of mouse mesenteric arteries \( (n \geq 9) \). The effects were inhibited by 4-AP (2 mM). These data show that adiponectin represents a novel potent arterial vasodilator in both rats and mice. Furthermore, the data suggest that vasorelaxation by adiponectin is produced by opening Kv channels. Since Kv channels in arterial smooth muscle cells are targets for ADRF [4,5] and adiponectin levels are high in perivascular adipose tissue, we next investigated whether or not adiponectin is ADRF. We used Apn \( 1^{-/-} \) mice to study the role of adiponectin in the paracrine control of vascular tone by perivascular adipose tissue.

3.3. Adiponectin is not ADRF

The mesenteric vascular bed of wild-type mice was first cannulated and perfused at a constant flow of 4–5 ml/min in the absence and presence of perivascular adipose tissue (Fig. 3). KCl (60 mM) induced similar increases in perfusion pressure in the presence \((+\) fat\) \((n=10)\) and absence \((-\) fat\) \((n=7)\) of perivascular fat (Fig. 3A and B). However, serotonin (100 and 300 nM) induced stronger increases in perfusion pressure in isolated \(-\) fat mesenteric vascular beds, compared to \(+\) fat mesenteric vascular beds of wild-type mice (Fig. 3A and C).

We next cannulated and perfused \(+\) fat mesenteric vascular beds of wild-type and Apn \( 1^{-/-} \) mice at a constant flow of 4–5 ml/min (Fig. 4). KCl (60 mM) induced similar increases in perfusion pressure in \(+\) fat isolated mesenteric vascular beds of wild-type \((n=10)\) and Apn \( 1^{-/-} \) mice \((n=5)\) (Figs. 4A and 3B). In addition, serotonin (100 and 300 nM) induced similar increases in perfusion pressure in \(+\) fat isolated mesenteric vascular beds of wild-type and Apn \( 1^{-/-} \) mice (Figs. 4A and 3C). K\(_c\) channel inhibition with 4-AP (2 mM) increased perfusion pressure in \(+\) fat mesenteric vascular beds of both Apn \( 1^{-/-} \) mice and wild-type mice (Fig. 4B). In contrast, 4-AP (2 mM) did not increase perfusion pressure in \(-\) fat mesenteric beds of wild-type mice (Fig. 4B).

We then performed isometric contraction measurements of isolated aortic and mesenteric arterial rings and generated dose–response curves to serotonin for both rings with \(+\) fat and without \((-\) fat\) (Fig. 5). KCl produced similar contractions of \(-\) fat and \(+\) fat mesenteric rings of wild-type mice (Fig. 5A). However, the contractile response to serotonin was markedly reduced in intact \(+\) fat vessels compared to \(-\) fat vessels (Fig. 5B). Similar effects were observed in mesenteric rings from Apn \( 1^{-/-} \) mice (Fig. 5C and D). K\(_c\) channel inhibition with 4-AP (2 mM) abrogated the anti-contractile effects of perivascular fat and induced similar increases in the response of \(+\) fat mesenteric rings of Apn \( 1^{-/-} \) mice to serotonin, compared to wild-type mice. Length–tension curves of differently sized mesenteric rings were not influenced by the presence of perivascular fat (Fig. 1 online). The small-conductance Ca\(^{2+}\)-activated K\(^+\) channel blocker apamin [2,3,5] (1 \muM, \( n=6 \)), the K\(_{ATP}\) channel blocker glibenclamide [5] (3 \muM, \( n=8 \)), the inward rectifier K\(^+\) channel blocker Ba\(^{2+}\) (3 \muM, \( n=3 \)) [5,21], and blockers of large-conductance Ca\(^{2+}\)-activated potassium (BK)
Serotonin induced similar contractions in (+) fat rings from 20-, 25- and 34-week-old mice (Fig. 6A). The contractile response to serotonin was markedly reduced in intact (+) fat vessels compared to (-) fat vessels at all ages. However, these anti-contractile effects decreased with age (Fig. 6B). Notably, the reduction in the anti-contractile effects was not associated with decreased adiponectin levels in NZO mice. Instead, serum adiponectin levels showed a tendency to increase with age. Serum adiponectin levels were 20.3±3.6 μg/ml in 48-week-old NZO mice (n=6), which is higher than in 12-week-old NZO mice. Serum adiponectin levels were 15.7±0.87 μg/ml in 12-week-old NZO mice, which is similar to 12-week-old and 48-week-old wild-type mice (16.0±2.2 μg/ml, and 14.3±3.6 μg/ml, respectively, n=6 each).

In addition, adiponectin levels were similar in 20-, 25-, and 34-week-old NZO mice (18.2±8.0, 20.0±4.8, 15.1±8.2 μg/ml, n=5 each). RT-PCR revealed the expression of the adiponectin receptors AdipoR1 and AdipoR2 mRNA in fat-removed NZO mouse mesenteric arteries; however, with no difference in the degree of expression level between 20- and 34-week-old NZO mice (not shown). Despite diminished anti-contractile effects to perivascular fat (Fig. 6), (-) fat mesenteric rings of NZO mice showed normal vasodilatory responses to recombinant mouse adiponectin (5 μg/ml) (Fig. 2C; n≥5). The vasodilatory effects were similar compared to control mice (p<0.05).

4. Discussion

Our study produced four novel findings. First, we found that serum concentrations of adiponectin (IC50, ∼8 μg/ml) produced vasorelaxation of rat aorta and mouse mesenteric arteries. The effects were not dependent on the endothelium and may be mediated AdipoR1 and/or AdipoR2. 4-AP inhibited the vasorelaxation, suggesting that opening of Kv channels was involved. Our report is the first to show a direct vasodilating action of adiponectin and to demonstrate a mechanism for this effect. Second, we demonstrate that like the rat, the mouse also exhibits ADRF. Third, despite high-normal adiponectin levels and more perivascular fat, the anti-contractile effects of perivascular fat were diminished in mesenteric arteries of NZO mice, suggesting malfunction of ADRF in this model. Fourth, our investigations of Apn 1−/− mice suggest that adiponectin is not ADRF.

We demonstrated earlier that periadventitial adipose tissue markedly attenuates the contractile response to serotonin, phenylephrine, and angiotensin II in aortic and mesenteric ring preparations of rats [2,5]. Inhibition of the contractile response by fat depended on the amount of fat on each ring. The effects were not dependent on the endothelium [2,5] We and others showed that periadventitial fat appears to release ADRF into the organ bath that induces vasorelaxation by opening smooth muscle K+ channels [3,6,27], with a major role of Kv channels in mesenteric arteries [5]. Malfunction of this pathway may result to increased vascular reactivity in obesity and
hypertension [4,28]. In accord, the anti-contractile effects of perivascular fat are reduced in SHR mesenteric artery rings compared with WKY rings [17]. Noteworthy, serum adiponectin levels are low in SHR compared to WKY [16]. Furthermore, Apn 1−/− mice develop hypertension on an atherogenic diet [14], which is aggravated by salt intake [29]. These findings prompted us to suggest that adiponectin might be involved in the reduced paracrine effects of perivascular fat.

We found that adiponectin levels in rat serum were ∼2.5 μg/ml, as previously reported for rats [30] and humans [31,32]. We studied the effects of adiponectin at these concentrations on vascular ring preparations and observed that serum concentrations of adiponectin relaxed rat aortas (IC50, ∼8 μg/l). The effects were reversible upon adiponectin washout, independent of the endothelium, and inhibited by 4-AP. Similar effects were observed in mouse mesenteric arteries. These results suggest that adiponectin represents a novel vasodilator in rats and mice at physiological concentrations that produces vasorelaxation by opening K+ channels.

We next studied adiponectin levels in different adipose tissues of rats. In subcutaneous fat of rats, the concentration of adiponectin was ∼0.2 ng/μg total protein, which is similar to adiponectin levels in human subcutaneous adipose tissue [33,34]. We found that adiponectin concentrations were similar in perivascular fat of the superior branch of the mesenteric artery and perivascular fat of the aorta, compared to visceral abdominal fat and subcutaneous fat. These results suggest that perivascular adipose tissue might serve as a paracrine adiponectin source to control vascular tone. Adiponectin represents a possible ADRF candidate because of its presence in perivascular adipose tissue, its ability to induce vasorelaxation of aortic and mesenteric rings, and its effects on K+ channels that are blocked by 4-AP. This notion is also supported by detection of a 28.7-kDa protein band in ADRF-containing bath solutions of rat aorta, which is close to the molecular mass of adiponectin (30 kDa) [6].

To test adiponectin as possible ADRF candidate, we studied Apn 1−/− mice. We perfused the isolated mesenteric vascular bed and at a constant flow in the absence and presence of serotonin. Inhibition of K+ channels with 4-AP induced a similar increase in perfusion pressure by serotonin in mesenteric vascular bed of Apn 1−/− mice, compared to wild-type mice. Our experiments with fat-removed mesenteric vascular beds showed that these effects were solely dependent on the presence of perivascular fat. Our report is the first to show a direct vasodilating action of perivascular fat on resistance vessels exhibiting myogenic tone [35] in a perfused organ and under flow. We next studied isometric contractions of (+) fat and (−) fat mesenteric arterial rings from Apn 1−/− mice and wild-type mice. We found that periadventitial adipose tissue markedly attenuated the contractile response to serotonin. The attenuation was not different between mesenteric rings from Apn 1−/− mice and from wild-type mice. Similar effects were observed in aortas from Apn 1−/− and wild-type mice. Furthermore, the anti-contractile effect of perivascular fat was antagonized by 4-AP. Blockers of other K+ channels (BK, KATP) in smooth muscle cells were not effective. The effects of 4-AP were not different between rings from Apn 1−/− mice and from wild-type mice. These results indicate that perivascular adipose tissue of the mouse harbors an ADRF, which is similar to ADRF in rats [5,17]. Despite high-normal adiponectin levels and more perivascular fat (Fig. 3 online), the anti-contractile effects of perivascular fat were diminished in mesenteric arteries of NZO mice, which have a severe metabolic syndrome associated with hypertension [18,19]. At first glance, the high-normal levels of adiponectin in NZO mice were surprising. However, hypoadiponectinemia is not observed in all human populations and rodent models with obesity, type 2 diabetes, and/or hypertension [36–39]. Nevertheless, the discordance between the adiponectin levels and anti-contractile effects of perivascular fat in NZO mice suggest that ADRF is not adiponectin. Moreover, the response of NZO mesenteric rings to adiponectin was normal. However, our data clearly demonstrate that ADRF is malfunctional in NZO mice. Therefore, we suggest that differences in visceral perivascular adipose tissue function may contribute to the increased vascular resistance observed in NZO mice.

Release of adiponectin is of interest in various pathophysiological conditions, including hypoadiponectinemia, obesity, and obesity-associated hypertension [11,40,41]. Our results demonstrate that NZO mice feature a metabolic syndrome without hypoadiponectinemia. Our results also demonstrate that the paracrine control of vascular tone by perivascular adipose tissue is disturbed in these mice and is not mediated by adiponectin but possibly by other substances released from adipocytes or other adventitial cells. The study of Apn 1−/− mice has advanced our search since we found a hitherto fore not appreciated vasodilatory mechanism for adiponectin. Nevertheless, the role and nature of ADRF in health and cardiovascular disease remains to be identified.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cardiores.2007.05.025.

References


