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A novel adipocytokine, omentin, inhibits monocrotaline-induced pulmonary arterial hypertension in rats

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ABSTRACT

Omentin is a novel adipocytokine mainly expressed in visceral rather than subcutaneous adipose tissue. Several epidemiological studies demonstrated the negative relationship between blood omentin level and occurrence of obesity, type 2 diabetes and hypertension. Increases of inflammatory responses, contractile reactivity and structural remodeling of vascular wall contribute to hypertension development. Our in vitro studies previously demonstrated that omentin inhibited those hypertension-related pathological processes. In addition, our in vivo study demonstrated that intravenously injected omentin acutely inhibited agonists-induced increases of blood pressure in rats. However, the chronic effects of omentin on hypertension development are not determined. In the present study, we tested the hypothesis that chronic omentin treatment may inhibit pulmonary arterial (PA) hypertension (PAH). PAH was induced by a single intraperitoneal injection of monocrotaline (MCT: 60 mg/kg) to rats. Omentin (18 μg/kg/day) was intraperitoneally treated for 14 days. Chronic omentin treatment inhibited MCT-induced increases in PA pressure. Omentin inhibited MCT-induced right ventricular hypertrophy as well as increase of lung to body weight ratio. Histologically, omentin inhibited MCT-induced PA hyperplasia. Further, omentin inhibited the impairment of both endothelium-dependent and -independent relaxations mediated by acetylcholine and sodium nitroprusside, respectively. In conclusion, we for the first time demonstrate that chronic omentin treatment inhibits MCT-induced PAH in rats via inhibiting vascular structural remodeling and abnormal contractile reactivity.

1. Introduction

Pulmonary arterial (PA) hypertension (PAH) is a disease that is characterized by increases in PA resistance and PA pressure. Increases of inflammatory responses, contractile reactivity and vascular structural remodeling contribute to the increases in pulmonary vascular resistance, finally leading to right heart failure (RHF) through PAH. There are currently several reports demonstrating that a tyrosine kinase inhibitor, imatinib could inhibit PAH via inhibiting platelet-derived growth factor-induced vascular structural remodeling [1,2]. However, there is a report demonstrating that a long-term imatinib treatment has several side effects [3]. As other therapeutic drugs for PAH, prostacyclin, endothelin receptor blocker and phosphodiesterase-5 inhibitor are known [4]. Since these drugs have different sites of actions and molecular mechanisms, they are often given together. Nonetheless, more attractive and effective drugs for PAH are urgently demanded.

Obesity-induced adipocyte hypertrophy causes an increase or decrease in the production and secretion of adipocyte-derived cytokines, named adipocytokine. Adipocytokine can control progression of obesity-related cardiovascular diseases including hypertension [5]. Omentin, also referred as intelectin-1 and intestinal lactoferrin receptor, is an adipocytokine originally discovered in omental fat [6,7]. Omentin is mainly expressed in visceral rather than subcutaneous adipose tissue [7]. Several epidemiological reports demonstrated the negative relationship between blood omentin level and occurrence of obesity, type 2 diabetes and hypertension [8,9]. In addition, another report demonstrated that serum omentin level decreases in patients with obstructive sleep apnea syndrome (OSAS), ultimately inducing PAH and RHF [10].

Abbreviations: PA, pulmonary arterial; PAH, pulmonary arterial hypertension; MCT, monocrotaline; RHF, right heart failure; OSAS, obstructive sleep apnea syndrome; SMCs, smooth muscle cells; NO, nitric oxide; BP, blood pressure; IPAs, intrapulmonary arteries; ACh, acetylcholine; SNP, sodium nitroprusside; NA, noradrenaline; RV, right ventricular; NOX, NADPH oxidase; LV, left ventricular.

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Our previous in vitro studies demonstrated that omentin inhibited vascular inflammatory responses and smooth muscle cells (SMCs) migration [11,12], which are important components for the development of vascular structural remodeling. In addition, we demonstrated that omentin induced vasodilation of isolated blood vessel through endothelium-derived nitric oxide (NO) [13]. Moreover, our in vivo study demonstrated that intravenously injected omentin acutely inhibited agonists-induced increases of blood pressure (BP) in rats [14]. Thus, we hypothesized that chronic omentin treatment may inhibit PAH. To test the hypothesis, we examined the effects of chronic omentin treatment on monocrotaline (MCT)-induced PAH in rats.

2. Materials and methods

2.1. Animal experiments

Animal care and treatment were conducted in conformity with institutional guidelines of The Kitasato University and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Male Wistar rats (Clea Japan, Tokyo, Japan) were maintained on a standard laboratory diet and tap water, and exposed to a 12 h/12 h light–dark cycle at 23 ± 2 °C. Rats (5-week-old) were randomly divided into three groups; control group (Control, $n = 8$), MCT-injected group (MCT, $n = 10$) and omentin-treated MCT-injected group (+Omentin, $n = 8$). PAH was induced by a single intraperitoneal injection of MCT (60 mg/kg) as previously described [15]. The rats in the Control were once intraperitoneally injected with saline. Saline (MCT) or recombinant omentin (+Omentin; 18 μg/kg/day) was intraperitoneally treated once daily for 14 days.

2.2. Mean PA pressure measurement

At the end of the treatment, PA pressure was measured under urethane (1.5 g/kg, i.p.) anesthesia as described previously [15]. The catheter filled with a heparin-saline solution was inserted into the pulmonary artery via the right external jugular vein as described previously [16]. Catheter was connected to MLT0670 BP transducer (ADInstruments Colorado Springs, CO, USA). Mean PA pressure was measured and digitally recorded using ML117 BP Amp (ADInstruments), ML825 PowerLab 2/25 (ADInstruments) system and Chart 5 software (ADInstruments).

2.3. Histological analysis

After PA pressure measurement, rats were euthanized by exsanguination under deep urethane (1.5 g/kg, i.p.) anesthesia, and hearts and lungs were isolated for histological examinations. The hearts were separated into right and left atrial or ventricular tissues. After measurement of isolated ventricular tissue and lung weight, a part of each tissue was fixed in 4% paraformaldehyde. Thin paraffin sections (4 μm) were made and stained with hematoxylin and eosin as described previously [12,17]. The images were obtained using a light microscope (BX-51, Olympus, Tokyo, Japan). Cross sectional area of cardiomyocytes (μm^2) was calculated using Image J software. Vascular structural remodeling was evaluated by calculating luminal to vessel area ratio (%) in the intrapulmonary arteries (IPAs) (diameter; <100 μm) using Image J software.

2.4. Measurement of isometric contraction

The intrapulmonary arterial rings (diameter; <1 mm) were placed in normal physiological salt solution, which contained (mM): NaCl 136.9, KCl 5.4, $CaCl_2$ 1.5, $MgCl_2$ 1.0, $NaHCO_3$ 23.8, glucose 5.5 and EDTA 0.001. The high KCl solution was prepared by replacing NaCl with equimolar KCl. These solutions were saturated with a 95% O_2–5% CO_2 mixture at 37 °C and pH 7.4. Smooth muscle contractility was recorded isometrically with a force–displacement transducer (Nihon Kohden, Tokyo, Japan) as described previously [18]. Each arterial ring was attached to a holder under a resting tension of 0.5 g. After equilibration for 30 min in a 3 ml organ bath, each ring was repeatedly exposed to 72 mM KCl solution, until the responses became stable. Concentration–responses curves were obtained by the cumulative application of acetylcholine (ACh; 1 nM–30 μM) or sodium nitroprusside (SNP; 100 pM–3 μM) to the artery precontracted equally by 100 nM noradrenaline (NA).

2.5. Materials

Recombinant omentin (BioVendor, Candler, NC, USA); MCT (Wako Pure Chemical, Osaka, Japan); ACh (Daiichi-Sankyo, Tokyo, Japan); NA and SNP (Sigma–Aldrich, St. Louis, MO, USA).

2.6. Statistical analysis

Data were shown as mean + SEM. Statistical evaluations were performed by one-way ANOVA followed by Bonferroni's test. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Effects of chronic omentin treatment on MCT-induced increases in mean PA pressure

We first examined the effects of chronic omentin (18 μg/kg/day, 14 days) treatment on MCT-induced increases in PA pressure of rats. Omentin significantly inhibited MCT (60 mg/kg)-induced increases in PA pressure (from 27.2 ± 2.6 to 18.7 ± 1.4 mmHg, $n = 8$–10, $p < 0.05$, Fig. 1).

3.2. Effects of omentin on MCT-induced increases in right ventricular (RV) hypertrophy

Increases of PA pressure contribute to RV hypertrophy. We next examined the effects of omentin on MCT-induced RV hypertrophy. Omentin significantly inhibited both RV to left ventricular weight ratio (from 0.36 ± 0.02 to 0.28 ± 0.02 g/g, $n = 8$, $p < 0.01$, Fig. 2A)

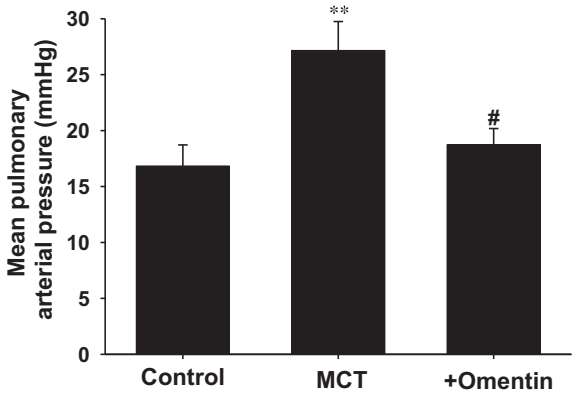

Fig. 1. Effects of chronic omentin treatment on monocrotaline (MCT)-induced increases in mean pulmonary arterial (PA) pressure of rats. After saline (Control, $n = 8$) or MCT (60 mg/kg) was intraperitoneally injected to rats (5-week-old), saline (MCT, $n = 10$) or omentin (+Omentin; 18 μg/kg/day, $n = 8$) was intraperitoneally treated everyday. After 14 days, mean PA pressure was directly measured by a cannulation method. $^{**}p < 0.01$ vs. Control; $^{\#}p < 0.05$ vs. MCT.

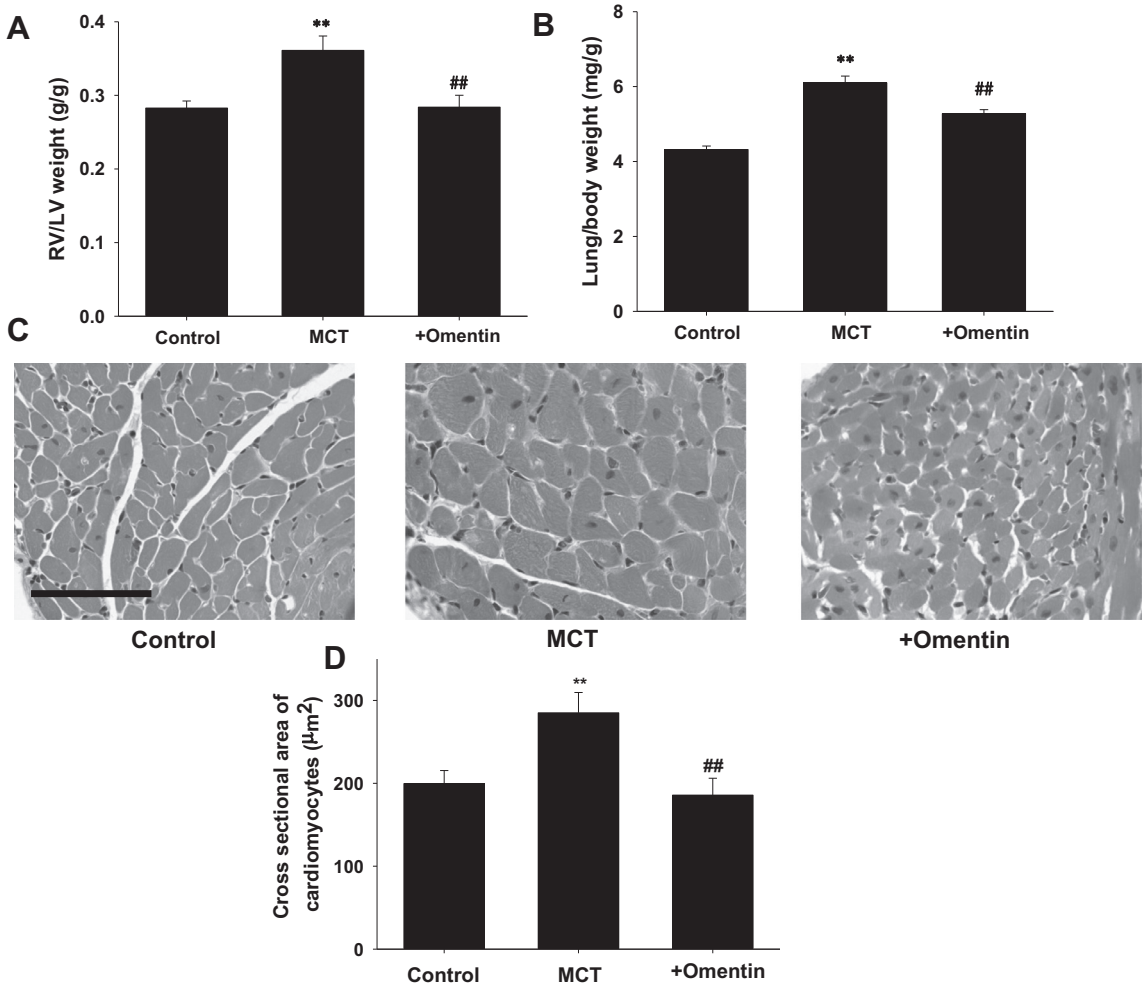

Fig. 2. Effects of omentin on MCT-induced right ventricular (RV) hypertrophy. After saline (Control) or MCT (60 mg/kg) was intraperitoneally injected to rats, saline (MCT) or omentin (+Omentin; 18 μg/kg/day) was intraperitoneally treated everyday. After 14 days, (A) RV to left ventricular (RV/LV) weight ratio (g/g, $n = 8$) and (B) lung to body weight ratio (mg/g, $n = 8$) were calculated and shown in the bar graph. (C) Representative hematoxylin and eosin stained sections for RV cardiomyocytes were shown ($n = 6$–8). (D) Cross sectional area of cardiomyocytes (μm^2) was calculated and shown in the bar graph ($n = 6$–8). $^{**}p < 0.01$ vs. Control; $^{\#\#}p < 0.01$ vs. MCT. Scale bar: 100 μm.

and lung to body weight ratio (from 6.1 ± 0.18 to 5.3 ± 0.1 mg/g, $n = 8$, $p < 0.01$, Fig. 2B). We further examined the effects of omentin on MCT-induced RV cardiomyocytes hypertrophy. Omentin significantly inhibited MCT-induced increases in cross sectional area of RV cardiomyocytes (from 285.0 ± 24.6 to 185.8 ± 20.3 μm^2, $n = 6$–8, $p < 0.01$, Fig. 2C and D).

3.3. Effects of omentin on MCT-induced PA hyperplasia

PA hyperplasia is very important for PAH development. To determine whether omentin affects PA hyperplasia, we next examined the effects of omentin on MCT-induced morphological changes of vascular wall in IPAs. Omentin significantly inhibited MCT-induced decreases in luminal to vessel area ratio of IPAs (from 10.6 ± 2.3 to 21.6 ± 2.7%, $n = 8$, $p < 0.01$, Fig. 3A and B).

3.4. Effects of omentin on MCT-induced impairment of vasorelaxing function in IPAs

Impairment of relaxing function in IPAs is also important for PAH development. Finally, we examined the effects of omentin on MCT-induced impairment of endothelium-dependent and -independent relaxations. In IPAs from Control, ACh (1 nM–30 μM) induced relaxation of the NA-induced precontraction in a concentration-dependent manner (closed circle, $n = 7$–9, Fig. 4A). In IPAs from MCT, the ACh-induced relaxation was significantly impaired from Control (open circle, $n = 9$–13, $p < 0.05$, 0.01, Fig. 4A). Chronic omentin treatment significantly inhibited the MCT-induced impairment of endothelium-dependent relaxation by ACh (open square, $n = 8$, $p < 0.05$, 0.01, Fig. 4A). In IPAs from Control, SNP (100 pM–3 μM) induced relaxation of the NA-induced precontraction in a concentration-dependent manner (closed circle, $n = 8$, Fig. 4B). In IPAs from MCT, the SNP-induced relaxation was significantly impaired from Control (open circle, $n = 8$, $p < 0.05$, 0.01, Fig. 4B). Chronic omentin treatment also significantly inhibited the MCT-induced impairment of endothelium-independent relaxation by SNP (open square, $n = 7$, $p < 0.05$, 0.01, Fig. 4B).

4. Discussion

In the present study, we for the first time demonstrated that chronic omentin treatment inhibited MCT-induced increases in PA pressure. In addition, omentin inhibited MCT-induced RV hypertrophy as well as increase of lung weight. Moreover, omentin inhibited MCT-induced intrapulmonary arterial hyperplasia. Further, omentin inhibited MCT-induced impairment of both endothelium-dependent and -independent relaxations. These data

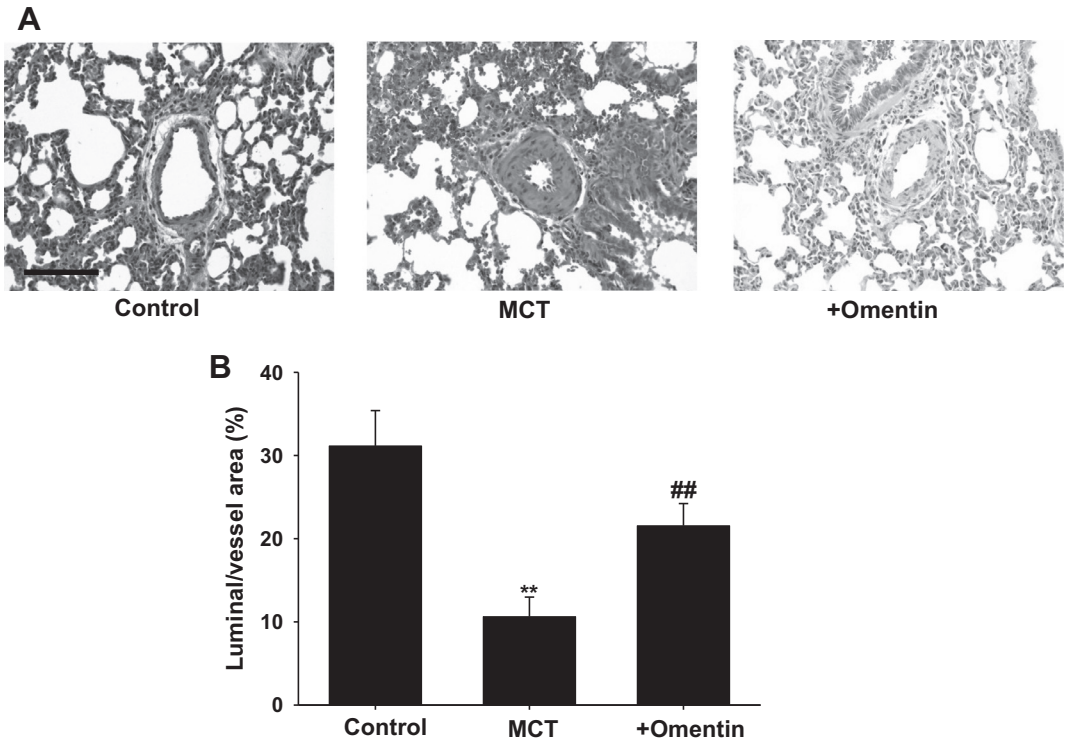

Fig. 3. Effects of omentin on MCT-induced PA hyperplasia. After saline (Control) or MCT (60 mg/kg) was intraperitoneally injected to rats, saline (MCT) or omentin (+Omentin; 18 μg/kg/day) was intraperitoneally treated everyday. After 14 days, lungs were harvested. (A) Representative hematoxylin and eosin stained lung sections for intrapulmonary arteries (IPAs) were shown ($n = 8$). (B) Luminal to vessel area ratio (%) of IPAs (diameter: <100 μm) was calculated and shown in the bar graph ($n = 8$). $^{**}p < 0.01$ vs. Control; $^{\#\#}p < 0.01$ vs. MCT. Scale bar: 100 μm.

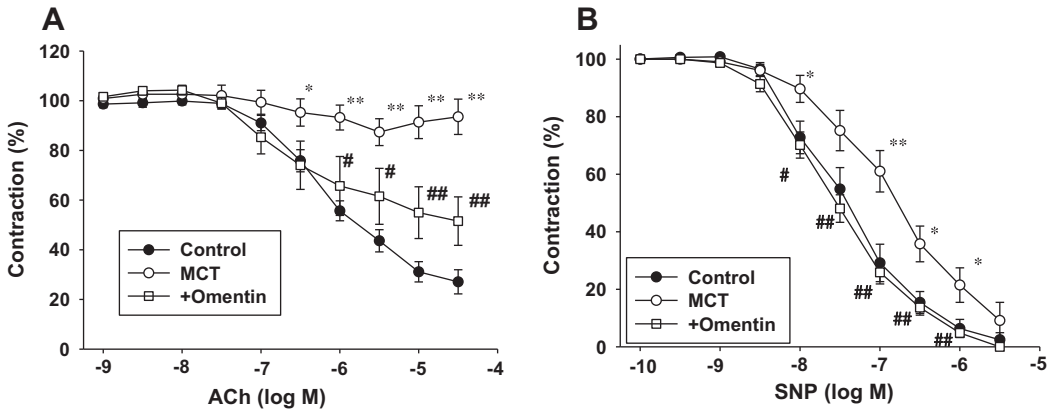

Fig. 4. Effects of omentin on MCT-induced impairment of endothelium-dependent and -independent relaxations mediated by acetylcholine (ACh, $n = 7–13$, A) and sodium nitroprusside (SNP, $n = 7–8$, B), respectively, in IPAs of rats. After saline (Control) or MCT (60 mg/kg) was intraperitoneally injected to rats, saline (MCT) or omentin (+Omentin; 18 mg/kg/day) was intraperitoneally treated everyday. After 14 days, IPAs were isolated. Contraction was expressed as relative to the precontraction induced by 100 nM noradrenaline. ACh (1 nM–30 μM) or SNP (100 pM–3 μM) was cumulatively applied. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. Control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. MCT.

collectively indicate that omentin is anti-PAH via inhibiting vascular structural remodeling and abnormal contractile reactivity.

PAH is characterized by increases in PA resistance and PA pressure. PAH is a disease that carries a very poor prognosis. As therapeutic drugs for PAH, a tyrosine kinase inhibitor, prostacyclin, endothelin receptor blocker and phosphodiesterase-5 inhibitor are known [1,2,4]. These drugs are often given together in clinical. In this study, chronic omentin treatment improved MCT-induced both vascular structural remodeling and abnormal contractile reactivity. Since omentin inhibited MCT-induced PAH through two different actions, it might be a more attractive molecule for developing drugs against PAH.

Increases of vascular contractile reactivity and hyperplasia contribute to the increases in pulmonary vascular resistance, finally leading to RHF through PAH. Inflammatory response is also important for the initiation and progression of abnormal vascular contractile reactivity and structural remodeling including hyperplasia. We have previously demonstrated that omentin inhibited TNF-α-induced inflammatory responses in cultured endothelial cells and SMCs [11,19]. In addition, we have recently demonstrated that omentin inhibited PDGF-BB-induced SMCs migration as well as neointimal hyperplasia in mouse carotid ligation model [12]. These data suggest that omentin inhibited PAH and subsequent RHF through anti-inflammatory and anti-migratory mechanisms.

Our previous studies also demonstrated that omentin is anti-inflammatory and anti-migratory through anti-oxidative mechanisms via the inhibition of NADPH oxidase (NOX) activity [12,19]. NOX activation is considered as one of the major contributors to PAH progression. There is a report demonstrating that NOX-4 expression increases in response to hypoxia [20]. NOX-4 overexpression contributes to pulmonary vascular structural remodeling in response to hypoxia [21]. Another report demonstrated that NOX-1 but not NOX-4 is responsible for proliferation and migration of PASMCs in MCT-induced PAH [22]. In addition, apocynin, a NOX inhibitor, increases NO-mediated vasodilation and inhibits reactive oxygen species-mediated vasoconstriction in pulmonary arteries [23]. Thus it is suggested in the present study that omentin may prevent MCT-induced PAH and subsequent RHF through inhibiting vascular structural remodeling and abnormal contractility at least in part via the inhibition of NOX-1/NOX-4 in IPAs.

Several epidemiologic studies demonstrated the negative relationship between blood omentin level and occurrence of obesity, type 2 diabetes and hypertension [8,24,25]. In addition, a recent report demonstrated that serum omentin level decreased in patients with OSAS compared with healthy controls [10]. Obesity is a major risk factor for OSAS progression [26]. Hypoxia is developed in the severe cases of OSAS and ultimately induces PAH and RHF. Considering that, omentin may prevent obesity-associated OSAS and subsequent PAH and RHF. It is well known that adiponectin, a member of good adipocytokine family, is anti-inflammatory, anti-vascular structural remodeling and anti-vascular constriction. A recent report also demonstrated that adiponectin inhibited obesity-related PAH progression [27]. Since there are many similarities between the effects of omentin and adiponectin, omentin should be a novel candidate member of good adipocytokine family against obesity-related cardiovascular disease.

We for the first time demonstrate that chronic omentin treatment inhibits MCT-induced PAH through the inhibition of vascular structural remodeling and abnormal contractile reactivity. Our novel findings indicate omentin as an attractive molecule for developing drugs against PAH.

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Disclosures

The authors have nothing to disclose.

References

[1] E. Berghausen, H. Ten Freyhaus, S. Rosenkranz, Targeting of platelet-derived growth factor signaling in pulmonary arterial hypertension, Handb. Exp. Pharmacol. 218 (2013) 381–408.
[2] H.A. Ghofrani, O. Distler, F. Gerhardt, M. Gorenflo, E. Grunig, W.E. Haefeli, M. Held, M.M. Hoeper, C.M. Kahler, H. Kaemmerer, H. Klose, V. Kollner, B. Kopp, S. Mebus, A. Meyer, O. Miera, D. Pittrow, G. Riemekasten, S. Rosenkranz, D. Schranz, R. Voswinckel, H. Olschewski, Treatment of pulmonary arterial hypertension (PAH): recommendations of the Cologne Consensus Conference 2010, Dtsch. Med. Wochenschr. 135 (Suppl. 3) (2010) S87–S101.
[3] R. Souza, O. Sitbon, F. Parent, G. Simonneau, M. Humbert, Long term imatinib treatment in pulmonary arterial hypertension, Thorax 61 (2006) 736.
[4] H. Watanabe, Pharmacological treatment of pulmonary hypertension at a turning point, Nihon Yakurigaku Zasshi 143 (2014) 165–172.
[5] H. Yamawaki, Mechanisms of action of novel adipocytokines on the vascular system, Nihon Yakurigaku Zasshi 137 (2011) 131–135.
[6] A. Schaffler, M. Neumeier, H. Herfarth, A. Furst, J. Scholmerich, C. Buchler, Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue, Biochim. Biophys. Acta 1732 (2005) 96–102.
[7] R.Z. Yang, M.J. Lee, H. Hu, J. Pray, H.B. Wu, B.C. Hansen, A.R. Shuldiner, S.K. Fried, J.C. McLenithan, D.W. Gong, Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action, Am. J. Physiol. Endocrinol. Metab. 290 (2006) E1253–E1261.
[8] C.M. de Souza Batista, R.Z. Yang, M.J. Lee, N.M. Glynn, D.Z. Yu, J. Pray, K. Ndubuizu, S. Patil, A. Schwartz, M. Kligman, S.K. Fried, D.W. Gong, A.R. Shuldiner, T.I. Pollin, J.C. McLenithan, Omentin plasma levels and gene expression are decreased in obesity, Diabetes 56 (2007) 1655–1661.
[9] S. Maruyama, R. Shibata, R. Kikuchi, Y. Izumiya, T. Rokutanda, S. Araki, Y. Kataoka, K. Ohashi, H. Daida, S. Kihara, H. Ogawa, T. Murohara, N. Ouchi, Fat-derived factor omentin stimulates endothelial cell function and ischemia-induced revascularization via endothelial nitric oxide synthase-dependent mechanism, J. Biol. Chem. 287 (2012) 408–417.
[10] Q. Wang, X. Feng, C. Zhou, P. Li, J. Kang, Decreased levels of serum omentin-1 in patients with obstructive sleep apnoea syndrome, Ann. Clin. Biochem. 50 (2013) 230–235.
[11] H. Yamawaki, J. Kuramoto, S. Kameshima, T. Usui, M. Okada, Y. Hara, Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells, Biochem. Biophys. Res. Commun. 408 (2011) 339–343.
[12] K. Kazama, M. Okada, H. Yamawaki, A novel adipocytokine, omentin, inhibits platelet-derived growth factor-BB-induced vascular smooth muscle cell migration through anti-oxidative mechanism, Am. J. Physiol. Heart Circ. Physiol. 306 (2014) H1714–H1719.
[13] H. Yamawaki, N. Tsubaki, M. Mukohda, M. Okada, Y. Hara, Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels, Biochem. Biophys. Res. Commun. 393 (2010) 668–672.
[14] K. Kazama, M. Okada, Y. Hara, H. Yamawaki, A novel adipocytokine, omentin, inhibits agonists-induced increases of blood pressure in rats, J. Vet. Med. Sci. 75 (2013) 1029–1034.
[15] M. Okada, T. Harada, R. Kikuzuki, H. Yamawaki, Y. Hara, Effects of telmisartan on right ventricular remodeling induced by monocrotaline in rats, J. Pharmacol. Sci. 111 (2009) 193–200.
[16] Y. Yamada, J. Maruyama, E. Zhang, A. Okada, A. Yokochi, H. Sawada, Y. Mitani, T. Hayashi, K. Suzuki, K. Maruyama, Effect of thrombomodulin on the development of monocrotaline-induced pulmonary hypertension, J. Anesth. 28 (2014) 26–33.
[17] M. Okada, R. Kikuzuki, T. Harada, Y. Hori, H. Yamawaki, Y. Hara, Captopril attenuates matrix metalloproteinase-2 and -9 in monocrotaline-induced right ventricular hypertrophy in rats, J. Pharmacol. Sci. 108 (2008) 487–494.
[18] M. Mukohda, T. Morita, M. Okada, Y. Hara, H. Yamawaki, Long-term methylglyoxal treatment impairs smooth muscle contractility in organ-cultured rat mesenteric artery, Pharmacol. Res. 65 (2012) 91–99.
[19] K. Kazama, T. Usui, M. Okada, Y. Hara, H. Yamawaki, Omentin plays an anti-inflammatory role through inhibition of TNF-α-induced superoxide production in vascular smooth muscle cells, Eur. J. Pharmacol. 686 (2012) 116–123.
[20] I. Diebold, A. Petry, J. Hess, A. Gorlach, The NADPH oxidase subunit NOX4 is a new target gene of the hypoxia-inducible factor-1, Mol. Biol. Cell 21 (2010) 2087–2096.
[21] S. Ismail, A. Sturrock, P. Wu, B. Cahill, K. Norman, T. Huecksteadt, K. Sanders, T. Kennedy, J. Hoidal, NOX4 mediates hypoxia-induced proliferation of human pulmonary artery smooth muscle cells: the role of autocrine production of transforming growth factor-{beta}1 and insulin-like growth factor binding protein-3, Am. J. Physiol. Lung Cell. Mol. Physiol. 296 (2009) L489–L499.
[22] F. Veit, O. Pak, B. Egemnazarov, M. Roth, D. Kosanovic, M. Seimetz, N. Sommer, H.A. Ghofrani, W. Seeger, F. Grimminger, R.P. Brandes, R.T. Schermuly, N. Weissmann, Function of NADPH oxidase 1 in pulmonary arterial smooth muscle cells after monocrotaline-induced pulmonary vascular remodeling, Antioxid. Redox Signal. 19 (2013) 2213–2231.
[23] S. Wedgwood, S. Lakshminrusimha, K.N. Farrow, L. Czech, S.F. Gugino, F. Soares, J.A. Russell, R.H. Steinhorn, Apocynin improves oxygenation and increases eNOS in persistent pulmonary hypertension of the newborn, Am. J. Physiol. Lung Cell. Mol. Physiol. 302 (2012) L616–L626.
[24] R. Shibata, N. Ouchi, R. Takahashi, Y. Terakura, K. Ohashi, N. Ikeda, A. Higuchi, H. Terasaki, S. Kihara, T. Murohara, Omentin as a novel biomarker of metabolic risk factors, Diabetol. Metab. Syndr. 4 (2012) 37.
[25] B.K. Tan, R. Adya, S. Farhatullah, K.C. Lewandowski, P. O'Hare, H. Lehnert, H.S. Randeva, Omentin-1, a novel adipokine, is decreased in overweight insulin-resistant women with polycystic ovary syndrome: ex vivo and in vivo regulation of omentin-1 by insulin and glucose, Diabetes 57 (2008) 801–808.
[26] M.L. Alonso-Alvarez, J.A. Cordero-Guevara, J. Teran-Santos, M. Gonzalez-Martinez, M.J. Jurado-Luque, J. Corral-Penafiel, J. Duran-Cantolla, L. Kheirandish-Gozal, D. Gozal, Obstructive sleep apnea in obese community-dwelling children: the NANOS study, Sleep 37 (2014) 943–949.
[27] R. Summer, K. Walsh, B.D. Medoff, Obesity and pulmonary arterial hypertension: is adiponectin the molecular link between these conditions?, Pulm Circ. 1 (2011) 440–447.