A Novel Adipocytokine, Omentin, Inhibits Agonists-Induced Increases of Blood Pressure in Rats

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ABSTRACT Omentin is a recently identified adipocytokine, and we previously demonstrated that omentin played anti-inflammatory roles in vascular endothelial and smooth muscle cells. We also demonstrated that omentin induced vasodilation in rat isolated blood vessels. However, effects of omentin on blood pressure (BP) are not determined. Here, we examined whether intravenously injected omentin acutely alters BP of Wistar rats. Omentin (0.06–18 µg/kg) alone did not alter BP of Wistar rats. On the other hand, omentin (18 µg/kg) significantly inhibited noradrenaline (NA; 2 µg/kg)-induced increases in systolic BP and mean BP. Omentin (18 µg/kg) significantly inhibited angiotensin II (1 µg/kg)-induced increases in diastolic BP. Omentin (18 µg/kg) significantly inhibited dimorpholamine (3 mg/kg)-induced increases in diastolic BP. Omentin (18 µg/kg) failed to inhibit the NA (0.02–2 µg/kg)-induced increases of systolic BP in the nitric oxide (NO) synthase inhibitor, Nω-nitro-l-arginine methyl ester (80 mg/kg, 1 day)-treated Wistar rats. In summary, we for the first time demonstrated that omentin inhibited agonists-induced increases in BP. The effect of omentin was suggested to be mediated likely via NO-dependent mechanism.

KEYWORDS: adipocytokine, blood pressure, nitric oxide, omentin.


Adipocytes can secrete a variety of cytokines, termed adipocytokine. Obesity with an accumulation of visceral fat is one of the main risk factors for cardiovascular diseases, including hypertension. Adipocytes enlarged by obesity may increase or decrease the production and secretion of adipocytokine. Adipocytokine is thought to regulate obesity-related hypertension by directly acting on vascular system [13, 14].

Omentin is a recently identified adipocytokine consisting of 313 amino acids [9]. Secretion and plasma concentration of omentin decrease in the obese patients, but increase after a weight loss [2]. We previously demonstrated that omentin was anti-inflammatory in cultured vascular endothelial and smooth muscle cells [5, 16]. In addition, we demonstrated that omentin induced vasodilation in rat isolated blood vessels via stimulating endothelial nitric oxide (NO) production [15]. While it is presumed that omentin could regulate blood pressure (BP) in vivo, effects of omentin on BP remain to be determined. Here, we for the first time provided the evidence that omentin can regulate BP in rats.

MATERIALS AND METHODS

Materials: Reagent sources were as follows: recombinant omentin (BioVendor, Candler, NC, U.S.A.); noradrenaline (NA) and angiotensin II (Ang II) (Sigma-Aldrich, St. Louis, MO, U.S.A.); dimorpholamine (Eisai Co., Ltd., Tokyo, Japan); Nω-nitro-l-arginine methyl ester (L-NAME) (Dojindo, Kumamoto, Japan).

Physical parameters of rats: Physical parameters of normal Wistar rats (Clea Japan Inc., Tokyo, Japan) or L-NAME-treated Wistar rats (6–10-week-old) were measured. Body weight, heart rate (HR), systolic blood pressure (BP) (SBP), mean BP (MBP) and diastolic BP (DBP) represent the average value (Table 1). Noninvasive BP in conscious rats was measured using a tail-cuff method after heating the rats (38°C) (Softron, Tokyo, Japan) [6, 11, 12]. L-NAME was dissolved in drinking water and given to rats (80 mg/kg, 1 day).

Direct BP measurement: BP and HR of male Wistar rats (130–350 g, 6–10-week-old) were measured under urethane (1.5 g/kg, i.p.) anesthesia as described previously [7, 17]. Briefly, the catheter filled with a heparin-saline solution was inserted into carotid artery with a small incision. Catheter was connected to MLT0670 BP transducer (ADInstruments, Colorado Springs, CO, U.S.A.). SBP, MBP and DBP were measured and recorded using ML117 BP Amp (ADInstruments), ML825 PowerLab 2/25 (ADInstruments) system and Chart5 software (ADInstruments). HR was calculated by a cyclic measurement of BP recording. After omentin (0.06–1.8 µg/kg) or saline was intravenously applied for 5 min through the catheter inserted into saphenous vein, NA (0.02–2 µg/kg), Ang II (0.01–10 µg/kg) or dimorpholamine (3 mg/kg) was applied. The differences of BP or HR before and after the addition of drugs were calculated. Animal care and treatment were conducted in conformity with the institutional guidelines of The Kitasato University.

Statistics: The results of the experiments were expressed as means ± SEM. Statistical evaluation of the data was performed by Student’s t-test in comparison between two groups or one-way ANOVA followed by Bonferroni’s test in comparison between four groups. A value of P<0.05 was taken as statistically significant.
RESULTS

Effects of omentin alone injection on BP of Wistar rats: We first examined whether omentin alone injection alters BP of Wistar rats. Omentin (0.06–18 µg/kg) alone treatment had no influence on BP of Wistar rats (Fig. 1, n=11).

Effects of omentin on agonists-induced increases in BP of Wistar rats: We next examined effects of omentin on agonists-induced increases in BP of Wistar rats. We used NA and Ang II to increase BP. Omentin (18 µg/kg) significantly inhibited NA (2 µg/kg)-induced increases in SBP (Control; 20.5 ± 2.0 mmHg increase vs. Omentin; 14.3 ± 1.1 mmHg increase, n=11, P<0.05, Fig. 2A and 2B) and MBP (Control; 21.5 ± 2.0 mmHg increase vs. Omentin; 16.7 ± 1.0 mmHg increase, n=11, P<0.05, Fig. 2A and 2C). Omentin also decreased NA (2 µg/kg)-induced increases in DBP, which was not statistically significant (Control; 22.2 ± 2.2 mmHg increases vs. Omentin; 16.8 ± 1.9 mmHg increase, n=11, Fig. 2A and 2D). Omentin (18 µg/kg) significantly inhibited Ang II (1 µg/kg)-induced increases in DBP (Control; 38.0 ± 1.7 mmHg increase vs. Omentin; 30.8 ± 1.2 mmHg increase, n=5, P<0.01, Fig. 3A and 3D), but not SBP (Fig. 3A and 3B) and MBP (Fig. 3A and 3C). NA and Ang II caused decreases in HR of Wistar rats. Omentin tended to inhibit the NA- and Ang II-induced decreases in HR, which was not statistically significant (Figs. 2E and 3E).

Effects of omentin on dimorpholamine-induced increases in BP of Wistar rats: Action on central nerve is also important for BP regulation in addition to peripheral control. Dimorpholamine is known to have the central actions. We thus examined effects of omentin (18 µg/kg) on dimorpholamine (3 mg/kg)-induced increases in BP of Wistar rats. Omentin significantly inhibited dimorpholamine-induced increases in DBP (Control; 19.2 ± 1.2 mmHg increase vs. Omentin; 14.0 ± 1.5 mmHg increase, n=7, P<0.05, Fig. 4A and 4C), but not SBP (Fig. 4B). Dimorpholamine caused decreases in HR of Wistar rats. Omentin tended to inhibit it, which was not statistically significant (Fig. 4D).

Effects of omentin on NA-induced increases of BP in L-NAME-treated Wistar rats: Since NO is one of the most important physiological substances which control arterial BP, we finally examined effects of omentin on NA-induced increases of BP in an NO synthase inhibitor, L-NAME (80 mg/kg, 1 day)-treated Wistar rats. Omentin (18 µg/kg) failed to inhibit the NA (0.02–2 µg/kg)-induced increases of SBP in L-NAME-treated Wistar rats (at 2 µg/kg NA, Control; 20.5 ± 0.6 mmHg increase, n=11, Omentin; 11.3 ± 0.5 mmHg increase, n=16, L-NAME; 33.3 ± 5.1 mmHg increase, n=5, L-NAME + omentin; 31.2 ± 7.2 mmHg increase, n=8, Fig. 5).

Table 1. Baseline characteristics of normal Wistar rats or L-NAME-nitro-l-arginine methyl ester (L-NAME; 80 mg/kg, 1 day)-treated Wistar rats

<table>
<thead>
<tr>
<th></th>
<th>Body Weight (g)</th>
<th>Age (week)</th>
<th>HR (b.p.m.)</th>
<th>SBP (mmHg)</th>
<th>MBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal rat (n=7)</td>
<td>265.4 ± 27.2</td>
<td>6–10</td>
<td>362.4 ± 10.4</td>
<td>114.9 ± 2.7</td>
<td>91.9 ± 1.7</td>
<td>80.6 ± 2.0</td>
</tr>
<tr>
<td>+ L-NAME (n=9)</td>
<td>219.1 ± 22.2</td>
<td>6–10</td>
<td>344.0 ± 16.1</td>
<td>132.5 ± 4.0**</td>
<td>109.1 ± 2.8**</td>
<td>97.6 ± 2.5**</td>
</tr>
</tbody>
</table>

Body weight, heart rate [HR, beats per minutes (b.p.m.)], systolic blood pressure (BP) (SBP), mean BP (MBP) and diastolic BP (DBP) were shown. Data were expressed as mean ± SEM. **P<0.01 vs. Normal rat.
OMENTIN INHIBITS INCREASE OF RAT BP

In this study, we investigated the acute effects of omentin on BP in Wistar rats. Omentin alone did not alter BP of Wistar rats (Fig. 1). On the other hand, omentin significantly inhibited the NA-, Ang II- and dimorpholamine-induced increases in BP (Figs. 2–4). It was further shown that omentin inhibited the NA-induced increases in SBP more than DBP, while it inhibited the increases in DBP but not SBP induced by Ang II and dimorpholamine. It thus seems likely that omentin may preferentially inhibit the agonists-induced increases in DBP. Although we cannot explain the exact mechanism, it may be at least partly due to the vasodilating effect of omentin [15] since DBP is more likely affected by a vascular resistance. Nonetheless, it remains to be determined why omentin inhibited the increases in SBP induced by NA, but not Ang II and dimorpholamine. To the best of our knowledge, this is the first report demonstrating that omentin can regulate BP in rats.

It was reported that blood omentin level decreased in the obese subjects (310 ng/ml) compared with the lean subjects (370 ng/ml) [2]. It was also reported that blood omentin level decreased in the obese diabetic women (119 ng/ml) compared with the non-diabetic obese women (207 ng/ml) [10]. The concentration of omentin (18 µg/kg) that we used in this study was ~300 ng/ml when it was estimated that a total blood volume was ~12 ml in 200 g body weight rat. Considering the concentration of omentin (300 ng/ml) that we used in the previous in vitro and ex vivo experiments [5, 15, 16] as well as the human blood level, the concentration of omentin used in this study might be within the physiologic ranges.

In the present study, we found that omentin inhibited the NA-induced increases in BP. Our previous result demonstrating that omentin inhibited the NA-induced contraction in rat isolated aorta and mesenteric artery [15] fits to the present in vivo data. We also showed that omentin failed to inhibit the NA-induced increases of BP in the L-NAME-treated Wistar rats (Fig. 5). Since our previous studies demonstrated that omentin produced NO from vascular endothelial cells [16]...
and induced vasodilation in isolated blood vessels [15], it is suggested that the BP lowering effects of omentin were at least partly mediated via NO-mediated endothelium-dependent mechanism. While the data were not shown, we investigated effects of omentin on BP in spontaneously hypertensive rats (SHR) and observed that omentin failed to inhibit NA-induced increase of BP in SHR (n=7–8). Because previous reports demonstrated that NO-mediated endothelium-dependent relaxation was impaired in the artery from SHR [6, 11, 12], this observation may support the idea that the effect of omentin was endothelial NO-dependent. However, since our previous results suggested the NO-independent component of vasodilation by omentin in isolated blood vessel [15], we cannot completely exclude the possibility that omentin may reduce the agonists-induced increases in BP via NO-independent mechanisms. Furthermore, we cannot exclude the possibility that the increase of BP by L-NAME may mask the inhibitory effects of omentin. In addition, we cannot observe the direct BP lowering effects of omentin. A previous report demonstrated that platelet-derived growth factor (PDGF)-BB caused NO-mediated endothelium-dependent vasodilation in isolated blood vessels and thereby directly lowered BP of rats after intravenous injection [4]. While we cannot explain the exact reason for this discrepancy, it may be at least partly due to the relatively lower vasodilating effects of omentin [15] compared with PDGF-BB.

There is no report so far examining whether chronic omentin treatment may affect the BP of rats. We previously showed that omentin was anti-inflammatory in cultured vascular endothelial and smooth muscle cells [5, 16]. Since inflammation plays an important role in the progression of hypertension, it is presumed that chronic omentin treatment may protect the vascular wall from inflammation and thereby inhibit the development of hypertension. That is an important target for our future experiments.

Recently, the central nervous control of BP via adipocytokine attracts an attention in addition to peripheral control [1, 3]. However, there is no report so far examining the central BP control via omentin. In this study, we showed that
omentin inhibited the dimorpholamine-induced increases in BP. The BP increasing mechanisms of dimorpholamine may involve both the central actions and the non-central actions, including direct vascular effects and stimulation of catecholamine release [8]. It is thus necessary to clarify effects of intraventricularly injected omentin on BP.

In summary, we for the first time determined that omentin inhibited agonists-induced increases in BP at least in part via NO-mediated endothelium-dependent mechanism. Further experiments to determine chronic effects of omentin on BP are necessary.

REFERENCES

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