Table 2 Changes of parameters in blood and urine tests

	Before	*3 h*	*18 h*	*27 h*	*Recovery*
Total protein, g dl^{-1}					
Vehicle	6.7 ± 0.1		6.7 ± 0.1		6.7 ± 0.1
Cnt-AM	7.1 ± 0.2		6.8 ± 0.1		7.2 ± 0.2
PA-AM	7.2 ± 0.1		6.6 ± 0.2*		7.1 ± 0.3
Mature adrenomedullin, fmol ml^{-1}					
Vehicle	2.4 ± 0.1	3.2 ± 0.9	2.7 ± 0.6	3.1 ± 0.7	2.3 ± 0.2
Cnt-AM	2.0 ± 0.4	8.1 ± 1.1**	13.4 ± 1.8**	11.8 ± 2.6**	1.6 ± 0.3
PA-AM	2.8 ± 0.4	9.6 ± 2.0*	18.8 ± 3.5**	12.2 ± 2.4*	2.8 ± 0.8
Noradrenaline, pg ml^{-1}					
Vehicle	226 ± 35	290 ± 52	219 ± 29	242 ± 27	219 ± 25
Cnt-AM	297 ± 31	336 ± 21	374 ± 30	316 ± 25	341 ± 55
PA-AM	384 ± 81	428 ± 110	487 ± 146	469 ± 122	417 ± 99
cAMP, pmol ml^{-1}					
Vehicle	11.7 ± 0.7	11.3 ± 0.7	12.5 ± 1.0	12.4 ± 0.4	12.4 ± 0.8
Cnt-AM	14.4 ± 0.8	15.1 ± 0.6	15.6 ± 0.8	14.9 ± 0.9	14.0 ± 0.6
PA-AM	13.2 ± 1.0	14.6 ± 1.1	13.8 ± 1.1	13.6 ± 1.0	12.5 ± 1.4
cGMP, pmol ml^{-1}					
Vehicle	4.5 ± 0.7	3.5 ± 0.8	3.2 ± 0.4	3.9 ± 0.5	3.3 ± 0.3
Cnt-AM	3.4 ± 0.3	3.9 ± 0.5	4.5 ± 0.8	3.6 ± 0.4	3.3 ± 0.2
PA-AM	2.6 ± 0.4	4.7 ± 0.5**	3.6 ± 0.3*	4.4 ± 0.6**	2.7 ± 0.3
ANP, pg ml^{-1}					
Vehicle	23.6 ± 4.1	19.6 ± 2.0	17.0 ± 1.6	20.9 ± 1.5	17.1 ± 1.6
Cnt-AM	15.6 ± 2.8	23.9 ± 6.8	29.6 ± 7.4	29.6 ± 9.1	18.6 ± 4.4
PA-AM	23.4 ± 9.8	40.0 ± 12.0*	41.0 ± 7.6*	49.8 ± 9.2**	29.0 ± 10.4
BNP, pg ml^{-1}					
Vehicle	18.9 ± 5.0	17.7 ± 4.4	15.1 ± 3.3	13.2 ± 2.9	10.6 ± 2.1
Cnt-AM	16.6 ± 3.3	12.7 ± 2.8	31.1 ± 7.4	61.1 ± 15.2**	53.0 ± 12.4**
PA-AM	55.8 ± 36.2	42.9 ± 24.8	79.8 ± 37.6	131.3 ± 53.5*	115.7 ± 56.3*
ACTH, pg ml^{-1}					
Vehicle	26.0 ± 5.9		21.7 ± 3.6		22.3 ± 3.8
Cnt-AM	20.6 ± 1.9		18.7 ± 5.3		22.1 ± 3.2
PA-AM	18.5 ± 2.8		18.2 ± 3.9		20.6 ± 5.9
Cortisol. μg dl^{-1}					
Vehicle	8.4 ± 0.5		11.2 ± 1.6		11.9 ± 1.3
Cnt-AM	10.7 ± 1.2		14.9 ± 2.5		13.2 ± 1.6
PA-AM	16.7 ± 3.6		17.8 ± 4.6		15.6 ± 1.9
8-Isoprostane, pg per mg creatinine					
Vehicle	256 ± 62		169 ± 23		237 ± 60
Cnt-AM	197 ± 25		206 ± 25		168 ± 19
PA-AM	207 ± 41		252 ± 46		253 ± 54
8-OHdG, ng per mg creatinine					
Vehicle	10.1 ± 1.3		10.1 ± 1.3		9.6 ± 1.1
Cnt-AM	7.8 ± 1.6		7.6 ± 0.9		7.7 ± 0.5
PA-AM	11.9 ± 5.1		9.4 ± 2.0		12.5 ± 2.9

Abbreviations: ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; Cnt-AM, control group with adrenomedullin infusion; 8-OHdG, 8-hydroxydeoxyguanosine; PA, primary aldosteronism group.
*P<0.05, **P<0.01 *vs.* before.

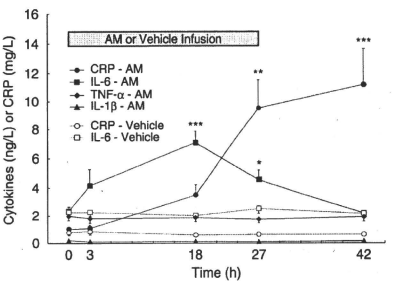

Figure 4 Changes in the serum concentration of cytokines and high-sensitivity CRP during infusion of adrenomedullin or vehicle. Data are summarized for all participants (control+PA group, n=12) and expressed as means ± s.e.m. *P<0.05, **P<0.01, ***P<0.0001, each *vs.* baseline. Abbreviations: IL-1β, interleukin-1β (high sensitivity); IL-6, interleukin-6; TNF-α, tumor necrosis factor-α (high sensitivity).

DISCUSSION

This is the only study to investigate long-term administration (over 24 h) of AM in humans.[14] The study put considerable strain on the participants, and hence the minimum number of participants required to achieve statistical significance was considered. Prolonged infusion of AM caused a hypotensive reaction, accompanied by improvements in arteriosclerotic markers (pulse wave velocity, augmentation index and elastic property of the carotid artery) in both the control group, with normal aldosterone levels, and in patients with PA. More importantly, we confirmed for the first time that AM infusion suppressed aldosterone release, producing a normal range in patients with PA.

AM is located in the zona glomerulosa of the adrenal cortex and Conn's adenoma.[2–4] AM has a direct inhibitory effect on aldosterone release from adrenocortical cells and Conn's adenoma cells.[15] Previous human experiments have produced varied results on the effects of intravenous infusion of AM on aldosterone release.[8–12] Our study showed that suppression of aldosterone release by AM in the control group was significant but quite limited (Figure 3). A hypotensive reaction due to AM infusion was observed over a wide dosage range, but the suppressive effect of AM on aldosterone release was time and dose dependent, suggesting that there may be relatively high thresholds for suppression.[8,16] We used a 'moderate' amount of AM (2.5 pmol kg^{-1} min^{-1} or 15 ng kg^{-1} min^{-1}), which led to a significant decrease in aldosterone release after 3 h of infusion (Figure 3). In a previous report, a similar amount of AM (16 ng kg^{-1} min^{-1}), infused for 2 h, did not change renin or aldosterone release in healthy volunteers.[9] The dose of AM was increased to 32 ng kg^{-1} min^{-1} and infusion was continued for another 2 h: a vigorous increase in renin release was reported, but there were no changes in aldosterone.[9] A large dose of AM infusion caused strong hypotension and strongly stimulated renin release as well as sympathetic nervous activity.[8] This may have interfered with the suppressive effect on aldosterone release. AM administration stimulates renin release.[8–12] On the other hand, AM can partially, but not completely, suppress increases in aldosterone induced by angiotensin II in humans.[17] In PA patients, renin activity is extremely suppressed, suggesting that AM could mediate essential aldosterone suppression. Under the conditions studied here

(2.5 pmol kg^{-1} min^{-1} for 3 h), AM may be useful as an alternative renin-stimulating (and aldosterone-suppressing) test for PA detection. In addition, it is important to elucidate the suppressive mechanism of AM because the lower aldosterone concentration in blood that results could benefit the cardiovascular system.

In this study, the plasma concentration of AM in PA patients was increased (Table 1). We and one other research group have previously reported this phenomenon.[18,19] The underlying mechanism remains to be elucidated: there may be a mutual relationship between aldosterone and AM. Aldosterone stimulates AM production in rat aortic adventitia or cardiac fibroblasts; increased AM, in turn, regulates the proliferative action of aldosterone in those cells.[5,6] Increased levels of AM were able to suppress blood pressure and aldosterone release in PA patients (Figures 2 and 3). AM may counteract or buffer the impact of hyperaldosteronism; however, AM stimulates or maintains cell proliferation in the adrenal zona glomerulosa as well as Conn's adenoma cells.[4,20,21] Letizia *et al.*[19] reported that the plasma level of AM was positively related to the tumor size of the adenoma in PA. It is highly probable that AM modulates the pathophysiological condition of PA, but further study is required to elucidate the participation of AM in PA.

AM administration caused several alterations in the humoral factors measured (Table 2). In particular, ANP was significantly increased, accompanied by continuous increases in cGMP, but only in PA patients. AM did not affect ANP or BNP levels in normal subjects or in patients with hypertension or heart failure.[9,10,12] The ANP-stimulating effect in PA patients is interesting, although the mechanism is unclear. ANP inhibits aldosterone secretion and is considered to be a key factor in aldosterone escape (or aldosterone breakthrough).[22,23] Thus, increased ANP may participate in the suppression of aldosterone release in PA. However, aldosterone-producing adenomas do not have a receptor for ANP and ANP did not suppress aldosterone release from the adenoma.[24] In addition, ANP infusion did not suppress aldosterone release in patients with PA.[25] The AM-induced ANP increase does not seem to be related to aldosterone suppression in PA by AM. ANP increased during AM infusion, whereas BNP was increased in both groups during the late phase of the experiment (Table 2). AM has a cAMP-dependent and -independent positive inotropic effect on myocardium.[26,27] In addition to the decrease in cardiac afterload induced by vasodilation, cardiac output was markedly increased by AM administration.[9–12] The cumulative increase in BNP may reflect cardiac overload induced by prolonged infusion of AM. Although none of the participants experienced adverse events, cardiac overload must be carefully avoided during longer term application of AM. AM has diuretic and natriuretic effects,[10–12] and AM administration increased ANP and BNP levels in this study; however, we did not study the diuretic and natriuretic effects of these factors. Participants would not agree to use an additional balloon catheter for accurate urine collection. Total saline infusion was only 135 ml over 27 h, so it should not have influenced urine samples in this experiment. Because total protein was decreased after AM administration (Table 2), significant decreases were measured in PA patients, while serum levels of sodium were not altered (control: 141.1 ± 1.1, 141.4 ± 0.8 and 140.9 ± 0.8 mEq l^{-1}; PA: 143.6 ± 0.5, 144.4 ± 0.5 and 143.4 ± 0.4 mEq l^{-1} before, during and after AM administration, respectively). The decreases in total protein may be due to vasodilation induced by AM. Decreases in hematocrit have been previously reported,[28] suggesting some hemodilution.

This is the first report suggesting that prolonged administration of AM can induce CRP production through IL-6 in humans. AM is known to inhibit strong inflammation, such as sepsis.[29] However, AM can exert both pro-inflammatory and anti-inflammatory effects, and it stimulates IL-6 production in macrophages.[30] As yet, there are no data on the effect of AM on CRP production in humans who do not exhibit accelerated inflammation. The time course of IL-6 and CRP changes (Figure 4) and the close relationship between both factors (relationship between maximum changes of CRP and IL-6; r=0.64, P=0.034) in the present study strongly suggest an interaction of IL-6 with CRP. Isumi *et al.*[31] reported that the stimulatory effect of AM on *IL-6* gene transcription took place immediately, reached a plateau within 30 min, and then decreased gradually. The short-term increase in IL-6 in the present study is compatible with the acute-phase stimulant nature of AM. However, IL-6 is a key factor in the regulation of CRP production in the liver, the main source of serum CRP.[31] As CRP has a higher rate of increase and longer half-life (about 19 h) in comparison with IL-6 or AM,[32] the extended increase in CRP observed in this study was not unexpected.

In addition to modulating the vascular tonus, AM influences the progression of atherosclerosis[1] and stimulates production of IL-6.[30] Moreover, AM and inflammatory markers, such as IL-6 and CRP, are elevated in patients with hypertension, CHD and peripheral artery disease: positive correlations between AM and IL-6 or CRP[1,33] have been reported. AM production is most likely stimulated in the vasculature, as a reaction to a variety of stress-related factors, including hormones, mechanical stresses, metabolic factors and cytokines.[34] In addition to inflammation, many kinds of stimuli to blood vessels would influence AM levels and consequently CRP. Although AM is merely one factor regulating CRP production, this intimate relationship of AM with CRP via IL-6 may represent a pivotal role for AM in a mechanism linking serum CRP and vascular alterations. However, prolonged elevation of AM in PA patients did not completely correlate with CRP elevation in PA patients (Table 1). Further studies to confirm the roles of AM in the regulation of CRP levels under various conditions are required.

In conclusion, we have shown that prolonged administration of AM can normalize blood pressure and aldosterone release in PA. The ability of AM to suppress autonomous release of aldosterone in PA seems to be substantial when compared with the suppressive properties of ANP in PA that are unrelated to aldosterone. AM may be an important modulator in PA, and AM seems to be a unique tool and potential target for research into aldosterone release in PA. In addition, AM mildly stimulates CRP production at baseline, through IL-6 or non-stimulated inflammatory conditions in humans. This pathway might participate in CRP elevation in cardiovascular disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Reciprocal Contribution of Pentraxin 3 and C-Reactive Protein to Obesity and Metabolic Syndrome

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Pentraxin 3 (PTX3) is an acute-phase protein that shares structural homology with C-reactive protein (CRP). PTX3 is produced in macrophages, endothelial cells, and adipocytes in response to inflammatory stimuli, whereas hepatocytes are the main source of CRP. Because obesity and metabolic syndrome (MetS) are considered chronic inflammatory states, PTX3 might be involved in the pathogenesis of obesity and MetS as well as CRP. Levels of CRP correlated positively with body weight, BMI, waist circumference (WC), fasting plasma glucose and interleukin (IL)-6, and negatively with high-density lipoprotein cholesterol and adiponectin in healthy males. In contrast, PTX3 correlated positively with adiponectin, and negatively with body weight, BMI, WC, and triglyceride. Plasma CRP significantly increased, whereas plasma PTX3 significantly decreased with increasing BMI. Plasma CRP and PTX3 levels were significantly higher and lower, respectively, in individuals who had more than one MetS component compared with those who had none. In conclusion, PTX3 and CRP antagonistically participate in the development of obesity or MetS.

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Obesity and metabolic syndrome (MetS) should be considered as chronic inflammatory states. C-reactive protein (CRP) belongs to the pentraxin family and it is a plasma marker of acute and chronic inflammation. It is mainly produced in the liver in response to inflammatory mediators, particularly interleukin (IL)-6 (ref. 1). Levels of CRP are elevated in obese persons, and can predict future cardiovascular risks (2). Pentraxin 3 (PTX3) is structurally related to other proteins of the pentraxin family but it is distinct from the classical pentraxins such as CRP (3). Various cells including macrophages, endothelial cells, smooth muscle cells, white blood cells, and adipocytes produce PTX3 in response to inflammatory cytokines such as IL-1 and tumor necrosis-α (4–7). Plasma PTX3 levels are positively associated with adhesion molecules and endothelial dysfunction in patients with chronic kidney disease (8,9), and rapidly increase in patients with acute coronary syndrome (10,11). However, the relationship between PTX3 and chronic inflammatory states such as obesity or MetS remains unknown. Because different cells within adipose tissue might produce PTX3 (7), it could be a more sensitive marker of inflammation caused by obesity and MetS than CRP. Here, we examined plasma PTX3 levels in 226 nonmedicated, healthy males to assess relationships between PTX3 and BMI as well as MetS components.

METHODS AND PROCEDURES

Participants

We enrolled 226 apparently healthy males (range 26–82 years) who presented at a public health center associated with Miyazaki Social Insurance Hospital for an annual routine health check and who provided written informed consent to participate in the study. None of them were under medication including nonsteroidal anti-inflammatory drugs and other over-the-counter drugs such as aspirin. We measured height, body weight, waist circumference (WC), blood pressure, and blood parameters. Smoking status was scored based on numbers of cigarettes smoked per day as: nonsmoker, 0; 1–9 cigarettes, 1; 10–19 cigarettes, 2; and ≥20 cigarettes, 3. The participants were assigned to group 1, 2, 3, or 4 based on BMI of 18–22; 22–25; 25–28, and 28–43, respectively. The participants were also classified according to the number of MetS components as follows: (i) none, (ii) one, (iii) two, and (iv) three or four. The MetS components were defined as: (i) WC of ≥85 cm measured at the level of the navel, (ii) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, (iii) triglyceride ≥150 mg/dl or high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, and (iv) fasting plasma glucose ≥110 mg/dl. The Ethical Committee of Miyazaki Social Insurance Hospital approved the study.

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Assays

Plasma levels of tumor necrosis-α (intra- and interassay coefficients of variation (CVs), 5.2 and 7.3%, respectively), adiponectin (intra- and interassay CV, 4.7 and 6.8%, respectively), and IL-6 (intra- and interassay CV, 4.2 and 6.4%, respectively) were determined using ELISA kits from R&D Systems (Minneapolis, MN). Plasma levels of IL-1β (intra- and interassay CV, 10.0 and 12.0%, respectively) and PTX3 (intra- and interassay CV, 4.1 and 4.3%, respectively) were determined using ELISA kits from RayBiotech (Norcross, GA) and Perseus Proteomics (Tokyo, Japan), respectively. Details of the PTX3 assay including the detection limit have already been published (10). Plasma CRP levels (intra- and interassay CV, 1.3 and 2.8%, respectively) were measured using high-sensitivity assays (Denka Seiken, Japan). All other plasma data were conventionally measured at Miyazaki Social Insurance Hospital.

Statistical analyses

All results are expressed as means ± s.e.m. We determined statistical differences among multiple groups using ANOVA, and pairwise differences between two groups using the Bonferroni test. Multiple groups were compared using analysis of covariance when adjustment for BMI was required. Relationships between CRP or PTX3 and other variables were determined by multiple regression analysis to adjust for age and smoking status. The normality of distribution for each parameter was confirmed using the Shapiro–Wilk analysis. All statistical calculations were performed using the Excel Tokei software series (Esumi, Tokyo, Japan.).

RESULTS

Characteristics of the participants

Table 1 shows the anthropological, clinical, and biochemical features of the participants.

Table 1 Clinical and biochemical characteristics of subjects

Parameter	Means ± s.d.
Age (years)	48.0 ± 9.6
BW (kg)	73.4 ± 12.5
Height (cm)	170.4 ± 6.4
BMI (kg/m^2)	25.2 ± 3.8
WC (cm)	88.4 ± 9.5
SBP (mm Hg)	121 ± 18
DBP (mm Hg)	78 ± 12
T-CHO (mg/dl)	208 ± 35
HDL-C (mg/dl)	55 ± 12
TG (mg/dl)	165 ± 166
FPG (mg/dl)	102 ± 27
TNF-α (pg/ml)	0.88 ± 0.58
Adiponectin (μg/ml)	4.03 ± 2.86
IL-6 (pg/ml)	1.74 ± 1.58
IL-1β (pg/ml)	1.61 ± 1.66
CRP (mg/dl)	0.12 ± 0.17
PTX3 (ng/ml)	1.79 ± 0.89

BW, body weight; CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; PTX3, pentraxin 3; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; WC, waist circumference.

Relationships between CRP or PTX3 and other parameters

Plasma CRP correlated positively with body weight, BMI, WC, fasting plasma glucose, and IL-6, and negatively with HDL-C and adiponectin levels after adjustment for age and smoking status. On the other hand, plasma PTX3 correlated positively with adiponectin and negatively with BMI, WC, and triglyceride (**Table 2**).

Plasma PTX3, CRP, adiponectin, and IL-6 levels among BMI groups

The numbers of individuals in groups 1, 2, 3, and 4 classified according to BMI were 39, 76, 65, and 46, respectively. Plasma CRP ($P < 0.05$) and IL-6 ($P < 0.05$) levels significantly increased with increasing BMI, whereas plasma PTX3 ($P < 0.01$) and adiponectin ($P < 0.01$) levels significantly decreased with increasing BMI (**Figure 1**).

Plasma PTX3, CRP, adiponectin, and IL-6 among groups classified by the number of MetS components

The numbers of individuals with none (Control), one (group 1), two (group 2) and three or four (group 3) MetS components were 40, 65, 80, and 41, respectively. Plasma PTX3 levels in groups 1 (1.63 ± 0.09 ng/ml), 2 (1.73 ± 0.10 ng/ml), and 3 (1.68 ± 0.09 ng/ml) were significantly lower than control values (2.29 ± 0.19 ng/ml) ($P < 0.01$). However, groups 1, 2, and 3 did not significantly differ. The differences in plasma PTX3 between the control group and groups with Mets components persisted even after adjustment for BMI. Likewise, plasma adiponectin levels in groups 1 (4.21 ± 0.37 μg/ml), 2 (3.42 ± 0.24 μg/ml), and 3 (2.88 ± 0.25 μg/ml) did not significantly differ but were all significantly lower than those of the Control group (6.16 ± 0.58 μg/ml; $P < 0.01$). On the other hand, plasma CRP levels in groups 1 (0.119 ± 0.016 mg/dl), 2 (0.124 ± 0.017 mg/dl), and 3 (0.120 ± 0.018 mg/dl) did not significantly differ, but were significantly higher than those of the Control (0.071 ± 0.021 mg/dl; $P < 0.05$). Plasma IL-6 and CRP levels were similar (data not shown).

DISCUSSION

CRP is mainly produced in hepatocytes in response to IL-6, whereas various types of cells including adipocytes locally and directly produce PTX3 (4,7,12). Given the cellular sources of PTX3 and the components of adipose tissue, we postulated that the PTX3 level would increase with chronic inflammation caused by obesity and MetS. However, the present findings suggested that PTX3 and CRP are inversely involved in obesity and MetS, which contradicted this hypothesis. An inverse relationship between plasma PTX3 and BMI in healthy individuals (13), patients with chronic kidney disease (9) and those on hemodialysis (14) has recently been reported. Malnutrition is also associated with an increased plasma PTX3 level in patients with chronic kidney disease (8) and in those on hemodialysis (14). Bosutti *et al.* demonstrated that plasma PTX3 levels inversely correlate with fat mass and that less body fat means decreased and increased plasma levels of CRP and PTX3, respectively (15). Our findings of reciprocal changes

Table 2 Correlations between CRP and PTX3 and other factors after adjustment for age and smoking status

	CRP		PTX3	
	Coefficient	*P* value	Coefficient	*P* value
BW	0.1766	0.0096†	−0.1693	0.0120*
Height	−0.0458	0.5420	−0.0355	0.6325
BMI	0.2079	0.0018†	−0.1628	0.0139*
WC	0.2238	0.0008†	−0.1706	0.0099†
SBP	0.0412	0.5632	−0.0621	0.3777
DBP	0.1288	0.0593	−0.0879	0.1935
T-CHO	0.0765	0.2538	−0.0946	0.1527
HDL-C	−0.1426	0.0348*	0.1089	0.1034
TG	−0.0194	0.7765	−0.1897	0.0046†
FPG	0.1358	0.0445*	−0.0404	0.5465
TNF-α	0.0682	0.3186	−0.0356	0.5989
Adiponectin	−0.1771	0.0111*	0.1572	0.0227*
IL-6	0.3953	0.0000†	−0.0009	0.9890
IL-1β	−0.0804	0.2315	−0.0586	0.3781
CRP	—	—	0.0463	0.4849
PTX3	0.0475	0.4849	—	—

BW, body weight; CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; PTX3, pentraxin 3; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; WC, waist circumference.
*$P < 0.05$; †$P < 0.01$.

between PTX3 and CRP in obesity are in accordance with these reports.

Expression of the *PTX3* gene is stimulated by HDL-C in cultured human umbilical vein and aortic endothelial cells (16). Thus, the decrease in plasma HDL-C might be responsible for the lower PTX3 levels in obese individuals or in those with MetS. However, the cause of the decreased PTX3 level in obesity or MetS cannot be explained simply by a relationship between PTX3 and HDL-C, because we could not identify a positive association between them. We found that the PTX3 level positively correlated with adiponectin, an adipocyte-specific plasma protein with antiatherosclerotic properties. Systemic clinical hypoadiponectinemia is closely associated with obesity, type 2 diabetes and coronary artery disease. The increased oxidative stress in adipose tissue that accumulates in obesity results in decreased adiponectin production (17). A similar oxidative stress-related mechanism might also, at least in part, affect PTX3 production in adipocytes of obese individuals.

Whether plasma PTX3 increases to protect against local inflammation or to exacerbate the expansion of tissue damage remains unknown. However, mice with induced *PTX3* genes are more resistant to endotoxic shock induced by lipopolysaccharide and to polymicrobial sepsis caused by cecal ligation and puncture (18). Additionally, PTX3-deficient mouse models of acute myocardial infarction caused by coronary artery ligation developed more myocardial damage, and this

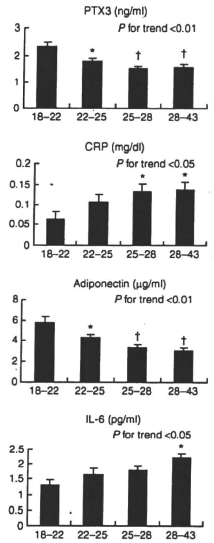

Figure 1 Plasma levels of pentraxin 3, C-reactive protein, adiponectin, and interleukin-6 in apparently healthy males. Participants were assigned to the following groups based on BMI as follows: group 1, 18–22; group 2, 22–25; group 3, 25–28; and group 4, 28–43. Data are shown as means ± s.e.m. *$P < 0.05$ and †$P < 0.01$ vs. 18–22 group. Plasma CRP ($P < 0.05$) and IL-6 ($P < 0.05$) levels significantly increased with increasing BMI, whereas plasma PTX3 ($P < 0.01$) and adiponectin ($P < 0.01$) levels significantly decreased with increasing BMI. Although plasma PTX3 levels in groups 2, 3, and 4 did not significantly differ, all of them were significantly lower than those in group 1. The findings for adiponectin were similar to those of PTX3. Plasma CRP levels in groups 3 and 4 did not significantly differ, but both were significantly higher than those in group 1. Plasma IL-6 was significantly higher in group 4 than in group 1. PTX3, pentraxin 3; CRP, C-reactive protein; IL-6, interleukin-6.

phenotype was reversed by exogenous PTX3 (19). Taken together, current evidence indicates that PTX3 plays tissue protective and anti-inflammatory roles. Both PTX3 and CRP can bind C1q, the recognition subunit of the classical complement pathway, which might be activated by CRP after binding to C1q and such binding might also contribute to tissue damage. Although PTX3 enhances binding between apoptotic cells and C1q, it inhibits CH50 and C1q hemolytic activity when incubated with normal human serum or human C1q, suggesting that PTX3 inhibits the classical complement pathway (20). These findings indicate that decreased plasma PTX3 levels in obese individuals or those with MetS accelerate chronic inflammation and atherosclerosis. In addition, complement fraction C1q is structurally homologous with adiponectin and interaction with PTX3 and adiponectin should be considered. However, this notion also requires further investigation.

Like CRP, PTX3 belongs to the pentraxin family and it is considered a surrogate marker of disease activity at sites of inflammation. Although PTX3 and CRP are weakly and positively related without significance, both markers reciprocally change in individuals who are obese or have MetS. Although HDL-C stimulation of the *PTX3* gene or PTX3 inhibition of the plasma complement pathway might account for the paradoxical change in PTX3, further study is needed for clarification. In conclusion, the plasma profiles of PTX3 and CRP in 226 nonmedicated males indicated that these proteins inversely participate in the development of obesity or MetS.

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DISCLOSURE

M.S. was a full-time employee of Perseus Proteomics Inc. Other authors declared no conflict of interest.

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