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Elevated plasma levels of soluble (pro)renin receptor in patients with obstructive sleep apnea syndrome: Association with polysomnographic parameters

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ABSTRACT

(Pro)renin receptor ((P)RR) is a specific receptor for both renin and its precursor prorenin. (P)RR was shown to be involved in pathophysiology of cardiovascular and renal diseases. Soluble (pro)renin receptor (s(P)RR), which is generated by furin from full length (P)RR, is present in blood. The aim of the present study is to clarify the association of plasma s(P)RR levels and the severity of OSAS. Plasma levels of s(P)RR were measured by ELISA in 58 male patients diagnosed as OSAS based on polysomnography, and 14 age-matched male control subjects. Blood samples were obtained at 6:00 a.m. just after overnight polysomnography. Plasma s(P)RR levels were significantly higher in patients with OSAS (9.0 ± 2.0 ng/mL, mean ± SD) than in control subjects (7.4 ± 1.5 ng/mL) ($P = 0.0026$). Plasma s(P)RR levels showed a significant negative correlation with % stage rapid eye movement (REM) sleep ($r = -0.377$, $p < 0.005$), and significant positive correlations with % stage 1 ($r = 0.374$, $p < 0.005$), arousal index ($r = 0.341$, $p < 0.01$), apnea hypopnea index (AHI) ($r = 0.352$, $p < 0.01$) and desaturation index ($r = 0.302$, $p < 0.05$). In 12 OSAS patients with AHI ≥20, plasma levels of s(P)RR were studied after 3-month treatment with nasal continuous positive airway pressure (nCPAP). Plasma s(P)RR levels were significantly decreased after the nCPAP treatment ($p = 0.0016$). The present study has shown for the first time elevated plasma s(P)RR levels in patients with OSAS. Plasma s(P)RR levels were associated with the severity of OSAS. Soluble (P)RR may serve as a plasma marker reflecting the severity of OSAS.

1. Introduction

(Pro)renin receptor ((P)RR) is a specific receptor for renin and prorenin [27,29,30]. Prorenin is an enzymatically inactive precursor of renin, and is present in blood at levels nine times greater than those of renin. Plasma concentrations of prorenin are increased in patients with diabetes mellitus and may be a marker of microvascular diabetic complications [23]. Prorenin binds to (P)RR and becomes active in converting angiotensinogen to angiotensin I by conformational change. In addition, (P)RR has various biological functions independent of the renin-angiotensin system (RAS) [27,30]. The binding of (pro)renin to (P)RR increased proliferation and/or hypertrophy of cells including vascular smooth muscle cells and mesangial cells [13,22,36], via the activation of the ERK1/2 and Akt, epidermal growth factor receptor [22], and TGF-β expression [13]. Several studies using animal models have suggested that (P)RR has important roles in the pathogenesis of vascular complications of diabetes mellitus, hypertension and other cardiovascular diseases [15,16].

(P)RR consists of 350 amino acids with single transmembrane domain [27,29,30]. Full length (P)RR is cleaved by furin into soluble (P)RR (s(P)RR) consisting of the extracellular domain, and a truncated form of (P)RR consisting of transmembrane and intracellular domain [7]. A truncated form of (P)RR was found to be associated with vacuolar-type H^+-ATPase (V-ATPase) [27]. V-ATPase is a large multi-subunit, membrane-associated protein complex that carries out active transport of protons across the membrane, thereby affecting the acidic environment of intracellular compartments and of the extracellular space. The complex formation of (P)RR and V-ATPase is essential for cell survival of murine cardiomyocytes [20] and podocytes [32]. The (P)RR and V-ATPase is also involved in the Wnt/β-catenin pathway, which is essential for stem cell biology, embryonic development and diseases [2,8].

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Table 1
Clinical characteristics of 58 patients with obstructive sleep apnea syndrome (OSAS) and 14 control subjects.

	Control ($n = 14$)	OSAS ($n = 58$)	p-Value
Age (year)	49.9 ± 14.0	56.9 ± 15.6	NS
BMI (kg/m^2)	23.2 ± 1.8	27.2 ± 6.2	$p < 0.05$
BUN (mg/dL)	13.6 ± 2.2	13.5 ± 3.4	NS
Cre (mg/dL)	0.8 ± 0.3	1.1 ± 1.8	NS
HbA1c (%)	5.3 ± 0.4	5.5 ± 0.3	$p < 0.05$
IRI (mg/dL)	7.1 ± 3.9	8.5 ± 5.3	NS
BG (mg/dL)	91.0 ± 8.3	93.7 ± 9.7	NS
HOMA-R	1.6 ± 0.9	2.0 ± 1.2	NS
Blood pressure (6 a.m.)			
Systolic (mmHg)	122.0 ± 13.1	131.0 ± 19.1	NS
Diastolic (mmHg)	75.6 ± 14.2	78.3 ± 15.3	NS
Mean (mmHg)	91.0 ± 13.2	95.9 ± 14.7	NS
Blood pressure (13 p.m.)			
Systolic (mmHg)	122.8 ± 10.9	128.8 ± 19.6	NS
Diastolic (mmHg)	76.0 ± 10.5	75.1 ± 15.4	NS
Mean (mmHg)	91.6 ± 9.6	93.0 ± 14.7	NS
ESS	5.1 ± 4.1	9.0 ± 5.3	$p < 0.05$
Sleep study			
TST (mins)	421.3 ± 75.6	405.4 ± 87.2	NS
Sleep efficiency (%)	74.5 ± 13.0	70.6 ± 14.4	NS
% Stage 1 (%)	14.6 ± 10.1	32.6 ± 18.9	$p < 0.005$
% Stage 2 (%)	55.1 ± 8.4	45.5 ± 16.3	$p < 0.05$
% Stage 3 + 4 (%)	11.0 ± 6.1	4.5 ± 5.6	$p < 0.0005$
% Stage REM sleep (%)	19.3 ± 5.0	17.3 ± 6.1	NS
Arousal index (events/h)	10.3 ± 5.9	29.7 ± 18.9	$p < 0.0005$
AHI (events/h)	3.1 ± 1.4	43.1 ± 25.2	$p < 0.0001$
SpO_2 mean (%)	95.2 ± 1.1	91.9 ± 3.4	$p < 0.001$
SpO_2 minimum (%)	88.9 ± 3.8	77.4 ± 8.6	$p < 0.0001$
Desaturation index (events/h)	5.2 ± 7.1	39.1 ± 23.9	$p < 0.0001$

Data are shown as mean ± S.D. NS, not significant.
BMI, body mass index; BUN, blood urea nitrogen; Cre, serum creatinine; HbA1c, glycosylated hemoglobin; IRI, immunoreactive insulin; BG, blood glucose; HOMA-R, homeostasis model assessment as an index of insulin resistance; ESS, Epworth Sleepiness Scale; TST, total sleep time; REM, rapid eye movement, SpO_2, oxygen saturation of peripheral artery; AHI, apnea hypopnea index.

Soluble (P)RR is present in human plasma [7,25], and plasma concentrations of s(P)RR were elevated in patients with chronic renal failure [10]. Increased plasma concentrations of s(P)RR at early pregnancy predicted a subsequent elevation in blood pressure [42], and the development of gestational diabetes mellitus later in pregnancy [43]. By contrast, plasma sPRR concentrations were independent of plasma concentrations of renin, prorenin and aldosterone in healthy subjects and in patients with contrasted degrees of RAS activity [28].

Obstructive sleep apnea syndrome (OSAS) is a common disease which affects 2–4% of total population [46]. Risk factors of OSAS include obesity [21], hypertension [33], diabetes mellitus [34], and the enlarged volume of the soft tissue structures surrounding the upper airway [37]. There has been accumulating evidence that indicates alteration in the endocrine system in patients with OSAS, such as the RAS [4,26], atrial natriuretic peptide [24], endothelin-1 [9], vascular endothelial growth factor [17], erythropoietin [17,44] and orexin-A [31,35]. It was reported that OSAS patients showed elevated aldosterone excretion and plasma aldosterone levels, with suppressed plasma renin activity (PRA) [26], whereas another study showed no significant changes in plasma aldosterone levels [39]. Plasma s(P)RR concentrations have not been studied in patients with OSAS.

The aim of the present study is therefore to study plasma s(P)RR concentrations in patients with OSAS, and to clarify correlation of the plasma levels with the severity of OSAS.

2. Materials and methods

2.1. Study participants

We included 78 Japanese male subjects who visited the Division of Behavioral Sleep Medicine, Iwate Medical University Hospital for evaluation of possible OSAS with overnight polysomnography (PSG) because of snoring and/or daytime sleepiness. Two patients with rapid eye movement (REM) sleep behavior disorder (RBD) and 18 patients with glycosylated hemoglobin (HbA1c) levels of 6.2 or more, or with treatment for diabetes mellitus were excluded from the study. Finally, 58 patients with OSAS and 14 age-matched control subjects without OSAS on PSG were included in the study. These control subjects did not have drug-resistant hypertension, diabetes mellitus, kidney disease, chronic heart disease, chronic obstructive pulmonary disease, Cheyne–Stokes respiration syndrome, or sleep disorders (Table 1, Fig. 1).

This study was approved by the Ethics Review Boards of Iwate Medical University and Tohoku University Graduate School of Medicine, and written informed consent was obtained from all subjects.

PSG testing was performed between 8:00 p.m. and 6:00 a.m. by using SomnoStar-α (SensorMedics, Yorba Linda, CA, USA) in a designated examination room equipped with an air conditioning system at the Iwate Medical University Hospital following the criteria of the American Academy of Sleep Medicine [14]. The severity of subjective excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [18].

2.2. Measurement of plasma s(P)RR levels

Blood samples were collected from cubital veins using aprotinin-added vacuum blood collection tubes at approximately 6:00 a.m. after undergoing PSG. Plasma was immediately isolated and stored at −60 °C until measurement.

Plasma s(P)RR levels were measured by the ELISA method (Immuno-Biological Laboratories Co. Ltd., Fujioka, Japan) [10,25,28,42,43] following the manufacturer's protocols in