Modulation of Plasma Sphingosine-1-Phosphate Levels via Dietary Salt Intervention in Chinese Adults:an Intervention Trial

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Research

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Abstract

Background Sphingosine-1-phosphate (S1P), a pleiotropic bioactive sphingolipid metabolite, is involved in various pathophysiological processes,including blood pressure regulation. Salt is a crucial factor for blood pressure modulation,especially in salt-sensitive individuals who may develop earlier, more severe subclinical target organ damage than salt-resistant individuals.However, the relationships among salt intake, circulating S1P levels, and blood pressure changes are unknown. Thus, we conducted this intervention trial to explore the effect of dietary salt intake on plasma S1P levels and examine the relationship between S1P and blood pressure in Chinese adults.

Methods Forty-two participants (aged 18–65 years) were recruited from a rural community in Shaanxi, China. All participants first maintained their normal diet for 3 days, then sequentially ate a low-sodium diet (3.0 g/day NaCl) for 7 days, followed by a high-sodium diet (18.0 g/day NaCl) for 7 days. We assessed their plasma S1P concentrations on the last day of each intervention phase by liquid chromatography–tandem mass spectrometry. We classified the subjects who demonstrated at least a 10% increase in mean arterial pressure upon transitioning from a low-salt to a high-salt diet as salt-sensitive and the others as salt-resistant. Differences in repeated measures were analyzed by repeated-measures analysis of variance.

Results Plasma S1P levels decreased significantly from the baseline to low-salt diet period and increased from the low-salt tohigh-salt diet period. We observed this response in both salt-sensitive and salt-resistant individuals. Plasma S1P levels positively correlated with 24-hour urinary sodium excretion, but not 24-hour urinary potassium excretion. In line with plasma S1P level responses to salt intervention, systolic blood pressure and mean arterial pressure decreased from the baseline to low-salt diet period and increased from the low-salt to high-salt period.Systolic blood pressure positively correlated with plasma S1P; the correlation was stronger in salt-sensitive individuals than in salt-resistant individuals.

Conclusion Low-salt intervention decreased plasma S1P levels, whereas high-salt intervention reversed this changein Chinese adults. This finding provides evidence that salt moderation may be a high-efficiency, low-cost intervention for regulating circulating S1P levels, with implications for salt-induced blood pressure modulation.

Trial registration:

NCT02915315.Registered 27 September,2016,http://www.clinicaltrials.gov

Introduction

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite that mainly acts as an intracellular messenger by directly binding to its G protein-coupled receptors (S1P receptor [S1PR] subtype 1–5)[1, 2]. It is involved in various cellular functions and biological systems, including the cardiovascular system[3–5]. S1P signaling contributes to cardiac remodeling and protects cardiomyocytes from hypoxic and

ischemia/reperfusion injury[6–8]. A growing body of literature suggests that it plays an essential role in vascular endothelial and smooth muscle cell functions, through which it modulates vascular tone and blood pressure (BP)[9–11]. Thus, manipulation of S1P signaling will offer new therapeutic approaches to cardiovascular diseases. Several pharmacological S1PR agonists and antagonists are available; they serve as important tools for targeting different cells and systems. Cantalupo et al. found that the S1PR1 selective agonist SEW2871 restores normal BP in hypertensive mice[12]. The administration of FTY720, a modulator of S1PRs, for a period of 10 days raised the BP of rats in a dose-dependent manner, whereas a single dose of FTY720 further increased the BP of spontaneously hypertensive rats at 24 hours post-administration[13, 14].

However, the levels of circulating S1P are relatively high (0.1–1 μM) compared to the potency of S1P on S1PR1[15]. Only a few studies have focused on the effects of circulating S1P on BP modification using in vivo models, with controversial results. Generation of S1P in response to anandamide reduce mean arterial pressure in mice[16],but Forrest et al. found that continuous infusion of S1P was predominantly associated with an increase in BP in both rats and mice[17]. Furthermore, although there are multiple S1PR intervention approaches, there are no simple and effective approaches to regulate the equally important circulating S1P levels.

Salt intake is thought to be the most critical environmental factor for BP regulation; nearly one-half of essential hypertensive patients have salt sensitivity[18], which is accompanied by risk of earlier, more severe target organ damage[19]. Many studies have demonstrated that salt overload strongly contributes to the development and progression of hypertension[20], whereas salt restriction plays an essential role in BP control and is recommended by guidelines worldwide[21–23]. Notably, S1P has recently been identified as a novel lipid diuretic factor that participates in sodium metabolism in the renal medulla[24]. This evidence emphasizes a possible role for S1P in the response to salt intervention and salt-induced BP change.

Thus, we investigated plasma S1P responses to salt intervention in Chinese adults and examined the relationship between S1P levels and BP to identify a potential intervention for regulating circulating S1P levels and a novel target to determine the mechanism of salt-induced BP change.

Methods

Subjects

Forty-two subjects (aged 18–65 years) with similar dietary habits were recruited from a rural community in Shaanxi, China. We used a standard questionnaire administered by professional staff to collect basic demographic information (age, sex, education, ethnicity, occupation, physical activity, cardiovascular disease-related history, and physical examination findings). Hypertension was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, and/ora history of hypertension with current use of anti-hypertensive medications.

The exclusion criteria included: stage 2 hypertension; secondary hypertension; history of cardiovascular disease, chronic liver disease, chronic kidney disease, or diabetes; pregnancy; and alcohol abuse.

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Medical School, Xi'an Jiaotong University (Code: 2015-128). All participants provided signed informed consent. The trial registration number was NCT02915315 (http://www.clinicaltrials.gov), with a date of registration of 27September, 2016.

Dietary salt intervention and physical examination

The dietary intervention included a 3-day baseline diet characterized by habitual salt intake, followed by a 7-day low-salt intervention (51.3 mM sodium or 3.0 g NaCl per day), and then a 7-day high-salt intervention (307.8 mM sodium or 18.0 g NaCl per day). Prepacked salt was added to salt-free meals cooked by the study kitchen; participants ate their breakfast, lunch, and supper under the supervision of professional staff during the whole intervention period to ensure compliance with the intervention protocol. Any food that was not provided by study personnel was forbidden. Physical examinations, including height, weight, and waist circumference measurements, were conducted twice on the last day of each period.We measured brachial-ankle artery pulse wave velocity at the same time.

BP measurement and salt sensitivity definition

BP was measured by certified physicians using standard mercury sphygmomanometers according to the protocol recommended by the American Heart Association. Participants were instructed to sit in a resting position for more than 5 minutes after avoiding exercise; smoking; and alcohol, coffee, or tea consumption for at least 30 minutes before BP measurement. BP was measured 3 times at 1-minute intervals on each day of baseline observation and on the last 2 days of the low- and high-salt intervention periods; we recorded the mean value. The BP of each participant was measured by the same physician using the same sphygmomanometer to avoid observation variation. Mean arterial pressure (MAP) was calculated as MAP = (SBP/3) + (DBP × 2/3). Due to the lack of an authoritative consensus on the definition of salt sensitivity based on BP, we classified subjects who demonstrated at least a 10% increase in MAP between the low-salt and high-salt diets as salt-sensitive (SS) and the others as salt-resistant (SR)[25].

Biochemical analyses

Blood samples were obtained by venipuncture on the last morning of each intervention phase. Within 2 hours of collection, staff centrifuged the samples at 3,000 ×*g* for 10 min to separate EDTA plasma and serum, which were shipped to a central laboratory via standardized procedures where they were stored at −80°C until further analysis. We measured serum creatinine, uric acid, fasting serum glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels using an automatic biochemical analyzer (model 7600; Hitachi, Tokyo, Japan).

Plasma S1P

We measured plasma S1P levels by liquid chromatography–tandem mass spectrometry. We used a previously described protocol with minor modifications[26]. Plasma (100 μL) was deproteinated by the addition of methanol (400 μL). The internal standard D-erythro-C17-sphingosine-1-phosphate (10 μL, 10 μM; Avanti Polar Lipids, Alabaster, AL, USA) was used to correct for variations in sample preparation and instrument response. We cleared the extracts by centrifugation (5810R Eppendorf, 12,000 rpm, 10 min; Eppendorf, Wesseling-Berzdorf, Germany). We subjected the cleared extracts to reverse-phase chromatography on an Agilent Eclipse XDB C-18 analytical column (2.1 mm × 150 mm, 3.5 μm; Agilent Technologies, Santa Clara, CA, USA) at a flow rate of 0.3 mL/min. S1P was eluted using a ballistic gradient (30% to 85% [v/v] methanol and 0.2% [v/v] formic acid) and measured with a Shimadzu high-performance liquid chromatography system coupled to an API 4000™ tandem mass spectrometer (Applied Biosystems/MDS SCIEX, Framingham, MA, USA). The quantification determination was performed using multiple reaction monitoring with the *m/z* 380.1 to 264.3 (M + H S1P parent ion). We generated a calibration curve (0.125–5 μM S1P) to calculate the S1P levels in the samples. The same sample was tested multiple times with a relative standard deviation <5% within 12 hours and <10% within 6 days when stored at room temperature.

24-hour urinary sodium and potassium determination

We collected 24-hour urine samples on the last day of each period, which we froze at −40°C until further analysis. We determined the urinary concentrations of sodium and potassium using ion-selective electrodes (Hitachi, Tokyo, Japan). The 24-hour urinary excretion of sodium and potassium were calculated as 24-hour excretion = [Na^+ or K^+] × 24-hour total urine volume.

Statistics analyses

We performed statistical analyses with SPSS Statistics 22.0 (IBM, Chicago, IL, USA). Continuous data are presented as the mean ± standard deviation. Categorical data are shown as frequency and percentage. Differences in repeated measures were analyzed by repeated-measures analysis of variance. Differences in characteristics between the SS and SR groups were analyzedby independent t-tests for continuous variables, where appropriate; they were otherwise analyzed by Mann–Whitney U test.We determined correlations by calculating Pearson's correlation coefficient, where the residuals were normally distributed, and by calculating Spearman's correlation coefficient in other cases. A two-tailed P-value ≤0.05 was considered statistically significant.

Results

1. Baseline characteristics of subjects

The basic characteristics of the subjects are outlined in Table 1. Of the 42 recruited subjects, 12 (28.6%) were classified as SS and the other 30 subjects (71.4%) were defined as SR individuals who showed little or no response to salt loading. No significant differences were found in age, body mass index, or BP

between the SS and SR groups. However, the prevalence of hypertension (50% versus 16.7%, $p = 0.026$), glucose levels (5.82 ± 0.71 mM versus 5.21 ± 0.70 mM, $p = 0.015$), and brachial-ankle pulse wave velocity (1665.08 ± 392.49 cm/s versus 1402.10 ± 200.26 cm/s, $p = 0.045$) in SS subjects were significantly higher than in SR subjects (Table 1).

Table 1
Baseline characteristics of subjects

Parameters	Overall	Salt-Sensitive Subjects	Salt-Resistant Subjects
N(%)	42	12(28.6%)	30(71.4%)
Age,years	51.8 ± 12.3	56.4 ± 9.2	50.1 ± 13.7
Body mass index,kg/m2	24.86 ± 3.22	25.62 ± 3.43	24.56 ± 3.14
Smoking,n(%)	5(5.7%)	0	5(16.7%)
Hypertension,n(%)	11(26.2%)	6(50.0%)*	5(16.7%)
SBP,mmHg	126.2 ± 18.3	131.2 ± 22.2	123.8 ± 16.3
DBP,mmHg	80.7 ± 9.7	83.3 ± 10.9	81.5 ± 9.4
MAP,mmHg	95.9 ± 11.4	99.3 ± 14.0	95.4 ± 10.8
Glucose,mmol/L	5.38 ± 0.75	5.82 ± 0.71*	5.21 ± 0.70
Total cholesterol,mmol/L	4.58 ± 0.90	4.58 ± 0.94	4.59 ± 0.89
Triglycerides,mmol/L	1.38 ± 0.81	1.42 ± 0.62	1.13 ± 0.59
LDL,mmol/L	2.56 ± 0.66	2.64 ± 0.83	2.53 ± 0.60
HDL,mmol/L	1.48 ± 0.42	1.40 ± 0.33	1.51 ± 0.45
Uric acid,μmol/L	256.07 ± 72.08	225.42 ± 68.21	268.33 ± 70.97
Serum creatinine,μmol/L	52.17 ± 7.26	50.43 ± 5.38	51.64 ± 8.08
baPWV,cm/s	1477.24 ± 290.09	1665.08 ± 392.49*	1402.10 ± 200.26

Values are presented as mean ± SD.SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP,mean arterial pressure;LDL, low-density lipoprotein; HDL, high-density lipoprotein; baPWV, brachial-ankle pulse wave velocity.* $p < 0.05$ vs salt-resistant subjects.

2. Effects of dietary salt intervention on BP and 24-hour urinary sodium and potassium excretion

We considered sodium excretion in 24-hour urine a reliable indicator of salt intake; we collected 24-hour urine on the last day of each period. We found that 24-hour urinary sodium excretion decreased significantly from the baseline to low-salt intervention period in all groups (whole cohort: 167.5 ± 89.7 mM/24 h versus 72.6 ± 28.1 mM/24 h, $p < 0.001$; SS group: 159.2 ± 120.7 mm/24 h versus 73.6 ± 22.2 mM/24 h, $p = 0.034$; and SR group: 178.0 ± 76.6 mM versus 68.2 ± 32.9 mM/24 h, $p = 0.004$). From

the low-salt to high-salt intervention period, 24-hour urinary sodium excretion increased (whole cohort: 72.6 ± 28.1 mm//24 h versus 302.1 ± 88.3 mM/24 h, $p < 0.001$; SS group: 73.6 ± 22.2 mM/24 h versus 297.9 ± 61.5 mM/24 h, $p < 0.001$; and SR group: 68.2 ± 32.9 mM/24 h versus 312.3 ± 106.4 mM/24 h, $p < 0.001$). These findings demonstrate that the subjects complied well with the dietary intervention protocol. Conversely, the 24-hour urinary potassium excretion did not change between the baseline and low-salt periods. It increased from the low-salt to high-salt period in the whole cohort (24.5 ± 9.4 mM/24 h versus 36.0 ± 11.2 mM/2 4 h, $p = 0.003$) and the SR group (24.3 ± 9.8 mM/24 h versus 39.1 ± 12.2 mM/24 h,$p = 0.049$), but not in the SS group.

In line with the changes in urinary sodium excretion, we observed decreases in SBP and MAP from the baseline to low-salt period (SBP: 126.2 ± 18.3 mmHg versus 117.7 ± 13.7 mmHg, $p < 0.001$; MAP: 95.9 ± 11.4 mmHg versus 91.3 ± 8.0 mmHg,$p = 0.035$) and increases from the low-salt to high-salt period (SBP: 130.7 ± 20.3 mmHg versus 117.7 ± 13.7 mmHg,$p < 0.001$; MAP: 91.3 ± 8.0 mmHg versus 97.7 ± 10.7 mmHg, $p < 0.001$) in the whole cohort. The SBP, DBP, and MAP of SS individuals significantly increased from the low-salt to high-salt period (SBP: 148.4 ± 19.6 mmHg versus 123.9 ± 15.2 mmHg, $p < 0.001$; DBP: 87.2 ± 6.1 mmHg versus 79.9 ± 5.8 mmHg, $p < 0.001$; and MAP: 107.6 ± 9.7 mmHg versus 94.6 ± 7.9 mmHg, $p < 0.001$). The readings of the SS individuals were much higher than those of the SR individuals in the high-salt period(SBP: 148.4 ± 19.6 mmHg versus 121.8 ± 14.2 mmHg, $p = 0.002$; DBP: 107.6 ± 9.7 mmHg versus 92.8 ± 7.4 mmHg, $p = 0.001$; and MAP: 87.2 ± 6.1 mmHg versus 78.3 ± 6.6 mmHg, $p = 0.008$, respectively) (Table 2).

Table 2
BP and 24-h urinary sodium and potassium excretion at baseline and during dietary intervention periods

	SBP,mmHg	DBP,mmHg	MAP,mmHg	UrinaryNa^+, mmol/24 h	UrinaryK^+, mmol/24 h
Overall					
Baseline	126.2 ± 18.3	80.7 ± 9.7	95.9 ± 11.4	167.5 ± 89.7	25.0 ± 9.9
LS	117.7 ± 13.7^{aaa}	78.1 ± 7.1	91.3 ± 8.0^{a}	72.6 ± 28.1^{aaa}	24.5 ± 9.4
HS	130.7 ± 20.3^{bbb}	81.2 ± 7.6^{b}	97.7 ± 10.7^{bbb}	302.1 ± 88.3^{aaabbb}	36.0 ± 11.2^{aabb}
SS subjects					
Baseline	131.2 ± 22.2	83.3 ± 10.9	99.3 ± 14.0	159.2 ± 120.7	20.6 ± 11.3
LS	123.9 ± 15.2	79.9 ± 5.8	94.6 ± 7.9	73.6 ± 22.2^{a}	21.8 ± 8.5
HS	148.4 ± 19.6^{abbb}**	87.2 ± 6.1^{bbb}**	107.6 ± 9.7^{bbb}**	297.9 ± 61.5^{bbb}	33.5 ± 10.1
SR subjects					
Baseline	123.8 ± 16.3	79.4 ± 9.2	94.2 ± 10.1	178.0 ± 73.6	28.0 ± 8.3
LS	114.6 ± 12.4^{aa}	77.3 ± 7.7	89.7 ± 7.8	68.2 ± 32.9^{aa}	24.3 ± 9.8
HS	121.8 ± 14.2^{bbb}	78.3 ± 6.6	92.8 ± 7.4^{b}	312.3 ± 106.4^{aabbb}	39.1 ± 12.2^{b}

Values are presented as mean ± SD.SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP,mean arterial pressure;LS, low- salt; HS, high-salt; SS, salt-sensitive; SR, salt-resistant.a $p < 0.05$ versus baseline,aa $p < 0.01$ versus baseline,aaa $p < 0.001$ versus baseline.b $p < 0.05$ versus low-salt diet,bb $p < 0.01$ versus low-salt diet,bbb $p < 0.001$versus low-salt diet.** $p < 0.01$ versus salt-resistant subjects.

3. Effects of dietary salt intervention on plasma S1P levels

Plasma S1P levels decreased significantly from the baseline period to low-salt diet period and increased from the low-salt to high-salt period in the whole cohort (baseline: 1.455 ± 0.390 μM, low-salt period: 1.017 ± 0.245 μM, and high-salt period: 1.395 ± 0.288 μM). Further analysis revealed that S1P levels showed the same trend in the SS group (baseline: 1.278 ± 0.255 μM, low-salt period: 0.849 ± 0.197 μM, and high-salt period: 1.294 ± 0.164 μM) and the SR group (baseline: 1.542 ± 0.423 μM, low-salt period: 1.101 ± 0.228 μM, and high-salt period: 1.445 ± 0.328 μM). However, the plasma S1P level during the low-salt period in the SS group was significantly lower than that in the SR group, with no significant

differences during the baseline and high-salt periods (low-salt period SS: 0.849 ± 0.197 μM versus low-salt period SR: 1.101 ± 0.228 μM, $p = 0.022$) (Fig. 1).

4. Correlations between S1P levels and 24-hour urinary sodium and potassium excretion

S1P levels positively correlated with 24-hour urinary sodium excretion in the whole, SS, and SR group ($r = 0.416$, $p = 0.001$; $r = 0.566$, $p = 0.007$; and $r = 0.328$, $p = 0.036$, respectively), but not with 24-hour urinary potassium excretion ($r = 0.145$, $p = 0.261$; $r = 0.233$, $p = 0.310$; and $r = 0.007$, $p = 0.963$, respectively) (Fig. 2).

5. Correlations between S1P levels and BP

We observed a positive correlation between S1P levels and SBP in the whole, SS, and SR groups ($r = 0.290$,$p = 0.021$; $r = 0.762$, $p < 0.001$; and $r = 0.350$, $p = 0.023$, respectively); the correlation reached a higher level of statistical significance in the SS individuals than in the SR individuals. Further analysis revealed that S1P levels also positively correlated with MAP and DBP in SS individuals ($r = 0.707$, $p < 0.001$ and $r = 0.612$, $p = 0.003$, respectively) but not in SR individuals ($r = 0.271$, $p = 0.082$ and $r = 0.127$, $p = 0.421$, respectively)(Figure 3).

Discussion

This is the first study to reveal that low-salt dietary intervention decreases plasma S1P levels, whereas high-salt intervention reverses that change, in SS and SR Chinese adults. The positive correlations between plasma S1P levels and 24-hour urinary sodium excretion, but not 24-hour urinary potassium excretion, and SBP and MAP indicate that plasma S1P levels are responsive to dietary salt intervention in Chinese adults and that circulating S1P levels may be involved in BP regulation in SS individuals. These findings suggest that moderation of salt intake could represent a high-efficiency, low-cost, non-pharmaceutical approach to regulating circulating S1P levels and circulating S1P may be involved in salt-sensitive blood pressure regulation.

S1P regulates the functions of multiple systems, such as the immune system, central nervous system, and cardiovascular system. It also contributes to the pathogenesis of a broad range of diseases, including atherosclerosis, pulmonary arterial hypertension, diabetes mellitus, and cancer[27–30]. Sphingolipids, including S1P and ceramides, are associated with vascular tone, BP regulation, cardiovascular outcomes, and mortality. Patients who experience pre-infarction angina have higher serum S1P levels than patients without pre-infarction angina[31], and ST segment elevation myocardial infarction patients have low plasma S1P concentrations and an accumulation of free sphingoid bases and their 1-phosphates in their erythrocytes[32], supporting the hypothesis that S1P mediates important cardiovascular protective functions.

However, S1P may have quite different effects on other systems. A cross-sectional study demonstrated that increased plasma S1P levels are associated with blood glucose levels and the accumulation of fat

mass, especially visceral fat mass, in men with type 2 diabetes mellitus[29]. Ardawi et al. found that plasma S1P levels were significantly higher in women with incident fracture than in those without osteoporosis-related fractures, and high S1P levels were strongly associated with increased fracture risk[33]. Decreasing circulating S1P levels to physiological levels will certainly benefit those patients. In our study, a low-salt intervention for 7 days decreased plasma S1P levels, suggesting that dietary salt restriction is a highly efficient and low-cost intervention to regulate circulating S1P levels. Circulating S1P is synthesized and degraded rapidly under the regulation of a specific enzyme; this dynamic process may explain why a short intervention was able to statistically decrease plasma S1P levels.

A growing number of studies have shown that S1P and its signaling pathway may participate in BP regulation and hypertension[34–36]. The effect of S1P on BP is the result of changes in both vascular and heart functions. S1PR1 and S1PR3 are expressed in the heart[37]; S1PR1 and S1PR3 in the endothelium mediate vasodilation, resulting in lower BP, whereas S1PR2 and S1PR3 in smooth muscle mediate vasoconstriction, resulting in higher BP[9–11, 38]. In our study, both S1P levels and BP decreased during the low-salt period and increased during the high-salt period, demonstrating a potential role for S1P in mediating salt-induced BP change. Notably, the plasma S1P levels in SS individuals during the low-salt period were significantly lower than those in SR individuals, but no significant differences were observed during the baseline and high-salt periods. Furthermore, the positive correlation between S1P and SBP was more significant in the SS group than the SR group. These results indicate that SS individuals are more sensitive to salt-induced plasma S1P changes and that S1P may be involved in salt sensitivity. In fact, EDG1 (also known as S1P1R) is a candidate for the control of salt sensitivity and hypertension in the stroke-prone spontaneously hypertensive rat model[39]. Zhu et al. found that S1P is a novel lipid diuretic factor in the renal medulla[24]. S1P produced NO-independent natriuretic effects by inhibiting ENaC activity via S1P1R to inhibit sodium reabsorption in the collecting tube and to increase urinary sodium excretion[24]. In accordance with those findings, our study verified a positive correlation between plasma S1P levels and 24-hour urinary sodium excretion. Taken together with the literature, our results indicate that S1P may be involved in determining salt sensitivity and BP regulation. Therefore, it constitutes a novel target for studying salt sensitivity and SS hypertension.

One limitation of our study is the small number of participants recruited from Northern China. Large, multiethnic clinical trials should be conducted to determine if the results of our study can be generalized to diverse populations. Moreover, further studies should be conducted to explore the underlying mechanism of salt-induced plasma S1P changes and to investigate the interaction between S1P and BP.

Conclusion

In conclusion, our study reveals that low-salt dietary intervention can decrease plasma S1P levels, whereas high-salt intervention reverses this change and S1P levels positively correlated with SBP,in Chinese adults. Further studies will determine if this high-efficiency, low-cost intervention approach is suitable for regulating circulating S1P levels in diverse populations. We expect that S1P regulates salt-induced BP changes and represents a potential target for treating SS hypertension.

Abbreviations

S1P
Sphingosine-1-phosphate
S1PR
Sphingosine-1-phosphateReceptor
BP
Blood Pressure
SBP
Systolic Blood Pressure
DBP
Diastolic Blood Pressure
MAP
Mean Arterial Pressure
LS
Low-salt
HS
High-salt
SS
Salt-sensitive
SR
Salt-resistant
EDTA
High-density Lipoprotein
HDL
High-density Lipoprotein
LDL
Low-density Lipoprotein
baPWV
Brachial-ankle Pulse Wave Velocity
SD
Standard Deviation

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from theethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (Code: 2015-128). All participatesprovided written informed consent. All steps of the study conformed to the Helsinki Declaration.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the experiments: JM CC QM. Performed the experiments: QM CC YX JH WZ YY KW YY YL CC. Analyzed the data: QM. Contributed reagents/materials/analysis tools: QM YX. Wrote the paper: QM. The author(s) read and approved the final manuscript.

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References

1. Blaho VA, Hla T. Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors. Chem Rev. 2011;111(10):6299–320.
2. Kluk MJ, Hla T. Signaling of sphingosine-1-phosphate via the S1P/EDG-family of G-protein-coupled receptors. Biochim Biophys Acta. 2002;1582(1–3):72–80.
3. Kunkel GT, Maceyka M, Milstien S, Spiegel S. Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. Nat Rev Drug Discov. 2013;12(9):688–702.
4. Wu X, Hou J, Li H, Xie G, Zhang X, Zheng J, et al. Inverse Correlation Between Plasma Sphingosine-1-Phosphate and Ceramide Concentrations in Septic Patients and Their Utility in Predicting Mortality. Shock. 2019;51(6):718–24.

5. Hoefer J, Azam MA, Kroetsch JT, Leong-Poi H, Momen MA, Voigtlaender-Bolz J, et al. Sphingosine-1-phosphate-dependent activation of p38 MAPK maintains elevated peripheral resistance in heart failure through increased myogenic vasoconstriction. Circ Res. 2010;107(7):923–33.
6. Zhang F, Xia Y, Yan W, Zhang H, Zhou F, Zhao S, et al. Sphingosine 1-phosphate signaling contributes to cardiac inflammation, dysfunction, and remodeling following myocardial infarction. Am J Physiol Heart Circ Physiol. 2016;310(2):H250–61.
7. Brakch N, Dormond O, Bekri S, Golshayan D, Correvon M, Mazzolai L, et al. Evidence for a role of sphingosine-1 phosphate in cardiovascular remodelling in Fabry disease. Eur Heart J. 2010;31(1):67–76.
8. Means CK, Xiao CY, Li Z, Zhang T, Omens JH, Ishii I, et al. Sphingosine 1-phosphate S1P2 and S1P3 receptor-mediated Akt activation protects against in vivo myocardial ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol. 2007;292(6):H2944–51.
9. Kerage D, Brindley DN, Hemmings DG. Review: novel insights into the regulation of vascular tone by sphingosine 1-phosphate. Placenta. 2014; 35 Suppl:S86-92.
10. Igarashi J, Michel T. Sphingosine-1-phosphate and modulation of vascular tone. Cardiovasc Res. 2009;82(2):212–20.
11. Schuchardt M, Tolle M, Prufer J, van der Giet M. Pharmacological relevance and potential of sphingosine 1-phosphate in the vascular system. Br J Pharmacol. 2011;163(6):1140–62.
12. Cantalupo A, Zhang Y, Kothiya M, Galvani S, Obinata H, Bucci M, et al. Nogo-B regulates endothelial sphingolipid homeostasis to control vascular function and blood pressure. Nat Med. 2015;21(9):1028–37.
13. Fryer RM, Muthukumarana A, Harrison PC, Nodop Mazurek S, Chen RR, Harrington KE, et al. The clinically-tested S1P receptor agonists, FTY720 and BAF312, demonstrate subtype-specific bradycardia (S1P(1)) and hypertension (S1P(3)) in rat. PLoS One. 2012;7(12):e52985.
14. Spijkers LJ, Alewijnse AE, Peters SL. FTY720 (fingolimod) increases vascular tone and blood pressure in spontaneously hypertensive rats via inhibition of sphingosine kinase. Br J Pharmacol. 2012;166(4):1411–8.
15. Cyster JG, Schwab SR. Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. Annu Rev Immunol. 2012;30:69–94.
16. Greig FH, Nather K, Ballantyne MD, Kazi ZH, Alganga H, Ewart MA, et al. Requirement for sphingosine kinase 1 in mediating phase 1 of the hypotensive response to anandamide in the anaesthetised mouse. Eur J Pharmacol. 2019;842:1–9.
17. Forrest M, Sun SY, Hajdu R, Bergstrom J, Card D, Doherty G, et al. Immune cell regulation and cardiovascular effects of sphingosine 1-phosphate receptor agonists in rodents are mediated via distinct receptor subtypes. J Pharmacol Exp Ther. 2004;309(2):758–68.
18. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension. 1996;27(3 Pt 2):481–90.
19. Titze J, Ritz E. Salt and its effect on blood pressure and target organ damage: new pieces in an old puzzle. J Nephrol. 2009;22(2):177–89.

20. Mente A, O'Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, Wielgosz A, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014;371(7):601–11.
21. Sun N, Mu J, Li Y, Working Committee of Salt evaluation, Blood Pressure Management Chinese Medical Association Hypertension Professional Committee Hypertension Group Chinese Society of Cardiology. An expert recommendation on salt intake and blood pressure management in Chinese patients with hypertension: A statement of the Chinese Medical Association Hypertension Professional Committee. J Clin Hypertens (Greenwich). 2019;21(4):446–50.
22. Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. Circulation. 2016;134(22):e505–29.
23. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
24. Zhu Q, Xia M, Wang Z, Li PL, Li N. A novel lipid natriuretic factor in the renal medulla: sphingosine-1-phosphate. Am J Physiol Renal Physiol. 2011;301(1):F35–41.
25. Elijovich F, Weinberger MH, Anderson CA, Appel LJ, Bursztyn M, Cook NR, et al. Salt Sensitivity of Blood Pressure: A Scientific Statement From the American Heart Association. Hypertension. 2016;68(3):e7–46.
26. Winkler MS, Nierhaus A, Holzmann M, Mudersbach E, Bauer A, Robbe L, et al. Decreased serum concentrations of sphingosine-1-phosphate in sepsis. Crit Care. 2015;19:372.
27. Jiang XC, Liu J. Sphingolipid metabolism and atherosclerosis. Handb Exp Pharmacol. 2013; (216):133–146.
28. Chen J, Tang H, Sysol JR, Moreno-Vinasco L, Shioura KM, Chen T, et al. The sphingosine kinase 1/sphingosine-1-phosphate pathway in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2014;190(9):1032–43.
29. Tanaka S, Kanazawa I, Sugimoto T. Visceral fat accumulation is associated with increased plasma sphingosine-1-phosphate levels in type 2 diabetes mellitus. Diabetes Res Clin Pract. 2018;143:146–50.
30. Ramanathan R, Raza A, Sturgill J, Lyon D, Young J, Hait NC, et al. Paradoxical Association of Postoperative Plasma Sphingosine-1-Phosphate with Breast Cancer Aggressiveness and Chemotherapy. Mediators Inflamm. 2017;2017:5984819.
31. Kiziltunc E, Abaci A, Ozkan S, Alsancak Y, Unlu S, Elbeg S, et al. The Relationship between Pre-Infarction Angina and Serum Sphingosine-1-Phosphate Levels. Acta Cardiol Sin. 2014;30(6):546–52.
32. Knapp M, Lisowska A, Zabielski P, Musial W, Baranowski M. Sustained decrease in plasma sphingosine-1-phosphate concentration and its accumulation in blood cells in acute myocardial infarction. Prostaglandins Other Lipid Mediat. 2013;106:53–61.
33. Ardawi MM, Rouzi AA, Al-Senani NS, Qari MH, Elsamanoudy AZ, Mousa SA. High Plasma Sphingosine 1-phosphate Levels Predict Osteoporotic Fractures in Postmenopausal Women: The

Center of Excellence for Osteoporosis Research Study. J Bone Metab. 2018;25(2):87–98.

34. Meissner A, Miro F, Jimenez-Altayo F, Jurado A, Vila E, Planas AM. Sphingosine-1-phosphate signalling-a key player in the pathogenesis of Angiotensin II-induced hypertension. Cardiovasc Res. 2017;113(2):123–33.
35. Fenger M, Linneberg A, Jeppesen J. Network-based analysis of the sphingolipid metabolism in hypertension. Front Genet. 2015;6:84.
36. Fenger M, Linneberg A, Jorgensen T, Madsbad S, Sobye K, Eugen-Olsen J, et al. Genetics of the ceramide/sphingosine-1-phosphate rheostat in blood pressure regulation and hypertension. BMC Genet. 2011;12:44.
37. Mazurais D, Robert P, Gout B, Berrebi-Bertrand I, Laville MP, Calmels T. Cell type-specific localization of human cardiac S1P receptors. J Histochem Cytochem. 2002;50(5):661–70.
38. Takuwa Y, Okamoto Y, Yoshioka K, Takuwa N. Sphingosine-1-phosphate signaling and biological activities in the cardiovascular system. Biochim Biophys Acta. 2008;1781(9):483–8.
39. Graham D, McBride MW, Gaasenbeek M, Gilday K, Beattie E, Miller WH, et al. Candidate genes that determine response to salt in the stroke-prone spontaneously hypertensive rat: congenic analysis. Hypertension. 2007;50(6):1134–41.

Figures

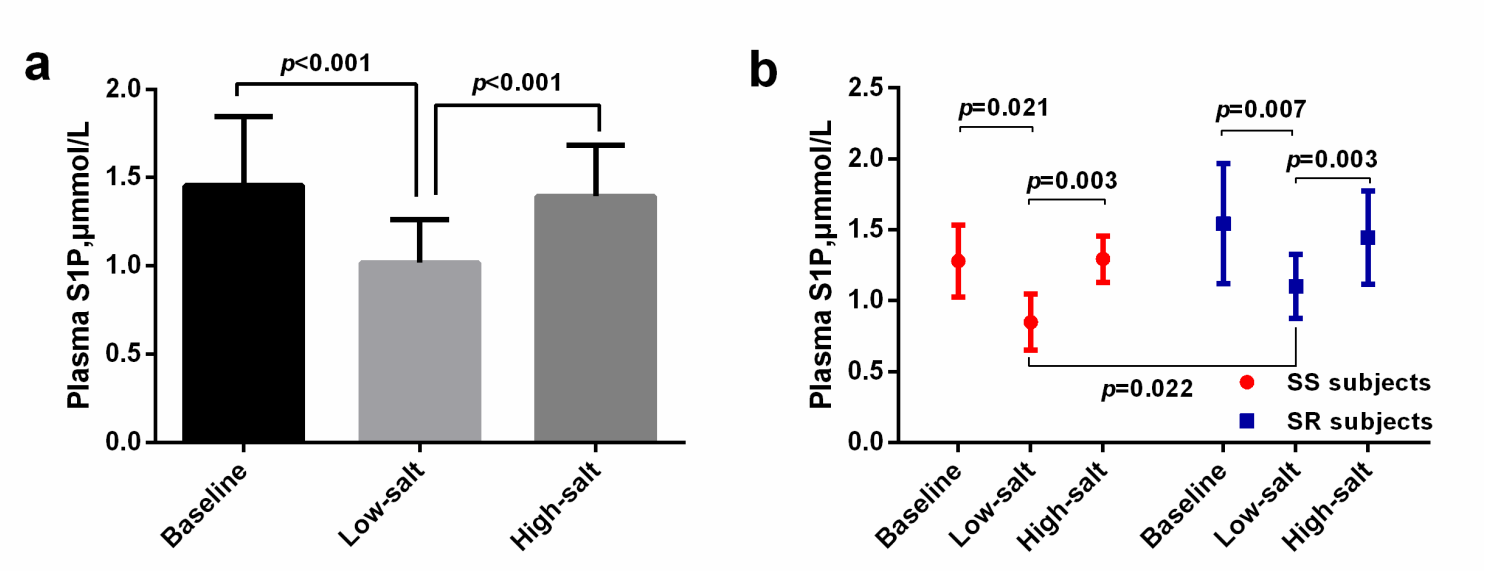

Figure 1

Effects of salt intervention on plasma S1P levels in the whole group(a)and in SS and SR subjects(b).S1P,Sphingosine-1-Phosphate;SS,salt-sensitive;SR,salt-resistant.

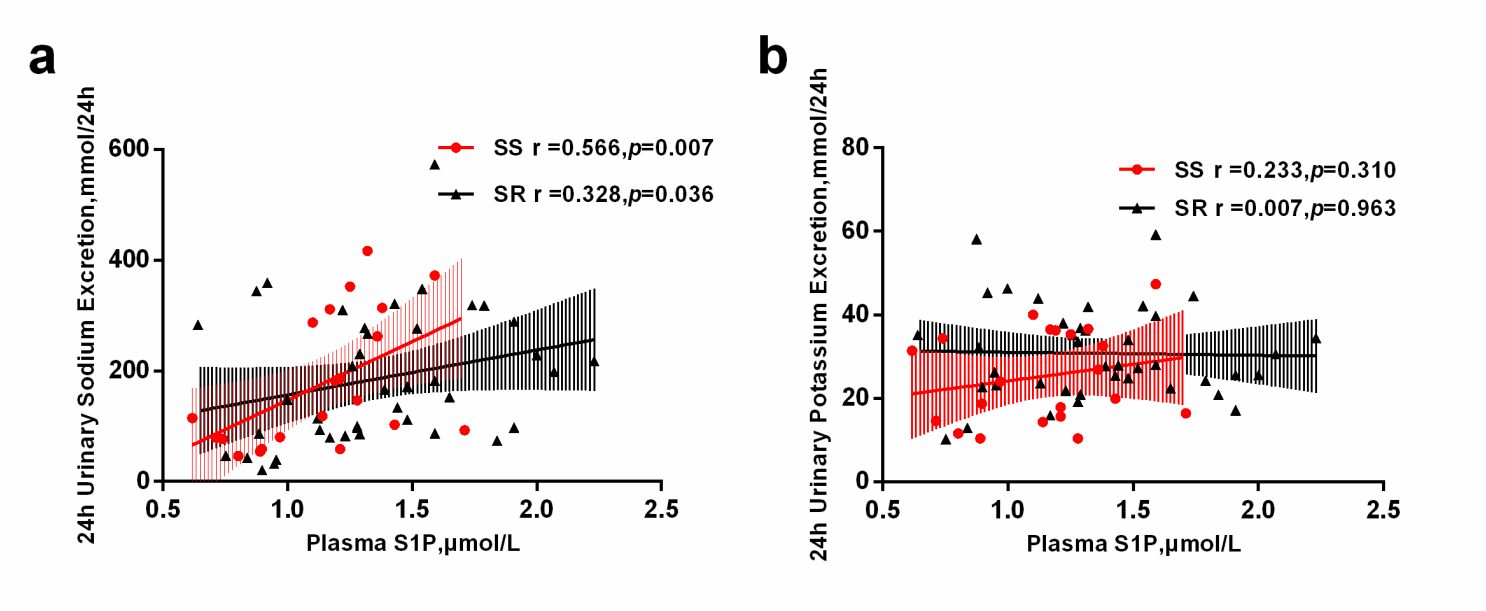

Figure 2

Correlations between S1P levels and 24-hour urinary sodium excretion(a) and potassium excretion(b) in SS and SR subjects.S1P,Sphingosine-1-Phosphate;SS,salt-sensitive;SR,salt-resistant.

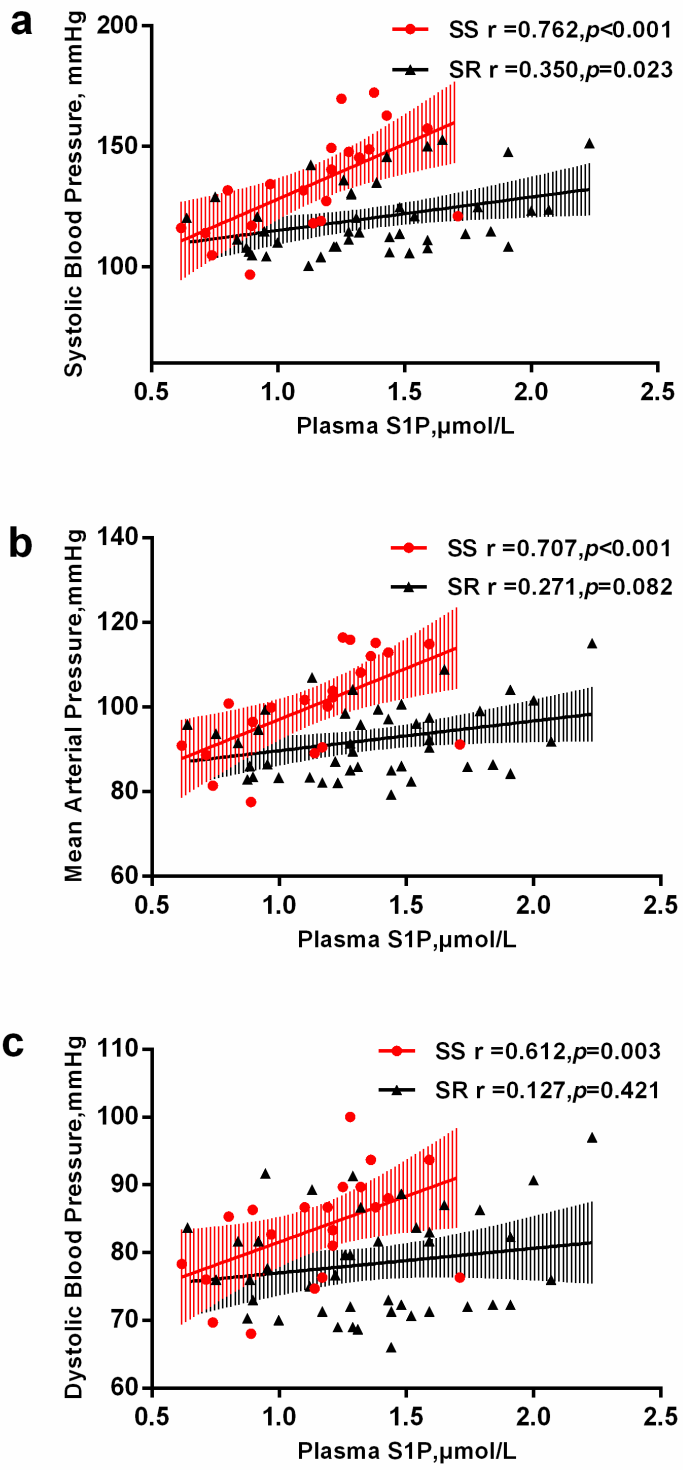

Figure 3

Correlations between S1P levels and systolic blood pressure(a),mean arterial pressure(b)and systolic blood pressure(c) in SS and SR subjects. S1P,Sphingosine-1-Phosphate; SS,salt-sensitive; SR,salt-resistant.