Research Article

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Water Ingestion Increases Plasma Somatostatin in the Course of the Osmopressor Response

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Abstract

Background: Studies in patients with an impaired efferent baroreflex led to the discovery that ingestion of water induces a robust increase in blood pressure and vascular resistance. This response was also present in healthy subjects with intact baroreflexes. We aimed to clarify the physiological role of the osmopressor response by determining the change of plasma somatostatin after water ingestion in young healthy subjects.

Methods and results: In a randomized, controlled, crossover fashion, 17 young healthy subjects (aged 22-35 years) ingested either 500 or 50 mL of water. Heart rate, blood pressure, cardiac index, and total peripheral vascular resistance were measured using a Finometer hemodynamic monitor. Blood sampling was performed at 5 min before and at 25 and 50 min after water ingestion. Plasma somatostatin was measured by ELISA. At 25 min after the ingestion of 500 mL of water, total peripheral resistance increased and plasma osmolality decreased, significantly. Plasma somatostatin increased significantly after ingestion of 500 mL of water, and the magnitude of change in plasma somatostatin strongly correlated with the change in total peripheral vascular resistance.

Conclusions: An increase in plasma somatostatin associated with the drop in osmolality after water ingestion might contribute to the physiology of the osmopressor response.

Keywords: Water ingestion; Osmopressor response; Somatostatin; Osmolality

Introduction

Previous studies in patients with an impaired efferent baroreflex led to the discovery that water ingestion induces a robust increase in blood pressure (BP) and vascular resistance [1,2]. Initially, Jordan et al. demonstrated that ingesting 473 mL (16 oz.) of water induces a profound increase in systolic BP averaging approximately40 mmHg in patients with autonomic failure and also elevated BP by approximately 11 mmHg in elderly subjects. This effect appears within 10 min, is maximal at 25-40 min, and largely dissipates by 90 min after water ingestion [1]. In young healthy subjects, water induces a maximal rise in peripheral vascular resistance at 25th min after ingestion without an associated increase in BP [3-5]. This prominent vascular response after water ingestion is termed the Osmopressor Response (OPR) [6].

Brown et al. suggested that the osmotic induced increase in cardiovagal tone after water drinking probably contributes to buffering of the vasoconstrictor response in young healthy subjects [7]. It has been suggested that water's relative hypo-osmolality acts as an afferent signal via osmoreceptive nerve fibers in the gut or portal circulation to elicit OPR in human [8,9]. To our knowledge, somatostatin release from gut is regulated by the autonomic nervous system with catecholamines inhibiting and cholinergic mediators stimulating peptide release. Mendonca et al. found that the mechanism of cardiovascular responses to water ingestion at rest most likely depend on reflex bradycardia of vagal origin [10]. Evidently, the somatostatin co-exists with acetylcholine in presynaptic vagal endings and may be released by high-frequency stimulation of the vagus nerve [11]. Somatostatin, a potent splanchnic vasoconstrictor, reduces the splanchnic vascular reservoir as compensation for the fall in cardiac filling pressure that

attends orthostasis [12]. Thus, we suggested that water ingestion may increase somatostatin release from gut by the cholinergic mediators stimulating somatostatin release during osmopressor response.

Water ingestion has been recommended for the management of orthostatic hypotension, orthostatic intolerance and syncope. Thus, we speculated that the gut hormone somatostatin may be involved in the physiology of OPR to improve tolerance to orthostatic stress in human. We hypothesized that water ingestion increase plasma somatostatin as part of presentation of the OPR. Thus, we assess the correlation between the change in plasma somatostatin concentration after water and the change in total peripheral vascular resistance in young healthy subject. This study will help clarify whether the physiological mechanism of the OPR involves splanchnic vasoconstriction by somatostatin.

Materials and Methods

Subjects

This study was approved by the Institutional Review Board (098-

032-312) of Tri-Service General Hospital, Taipei, Taiwan and was performed in the Pain Department Laboratory. Informed consent was obtained from each volunteer. We studied 17 healthy normal young adults who had no history of syncope and who were currently using no prescription or over-the-counter medications.

Study protocol

The subjects were asked to empty their bladder before beginning the test to avoid urinary bladder or stomach distension, which are known to affect peripheral sympathetic activity. Study sessions took place in a quiet, dimly lit room at a comfortable ambient temperature (21-24°C).We used a randomized, crossover study design. Each subject underwent the study protocol on two separate days. Subjects received either 500 mL or 50 mL water in their initial study, with the alternative in their second test. As water ingestion increases total systemic vascular resistance in healthy young subjects within 5 min after ingestion, reaches a maximum in 20–40 min, and is maintained for more than 1 h, the 25-min time point after water ingestion was taken as representative of the maximal osmopressor response, and the 50-mintime point as the terminal phase of OPR in comparison with the baseline level before water ingestion [1].

Instrumentation

An antecubital venous catheter was inserted for blood sampling at least 15 min before the beginning of the test, with the patient in the sitting position. Hemodynamic parameters including heart rate (HR), BP, Stroke Volume (SV), Cardiac Index(CI), and Total Peripheral Vascular Resistance (TPR) were measured using a Finometer (FMS, Finapres Measurement Systems, Arnhem, The Netherlands). Computation of stroke volume and cardiac output using the Model flow method was based on the finger arterial pressure [13]. The hemodynamic parameters were averaged over one minute from the continuous Finometer recording. Skin Blood Flow (SkBF) was recorded and measured using a flowmeter (DRT4 Instrument, Moor Instrument, Axminster, UK) over the right palmar region [14].

Blood sampling for plasma osmolality

Blood samples (2 mL) were collected at time points of -5 min (baseline), 25, and 50 min after water ingestion. Plasma osmolality was analyzed by the freezing point depression method using an Advanced osmometer model 3900 (Advanced Instruments, Norwood, MA, USA) [15].

ELISA to determine plasma somatostatin

A K2EDTA-containing tube (Becton Dickinson, Franklin Lakes, NJ, USA) was used to collect 10 ml whole blood. The sample was centrifuged at 17,000 g for 15 minutes at 4°C, and then the supernatant was aliquoted and stored at −80°C until analysis. The levels of somatostatin were measured using an ELISA kit (USCNK Life Science Inc., Wuhan, China) according to the manufacturer's protocol [16].

Statistical analysis

The primary objective was to evaluate the relative changes of plasma somatostatin after water in comparison with before water for water-ingesting (500 ml) and control (50 ml) groups. A sample size of 17 was estimated to have 65% power to detect the effect size of 0.5 by the paired t-test with a significance level of 0.05 [17]. A repeated-measures ANOVA was used to assess changes of osmolality or somatostatin between the water-ingesting (500 mL) and control (50 mL) sessions. Appropriate parametric (Student's t-test) tests for

paired data were used for the analysis. Values are reported as the mean ± Standard Deviation (SD), unless otherwise noted. P values of <0.05 were considered statistically significant, and all tests were two-tailed. Pearson correlation coefficient was used for testing the correlations between the variables. The level of significance was set at 5%. Statistical analyses were performed using SPSS (SPSS ver. 13.0, SPSS, Chicago, IL, USA).

Results

Demographic data, basal hemodynamic variables and plasma osmolality for all 17 subjects are shown in table 1.

Hemodynamic variables

There were no significant differences in hemodynamic variables [including the HR, systolic BP, diastolic BP, and mean arterial BP] between the baseline and 25 min and 50 min after ingestion of 50 ml of water. Twenty-five min after ingestion of 500 ml water, the HR had significantly decreased from 71.5 ± 8.6 beats/min at the baseline to 67.1 ± 8.1 beats/min at 25 min (p=0.004). Twenty-five minutes after 500 ml water, the TPR increased significantly from 1370 ± 221.9 dyne·sec·cm^{-5} at the basal level to 1740 ± 346.9 dyne·sec·cm^{-5} at 25 min (p<0.001). Five hundred ml of water reduced the SkBF from a baseline level of 213.0 ± 83.5 dyne·sec·cm^{-5} perfusion units to 71.0 ± 47.1 dyne·sec·cm^{-5} perfusion units (p<0.001; Table 2).

Water reduced plasma osmolality at 25 min after ingestion of 500 mL

There was significant difference in the plasma osmolality over time between the water-ingesting (500 mL) and control (50 mL) sessions (p=0.022). Ingestion of 500 ml water lowered the plasma osmolality from 285.6 ± 0.71 mOsm/kg to 281.9 ± 0.72 mOsm/kg and 282.8 ± 0.9 mOsm/kg at 25 and 50 min, respectively (p=0.0001 and p=0.038; Figure 1). There was no statistical significant change of plasma osmolality in the control session.

Plasma somatostatin after water ingestion

There was a significant difference in the plasma somatostatin over time between the water-ingesting (500 mL) and control (50 mL) sessions (p=0.031). After ingestion of 500 mL water, plasma somatostatin increased significantly from 106.7 pg/mL to 121.8 pg/ml and 120.7 pg/ml at 25 and 50 minutes, respectively (p=0.033 and p=0.003; Figure 2). There was no statistical significant change of plasma somatostatin in the control session.

Correlation between the change of total peripheral vascular resistance and somatostatin at 25th min after water

There was a strong correlation between the changes of plasma somatostatin and total peripheral vascular resistance at the 25th minute after ingestion of 500 mL water (n=17; r=0.6159; r^2=0.3794; p=0.0085; Figure 3).

Parameter Names	Mean (SD)	Range
Age, year	25.8 (3.6)	(22~35)
Gender, male: female	4:13	
Weight, kg	61.0 (8.1)	(47~80)
Height, cm	166.1 (6.1)	(154~177)
Body-mass index, kg/m^2 *	22.0 (1.8)	(20.0~26.0)

*The body mass index is the weight in kilograms divided by the square of the height in meters

Table 1: Characteristics of the 17 subjects examined at baseline before water ingestion.

Paramter	Water 50 mL			Water 500 mL		
Names	Baseline	25 min	50 min	Baseline	25 min	50 min
HR, beats/min	72.5 (9.6)	69.6 (9.8)	70.3 (9.5)	71.5 (8.6)	67.1* (8.1)	70.1 (8.5)
SBP, mmHg	121.6 (9.9)	131.8 (13.1)	138.6 (14.0)	120.1 (13.4)	135.8 (13.5)	135.5 (15.8)
MABP, mmHg	99.1 (12.7)	102.2 (11.9)	106.6 (11.4)	98.5 (8.1)	102.6 (9.9)	101.8 (13.8)
DBP, mmHg	71.7 (6.5)	77.7 (10.1)	81.9 (11.7)	69.8 (8.7)	79.5 (10.4)	76.5 (11.5)
SV, ml/min	75.0 (13.6)	73.9 (15.8)	72.9 (16.5)	76.8 (15.7)	76.4 (13.4)	76.8 (15.9)
TPR, dyn·sec·cm^5	1447 (300.4)	1668 (413.2)	1653 (463.9)	1370 (221.9)	1740*(346.9)	1508 (410.4)
SkBF, perfusion units	186.2(108.9)	127.1 (95.1)	108.6 (77.1)	213.0 (83.5)	71.0 * (47.1)	98.1 (60.5)

Values are the mean (SD); HR, heart rate; SBP, systolic blood pressure; MABP, mean arterial blood pressure; DBP, diastolic blood pressure. SV, stroke volume; TPR, total peripheral vascular resistance. SkBF, Laser Doppler skin blood flow * $p<0.05$ indicate a significant difference between baseline and 25th min after ingestion

Table 2: Hemodynamic variables at 5 min before (baseline) and 25 min and 50min after ingestion of either 500 or 50 mL of water in the same subjects (n=17).

Correlation between the change of plasma osmolality and somatostatin at 25th min after water

There was a good correlation between the changes of plasma somatostatinand osmolality at the 25th minute after ingestion of 500 mL water (n=17; r^2=0.2818; p=0.0284; Figure 4).

Discussion

The novel finding of this study was that water ingestion increased plasma somatostatin concentration during the osmopressor response. In addition, 1) water reduced skin blood flow was associated with the increase total peripheral vascular resistance; 2) Water ingestion reduced plasma osmolality simultaneously with an increase of plasma somatostatin; and 3) there was a good correlation between the changes in plasma somatostatin and total peripheral vascular resistance at the 25th min after water.

Drinking water increases leg vascular resistance and TPR in healthy young subjects proportional to the increase in muscle sympathetic nerve activity of nerves supplying the calf region, direct evidence for sympathetic vasoconstrictor activation after water ingestion [3,4]. Change in vascular tone of the limbs after ingesting water is thought to be partially compensated for by opposing changes in other vascular beds [4]. Our previous study demonstrated that ingesting water induces sympathetic vasoconstriction associated with a decrease in palmar skin blood flow, which could be a characteristic of the osmopressor response in young healthy subjects [14]. A baroreflex-mediated increase in cardiovagal tone has also been suggested to contribute to buffering the vasoconstrictor response and preventing an apparent change in BP [18]. Consistent with these previous studies, the present study showed that ingestion of water produced a maximal rise in TPR and an apparent decrease in SkBF without a prominent change in BP.

The actual site and type of water stimulus that elicits the OPR remains controversial. Several potential stimuli have been considered including duodenal stretch, vasoactive hormones, osmotic factors, and the change in plasma volume after water ingestion [1]. The absence of a pressor response following a saline infusion via nasogastric tube makes luminal stretch an unlikely explanation for the increase in BP or osmopressor response to water because both fluids would induce an equal duodenal stretch. Hydration status may affect BP, but acutely increasing plasma volume via an intravenous saline infusion fails to elicit the pressor response seen with duodenal water administration [19]. In fact, it is not easy to investigate how water affects luminal osmolality of the gastrointestinal tract in humans. There was an animal study provides evidence that duodenal infusion of water produces relative hypo-osmolality in the portal circulation, which indicates the hypo-osmotic nature of water [20]. Our present study demonstrated that a water-induced decrease in plasma osmolality was associated

with the elicitation of the OPR. The OPR should depend mainly on the hypo-osmotic nature of water itself to act as an afferent input via gastrointestinal stimulation because only water and not saline ingestion is effective at raising BP. These results and the lack of OPR after saline ingestion suggest that the OPR depends mainly on the hypo-osmotic nature of water to act as a stimulus in the gastrointestinal tract. In patients with efferent baroreflex impairment, the OPR happens prominently after either intragastric or intraduodenal infusions of water, suggesting that the location of water's actions is at or distal to the duodenum. In *in vivo* and *in vitro* studies, Lechner et al. have identified a specific population of TRPV4-positive hepatic sensory afferents that detect physiological changes in blood osmolality [21]. According to May et al., liver afferents may contribute to water drinking-induced sympathetic activation in human subjects [6,22]. The portal vein can exhibit a wider range of osmolality than the systemic circulation because of the water absorbed by the gastrointestinal tract and can trigger osmosensitive mechanisms in the portal system after water ingestion [21].

The splanchnic circulation is the most compliant vascular bed in humans and it receives a large fraction (25%) of the total cardiac output at rest. Patients with autonomic dysfunction usually suffer from orthostatic intolerance or orthostatic hypotension due to impaired capacity to raise vascular resistance in the splanchnic circulation during standing [12,23]. Impaired vasoconstriction allows splanchnic blood flow, and thus splanchnic blood volume, to remain high during standing. A high standing splanchnic blood volume leads to a marked fall in right atrial pressure and results in a reduced cardiac output which produces orthostatic hypotension [24].

The control of cardiovascular system is provided not only by regulatory influence of classical neurotransmitters, acetylcholine and noradrenaline, but also some regulatory peptides have very important physiological significance. Somatostatin, a peptide which possesses pronounced cardiotropic activity is found in the pancreas and gastrointestinal tract, including the visceral autonomic nervous system, the endocrine D cells and the gut lumen [11]. Somatostatin-28 (SS-28) acted within the Central Nervous System (CNS) to produce a dose-dependent elevation of Mean Arterial Pressure (MAP), a reduction of Heart Rate (HR), and an elevation of the plasma concentration of vasopressin. So far not much is known on the physiological effects of somatostatin in the gastrointestinal tract during osmopressor response [25].

This is the first human study to elucidate the hypo-osmotic nature of water increase plasma somatostatin level and suggested its physiological effect in the splanchnic circulatory control in simultaneous with OPR. Rudholm et al. demonstrated the release of regulatory gut peptides somatostatin by hyperosmolal solutions
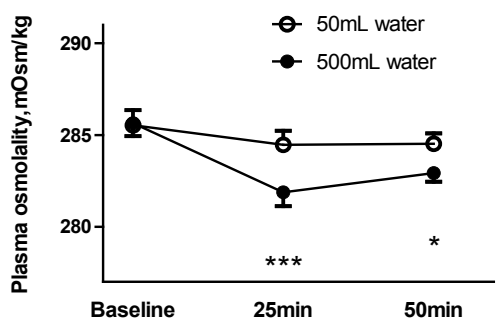
Figure 1: Change of plasma osmolality from the baseline (-5 min before), 25 and 50 min after either ingestion 500 mL (-●-) or 50mL (-○-) of water. There was statistical significant difference in decrease of plasma osmolality over-time between the water-ingesting (500 mL) and control (50 mL) sessions. (p=0.022)The bars indicate mean ± SEM. (n=17).
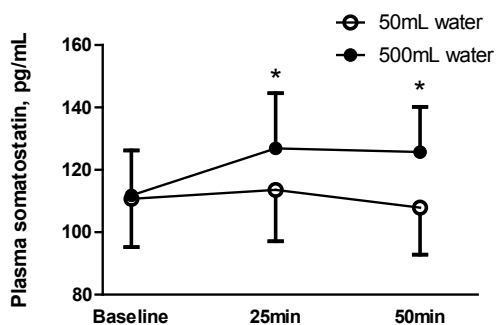

Figure 2: Plasma somatostatin concentration at baseline, 25 and 50 min after either ingestion500 mL (-●-) or 50mL (-○-) of water. There was statistical significant difference in increase of plasma somatostatin over- time between the water-ingesting (500 mL) and control (50 mL) sessions.(p=0.031) The bars indicate mean ± SEM. (n=17).

$$y=263.7+7.047x$$
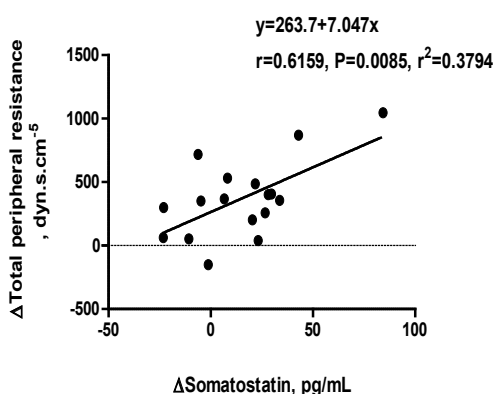$$r=0.6159, P=0.0085, r^2=0.3794$$

Figure 3: There was a significant correlation between increase of plasma somatostatin and increase of total peripheral vascular resistance (ΔTPR) at the 25th minute after ingestion of 500mL water.(p=0.0085; r2=0.3794; n=17).

in the intestine in conscious rats [26]. On the contrary, our study demonstrated water decreased plasma osmolality consistent with an increase of plasma somatostatin. As somatostatin has a very short plasma half-life and requires administration by continuous infusion

to maintain therapeutic levels, stable long-acting analogues has been developed. The analogue octreotide has been shown to have a plasma half-life of 113 minutes and to produce a profound selective inhibition of growth hormone. Circumstantial evidence is provided indicating that the mechanisms of action of somatostatin and octreotide in the therapy of bleeding oesophageal varices are mainly mediated by a splanchnic vasoconstrictive effect [27]. Octreotide, a derivative of somatostatin, also significantly attenuates orthostatic hypotension in patients with severely impaired baroreflex. The pressor effect of the octreotide in patients with autonomic neuropathy has been proven to be associated with increased splanchnic, forearm vascular resistance and with cardiac output [12].

The present study demonstrated that there was a significant correlation between the increase of plasma somatostatin and the increase of total peripheral vascular resistance at the 25th min ingestion after 500 ml of water. To our knowledge, there is still no evidence supporting the concept that water's hypo-osmolality in the gut can stimulate somatostatin release from gut into circulating blood, or an increase of plasma somatostatin after water ingestion is involved in the OPR or splanchnic vasoconstriction. Previous studies have demonstrated that ingesting water may lower portal plasma osmolality to a greater extent than systemic plasma osmolality to produce the OPR because the intraduodenal saline infusion does not alter portal/systemic osmolality or raise BP in patient with autonomic failure [19,20]. Additionally, our recent unpublished data also displayed that there was little change in plasma somatostatin after ingestion of 500 mL normal saline. Thus, we suggested that the water's hypo-osmolality might be crucial to facilitate the release of gut somatostatin, a potential vasocontrictive hormone, into systemic circulation. Pharmacologically, the octreotide, an analogue of somatostatin, has been proven to provoke the increase of splanchnic vascular resistance and the cardiac output in patients with autonomic neuropathy [27]. Thus, we propose that the water induced increase of somatostatin might explain why water ingestion improves orthostatic hypotension, orthostatic intolerance and as a prophylaxis against syncope in young healthy subjects.

Two limitations should be discussed in this study. The main limitation of our study is the open design. However, it is almost impossible to test the effect of water drinking in a double-blind fashion. Second, we did not determine the correlation of the change between abdominal splanchnic circulatory reservoir and the plasma somatostatin level during the OPR. This study suggested that the
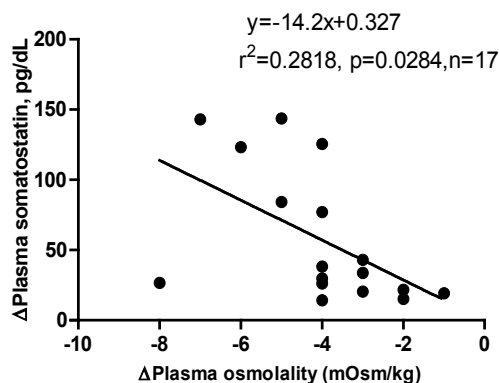

$$y=-14.2x+0.327$$
$$r^2=0.2818, p=0.0284, n=17$$

Figure 4: There wasa significant correlation between the increase of plasma somatostatin and decrease of plasma osmolality at the 25th minute after ingestion of 500mLwater.(p=0.0284; r²=0.2818; n=17).

increased plasma somatostatin after water ingestion might participate in the physiology of OPR.

In conclusion, water ingestion-induced increase of plasma somatostatin could be used as a biomarker of OPR, and suggests a potential physiological effect of plasma somatostatin on the splanchnic circulation. Perhaps, sympathetic vasoconstriction associated with water ingestion works synergistically with the somatostatin-induced splanchnic vasoconstriction, providing greater protection against syncope or orthostatic tolerance in young healthy subjects, but this requires further investigation.

Perspectives

Ingestion of water is proving to be therapeutic to relieve debilitating hypotension episodes. Identifying the exact mechanism of water-induced sympathetic activation may provide novel targets for treating orthostatic and vasovagal syncope. The osmopressor response link to plasma somatostatin release may reflect its physiological effect on splanchnic circulatory control during orthostatic stress.

Acknowledgement

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