Water drinking is recognized to be an essential behavior for fluid homeostasis and is frequently and necessarily observed in daily life. Water drinking causes many physiological changes, including fluctuations in endocrine function, cardiovascular system, and fluid balance during or immediately after drinking [1–7]. Because these changes occur in the early phase of drinking, the contribution of absorbed water from the gastrointestinal tract may be little, if any, but neural factors such as reflex, as with receptors in the oral, pharyngeal, esophageal, or gastric regions, have been suggested. Stimulation of the oropharyngeal region with water results in a decreased release of vasopressin and causes hypotonic diuresis in humans [1]. Recently, we have demonstrated that water drinking caused a biphasic change in blood volume; an initial hemoconcentration followed by hemodilution in humans [2]. The initial hemoconcentration was likely to be induced by a transient rise in blood pressure (BP) immediately after the onset of drinking. The rise in BP following water drinking by animals and humans might be attributed to stimuli from the oropharyngeal region, swallowing-induced factors, and/or a feedforward mechanism by a central descending signal from the higher brain centers. [Japanese Journal of Physiology, 52, 421–427, 2002]

Changes in Blood Pressure and Muscle Sympathetic Nerve Activity during Water Drinking in Humans

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Abstract: To investigate the possible involvement of the sympathetic nervous system in pressor response during water drinking, muscle sympathetic nerve activity (MSNA), blood pressure (BP), and heart rate (HR) were continuously measured in healthy young volunteers throughout the experiments of a 5-min control, 2 min of drinking 500 ml water, and a 28-min recovery. To avoid the effects of water passing through the oropharyngeal and esophageal regions and/or effects of swallowing, an equal amount of water was directly infused to the stomach through a stomach tube for 2 min. Water drinking caused a transient increase in mean arterial pressure (MAP) and HR immediately after drinking ($\Delta$MAP, 12.6±2.1 mmHg; $\Delta$HR, +19.9±1.7 beats/min at the peak). An abrupt decrease of MSNA was observed directly during water drinking ($\Delta$burst rate, −6.9±1.3 bursts/min; $\Delta$total activity, −2,606±491 U/min), and it increased to the baseline level thereafter. Gastric infusion had little or no effect on MAP, HR, and MSNA. The present study demonstrated that a pressor response during water drinking was associated with the attenuation of MSNA and not generated by gastric infusion of water at the same rate as in this drinking manner. In conclusion, the rapid rise in BP might be caused through stimulations from the oropharyngeal region, swallowing-induced factors, and/or a feedforward mechanism by a central descending signal from the higher brain centers. [Japanese Journal of Physiology, 52, 421–427, 2002]

Key words: pressor response, microneurography, water ingestion, gastric distension, human.

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Abbreviations: BP, blood pressure; ECG, electrocardiogram; HR, heart rate; MAP, mean arterial pressure; MSNA, muscle sympathetic nerve activity.

associated changes in BP remain unsolved. An enhanced sympathetic activity during drinking was suggested to play a role in the rise in BP [3, 6].

Therefore, the present study was designed to investigate whether or not the rise in BP during water drinking was directly caused by an increase in sympathetic nerve activity in humans. We measured muscle sympathetic nerve activity (MSNA) before, during, and after water drinking, and simultaneously measured BP and heart rate (HR). Further, we tested the possible effects of water passing through the oropharyngeal and esophageal regions as well as gastric stimulation on the drinking-associated changes in MSNA, BP, and HR.

METHODS

Subjects. A total of 19 healthy young male volunteers (22.3±0.3 years, 66.5±1.7 kg body wt., 172.4±1.3 cm height) participated in the experiments. The study was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, and all subjects gave their written consent after being fully informed about the procedures, risks, and protocol. All subjects were requested to refrain from eating and drinking after 2200 h on the day prior to the experiment in the case of the experiment being conducted in the morning or after taking breakfast on the experimental day in the case of the experiment being conducted in the afternoon.

Procedure. On the experimental day, each subject reported to the laboratory at 0900 h in the morning or 1300 h in the afternoon. The subjects rested in a thermoneutral room (28°C; 60% relative humidity) for 1 h, while they were instrumented with electrodes for electrocardiogram (ECG), a BP cuff which was maintained at heart level, and a thermocouple (copper-constantan) at the nostril for monitoring respiration, and then prepared for MSNA measurement. They were kept in sitting position throughout the experimental period. After a 5-min control period, they took half a liter of tap water at 25.0°C within 2 min, followed by a 28-min recovery period of recording. In the first experiment, they drank a half a liter water in 2 min (water drinking test, n=9). In the second experiment, the subject was infused the same amount of water in 2 min using a syringe and stomach tube (Safeed feeding tube, Terumo, Tokyo, Japan), which was swallowed to the stomach beforehand, and which the position in the stomach was verified by brief aspiration of gastric juice (gastric infusion test, n=10). During the control experiment, 5 subjects who participated in either of the tests were only kept in sitting position without drinking water over the experimental time (35 min). The MSNA recordings failed for some subjects during the water drinking test (n=3) and gastric infusion test (n=4).

Measurements.

Microneurography. Recording of MSNA was performed using a tungsten microelectrode (UN (KS1), Frederick Haer, Brunswick, ME, USA) that was manually inserted through intact skin into the right peroneal nerve fascicles without local anesthesia, as previously reported [11–14]. A reference electrode was placed on the skin near the recording electrode. The original nerve signals were amplified by a differential amplifier subsequently fed through a band-pass filter with a bandwidth of 200–3,000 Hz, which in turn filtered the signal through a band-pass filter (E3201A, NF Electronic Instruments, Yokohama, Japan) with a bandwidth of 500–1,500 Hz. The filtered neurogram, which was made audible through a loudspeaker, was routed through a resistance-capacitance integrator unit with a time constant of 0.1 s (1322 Integrate unit, NEC San-Ei, Tokyo, Japan), from which an average voltage display of the nerve signal was obtained. The identification of MSNA was performed according to the following criteria, as previously described [15–17]: (1) weak and intermittent internal electrical stimuli caused involuntary muscle twitches but no paresthesia of the leg, (2) the signals showed spontaneous, intermittent, and pulse-synchronous bursts, and (3) the signals were increased by the Valsalva maneuver. Sympathetic bursts were detected by inspecting the integrated neurogram. The amplitude of each burst was determined by direct observation.

Hemodynamics. BP was determined by a Finapres finger photoplethysmography (Finapres, model 2300, Ohmeda, Engelwood, CO, USA) and the pressure checked occasionally by a Dynamap automated oscillometric blood pressure device (Critikon Model 8100, Tampa, FL, USA). Mean arterial pressure (MAP) was calculated as the electronic mean of the Finapres signal. HR was determined from ECG.

Data analysis. Both filtered and integrated neurograms, beat to beat arterial BP and ECG were stored in an eight-channel digital tape recorder (RD-135T DAT Data Recorder, TEAC, Tokyo, Japan) and recorded on an eight-channel recorder with a maximum frequency response of 2.5 kHz (8M24, NEC San-Ei). In addition, the data of BP and HR were also sampled and calculated every 5 s and stored in a NEC computer. Further, correlation between changes in MAP and MSNA for the drinking duration was computed using Pearson’s correlation coefficient.
MSNA was expressed in terms of both burst rate (bursts/min) and total activity, which was calculated by burst rate × mean burst amplitude (arbitrary unit) and expressed in U/min.

Comparison of the data was made by analysis of variance (ANOVA) for repeated measurements in the same subjects. When significant F ratios were obtained, least significant differences were calculated for comparisons of the mean data between baseline control and during or after the episode. The significance level was set at \( p<0.05 \). Results are expressed as means±SE.

**RESULTS**

**Water drinking test**

A typical recording of HR, BP, respiration rate, and MSNA during the baseline control, water drinking, and the recovery period is shown in Fig. 1. Water drinking transiently increased MAP and HR, and reduced MSNA (Table 1 and Figs. 2, 3). MAP was stable at 88.4±1.9 mmHg during the control period, increased immediately after the start of drinking and further increased to reach the peak value of 100.7±3.1 mmHg in 1.92 min during drinking. After the cessation of drinking, MAP returned to the baseline level in 20 s (Fig. 3). HR was stable at 59.9±3.4 beats/min during the control period, rapidly increased to 79.9±4.2 beats/min 30 s after the start of drinking and then gradually decreased to 71.3±3.4 beats/min at the termination of drinking. HR returned to the baseline level about 30 s after the termination of drinking (Fig. 3). Thereafter, both MAP and HR were stable until the end of the experiments, as shown in Fig. 2.

MSNA was stable during the control period and decreased during drinking (burst rate, 13.3±1.6 bursts/min in the first min and 13.5±2.0 bursts/min in the second min; total activity, 4,954±608 U/min in the first min and 5,177±790 U/min in the second min), as shown in Table 1 and Fig. 3. Thereafter, MSNA values increased to the baseline level and appeared to be sta-

**Table 1. Changes in mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) during and after water drinking.**

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Period</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Drinking or GI</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88.4±1.9</td>
<td>97.5±2.9**</td>
</tr>
<tr>
<td></td>
<td>87.9±2.4</td>
<td>89.5±2.3</td>
</tr>
<tr>
<td></td>
<td>86.4±4.1</td>
<td>85.1±4.4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>59.9±3.4</td>
<td>73.8±3.5**</td>
</tr>
<tr>
<td></td>
<td>61.4±3.6</td>
<td>61.4±3.7</td>
</tr>
<tr>
<td></td>
<td>63.7±3.5</td>
<td>65.1±3.2</td>
</tr>
<tr>
<td>MSNA bursts (bursts/min)</td>
<td>20.2±1.6</td>
<td>13.4±1.7**</td>
</tr>
<tr>
<td></td>
<td>21.7±2.9</td>
<td>20.0±2.8</td>
</tr>
<tr>
<td></td>
<td>21.5±2.4</td>
<td>21.6±1.8</td>
</tr>
<tr>
<td>Total MSNA (U/min)</td>
<td>7,560±546</td>
<td>5,066±692**</td>
</tr>
<tr>
<td></td>
<td>8,189±1.711</td>
<td>7,738±1,550</td>
</tr>
<tr>
<td></td>
<td>7,903±845</td>
<td>8,462±605</td>
</tr>
</tbody>
</table>

Values are means±SE. GI, gastric infusion; NS, not significant. ** \( p<0.01 \) vs. baseline values.
Fig. 2. Changes in mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) during and after water drinking or gastric infusion (GI) of water. Values are means±SE.

As shown in Fig. 4, the correlation between changes in MAP and MSNA during water drinking was significant and negative (Pearson’s correlation coefficient, \( r = -0.668, p < 0.05 \); i.e., as MAP increased, MSNA decreased).

**Gastric infusion test**

MAP was stable at 87.9±2.4 mmHg during the control period and remained unchanged throughout the experiment (Table 1 and Figs. 2, 3). HR was stable at 61.4±3.6 beats/min during the control period, transiently increased by 5.0±2.5 beats/min 1.5 min after the termination of infusion and then stabilized at baseline level afterward (Figs. 2, 3). MSNA was stable during the control period and tended to decrease transiently during gastric infusion, but these changes were not statistically significant (Figs. 2, 3). In the recovery period, MSNA was stable at the baseline level (Fig. 2).

**Time control**

As shown in Table 1, in the time control experiment, all of the variables measured in this study, in-
including MAP, HR, and MSNA, were stable only when in the sitting position without water drinking or gastric infusion.

**DISCUSSION**

The present study clearly revealed that water drinking causes a rapid and marked rise in BP and HR and decrease in MSNA. The present findings confirmed an increase in HR and BP during water drinking in humans [2] and other animals such as rats [3, 6], goats [4, 5], and dogs [7].

MSNA has been recognized to consist of vasoconstrictor signals into the muscle vasculature and may be under baroreceptor reflex control [18], resulting in an inverse relationship between changes in BP and MSNA [16, 18, 19]. The present data also demonstrated a negative correlation coefficient between changes in MAP and MSNA during water drinking. Hoffman et al. [3] reported tachycardia and increased BP during water drinking in rats. They also observed abolishment of the pressor response by α-adrenergic blockade, thus the drinking-associated tachycardia and increased BP seemed to be associated with the enhancement of sympathetic activity. On the contrary, in the present study, MSNA significantly decreased during water drinking. The reason for the discrepancy appears to be dependent on the animal species used, rats in their study and humans in our present study, and/or appears to be dependent on the regional difference of the sympathetic nerve activities [20]. Regarding the latter, sympathetic nerve activities to other regions including the heart might have been stimulated during water drinking while MSNA were attenuated. In accordance with this speculation, it has been demonstrated that sympathetic nerve activities to the heart and kidneys are stimulated during feeding or drinking activity, resulting in the initial pressor response [20, 21], and sympathetic nerve activities increased almost simultaneously with the onset of eating followed by increases in BP and HR after a few seconds lag time [22]. These responses might be caused through a feed-forward mechanism activated by a central descending signal from the higher brain centers, not by baroreflexes [21]. What, if any, may be the other mechanisms responsible for the water drinking–associated rise in BP?

Rossi et al. [9] observed increased MSNA and BP by increasing intragastric pressure by means of inflating a balloon in the stomach, and the magnitude of the increase was in proportion to the intragastric pressure. What is the reason for the discrepancy as compared to the present experiment? In this study, water drinking or gastric infusion of 500 ml of water in 2 min may not have resulted in sufficient intragastric pressure to trigger the responses observed by Rossi et al. [9]. The data on gastric infusion revealed no significant effects on BP, HR, and MSNA, in accordance with a previous observation in rats [6]. Gastric factors might not be involved in the water drinking–induced rise in BP, at least in this drinking manner.

Stimulation from the esophageal region has been reported to modulate cardiac function because of a close relationship between the vagal and sympathetic innervations of the esophagus and the heart [23]. Tougas et al. [23] observed that electric and mechanical stimulation of the esophagus caused a sympatho-inhibitory effect and vagal acceleration in association with a decrease in HR, which is likely to be the reverse direction of the present findings. Furthermore, it has been reported that stimulation to regions innervated by trigeminal afferent nerves produces an increase in BP and HR by activating cardiovascular sympathetic efferents and decreasing vagal efferents in anesthetized rats [24, 25]. Accordingly, stimulation of the oropharyngeal region rather than the esophagus during water drinking may play a role in the drinking-induced pressor response as observed in the present study. Takeshima and Dohi [26] reported that swallowing saliva twice only caused a transient increase in BP and HR in humans. The possibility that hypoxemia after asphyxiation due to a glottis closure when swallowing water may activate the chemoreceptors and result in an acute rise in BP has been ruled out since breathing 95% oxygen fails to prevent a rise in BP [3]. Therefore, swallowing-induced factors other than hypoxemia may cause a rapid rise in BP during water drinking. Drinking water necessitates instantaneous and repeated glottis closure, which could have an effect on BP through influences on the respiratory functions. In Valsalva maneuver, increased intrathoracic pressure causes an elevation of systemic arterial pressure with brief reductions of MSNA during the initial phase of Valsalva straining [27, 28]. Accordingly, such an elevation of intrathoracic pressure during water drinking might cause a pressor response as observed in the present study. However, respiration was instantaneously and intermittently stopped, but not breath-holding, at least in the drinking manner in the present study. It has been also elucidated that Valsalva maneuvers cause an elevation of BP and abrupt decrease in HR [28], different from our present results. In any case, the cardiovascular responses observed in the present study might be slightly attributed to changes in intrathoracic pressure during the drinking activity.
It has been reported that water drinking could not cause a significant change in BP in young subjects [29, 30], and Scott et al. [31] reported, in normal human subjects, that the drinking of 500 ml water in 5 min increases MSNA in 20 to 40 min after ingestion, without significant changes in BP. These researchers might have ignored or failed to observe the initial rise in BP during drinking because the phenomenon was observed only during drinking and/or they focused on the changes in BP in the later phase, probably due to the post-absorptive effect of ingested fluid.

We do not know whether or not drinking a smaller amount of water or at slower rate, as usually done in our daily life, can induce similar responses. The drinking-associated rise in BP has been observed in rats after ad libitum water drinking [3]. Furthermore, we have demonstrated that drinking 1 l of water by humans caused a rise of over 20 mmHg in MAP [2], a greater increase than that shown in the present experiment when drinking 500 ml of water. Recently, water ingestion has been reported to increase BP over 30 min after drinking in aged healthy humans, but not the younger controls [30, 31]. Further, it has been reported that drinking 480 or 500 ml of water increases BP to a greater magnitude in patients with autonomic failure [32]. Therefore, the degree of drinking-induced rise in BP is likely to be dependent on the volume of water drunk, the rate of drinking, age, and types of disease such as autonomic failure.

In conclusion, our present study revealed that water drinking causes a rapid and marked rise in BP in concurrence with the attenuation of MSNA in humans. On the other hand, gastric infusion had no significant effect on BP, HR, and MSNA. The present findings suggest that water drinking causes a rise in BP, probably through stimulations from the oropharyngeal region and/or swallowing-induced factors, resulting in an increase in cardiac sympathetic efferent nerve activity. Furthermore, a feedforward mechanism activated by a central descending signal from the higher brain centers might be also involved in the pressor response during water drinking. To examine the pressor mechanism associated with water drinking in more detail, further work is warranted.

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REFERENCES

17. Vallbo ÅB, Hagbarth HE, Torebjörk HE, and Wallin BG:...
Pressor Response during Water Drinking

Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. Physiol Rev 59: 919–957, 1979


