The osmopressor response to water drinking

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May M, Jordan J. The osmopressor response to water drinking. Am J Physiol Regul Integr Comp Physiol 300: R40 –R46, 2011. First published November 3, 2010; doi:10.1152/ajpregu.00544.2010.—Water drinking elicits profound pressor responses in patients with impaired baroreflex function and in sinoaortic-degenerated mice. Healthy subjects show more subtle changes in heart rate and blood pressure with water drinking. The water-induced pressor response appears to be mediated through sympathetic nervous system activation at the spinal level. Indeed, water drinking raises resting energy expenditure in normal weight and obese subjects. The stimulus setting off the response is hypoisomolarity rather than water temperature or gastrointestinal stretch. Studies in mice suggest that this osmopressor response may involve transient receptor potential vanilloid 4 (Trpv4) receptors. However, the (nerve) cell population serving as peripheral osmosensors and the exact transduction mechanisms are still unknown. The osmopressor response can be exploited in the treatment of orthostatic and postprandial hypotension in patients with severe autonomic failure. Furthermore, the osmopressor response acutely improves orthostatic tolerance in healthy subjects and in patients with neurally mediated syncope. The phenomenon should be recognized as an important co-founder in cardiovascular and metabolic studies.

osmoreceptors; autonomic failure; syncope; blood pressure

WATER CONTENT OF THE HUMAN body decreases substantially from birth to an old age. Yet, the water molecule remains by far the dominating body constituent throughout lifetime. In mammals the relationship between free water and solutes in extra- and intracellular compartments, which determines osmolality, is tightly regulated through adjustment in water ingestion and excretion (3, 24, 69, 82). Even mild abnormalities in systemic osmoregulation can have grave consequences (2, 38, 44, 61, 69). Water intake is affected by thirst and psychosocial factors as water drinking is considered a healthy habit. Water excretion is primarily regulated through adjustment in water permeability in renal distal tubules and collecting ducts. The response is mediated largely through a rapid decrease in vasopressin release with subsequent aquaporin downregulation. These reflex mechanisms are governed by osmoreceptors detecting small changes in extracellular fluid osmolality. Central osmoreceptors located in the organum vasculosum of the lamina terminalis and subfornical organ (49, 51, 79), such as brain nuclei with no blood/brain barrier (4, 7, 25, 30), play a crucial role in osmoregulation. These mechanisms have been extensively studied and reviewed elsewhere. In addition, there is evidence for hitherto poorly characterized peripheral osmosensitive neurons (29, 52, 73). We review data suggesting that local changes in osmolality through water drinking may elicit a powerful pressor response and changes in energy metabolism through sympathetic nervous system activation. This osmopressor response may involve activation of transient receptor potential vanilloid 4 (Trpv4) receptors, which may be located on putative peripheral osmoreceptors. The osmopressor response has to be differentiated from immediate changes in sympathetic activity and in blood pressure elicited by stimulation of the oropharyngeal region or swallowing in animals (77) and in human subjects (11, 21).

Water-Induced Pressor Response

The fact that water drinking may elicit acute cardiovascular effects came to our attention through patients with severe orthostatic hypotension due to autonomic failure. Autonomic failure ensues when the sympathetic and parasympathetic nerves comprising the efferent baroreflex portion are interrupted. Neuronal degeneration within the brain or in the periphery (9, 70), enzymatic defects in catecholamine synthesis (45, 57), and autoimmune disorders (64, 80) can be causative. Common to all of these syndromes is debilitating orthostatic and postprandial hypotension. Some patients are unable to stand for more than a few seconds before presyncopal symptoms occur. Some autonomic failure patients reported rapid symptomatic improvement with water drinking. Subsequently, we tested the response to drinking 480 ml tap water in these patients (33, 35). In patients with central autonomic failure due to multisystem atrophy, seated systolic blood pressure increased 33 mmHg. In patients with peripheral autonomic degeneration due to pure autonomic failure, seated systolic blood pressure increased 37 mmHg (33). The pressor response had an onset within 5 min after water drinking, reached a maximum in 30–40 min, and was maintained for more than 1 h (Fig. 1). The response was reproduced by other groups (12). In elderly healthy subjects drinking 480 ml tap water, we observed a slight increase in systolic blood pressure of up to 11 mmHg above baseline (33, 35). In contrast, water
drinking in healthy young subjects did not elicit a pressor response (33, 65).

More detailed hemodynamic studies provided important insight in potential underlying mechanisms. These studies suggested that an increase in systemic vascular resistance rather than cardiac output mediates the pressor response in autonomic failure patients (12). Similarly, healthy young subjects showed an increase in calf vascular resistance, while systemic vascular resistance and blood pressure remained unchanged (65). Volume expansion is unlikely to contribute to the pressor response because free water is distributed throughout the extra- and intracellular space. Furthermore, drinking 480 ml water elicited a much greater pressor response than intravenous infusion of the same volume of 5% dextrose in water (33). Finally, water drinking did not induce major changes in plasma volume (33) or thoracic bioimpedance (63). Thoracic bioimpedance is related to thoracic blood volume (19). Together, these observations suggest that water drinking elicits changes in vascular tone that are unmasked in individuals with aging-associated changes in baroreflex regulation and more so in patients with profound baroreflex abnormalities due to neurodegenerative diseases. The cardiovascular portion of the efferent baroreflex arc is severed in cardiac transplant recipients. These patients show a moderate blood pressure increase with water drinking (60, 76). These ideas are supported by recent experiments in anesthetized mice given 25 μl/g body wt water through gastric or duodenal catheters over 6 min (48). Mice with intact baroreflexes did not respond to water. In contrast, water elicited a substantial increase in blood pressure after interruption of the afferent baroreflex arc through sinoaortic denervation. Remarkably, the time course of the pressor response to water in mice resembled the time course of the response to water drinking in human subjects.

Evidence for Water-Induced Sympathetic Activation

When we first observed the water drinking-induced pressor response in autonomic failure patients, we were convinced that sympathetic activation could not be involved given the underlying pathology. Indeed, sympathetic responses to cold pressor testing, handgrip testing, and other sympathetic stimuli are commonly attenuated in autonomic failure patients. One of the more puzzling findings in autonomic failure patients is that even in severely affected patients, loss of efferent sympathetic function is rarely complete. Some residual efferent nerves appear to be disconnected from central nervous system input, making them truly autonomic. Therefore, pharmacological blockade of autonomic ganglia with trimethaphan reduces blood pressure in a subgroup of pure autonomic failure patients and in virtually all patients with multiple system atrophy (68). Conversely, the α2-adrenergic receptor antagonist yohimbine engages residual sympathetic efferents, thus, raising blood pressure in a large proportion of autonomic failure patients (6, 32, 58). Yohimbine increases sympathetic activity by blocking the α2-adrenergic receptors in the central nervous system and in presynaptic adrenergic neurons (58). Patients with complete loss of efferent sympathetic function do not respond to yohimbine.

To address the question of whether residual sympathetic function is required to express the water-drinking pressor response, we tested yohimbine and water in autonomic failure patients. Patients with a complete loss of sympathetic efferent function suggested by absence of a pressor response to yohimbine showed no changes in blood pressure after water drinking. Patients with residual sympathetic function indicated by a large response to yohimbine also showed a large water drinking-induced pressor response (33). In two patients with autonomic failure, we tested the response to water with and without trimethaphan infusion. Trimethaphan abolished the water-induced pressor response (33). In sinoaortic-denervated mice, α1-adrenergic receptor blockade with prazosin attenuated the pressor response to water (48).

The idea that sympathetic nerves releasing norepinephrine are required to express the water-induced pressor response is supported by observations in mice with genetic deletion of the gene encoding dopamine-β-hydroxylase. The enzyme is required for conversion of dopamine to norepinephrine. Dopamine-β-hydroxylase deficiency is a rare cause of human autonomic failure (45). Plasma and urine norepinephrine and epinephrine are hardly detectable in dopamine-β-hydroxylase-deficient human beings and mice. Dopamine-β-hydroxylase-deficient mice did not show a pressor response to water (48). When we tested water drinking in a middle-aged woman with dopamine-β-hydroxylase deficiency, she did not respond either (Jordan J, Shannon JR, and Robertson D, unpublished observation).

While changes in blood pressure after water drinking require impairment in baroreflex function, sympathetic activation appears to be a more universal phenomenon. Water drinking increases muscle sympathetic activity in healthy subjects in the absence of a pressor response (65). Moreover, venous plasma norepinephrine concentrations increased significantly with water drinking in younger and in older healthy subjects (23, 33, 65) as well as in autonomic failure patients (55).

The sympathetic nervous system has a central role in the regulation of energy expenditure. Therefore, a change in sympathetic activity should lead to concomitant metabolic responses. Using whole-room indirect calorimetry and microdialysis we assessed the response to drinking 500 ml water on overall energy balance, substrate oxidation rates, and lipid mobilization in young healthy subjects (8). With water drinking, resting metabolic rate increased ~30% reaching a maximum after 30–40 min (Fig. 2). The response was predominantly fueled by lipid oxidation in men and carbohydrate...
The thalamus, midbrain, and medulla build a central autonomic system that involves neurons in the hypothalamus, which are activated by water intake, and there is not necessarily a general increase in muscle sympathetic activity and energy expenditure. The increase in sympathetic activity raises blood pressure buffering and increased vascular sensitivity, and blood pressure increases. Moreover, intragastric and intraduodenal fluid infusion induced an identical pressor response in sinoaortic-denervated mice.

Recent studies uncovered potential stimuli activating the spinal sympathetic response to water drinking. In autonomic failure patients, the magnitude of the water-induced pressor response was not related to water temperature. Only one third of the increase in resting energy expenditure could be explained by warming the water from 22°C to 37°C. Even drinking water at 37°C increased the metabolic rate. Gastric distention increases sympathetic activity in humans. Sympathetic activation elicited by gastric distention may attenuate postprandial hypotension (26). Yet, the maximal response to water drinking was observed after ~40 min. At this time, only 25% of the ingested water remains in the stomach. In some patients with autonomic dysfunction, small amounts of water were sufficient to trigger significant and sustained blood pressure increases. Moreover, intragastric and intraduodenal fluid infusion induced an identical pressor response in sinoaortic-denervated mice. Thus, the afferent structure responding to water is likely located distally from the stomach. Temperature or gastric distention is not sufficient to set off the spinal sympathetic activation. Water drinking raises blood pressure both in multiple system atrophy and in high spinal cord-injured patients. In multiple system atrophy patients, the lesion to the efferent part of the autonomic nervous system is located in the brain stem. Other distal efferent sympathetic structures are at least, in part, intact.

Pathways Mediating Sympathetic Activation with Water Drinking

Activity of postganglionic adrenergic neurons, which ultimately mediates all of the hemodynamic and metabolic responses to water drinking, could be engaged through various mechanisms. Brain stem and spinal pathways are prime candidates. It appears less likely that water drinking produces a signal directly affecting postganglionic adrenergic activity in peripheral tissues. The underlying pathology in water-responsive patients and the heart rate response to water drinking helped with localizing the neural substrate for water-induced sympathetic activation. Water drinking raises blood pressure in patients with high spinal cord injury. In contrast, physiological central-mediated sympathetic activation typically produces sympathetic efferent nerves. This idea is supported by the observation that heart rate decreases with water drinking, whereas heart rate variability increases. The response likely results from baroreflex activation of cardiac parasympathetic efferent nerves. Similarly, spinal sympathetic activation induced by bladder distention elicits hypertension and bradycardia in patients with high spinal cord injury. In high spinal cord-injured patients, spinal sympathetic neurons are intact but disconnected from brain stem input. Postganglionic sympathetic neurons can be activated by spinal reflexes but not by reflexes travelling through the brain stem, including baroreflexes. Thus, water drinking engages a spinal reflex-like mechanism that activates sympathetic efferent nerves. Notable exceptions are diving and Cushing reflexes. Finally, bilateral subdiaphragmatic vagotomy did not abolish the pressor response to water drinking in sinoaortic-denervated mice.

Oxidation in women. The additional energy expenditure associated with drinking 500 ml water averaged 100 kJ. A moderate single oral beta-blocker dose attenuated the response. Other groups, measuring energy expenditure with a ventilated hood, did not observe changes in energy expenditure with water drinking. Together, all of these observations suggest that water drinking raises sympathetic activity. The increase in sympathetic activity drives a pressor response in the setting of impaired baroreflex function. In addition, sympathetic activation raises energy expenditure even in healthy young subjects.

With water drinking, a similar increase in endogenous norepinephrine produces a much greater blood pressure increase in autonomic failure patients compared with healthy subjects. Autonomic failure patients are also extremely hypersensitive to exogenous α-adrenergic agonists. Loss of baroreflex blood pressure buffering and increased vascular sensitivity may contribute to the pressor hypersensitivity.

While some parts of the sympathetic nervous system (e.g., muscle sympathetic activity and energy expenditure) are activated by water intake, there is not necessarily a general sympathetic activation. Multiple, interacting, but modality-specific, hierarchical systems involving neurons in the hypothalamus, midbrain, and medulla build a central autonomic network and allow a selective regulation of the vascular resistance of different vascular beds and for the expression of patterned autonomic responses. The organization of neural circuits specifically reacting to water ingestion remains to be elucidated.
water response leaving local/regional hypoosmolarity as a likely trigger.

Drinking water is hyposmolar compared with extracellular fluid. When liquids with different osmolarities were infused into the stomachs of dogs, distilled water showed a twofold greater increase in blood pressure compared with isotonic saline (29). In rats, infusion of hypoosmolar solutions into the portal vein with concomitant infusion of hyperosmolar solutions into the vena cava elicited robust increases in diuresis (29). The experimental setup led to selective hypoosmolar stimulation of the liver, whereas central osmoreceptors were exposed to isoosmolarity. The diuretic response was attenuated when the infusions were switched. The observation suggested the presence of hepatic osmoreceptors. Though others did not reproduce the findings (62), there are investigations giving evidence for hepatic osmoreceptors (13, 37).

Infusion of water elicited a much greater pressor response compared with isotonic saline infusions in sinoaortic-denervated mice (48). Moreover, in patients with autonomic failure due to multiple system atrophy, water given through a nasogastric tube increased blood pressure more than the same volume of normal saline (41). Similarly, addition of sodium chloride to drinking water attenuated the pressure response in autonomic failure patients (55). Finally, in healthy subjects, hyposmolar fluid given through a gastric tube increased sweat production, which could be sympathetically mediated, to a greater extent than infusion of isoosmolar solutions (29). All of these findings support the idea that hypoosmolarity is the stimulus for water-induced sympathetic activation. Water ingestion likely results in particularly large osmolality changes in the portal tract and in the liver. Therefore, we speculate the osmosensitive afferent neurons may be located in this anatomical area. Indeed, in mice, changes in portal vein osmolality coincide with changes in blood pressure (48). In the same set of experiments, systemic osmolarity remained unchanged (48).

The molecular transduction mechanisms involved in sensing hypoosmotic signals in peripheral tissues are poorly understood. The transient receptor potential (Trp) channel family including the vanilloid subfamily Trpv is involved in recognition of noxious environmental stimuli including osmolality, temperature, and pain. Trpv4 is a prime suspect given its sensitivity to osmotic changes (39, 40, 56, 74, 75). Indeed, although portal osmolality decreases after water application in wild-type and Trpv4−/− mice (all had undergone sinoaortic denervation), only wild-type animals showed a pressor response (Fig. 3). Yet, wild-type and Trpv4−/− mice showed a similar increase in blood pressure due to restraint stress (48). This observation suggests that effenter sympathetic function was intact in both strains. Thus, the presence of Trpv4 is required to express the osmopressor response. We speculate that Trpv4 channels on hepatic and/or portal spinal afferent neurons could be involved.

Therapeutic Utility of Water Drinking

Recognition of the osmopressor response has had an important impact on the management of autonomic nervous system disorders, particularly in patients with autonomic failure and with neurally mediated (vasovagal syncope). Water drinking improves standing blood pressure and orthostatic tolerance in a large subgroup of patients with autonomic failure (66). The maximal pressor response to water is reached when other pressor agents are only beginning to act. Furthermore, water drinking attenuates postprandial hypotension (66). We recommend that water should be ingested before meals and when orthostatic symptoms are worst. Water ingestion is particularly useful in the morning before arising with or without the addition of pressor drugs. Most patients experience particularly severe orthostatic symptoms in the morning due to sodium loss throughout the night. Patients with supine hypertension should avoid water drinking at least 1 h before bedtime (68). The effects of pressor agents, such as pseudoephedrine and phenylpropanolamine, are potentiated by water drinking (34). These drug interaction effects can be exploited in the treatment of orthostatic hypotension. However, the interaction can also lead to potentially dangerous blood pressure surges. Excessive water ingestion should be avoided, particularly in patients with multiple system atrophy because potential life threatening hyponatremia could ensue.

Water drinking could have a therapeutic benefit in patients with postural tachycardia syndrome (idiopathic orthostatic intolerance), a syndrome that is more common than autonomic failure. True to its name, postural tachycardia syndrome is associated with tachycardia while standing in the absence of significant orthostatic hypotension (42, 72). Drinking 480 ml water lowered upright heart rate 15 and 10 beats/min after standing 3 and 5 min, respectively (66).

Influences of water drinking on orthostatic tolerance in healthy subjects and in patients with neurally mediated (vasovagal) syncope have been studied using head-up tilt testing combined with lower body negative pressure according to the Leeds protocol (20) or with regular head-up tilt testing. Studies were conducted in a crossover fashion. In young healthy subjects water drinking can delay or even prevent syncope during head-up tilt testing with or without lower body negative pressure (43, 63). Patients with neurally mediated syncope showed similar improvements in orthostatic tolerance with ingestion of 500 ml water (14). Water drinking decreases the risk for blood donation-related vasovagal reactions (1, 22, [Fig. 3 from McHugh et al. (48)]]
50) and may be beneficial in individuals with postexercise syncope (78).

On the basis of acute metabolic responses to single water applications in the metabolic chamber, we speculated that increasing water intake by 1.5 l/day could raise energy expenditure by ~200 kJ/day (8). Over 1 yr, energy consumption would increase 73,000 kJ (17,400 kcal) corresponding to the energy content of 2.4 kg adipose tissue. In comparison, administration of 50 mg ephedrine three times a day increased energy expenditure about 320 kJ/day (67). Whether water drinking as a cost-free intervention has a significance in the treatment of excess weight and obesity has not been assessed in prospective studies. However, in overweight and obese women, drinking water was associated with improved weight loss even after adjustment for nutrition and physical activity (71).

**Perspectives and Significance**

Drinking water elicits a sympathetically mediated pressor response in the setting of impaired baroreflex function in both human beings and animals. The increase in sympathetic activity is associated with significant increases in resting energy expenditure. Studies in patients with high spinal cord injury suggest a spinal reflex-like mechanism. The signal setting off the pressor response seems to be hypnoosmolality. Transduction of the hypoosmotic signal requires the presence of Trpv4. We speculate that these osmosensors may be located in liver and portal vasculature. However, the (nerve) cell population serving as peripheral osmosensors and the exact transduction mechanisms are still unknown. Moreover, the physiological role of peripheral osmosensors in human beings is not fully understood. It is possible that liver and portal osmosensors, which are exposed to relatively large swings in blood osmolality with feeding and drinking, serve as a first line of defense for maintenance of systemic osmolality. Conditions in which hepatic perfusion through the portal vein or hepatic innervation is disturbed may provide relevant models for physiological investigations. Remarkably, hyponatremia is common in patients with end-stage liver disease. Perhaps, manipulation of peripheral osmosensors via Trpv4 could be clinically applied in these patients. On the other hand, sympathetic activation elicited by hypnoosmolality can be therapeutically exploited. Indeed, the osmopressor response provides an effective and inexpensive treatment of orthostatic syndromes. The increase in metabolic rate with water drinking could be systematically applied in the prevention of weight gain and associated metabolic and cardiovascular risk factors. In essence, water drinking provides negative calories. In the event, a recent study applied in the prevention of weight gain and associated metabolic and cardiovascular risk factors. In essence, water drinking provides negative calories. In the event, a recent study

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).


