Increased osmolality of conscious water-deprived rats supports arterial pressure and sympathetic activity via a brain action

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Submitted 20 September 2004; accepted in final form 6 January 2005

Brooks, Virginia L., Yue Qi, and Theresa L. O’Donaughy.
Increased osmolality of conscious water-deprived rats supports arterial pressure and sympathetic activity via a brain action. Am J Physiol Regul Integr Comp Physiol 288: R1248–R1255, 2005. First published January 20, 2005; doi:10.1152/ajpregu.00638.2004.—To test the hypothesis that high osmolality acts in the brain to chronically support mean arterial pressure (MAP) and lumbar sympathetic nerve activity (LSNA), the osmolality of blood perfusing the brain was reduced in conscious water-deprived and water-replete rats by infusion of hypotonic fluid via bilateral nonoccluding intracarotid catheters. In water-deprived rats, the intracarotid hypotonic infusion, estimated to lower osmolality by -2%, decreased MAP by 9 ± 1 mmHg and LSNA to 86 ± 7% of control; heart increased by 25 ± 8 beats per minute (bpm) (all P < 0.05). MAP, LSNA, and heart rate did not change when the hypotonic fluid was infused intravenously. The intracarotid hypotonic fluid infusion was also ineffective in water-replete rats. Prior treatment with a V1 vasopressin antagonist did not alter the subsequent hypotensive and tachycardic effects of intracarotid hypotonic fluid infusion in water-deprived rats. In summary, acute decreases in osmolality of the carotid blood of water-deprived, but not water-replete, rats decreases MAP and LSNA and increases heart rate. These data support the hypothesis that the elevated osmolality induced by water deprivation acts via a region perfused by the carotid arteries, presumably the brain, to tonically increase MAP and LSNA and suppress heart rate.

Lumbar sympathetic nerve activity; heart rate; vasopressin; intracarotid infusion

Although it is well established that body fluid osmolality is a sensitive, critical regulator of vasopressin secretion and thirst, more recently, evidence increasingly supports a similar role in the modulation of blood pressure and activity of the sympathetic nervous system [for review, see (37)]. Acute increases in osmolality increase arterial pressure and activate the sympathetic nervous system in a regionally specific manner (1, 12, 40). Studies in water-deprived animals, in which plasma osmolality is more chronically increased, suggest that this rapid sympathoexcitatory effect can be sustained. First, there is evidence that the basal tone of sympathetic nerves activated by acute increases in osmolality is elevated; adrenal nerve activity and lumbar sympathetic nerve activity (LSNA) appear to be increased (6, 29), but basal renal nerve activity may not be altered (30). One index of overall sympathetic tone, plasma catecholamines, consistently exhibits a 50% elevation; however, this elevation has not always reached statistical significance (2, 10, 18, 38). Nevertheless, the depressor response to ganglionic blockade is usually enhanced (13, 34), consistent with the concept that water deprivation is associated with a teleologically appropriate activation of the sympathetic nervous system.

Second, increased osmolality per se contributes to increased LSNA and supports arterial pressure during water deprivation (29). An acute decrease in osmolality from elevated levels due to intravenous infusion of water in conscious water-deprived rats was associated with profound decreases in LSNA; a similar infusion in water-replete rats did not alter LSNA. Arterial pressure also fell in the water-deprived animals. Heart rate did not change; however, an infusion of isotonic saline at a rate that mimicked the volume loading of the water infusion elicited dramatic bradycardia, indirectly suggesting that the fall in osmolality with water infusion tended to increase heart rate. Thus the hypertonicity may also act to tonically suppress heart rate.

These data suggest that high osmolality during water deprivation can influence activity of the autonomic nervous system. However, the site at which osmolality is sensed to trigger these changes is unknown. Osmoreceptors that participate in control of arterial pressure and sympathetic activity have been identified in the brain and the liver (26, 37). Because the most sensitive osmoreceptors, at least in the regulation of thirst and vasopressin secretion, appear to reside in circumventricular organs (CVOs) of the brain (25, 36), this study tested the hypothesis that the high osmolality during water deprivation acts in the brain to support arterial pressure and LSNA and suppress heart rate. To test this hypothesis, rats were chronically prepared with nonoccluding catheters implanted into both carotid arteries. If high osmolality acts centrally, then acute decreases in osmolality to the brain, by infusion of hypotonic fluid via the carotid arteries, should decrease arterial pressure and LSNA and increase heart rate. To test this hypothesis, rats were chronically prepared with nonoccluding catheters implanted into both carotid arteries. If high osmolality acts centrally, then acute decreases in osmolality to the brain, by infusion of hypotonic fluid via the carotid catheters, should decrease arterial pressure and LSNA and increase heart rate in water-deprived, but not water-replete, conscious rats.

Methods
Experiments were performed using male Sprague-Dawley rats (300–350 g) housed individually with free access to 0.4% NaCl diet (LabDiet 5001, Richmond, IN). The housing facility was maintained at a temperature of -22°C with a 12:12-h light-dark cycle. All procedures were conducted in accordance with the National Institutes of Health Guide for the Health and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee.

Surgery
Rats were anesthetized with 2% isoflurane in oxygen. Femoral arterial and venous catheters [4 cm Micro-Renathane tubing (0.025 in. outside diameter, OD); Braintree, MA] welded to PE-50 were im-
planted for measurement of arterial pressure and for infusions, respectively. Nonocclusive intracarotid (ic) catheters, constructed using Micro-Renathane tubing (Braintree, MA) drawn out to a small tip [~0.01 in. outside diameter (OD)], were then implanted. After a midline incision of the skin of the neck, a large segment of each common carotid was dissected free, taking care to avoid disturbance of the carotid sinus, and two ligatures were placed loosely around the vessel. To ensure that fluids were directed to the brain, the external carotid and occipital arteries were ligated. While briefly occluding flow by tension on the ligatures, a small hole was made in the vessel between the ties, and the catheter was inserted and glued in place using Vet Bond (3M Animal Care Products, St. Paul, MN). Distal ends of the catheters were tunneled subcutaneously to exit at the nape of the neck, and all incisions were sutured closed. Rats were allowed at least 3 days, but usually 5 days, for recovery before any other procedures were performed. When not in use, catheters were filled with heparinized saline (500 U/ml, carotid catheters; 200 U/ml, femoral catheters). To maintain patency, intracarotid catheters were flushed daily, and femoral catheters were flushed every 2 days.

In a subset of the rats, a stainless steel bipolar recording electrode was implanted to record LSNA during a second surgery, at least 4 days following catheter surgery, as previously described (29, 42). Briefly, after rats were anesthetized with 2% isoflurane in oxygen, a midline abdominal incision was made. The intestines were retracted, and the aorta and vena cava were gently pulled aside to expose the lumbar nerves. A small segment of a nerve was dissected free, placed on hooks at the end of the bipolar electrode lead, and cemented in place using lightweight dental silicone (Bisico, Bielefeld, Germany). After the electrodes were tunneled subcutaneously and exteriorized at the nape of the neck, the incision was sutured closed.

To document the magnitude of carotid blood flow in conscious, undisturbed rats, a flow probe (Transonic, ISB) was implanted around the common carotid artery at the time of catheter surgery in one additional rat.

**Data Acquisition**

The arterial catheter was connected to a Grass bridge amplifier (7P1) for measurement of phasic and mean arterial pressure (MAP). The pulsatile signal was directed to a Grass tachograph amplifier (7P4) for determination of heart rate. Raw lumbar nerve activity was band-pass-filtered to transmit frequencies between 100 and 3,000 Hz, amplified (20,000–50,000×), whole-wave rectified and integrated (Grass 7P10) over 1-s intervals. MAP, heart rate, and LSNA signals were recorded on a Grass polygraph (7D). At the end of the experiment, background noise was quantified after ganglionic blockade with hexamethonium (30 mg/kg iv), and increases in arterial pressure by intravenous infusion of phenylephrine. This background level was subtracted from values of LSNA recorded during the experiment. LSNA was normalized to baseline nerve activity before the experimental protocol was initiated (% baseline).

**Experimental Protocols**

Rats remained in their home cages during experiments. The vascular catheters and electrode leads were connected to recording equipment or infusion pumps, and the rats were allowed at least 2 h habituation before one of the following protocols was performed. Some rats were used for more than one protocol; however, rats were not water-deprived more than once a week.

**Protocol 1.** This protocol tested the hypothesis that the increase in osmolality induced by water deprivation acts in the brain to support MAP and suppress heart rate. To test this hypothesis, it was determined whether intracarotid infusion of hypotonic fluid in 48-h, water-deprived rats decreases MAP and increases HR. The composition of the hypotonic fluid was (in mM): 4 KCl, 2.2 CaCl2, 0.9 MgCl2, 1.3 Na2HPO4, 20 NaHCO3; the osmolality of the fluid was ~40 mosmol/kH2O. The pH of the fluid was adjusted to 7.4 before each use. A control blood sample (400 μl) was collected for measurements of plasma sodium, chloride, protein concentration, and hematocrit and was replaced with an equal volume of isotonic saline injected intravenously. Control measurements of MAP and heart rate were recorded for 15 min, while rats remained quiet and usually asleep. Bilateral intracarotid infusion of hypotonic fluid then commenced at 0.1 ml/min per artery. Upon initiation of the infusion, most rats moved for a few minutes before settling back down; data were not collected while the rats were moving. After 15 min, the infusion was stopped, and measurements were continued during a 15-min recovery period. The experiment was terminated with a second blood sample that was collected and replaced as for the first blood sample. In separate groups of water-deprived rats, an identical protocol was performed, except the hypotonic fluid was infused into the carotids at 0.05 or 0.15 ml/min per artery. Additional control experiments included intracarotid infusion of isotonic fluid (128 mM NaCl added to hypotonic fluid; osmolality of the fluid was −300 mosmol/kH2O) for 15 min in water-deprived rats and intracarotid infusion of the hypotonic fluid in water-replete rats.

**Protocol 2.** To establish that any effects of intracarotid infusion of the hypotonic fluid were due to an action in the brain, the fluid was infused intravenously (0.2 ml/min) in a separate group of rats.

**Protocol 3.** To determine whether changes in MAP and heart rate were different in plasma vasopressin concentration, 48-h water-deprived rats were pretreated with the V1 vasopressin antagonist (Manning Compound; 5 μg) 15–30 min before intracarotid infusion of the hypotonic fluid as in protocol 1. At the completion of all experiments in this protocol, a bolus intravenous injection of 30 ng of vasopressin was administered to verify adequate blockade of V1 receptors. In no case was a significant pressor response observed, indicating an effective blockade.

**Protocol 4.** This protocol tested the hypothesis that the increase in osmolality induced by water deprivation acts in the brain to support LSNA. At least 3 days after catheter surgery, drinking water was removed. The next day, lumbar nerve electrodes were implanted. The following day (after 48 h of dehydration), hypotonic was infused intracarotidly or intravenously as described above in protocols 1 and 2.

**Data Analysis**

Between-group differences in the changes in MAP, heart rate, and LSNA in response to fluid infusion were determined using ANOVA for repeated measures. After performing an ANOVA that included all data from protocols 1–3, the data were then grouped for ANOVA analysis to answer specific questions: 1) Is the effect of intracarotid hypotonic fluid infusion on MAP and heart rate in water-deprived rats different from effects in water-replete rats and from effects of intracarotid isotonic fluid infusion in water-replete rats? 2) Are the effects of intracarotid hypotonic fluid infusion in water-deprived rats different from effects of intravenous infusion? 3) Does prior V1 vasopressin blockade alter the responses? A separate two-way ANOVA for repeated measures determined differences in data from protocol 4. Between-group differences were indicated by a significant interaction (P < 0.05). More specific between- and within-animal changes were assessed with the Bonferroni correction. Differences in basal values between water-deprived and water-replete rats were determined using a Student’s t-test.

**RESULTS**

**Basal Values**

As summarized in Table 1, compared with water replete animals, water-deprived rats exhibited higher plasma sodium concentration and osmolality, as well as elevated plasma protein concentration and hematocrit; plasma chloride concentration was not significantly different between groups. Basal
levels of MAP were elevated in water-deprived animals, but heart rate was similar between groups. After at least 1 wk of recovery from surgery, carotid blood flow in one rat averaged 5.5 ml/min, similar to previous reports [−1.5 ml·min⁻¹·100 g⁻¹ (15, 35)], and this flow was not significantly altered by intracarotid fluid infusion. Thus intracarotid infusion rates of hypotonic fluid at 0.05, 0.1, and 0.15 ml/min reduces the osmolality of carotid blood by about 1, 2, and 3%, respectively.

**Action of Increased Osmolarity on Brain**

A repeated-measures ANOVA, including all groups from protocols 1–3, revealed significant between-group differences in MAP (ANOVA group, time and interaction all P < 0.001) and heart rate (ANOVA group, P < 0.05; time and interaction, P < 0.001). More specific analysis indicated that the MAP and heart rate responses to intracarotid hypotonic fluid infusion in water-deprived rats were significantly different from the responses in other control groups. As shown in Fig. 1, a reduction in the osmolality of blood perfusing the brain in water-deprived rats produced a prompt decrease in MAP and an increase in heart rate (P < 0.05); both variables rapidly returned to control upon termination of the infusion. However, when the hypotonic fluid was infused intracarotidly in water-replete animals, neither MAP nor heart rate were significantly altered (Fig. 1). Similarly, intracarotid infusion of isotonic fluid in water-deprived rats did not decrease MAP or alter heart rate (Fig. 1), indicating that the responses were not secondary to an action of the infusion per se.

As shown in Table 2, the intracarotid hypotonic infusion decreased plasma osmolality, as well as plasma protein concentration and hematocrit. Plasma sodium and chloride concentrations tended to fall as well, but these changes failed to reach statistical significance. Two inferences can be made from these observations. First, because systemic osmolality ultimately decreased by ~2%, the decrease in osmolality of blood to the brain became progressively larger as the intracarotid hypotonic infusion mixed with systemic blood to reach a maximum fall of ~4% by the end of the infusion. Second, because systemic osmolality decreased, these data do not establish that the effect of the intracarotid infusion was mediated via an action in the brain. Therefore, the hypotonic fluid was also infused intravenously. Despite similar falls in plasma osmolality, protein, and hematocrit (Table 2), the hypotensive and tachycardic responses to the intracarotid hypotonic infusion were significantly greater than the effects of the same infusion intravenously (Fig. 2). In addition, intracarotid infusion of the hypotonic fluid at a lower rate that did not significantly alter systemic osmolality (Table 2) also produced a hypotensive response (Fig. 3). The higher infusion rate did not lower blood pressure more (ANOVA, interaction, ns); however, the tachycardic response grew larger as the infusion rate increased (Fig. 3; ANOVA, interaction, P < 0.05). Thus, when the data were combined, there was no relationship between the fall in MAP and the rise in heart rate (r² = 0.0002; P = 0.96). Collectively, these data support the hypothesis that the high osmolality of water-deprived rats acts in the brain to support MAP and suppress heart rate.

Additional experiments assessed whether the effect of elevated osmolality to support MAP was via actions on vasopressin secretion or on activity of the sympathetic nervous system. If the decrease in MAP were due to decreasing vasopressin levels, then the depressor response should be reduced or eliminated by prior V1 vasopressin blockade. Injection of the V1 antagonist decreased MAP by −7.0 ± 0.7 mmHg (P < 0.05) and increased heart rate by 30 ± 9 bpm (P < 0.05). However, the depressor response produced by subsequent intracarotid infusion was not significantly modified (Fig. 4). Thus it appears that a fall in vasopressin levels is not a major contributor to the depressor response elicited by intracarotid hypotonic fluid infusion in water-deprived rats.

Fig. 1. Effect of intracarotid infusion of hypotonic fluid (IC Hypo) in water-deprived (WD) and water-replete (WR) rats and of intracarotid infusion of isotonic fluid (IC Iso) in WD rats on mean arterial pressure (MAP) and heart rate (HR). Control values of MAP (in mmHg) were 121 ± 2 (IC Hypo WD), 110 ± 3 (IC Hypo WR), and 113 ± 2 (IC Iso WD). Control values of HR (in bpm) were 345 ± 10 (IC Hypo WD), 339 ± 14 (IC Hypo WR), and 361 ± 17 (IC Iso WD). *Significant interaction (P < 0.05) by ANOVA.
 Bonferroni correction. IC, intracarotid; IV, intravenous; Hypo, hypotonic fluid infusion; Iso, isotonic fluid infusion; WD, water deprived; WR, water replete; V1

Values are presented as means ± SE. *P < 0.05, Pre (before infusion) compared to Post (after infusion), determined by ANOVA followed by the post hoc Bonferroni correction. IC, intracarotid; IV, intravenous; Hypo, hypotonic fluid infusion; Iso, isotonic fluid infusion; WD, water deprived; WR, water replete; V1 vasopressin blockade; 1%, 2%, 3%, approximate percent decrease in blood osmolality.

osmolality of blood perfusing the brain is decreased. As shown in an individual experiment in Fig. 5, and in grouped data in Fig. 6, intracarotid hypotonic fluid infusion decreased LSNA as it decreased MAP, but intravenous infusion had no significant effects. Nevertheless, it is noteworthy that the LSNA response was variable (range of the decrease in LSNA: −4% to −45%). As illustrated in the individual tracing, heart rate also usually increased. However, overall, the mean increase in heart rate (8 ± 2 bpm) was not significant, due primarily to a bradycardic response exhibited by one animal. These data indicate that high osmolality in conscious water-deprived rats acts in the brain to support LSNA.

**DISCUSSION**

The purpose of the present study was to investigate the brain actions of increased osmolality during water deprivation in the support of MAP and sympathetic nerve activity. The major

Fig. 2. Effect of intravenous (IV Hypo) and intracarotid (IC Hypo) infusion of hypotonic fluid in WD rats on MAP and HR. Control values of MAP (in mmHg) were 121 ± 2 (IC Hypo WD) and 121 ± 3 (IV Hypo WD). Control values of HR (in bpm) were 345 ± 10 (IC Hypo WD) and 337 ± 9 (IV Hypo WD). *Significant interaction (P < 0.05) by ANOVA.

Fig. 3. Changes in MAP and HR following intracarotid infusions of hypotonic fluid at 0.05 (−1% decrease), 0.1 (−2% decrease) and 0.15 (−3% decrease) ml/min per artery in water-deprived rats. Changes are the difference between the average control values and the mean of values obtained at 9, 12, and 15 min after starting the hypotonic infusion. Control values of MAP (in mmHg) were: 122 ± 3 (1%), 122 ± 2 (2%) and 120 ± 2 (3%). Control values of HR (in bpm) were 342 ± 9 (1%), 348 ± 9 (2%) and 369 ± 24 (3%). *Significant response (P < 0.05) by 1-way ANOVA (analysis of all values within a group) and t-test (differences different from zero). Two-way ANOVA revealed that HR responses were dose dependent (P < 0.05), but MAP responses were not.
new findings are 1) decreases in osmolality of blood perfusing the brain, via intracarotid infusion of hypotonic fluid, decreased MAP, and increased heart rate in conscious water-deprived rats, but a similar intracarotid infusion in water-replete rats or intravenous in water-deprived rats was without effect; 2) the hypotensive and tachycardic effects of intracarotid hypotonic fluid infusion in water-deprived rats was unaltered by prior V1 vasopressin blockade; and 3) intracarotid, but not intravenous, hypotonic fluid infusion decreased LSNA in water-deprived rats. Collectively, these data support the hy-

Fig. 4. Effect of intracarotid infusion of hypotonic fluid in intact (IC Hypo) and V1 vasopressin-blocked (IC Hypo+V1) WD rats on MAP and HR. Control values of MAP (in mmHg) were: 121 ± 2 (IC Hypo WD) and 120 ± 3 (IC Hypo+V1 WD). Control values of HR (in bpm) were 345 ± 10 (IC Hypo WD) and 354 ± 19 (IC Hypo+V1 WD).

Fig. 5. Tracing from an individual water deprived rat showing the effect of bilateral intracarotid (ic) infusion of hypotonic fluid on MAP, HR and LSNA. The infusion was begun at time zero and was terminated after 15 min.

Fig. 6. Effect of intracarotid (IC Hypo WD) or intravenous (IV Hypo WD) infusion of hypotonic fluid in water-deprived rats on MAP, HR and lumbar sympathetic nerve activity (LSNA). Control values of MAP (in mmHg) were 106 ± 2 (IC Hypo WD) and 110 ± 2 (IV Hypo WD). *Significant interaction (P < 0.05) by ANOVA.
hypothesis that water deprivation-induced increases in osmolality act in the brain to support MAP at least in part by activation of the sympathetic nervous system.

Water deprivation is associated with increases in body fluid osmolality and decreases in blood volume, as indicated in the present study indirectly by increases in plasma protein concentration and hematocrit. Despite volume depletion, arterial pressure does not fall due, in part, to homeostatic increases in plasma vasopressin concentration and in basal sympathetic tone. Previous research indicated that increased osmolality supports MAP and contributes to elevated levels of LSNA (29); the present study investigated the role of the brain. The finding that in water-deprived rats intracarotid, but not intravenous, hypertonic fluid infusion rapidly decreases MAP indicates that the hypertonicity acts in a region perfused by the carotid arteries, presumably the brain, to support MAP.

McKinley et al. (24) investigated in conscious water-deprived sheep the brain actions of increased cerebrospinal fluid (CSF) sodium. They reported that dilution of CSF sodium levels by intracerebroventricular infusion of an isotonic mannitol solution decreased sodium excretion but did not alter arterial pressure. Differences in the access of the diluting infusion to brain CVOs, from the blood vs. the cerebroventricular side, may explain the difference between their finding and the current study.

In the present study, additional experiments investigated the role of vasopressin and the sympathetic nervous system in the responses. A decrease in vasopressin secretion does not appear to be a major contributor to the depressor response, since prior V1 vasopressin blockade did not alter it. On the other hand, the rapid time course of the response indirectly suggested that a decrease in sympathetic nerve activity might underlie the fall in MAP. More direct evidence to support this possibility was that intracarotid hypertonic fluid infusion was found to decrease LSNA as it decreased MAP. Nevertheless, the degree of sympathoinhibition was variable. One possible explanation for the variability may be that the decreases in LSNA elicited by decreases in osmolality of carotid blood may be variably offset by other factors. Countering factors might include baroreflex responses to the fall in MAP and a direct inhibitory action on carotid baroreceptor afferents of small decreases in sodium concentration (19, 20).

Infusion of hypertonic fluid into the carotid arteries of water-deprived rats also increased heart rate. One explanation for this finding is that the concurrent hypotensive response triggered a reflex tachycardia. However, changing the rate of the hypertonic infusion did not similarly alter MAP and heart rate, and there was no relationship between the degree of hypotension and the tachycardic response, suggesting that it was not baroreflex mediated. Instead, it may be that elevated systemic osmolality acts in the brain to tonically suppress heart rate, and this action is reversed when the osmolality of carotid blood is reduced.

Given that the high osmolality appears to act centrally to support MAP and LSNA during water deprivation, the next question is which brain sites are involved? Because carotid blood flow is restricted to the forebrain (11, 28), anterior CVOs, the organum vasculosum of the lamina terminalis (OVLT), and the subfornical organ (SFO) are the most likely osmosensitive sites involved. Nevertheless, a functional link between these CVOs and osmotic control of the sympathetic nervous system has not been established. From osmoreceptors, anatomic viral tracing studies suggest that direct and indirect (e.g., via the median preoptic nucleus) projections to the paraventricular nucleus (PVN) may be the next segment of the circuit (23, 41). Moreover, neurons in the OVLT and SFO, identified as projecting to the PVN or polysynthetically to the kidney, express c-fos following acute increases in osmolality (21, 32). Recent studies by Stocker et al. (34) suggest that the PVN is a critical brain region in the support of increased sympathetic tone during water deprivation, since nonspecific blockade of the PVN with muscimol microinjections produced profound decreases in MAP, LSNA, and renal sympathetic nerve activity; similar microinjections in water-replete rats were without effect.

PVN parvocellular neurons may influence the activity of sympathetic preganglionic neurons in the cord via several descending pathways, but, in particular, by a projection to the RVLM. PVN neurons antidromically identified as projecting to the RVLM are activated by increases in osmolality (37). Moreover, water deprivation evokes Fos expression in PVN neurons that project to spinal cord and RVLM, although a greater percentage of Fos-positive neurons are RVLM-projecting (33). Increases in osmolality appear to excite the RVLM at least in part by increasing the action of excitatory amino acids on vasomotor neurons. More specifically, nonselective blockade of ionotropic excitatory amino acid (EAA) receptors in RVLM decreases MAP dramatically in water-deprived but not water-replete rats (4, 5). It is not known whether this increased EAA tone is secondary to increased EAA release or activity or to the loss of convergent inhibition. Nevertheless, it is noteworthy that the hypertensive response is highly correlated to the degree of hypertonicity and can be attenuated by normalization of the high osmolality, but not the reduced blood volume, of water-deprived rats (4, 5). Finally, acute increases in osmolality, due to intravenous hypertonic saline infusion in water-replete rats, have been shown to increase EAA drive of the RVLM as it increases LSNA (5). Collectively, these data support key roles for the PVN and EAA drive of the RVLM in the increased sympathetic tone exhibited during water deprivation.

Intracarotid infusion of hypertonic fluid did not alter MAP or LSNA in water-replete rats. This finding is consistent with our previous reports showing that global decreases in osmolality in water-replete rats, due to intravenous infusion of 5% dextrose in water, also do not alter MAP, heart rate, LSNA, or renal sympathetic nerve activity (29, 30). Therefore, while decreases in osmolality decrease the activity of brain osmosensitive neurons and vasopressin secretion in normal animals (3, 39), indicating that basal osmolality levels provide a tonic stimulatory input to vasopressin secretion, the same level of basal support does not appear to exist for the tonic activity of the sympathetic nervous system or MAP. One explanation for this dichotomy may be that an intermediate relay station between the osmoreceptors and sympathetic preganglionic neurons, such as the median preoptic nucleus or the PVN, does not provide tonic excitatory input to the sympathetic nervous system under normal conditions. As a result, decreased input from osmoreceptors to this region will be ineffective, but excitation of osmoreceptors will activate this site. In support of this notion, it has been shown that acute blockade of the PVN due to muscimol microinjection does not significantly alter
MAP or sympathetic activity in normotensive rats (17, 34). However, if basal activity of this intermediate brain region is increased by another factor, then the effects of changes in osmolality on sympathetic outflow might be amplified. In this context, it is important to note that blood volume is decreased during water deprivation, which may, via unloading of cardiopulmonary receptors or increased plasma ANG II levels, interact with and facilitate the osmotic signal to increase LSNA and MAP.

In summary, we have shown for the first time that water deprivation-induced increases in osmolality act in the brain to support MAP and LSNA in conscious animals. These data indicate that osmolality, via a central action, can be a sensitive and important regulator of the sympathetic nervous system as it is of thirst and vasopressin secretion.

Perspectives

The present results indicate that high osmolality, secondary to water deprivation, acts in the brain to support MAP and activate the sympathetic nervous system. A question that logically follows is whether this action underlies sympathoexcitation in other pathophysiological states. One such state is salt-sensitive hypertension, in which increases in dietary salt increase sympathetic tone in parallel with MAP (7, 8, 22). However, the mechanism is unknown. Because increased salt intake increases plasma sodium chloride concentrations (9, 14, 31), and increased dietary salt sensitizes brain regulation of sympathetic outflow (16, 27), we speculate that central nervous system actions of the hypertonicity may underlie the activation of the sympathetic nervous system that is a hallmark of this disorder.

ACKNOWLEDGMENTS

The authors are grateful for the excellent technical assistance by Ling Xu and suggestions made by R.A.L. Dampney during preparation of the manuscript.

GRANTS

This work was supported in part by National Institutes of Health Grants HL-35872 and HL-70962. T. L. O’Donnaya was supported in part by a fellowship from the American Heart Association, 0325552Z.

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