Body sodium and volume homeostasis

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MAINTENANCE OF A “MILIEU INTERIEUR,” which allows our cells to function away from the ancient sea, is one of the most important functions of the body. Maintenance of constant extracellular osmolarity and sodium concentration depends on a precise balance between intake and excretion of sodium and water. Intakes of water and sodium are governed by an urge driven by the lack of these substances, by habit, or by more or less well-founded recommendations (43). Regulated excretion of the substances takes place mainly in the kidney.

The aim of this “In Focus” article is to give a short overview of the regulation of body sodium and volume homeostasis, with an emphasis on recent developments, and focus on papers published in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.

Regulation of water and sodium intake. Variations in the composition of blood plasma are picked up in the brain by the small areas that lack a blood-brain barrier. These areas, the circumventricular organs, surround the ventricular system. Three of these are involved in body fluid homeostasis: the subfornical organ (SFO) and organum vasculosum laminae terminalis (OVLT), which are located in the anteroventral third ventricle, and the area postrema (AP), which is located at the transition of the fourth ventricle and the central canal of the spinal cord (12).

Thirst. Hyperosmolarity is a strong stimulus for water intake. When exposed to hyperosmolality, osmoreceptor cells in the SFO and OVLT activate neurons projecting to the paraventricular nucleus (PVN) and supraoptic nucleus (SON) in the hypothalamus to stimulate thirst. The protooncogene c-Fos is an immediate-early response gene, which has become an excellent mapping tool to identify active cells in the nervous system. It is activated in response to a wide range of stimuli and its expression is barely detectable under basal conditions (18). Consistent with this, dehydration increased the expression of c-Fos in the OVLT, SFO, and SON in rats (11).

Thirst is also induced by profound volume contraction, which is probably detected by stretch receptors in the heart (39). A fall in arterial blood pressure increases thirst in response to intracerebroventricular ANG II (41). Conversely, thirst is inhibited by increased arterial blood pressure, which is detected by arterial baroreceptors (36) and inhibits thirst induced by ANG II infusion, hypovolemia, or hyperosmolarity (35).

ANG II is a strong dipsogenic agent. Circulating ANG II stimulates AT1 receptors in the SFO of rats (39), and intracerebroventricular injection of ANG II stimulates c-Fos expression in median preoptic nucleus (MnPO), SFO, PVN, and SON (21). On repetitive stimulation, there is desensitization to this response, which is associated with an increase in AT1 receptor protein expression (21). Thirst induced by intracerebroventricular hypertonic saline in sheep is inhibited by administration of intracerebroventricular losartan, which is an AT1 receptor antagonist (44). Upregulation of AT1 receptors in most regions inside the blood-brain barrier is one of the characteristics of the TGR(ASrAOGEN)680 transgenic rat and, in keeping with this, the drinking response to intracerebroventricular injection of ANG II is enhanced compared with controls (22). Lactating rats have increased dipsogenic responsivity to intracerebroventricular ANG II. An AT1 antagonist reduced drinking in lactating rats, but not in control rats, again pointing to a central role for ANG II in the control of thirst (33). In mice lacking the AT1a receptor, dehydration caused a smaller increase in plasma vasopressin concentration than in control mice. At the same time there was an enhanced response in the expression of c-Fos and vasopressin mRNA in the PVN (23), suggesting that the role of AT1 receptor activation is not a simple one. In the baboon, intracerebroventricular infusions of ANG III were as potent as ANG II in stimulating thirst and intake of NaCl solution, suggesting that ANG III could be a major effector peptide in the regulation of ingestive behavior (6). As shown before in rats, it has now been demonstrated in primates (baboons) that subcutaneously injected aldosterone acts synergistically with intracerebroventricular ANG II to induce thirst (31). Central thromboxane A2/prostaglandin H2 (TP) receptors may contribute to the dipsogenic response to ANG II, inasmuch as intracerebroventricular treatment with an antagonist of TP receptors decreased the dipsogenic response to ANG II and because a TP agonist enhanced the response to ANG II (17).

In addition, thirst is stimulated by gastric sodium loading, which is detected by sodium receptors in the abdominal viscera, such as hepatic portal osmoreceptors, before any increase in systemic plasma osmolality (37). The response is enhanced by simultaneous stimulation of the central osmoreceptors by dehydration and salt loading (37). Lesions in the SFO disrupt drinking after intragastric sodium loading, and the same

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happens after a dry chow meal, suggesting that results obtained with gastric saline loading are physiologically relevant (34). In keeping with this view, thirst is inhibited when gastric sodium concentration is reduced by gastric water loading (39).

Thirsty and dehydrated rats may gain water by drinking hypertonic saline, as long as they can excrete more concentrated urine (38). This works well when the rats are given 0.3 M saline, but osmoregulation is not achieved with 0.5 M saline and the rats drink much less. Analysis of drinking patterns suggested that the high salinity is detected in the gastrointestinal tract. Thus, in this situation, avoidance of salt intake is given preference over stimulation of fluid intake. After lesions of the AP, NaCl intake was kept high, even at 0.5 M saline, suggesting that the AP is involved in mediating the inhibitory signal to salt intake, which is elicited from the gastrointestinal tract (38).

The peptide adrenomedullin (AM) has been suggested to inhibit drinking responses. Taylor and Samson (40) constructed a ribozyme (a catalytic RNA molecule), which specifically cleaves transcripts of AM. In vascular myocytes, ribozyme treatment lowered AM mRNA and reduced peptide content. Furthermore, intracerebroventricular administration of the ribozyme reduced the AM content of the hypothalamus and led to an exaggerated drinking response in rats, suggesting that endogenous, brain-derived AM is also involved in the short-term control of water intake.

Sodium appetite. Many stimulators of thirst also induce sodium appetite, which is generally slower to develop and more persistent than increases in thirst (12). The osmoreceptors that trigger sodium appetite are the same as those eliciting thirst and are located in the OVLT and SFO. Sodium appetite is stimulated by sodium deficiency, by hypovolemia, by ANG II, and by mineralocorticoids. More variable stimulation has been ascribed to the hormones of pregnancy and lactation (e.g., Ref. 7) and the stress hormones of the hypothalamo-pituitary-adrenocortical axis. In studies of salt appetite, rats are usually first depleted of sodium, because rats maintained on standard laboratory diet have an excess body sodium that acts as a buffer when natriorexigenic stimuli are applied (12). The dependency of sodium appetite on the preexisting sodium and volume status is exemplified by the observation that hypotension in fluid-depleted animals increased sodium appetite in response to intracerebroventricular ANG II, but did not do this in fluid-replete animals (41). It has been suggested that oral NaCl receptors contribute to the satiation of NaCl intake in sodium-deficient rats, but results from comparisons of NaCl eaten normally and fed with a gastric tube could reject this hypothesis (42).

The renin-angiotensin system is a strong stimulator of sodium appetite. The SFO, OVLT and AP contain ANG II receptors that are accessible to circulating ANG II (12). Increased circulating ANG II seems to play a major role in the stimulation of sodium appetite after sodium deficiency, because in sodium-deprived and adrenalectomized rats, captopril treatment reduced sodium intake by a peripheral effect (intracerebroventricular infusion of ANG I still stimulated water and salt intake), and ANG II infusion restored sodium intake (28). Similarly, stimulation of sodium appetite in rats by dehydration followed by rehydration with water increased plasma renin activity and c-Fos expression specifically in the SFO. This is consistent with a role of the circulating renin-angiotensin system in the regulation of sodium appetite via this circumventricular organ (11). Central ANG II seems also to be involved in the control of sodium appetite. Thus, in sheep, intracerebroventricular losartan inhibits the sodium appetite induced by both a reduction in cerebral Na concentration and intracerebroventricular hypertonic saline (44). Similar to the results with induction of thirst, intracerebroventricular infusions of ANG III in the baboon were as potent as ANG II in stimulating intake of NaCl solution (6). Aldosterone is an independent stimulator of sodium appetite (12), and, as is the case with thirst, ANG II and aldosterone act synergistically to stimulate NaCl intake. This interaction has now also been demonstrated in baboons (31). At the same time, food intake, vasopressin release, ACTH release, and blood pressure regulation appear to be activated by the same type of synergy. The interaction of aldosterone and ANG II may involve central oxytocin (OT) neurons, which limit intracerebroventricular ANG II-induced NaCl intake. Measurements of c-Fos immunoreactivity and OT and vasopressin secretion in rats after DOCA treatment allowed Roesch et al. (27) to conclude that mineralocorticoids attenuated the responsiveness of OT and vasopressin neurons to ANG II. The inhibitory role of OT on salt appetite has been further demonstrated in mice where the OT gene was deleted (1). The OT-deficient mice drank about seven-fold more saline than wild-type mice after overnight fluid deprivation.

Injection of vasopressin into the lateral ventricle has been shown to decrease NaCl intake by sodium-deficient rats and to induce major motor disturbances. However, injection of V₁/V₂ and V₁ receptor antagonists suppressed NaCl intake without causing motor disturbances, suggesting that endogenous vasopressin actually stimulates salt appetite through V₁ receptor activation (13).

In addition to the forebrain structures that stimulate sodium appetite, a serotonergic hindbrain circuit including the lateral parabrachial nucleus (LPBN) has been suggested to inhibit sodium intake. This system includes the neural circuitry of the AP, the nucleus of the solitary tract (NTS), and the LPBN. Fos expression in many of these cells was decreased when the animals were sodium depleted, and Fos expression was increased when the animals were in near normal sodium balance (14). These authors suggest that under conditions of satiety, the raphe 5-HT system tonically inhibits sodium intake and that 5-HT neurons are activated in the process of sodium ingestion to limit excess NaCl intake. Consistent with this suggestion, injection of the serotonin antagonist methysergide into the LPBN increases salt intake. Menani et al. (20) observed that
central cholinergic stimulation with intracerebroventricular carbachol only induced thirst but carbachol in combination with methysergide increased sodium appetite, supporting the view that serotonergic mechanisms of the LPBN inhibit sodium appetite. De Gobbi et al. (10) studied the interaction of serotonin and cholecystokinin in inhibiting NaCl and water intake in the LPBN. The effects of the combined administration of serotonergic and cholecystokininergic agonists and antagonists into the LPBN on NaCl intake suggested that the two neurotransmitters interact in the control of sodium intake, although such an interaction was not observed in water intake.

Regulation of water and sodium excretion. The whole body control of salt and volume homeostasis is controlled not only by intake, but also by excretion, which is regulated by the kidneys. The regulation of water excretion by the kidney is mainly governed by the hormonal control via vasopressin, and salt excretion is mainly controlled by a combination of the renin-angiotensin-aldosterone system, the renal sympathetic nerves, which stimulate renin release and increase tubular sodium reabsorption, and the nitric oxide (NO) system, which promotes salt excretion.

The osmoreceptors that trigger vasopressin release are located in the OVLT and SFO and project to the vasopressinergic neurons originating in the PVN and SON in the hypothalamus, but are separate from those that trigger thirst and sodium appetite. Stimulation of release of vasopressin is also induced by ANG II, by hypovolemia, and by a fall in arterial blood pressure. Release of renin from the juxtaglomerular (JG) cells is stimulated by the renal sympathetic nerves, via β1-adrenoceptors on the JG cells, by a fall in NaCl concentration at the macula densa, by a fall in blood pressure, which is detected probably as a change in arteriolar wall stress, and by local and circulating hormones including ANG II, NO, and prostaglandins.

Renal sympathetic nerve activity (RSNA) is suppressed by increased arterial blood pressure via the arterial baroreceptors and probably also by acute increases in systemic plasma osmolality. Sly et al. (32) provided a neural substrate for osmotic control by showing that neurons in the lamina terminalis, which project to the kidney, reacted to 24 h dehydration, intravenous hypertonic saline, or intracerebroventricular ANG II with c-Fos induction. Sustained (48 h dehydration) increases in plasma osmolality and vasopressin, however, did not affect RSNA (30). The osmosensitive regions of the lamina terminalis innervate autonomic neurons in the hypothalamic PVN, which express AT1 receptors. Central hyperosmotic stimuli given through the internal carotid artery elevated RSNA in conscious rats (8). This response was inhibited by injection of losartan into the PVN, suggesting that AT1-receptor activation within the PVN was involved in the response.

The central role of the renin-angiotensin-aldosterone system in the control of sodium excretion has been confirmed in many different situations. Heinz and Gray (16) infused saline into Pekin ducks and observed an increase in salt excretion by the kidneys and salt glands, which was associated with a decreased plasma ANG II concentration and which was counteracted by infusion of ANG II, suggesting that the fall in ANG II was centrally involved in the increased salt excretion by the kidneys and salt glands. Essentially the same observation was made in humans where central hypovolemia was induced by lower body water immersion (29). The neuroendocrine link between volume sensing and renal function was preserved in patients with compensated chronic heart failure, in whom water immersion suppressed ANG II and aldosterone concentrations and elicited natriuresis (15).

Although ANG II by itself promotes salt retention, it also increases blood pressure, which may inhibit RSNA and thereby reduce sodium retention in the kidney. This pathway was demonstrated to be operative by Lohmeier et al. (19), who observed that chronic ANG II infusion in conscious dogs with an innervated and a denervated kidney led to a greater rate of sodium excretion from the innervated kidneys, indicating chronic suppression of sodium excretion by RSNA and supporting the contention that baroreflex suppression of RSNA is sustained during chronic ANG II hypertension (19).

The interplay between the NO system and ANG II in the control of salt excretion during volume expansion in conscious dogs has been investigated in several studies (2, 3, 25). NO synthase inhibition increased plasma renin and ANG II concentrations and largely abolished natriuresis after volume expansion, whereas acute AT1 blockade exaggerated the natriuresis. With a combination of NO synthase inhibition and AT1 blockade, volume expansion induced only a very modest natriuresis. Consistent with these results, infusion of L-arginine as a substrate for NO synthase exaggerates the natriuretic response to volume expansion and counteracts the effect of NO synthase inhibition (2, 3, 25). These results indicate that NO synthase inhibition abolishes the natriuresis after volume expansion, in part by preventing the suppression of the renin-angiotensin-aldosterone system and show that the NO system plays a dominant role in the hierarchy of control systems that control salt excretion.

Changes in renal and cardiovascular function when exposed to variations in dietary sodium intake have been investigated in conscious humans. During high sodium intake (250 mmol/day), the hormones of the renin-angiotensin system were suppressed compared with low sodium intake (70 mmol Na/day) (9), thus explaining how sodium excretion is balanced by sodium intake. Because plasma sodium concentration, osmolality, and arterial blood pressure were unchanged, the suppression of the renin-angiotensin system was likely related to a decreased sympathetic nervous activity, as reflected in a decreased plasma norepinephrine concentration. The error signal perceived by the nervous system during high sodium intake may well be initiated from low-pressure baroreceptors, because the plasma volume was 9% higher...
than with low sodium intake, and plasma concentration of ANP was increased (9).

Infusion of hypertonic NaCl solution into humans causes a larger natriuresis and greater plasma sodium and vasopressin concentrations than when the same NaCl load is given as an isotonic infusion (4). In this situation the signal perceived by the kidneys was uncertain, because there were no differences in blood pressure, glomerular filtration rate, the renin system, or ANP.

Body posture plays a role for renal and cardiovascular function and responses to sodium loading. One-week-long head-down bed rest induced hypovolemia, decreased body weight, increased plasma osmolality, and elicited antinatriuretic endocrine signals (5). In this situation the natriuretic response to isosotic saline infusion was augmented, whereas the response to hypertonic saline was unaltered. Pump et al. (26) compared cardiovascular and renal variables in humans lying on the back (supine), on the belly (prone), and on the side (left lateral). Compared with supine, the prone position slightly increased free water clearance and diuresis with no effect on renal sodium excretion, mean arterial pressure, and left atrial diameter. The prone position induced an increase in heart rate, total peripheral vascular resistance, venous plasma concentration of norepinephrine, and ANP, whereas stroke volume decreased. The left lateral position had no effect on renal variables, whereas left atrial diameter increased and mean arterial pressure decreased. In conclusion, the prone position reduced stroke volume and increased sympathetic nervous activity, possibly because of mechanical compression of the thorax with slight impendiment of arterial filling. Taken together, these results show that very stringent experimental conditions have to be applied to obtain valid results on renal and cardiovascular function in humans.

As indicated above, terrestrial animals, including humans, developed to cope with a low-sodium environment and, indeed, are very good at conserving salt, mainly through activation of the renin-angiotensin-aldosterone system. The situation is different in marine animals, such as elephant seal pups (24), where natriuresis in response to hyperosmolality was achieved by an immediate and sustained elevation in glomerular filtration rate and independent of an increase in ANP and decreases in ANG II and aldosterone.

In conclusion, the study of body sodium and volume homeostasis is a core area of interest for this journal. As shown by this short review, we have learned a lot within the last few years, but there is more to come, and new insights can be expected to be generated from classical physiological models, as well as increased use of genetically modified mouse models and discovery-based science working both on the gene-activation level and on the protein level.

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