The Natriuretic Response to Hydromineral Imbalance

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SUMMARY Many recent investigations of the mechanism of volume-expansion natriuresis fail to appreciate that the observed renal sodium excretion may not be dependent on an increase in intravascular volume, but rather on the infused sodium load or extracellular fluid volume expansion. With this in mind, the natriuresis of isotonic volume expansion, hypertonic saline infusion, and dehydration have a common basis: they present a relative or absolute sodium load. Lesions of forebrain periventricular tissue prevent the natriuretic response to these three states of body fluid imbalance. In this review we discuss the evidence for a common central nervous system-mediated natriuretic mechanism in response to disturbances of fluid and electrolyte balance. We also propose a role for pars intermedia-derived, proopiomelanocortin-derived peptides as humoral mediators of renal sodium excretion. Evidence from our laboratory, as well as others, provides data for a testable hypothesis to explain central nervous system-mediated natriuresis, as well as an explanation of how central nervous system lesions or neurochemical perturbations affect the renal response to body fluid imbalance.

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KEY WORDS • natriuresis • fluid-electrolyte balance • central nervous system • natriuretic hormones

MANY studies of the renal mechanism of volume-expansion natriuresis agree that the natriuretic response is not correlated to an increase in intravascular volume, but rather to the infused sodium load or extracellular expansion. Intravascular volume-expansion with sodium-free solutions of hyperoncotic dextran, hyperosmotic glucose, hyperoncotic albumin, or hypotonic sodium chloride produces little increase in sodium excretion.1,2 Expansion with saline or blood, however, challenges that produce an expansion of the extracellular fluid volume and present a sodium load, results in a significant increase in urinary sodium excretion.1,2 The hemodynamic response to “pure” intravascular expansion, isotonic saline expansion, or volume expansion with blood is quite similar. These data suggest that an increase in intravascular volume per se is not an effective natriuretic stimulus, but that a sodium load or an increase in extracellular volume is the crucial component necessary to evoke the response.

While most work on producing a natriuretic hormone-dependent natriuresis has used isotonic volume expansion, intracarotid or intraventricular infusion of hypertonic sodium chloride (in a relatively small volume) also produces a natriuresis that may be dependent on a similar mechanism. The specificity of this natriuretic response was demonstrated by the lack of effect after hyperosmotic glucose or hypertonic choline chloride infusions.3 This study also noted a significant pressor effect. Since the increase in blood pressure paralleled the increase in sodium excretion, a cause-effect relationship was suggested. However, it has been shown that chronic infusions, as opposed to bolus injections,4 of hypertonic sodium chloride evoke a natriuretic response with no change in blood pressure.5 Another similarity between saline expansion and hypertonic saline natriuresis is found in the recent report of Gilmore and Nemeh,6 in which sodium-depleted/volume-replete dogs did not have a natriuretic response to intracarotid hypertonic saline infusions. Thus a similar conclusion could be reached as in the previously mentioned experiments on hypotonic or hyperoncotic volume expansion, namely, that the total-
body sodium load is the major determinant of a natriuretic response.

Central Nervous System and Natriuresis

Both hypophyseal and hypothalamic lesions have been shown to affect natriuresis. Benesath and coworkers demonstrated that hypophysectomized rats do not exhibit natriuresis in response to a saline load, although a diuretic response was evident. Keeler first demonstrated that basal hypothalamic lesions decreased sodium excretion. These experiments were predicated on the hypothesis that a central sodium receptor was located in or near the third cerebral ventricle. In the late 1960s and early 1970s anatomical studies of the brain focused attention on a group of periventricular areas with a common specialized structure. These so-called circumventricular organs (CVOs) are highly vascularized and contain capillaries with a fenestrated structure. The latter feature is indicative of the lack of a blood-brain barrier. Studies with labeled compounds showed that CVOs are areas of the brain in which peripherally circulating substances can gain access to the central nervous system (CNS). In particular, the subfornical organ of the anterior third ventricle was suggested to be in an anatomical location uniquely suited to monitoring the composition of forebrain cerebral arterial blood. Thornborough et al. created subfornical organ lesions in cats and demonstrated a blunting of the natriuretic response to intracarotid infusions of hypertonic saline. This provided the first experimental evidence for a specific receptive function for a CVO.

Bealer et al. investigated the possibility that rats with electrolytic lesions of the third-ventricle CVOs were insensitive to perturbations in blood volume by challenging them to an isotonic saline load. They further measured the sodium transport inhibitory activity in blood from lesioned and sham-lesioned volume-expanded rats using isolated toad bladders (a model of the distal renal tubule and collecting duct). The experimental results suggested that ablation of this periventricular tissue attenuated the natriuresis induced by isotonic volume expansion, with no change in renal hemodynamics, and that lesioned rats did not have an appropriately high level of natriuretic hormone-like activity in their blood. The basic findings of this experiment were confirmed by Pammanni et al. with the use of a different ion transport assay.

Bealer extended his studies of the rat model with a lesion in the periventricular tissue of the anteroventral region of the third ventricle (AV3V) to other aspects of sodium balance. As might be expected from the work of Thornborough et al., these rats have a blunted natriuretic response to intraventricular hypertonic saline infusions.

When considered together, forebrain CVOs appear to play a crucial role in regulating the natriuretic response to isotonic volume expansion as well as decreases in extracellular volume, that is, increases in extracellular sodium. The CNS should therefore be viewed as an integrator of information on both blood volume and total-body sodium load. The decision to activate a natriuretic mechanism(s) would appear to be dependent on the detection of either an inappropriately high sodium concentration relative to blood volume (hypertonic saline infusion or dehydration-induced natriuresis) or a volume load with an isotonic sodium concentration. In the former case, natriuresis seeks to bring the total-body sodium load to a level commensurate with extracellular fluid volume, with a concomitant increase in vasopressin secretion to reduce renal free-water clearance. In the latter example, the detection of an isotonic saline load produces both natriuresis and diuresis.

A Putative Natriuretic Hormone of CNS Origin

Humoral regulation by the CNS of other organ systems is often accomplished through the secretion of specific pituitary polypeptides. The lack of a natriuretic response to saline expansion in hypophysectomized rats lends support to the concept of a pituitary-derived natriuretic hormone. Natriuretic activity has also been detected in several pituitary-derived peptides, including adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone (αMSH), and βMSH.

Several years ago we began to question if it was possible that the natriuretic activity noted in these peptides was related to common structural features, features that might be shared by a physiological natriuretic hormone. We compared the structures of these known natriuretic pituitary peptides and found they had a common core sequence, ACTH, αMSH, βMSH (Figure 1). We then determined that the natriuretic activity of these peptides resided in this common sequence.

Previous work on a natriuretic hormone had proposed αMSH (or a related peptide) as a candidate. This hypothesis was based on 1) the natriuretic activity of the peptide and 2) its origin from the intermediate lobe (pars intermedia; PI) of the pituitary. Selye and Hall first reported alterations in PI structure during states of fluid and electrolyte disturbance. Legait and Legait found that the size of the PI predicted the ability of an animal to withstand dehydration. Since these early reports, other investigators have found that hydromineral imbalance results in a histological appearance of PI cells suggestive of hyperactivity and an increase in αMSH secretion. Levitin et al. showed that rats bearing PI transplants had heightened natriuretic responses to volume loads. Releasing factors for PI hormones, such as serotonin agonists or corticotropin-releasing factor, appear to produce centrally mediated natriuresis.

A problem in the consideration of αMSH as a natriuretic hormone is the dose needed to evoke a significant response (μg/kg body weight). We therefore concluded that if the CNS produced a natriuretic hormone it might have an αMSH-like structure (i.e., have a sequence similar to αMSH) but would not be αMSH itself.

During the course of our work with ACTH we become aware of a relatively new class of pituitary peptides containing an ACTH-like sequence, the...
The pharmacological regulation of these intermediate lobe cells is analogous to those of lower mammals, however, demonstrating the existence of an intermediate-cell zone in the pars distalis of humans. Recent anatomical studies have noted with forebrain CVO damage in lower mammals, nonhuman primates, and humans regarding body fluid balance have not as yet been described when comparing the function of the cardiac atria to forebrain peri ventricular structures. While atrial stretch may play a role in body fluid homeostasis in lower mammals, evidence exists that this analogy may not be applicable to primates. Stretching the atria of nonhuman primates does not produce a renal response, although volume expansion natriuresis can be demonstrated.

In addition, chronic cardiac denervation in monkeys, in contrast to dogs, also has no effect on the renal response to volume expansion. Thus the parallels that have been noted with forebrain CVO damage in lower mammals, nonhuman primates, and humans as regards body fluid balance have not as yet been described when comparing the function of the cardiac atria among these species. The basis for this difference may be the relative insensitivity of low pressure baroreceptors in bipeds as opposed to quadrupeds. While the precise mechanism of CNS regulation of sodium balance is not yet established, many clinical states of hydromineral imbalance have been reported to be associated with altered levels of "natriuretic hormones" (reviewed in Reference 39).

**Figure 1.** A comparison of the analogous "core" sequences of ACTH, α-melanocyte stimulating hormone (αMSH), βMSH (βLPH), and γMSH. While the identical heptapeptide sequence appears in the first three peptides, the γMSH core sequence has an acidic residue-glycine transposition. γMSH is a des-Gly12, C-terminal amide derivative of γMSH. Larger molecular forms of γMSH (due to an N-terminal extension) have been reported; γMSH is a 15-residue C-terminal extension of γ2MSH.

γMSHs (see Figure 1). We showed in a rat bioassay that several peptides of the γMSH family produce a natriuresis that is qualitatively similar to ACTH or αMSH, but can be demonstrated at 1/1000 the dose. As in some early studies with αMSH or in our studies with ACTH, a significant diuresis or kaliuresis could not be demonstrated.

Independent support for the concept of a γMSH-like natriuretic hormone was presented by Lin et al. They initially showed that the natriuresis produced by acute unilateral nephrectomy (AUN) in rats was dependent on an intact pituitary. The natriuretic response was then correlated with an increase in circulating levels of pro-γMSH. Subsequent work by this group showed that circulating levels of immunoreactive γMSH (γ,MSH) correlated with the natriuretic response to AUN. Rats treated with γMSH antibodies prior to AUN failed to manifest an appropriate natriuretic response. As with our investigations of γMSH, kaliuresis appeared to be controlled by an unrelated mechanism.

Finally, the apparent lack of an intermediate pituitary lobe in humans would appear to provide little or no clinical applicability to research on intermediate-lobe peptides of lower animals. Recent anatomical studies, however, demonstrated the existence of an intermediate-cell zone in the pars distalis of humans. The pharmacological regulation of these intermediate lobe cells is analogous to those of lower mammals, including the rat. A previous problem in identifying an intermediate lobe in humans was using immunohistochemical localization of αMSH as a criterion for its existence. Adult human intermediate lobe cells do not typically process proopiomelanocortin (POMC) to produce an immunologically active form of αMSH; however, γMSH or β-endorphin immunohistochemistry clearly defines these cells.

In conclusion, we feel considerable evidence exists that the CNS regulates a natriuretic mechanism that normally operates in states of eunatremic hypervolemia (e.g., isotonic saline volume expansion) or hypernatremia (e.g., dehydration). The factors involved in this response may be neural (as detailed here) as well as neural. The latter possibility is based on several reports that suggest that withdrawal of sympathetic tone is associated with CNS-mediated natriuresis. Work from several laboratories has implicated peptides derived from the N terminus of POMC (γMSHs) as potential humoral mediators of CNS natriuresis. The potential clinical significance of a CNS-natriuretic mechanism is seen in the fact that lower mammals with forebrain CVO lesions that disrupt body fluid homeostasis have striking parallels to clinical reports of idiopathic hypernatremia, which also appears to involve damage to forebrain periventricular structures. While atrial stretch may play a role in body fluid homeostasis in lower mammals, evidence exists that this analogy may not be applicable to primates. Stretching the atria of nonhuman primates does not produce a renal response, although volume expansion natriuresis can be demonstrated.

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