Physiological studies have clarified the role that the brain has in the interplay between salt balance and hypertension. Neural mechanisms and endocrine secretions play a pivotal role in the adaptation of mammals to changes in the intake and excretion of sodium. Maneuvers that alter the concentration of sodium in the plasma modify the sensitivity of baroreceptor reflexes and alter vascular reactivity. These changes may be mediated in part by the release of vasopressin. The research also suggests that the brain indirectly modulates the ability of the vascular endothelium to release vasoactive factors. Collectively, these studies illustrate the multiple effects of the sodium ion on the peripheral neural and central endocrine mechanisms that participate in the regulation of arterial pressure.

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The relation between arterial hypertension and dietary salt intake is complex and often obscured by the added influence of other risk factors. Nonetheless, several lines of evidence suggest that alterations in the distribution of sodium chloride (NaCl) between the intracellular and extracellular spaces of the body contribute to the pathogenesis of high blood pressure. For many investigators this relation may be explained by sodium retention and body fluid expansion. Yet other studies suggest a concomitant influence of the brain and central endocrine secretions in the regulation of total body sodium. Analysis of the neurohormonal adjustments that result from changes in blood volume and extracellular sodium (Na\(^+\)) concentration suggest that these factors act synergistically in the long-term regulation of arterial pressure.

This presentation aims at describing the interlocking characteristics of the peripheral and central neurohormonal mechanisms that are altered by a change in the extracellular concentration of Na\(^+\). We include an assessment of what seems to be a new possibility. Through the collective analysis of studies done in this and other laboratories, we advance the hypothesis that the brain modulates the function of the vascular endothelium.

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FIGURE 1. Schematic representation of various factors that influence intrinsic reactivity of blood vessels. Studies described in text suggest that central nervous system (CNS) may modulate activity of vascular receptors through mechanisms that entail modifications of extracellular concentration of sodium (Na+) and secretion of endothelium-derived vasoactive factors. These paracrine actions of the endothelium may result in sensitization of baroreceptor endings, prejuditional modulation of the release of adrenergic transmitters, or both. Therefore, it is possible that vascular nerve endings and the endothelium constitute separate limbs of an integral central system that is modifiable by alterations in the extracellular concentration of Na+. Evidence that supports these interactions is reviewed below.

Sodium and the Central Nervous System

The movement of many circulating agents to and from the central nervous system is impeded by the blood–brain barrier. The structural and functional characteristics of this barrier is one reason that in most mammals, the concentration of Na+ within the CSF is higher than that of the plasma. Nevertheless, the brain is fastidious about variations in the concentrations of its cations. It has been known for a long time that small increases in CSF Na+ produce marked hypertensive responses. But only recently has it been fully appreciated that the excitatory actions of Na+ in the brain are quite specific. This is evidenced in Figure 2. It contrasts the hemodynamic and neurohumoral effects of an acute injection of hypertonic NaCl into either the third ventricle or the cisterna magna. In either situation hypertonic NaCl elevates blood pressure and heart rate. But the neurohumoral response that accompanies the hemodynamic effects of an acute injection of NaCl is of a different nature when the agent is injected at various sites within the cerebral ventricles. A rise in CSF Na+ within a lateral or third cerebral ventricle increases plasma levels of catecholamines, AVP, and cortisol and decreases plasma renin activity. In addition, sympathetic nerve activity to the kidneys falls because of a selective inhibition of renal sympathetic motor neurons by cardiopulmonary baroreceptors. In contrast, injection of the same amounts of NaCl into the cisterna magna causes no changes in renal sympathetic nerve activity or hypophyseal secretions (Figure 2). In keeping with these findings, removal of the area postrema in the fourth ventricle eliminates the pressor response produced by increased CSF Na+ at the level of the cisterna magna but not within a lateral cerebral ventricle. The latter response is prevented, however, by blockade of the periventricular tissue of the hypothalamus. These data show that the actions of Na+ in the brain are specific and that they are mediated through separate sites and mechanisms.

The baroreceptors are another system influenced by changes in sodium balance. In sodium-depleted dogs, Szilagyi and colleagues found that the pressor response to carotid occlusion was blunted before but not after removal of cardiac vagal afferents. Subsequent experiments by Trampisch et al showed that sodium loading had the opposite effect. In this situation, the pressor response to carotid occlusion was...
markedly potentiated and not modified by the elimination of vagal afferents. In other words, decreased salt intake enhanced the inhibitory input provided by the low-pressure baroreceptors. Conversely, increased salt intake produced a significant reduction of their activity.\(^1\)

These findings may be useful in understanding the participation of neural mechanisms in the pathogenesis of salt-sensitive types of experimental hypertension. For example, mineralocorticoid-induced hypertension is associated with both salt and fluid retention.\(^1\) Yet other data suggest a participation of the sympathetic nervous system.\(^1\) We investigated this possibility in instrumented dogs in which steroid hypertension was induced by subcutaneous injections of deoxycorticosterone (DOC) pivalate (20 mg/kg, i.m.). In this model of experimental hypertension, we found that both CSF and plasma AVP increased as early as 7 days after the administration of DOC.\(^20,21\) Furthermore, hypernatremia was present in association with a decrease in the activity of the peripheral renin-angiotensin system.\(^20,21\) Parallel studies of the carotid occlusion reflex revealed an enhanced pressor responsiveness that coincided with the phase of hypernatremia. Cardiopulmonary reflexes had a diminished influence in regulating the increase in sympathetic nerve activity because vagotomy caused no further potentiation of carotid occlusion responses.\(^21,22\) When similar studies were repeated during the more chronic phase of DOC-induced hypertension, we found, in contrast, a diminished activity of sympathetic pressor reflexes.\(^21\) At this late stage of the hypertension, the concentrations of Na\(^+\) and AVP in the plasma were within normal values.

The apparent associations between plasma Na\(^+\), AVP, and sympathetic activity found in dogs exposed to changes in salt intake\(^20,21\) or steroid-induced hypertension\(^20,22\) seemed to us most intriguing. Thus, we explored further whether increases in AVP influence sympathetically mediated responses that are triggered by the carotid occlusion reflex. As done in earlier experiments, conscious dogs previously instrumented with aortic flow probes and vascular catheters received one injection of either DOC or peanut oil (vehicle). The hemodynamic and hormonal changes observed in these new experiments were not different from those reported earlier.\(^22\) Hypernatremia again coincided with increases in plasma AVP and enhanced pressor responses to carotid occlusion. We then determined the effect of the AVP antagonist on both baseline hemodynamics and the carotid occlusion response of DOC-treated dogs. The injection of \([d(CH_2)_2Tyr(Me)]AVP (20 mg/kg, i.v.)\) caused decreases in both blood pressure and total peripheral resistance but marked rises in cardiac output and heart rate. Moreover, blockade of AVP receptors markedly attenuated the pressor response produced by carotid occlusion in these DOC-treated dogs. Intravenous injection of hexamethonium bromide further decreased the blood pressure of DOC-treated animals. The hypotension was accounted for by a large decrease in cardiac output without further reductions in total peripheral resistance.\(^22\) In the sham group of dogs, blockade of \(V_1\) AVP receptors had no effect on the hemodynamic response elicited by the carotid occlusion reflex. These experiments again showed the importance of the interfering relations between neural, hormonal, and humoral factors in the regulation of adrenergic vasoconstrictor drive.

Vasopressin modulates the activity of the sympathetic nervous system\(^23-25\) and participates in the expression of several forms of experimental hypertension.\(^22,26\) The studies done in our dogs suggested an important role of AVP in modulating adrenergic vasoconstrictor drive in DOC-induced hypertension. In retrospect, this was not a new idea as others\(^23-25\) had found that AVP and its analogues interact with prejunctional and postjunctional adrenergic sites to facilitate effects of adrenergic agonists. Furthermore, potentiation of vasoconstrictor responses to norepinephrine has been previously observed in DOC acetate salt-treated animals.\(^27,28\)

Interplay Among Na\(^+\), Angiotensin II, and the Brain

Other work stresses the importance of an integral central mechanism in the regulation of sodium and body fluid balances. Studies from this\(^29\) and other laboratories\(^30\) found that sodium balance alters the interplay between the brain, renin-angiotensin, and the sympathetic control mechanisms. Circumventricular organs and neuronal pathways that participate in the control of arterial pressure contain receptors for Ang II.\(^31\) Furthermore, either acute or chronic deviations in salt balance are associated with changes in the CSF content of Ang II\(^17\) and the density of Ang II receptors present within or in the near vicinity of circumventricular organs.\(^32\) The periventricular region of the third ventricle (AV3V) is one area where the neuronal substrata may determine interactions among AVP, Ang II, and the interstitial concentration of Na\(^+\).\(^33\) This area of the brain has attracted much interest since Andersson and McCann\(^34\) first suggested that it was involved in the control of thirst. Although the role of the AV3V region in the control of hydromineral balance has long been accepted, there are still conflicting opinions concerning the role that this area plays as the site for the neurogenic actions of Ang II.\(^35\)

Lesions of the AV3V area produce chronic hypernatremia and a significant blunting of the pressor responsiveness to peripheral administration of Ang II and norepinephrine. The occurrence of hypernatremia in the rat with AV3V lesions led us to examine its potential influence in determining vascular reactivity to agents such as Ang II. We lesioned the AV3V area of dogs by lowering a microknife after surgically exposing the ventral surface of the brain through the upper palate.\(^35\) This procedure denervated the organum vasculosum of the lamina terminalis (OVLT), the nucleus medianus, and the medial
preoptic nucleus. After 2–4 days, conscious AV3V-lesioned dogs displayed adipsia, hypernatremia (175±2 meq/l) and an elevated plasma osmolality. Cardiac rate was faster in AV3V-lesioned dogs, but their mean arterial pressure was within normal values. These changes were accompanied by an almost 18-fold increase in the plasma levels of immunoreactive Ang II (irAng II). In contrast, plasma AVP levels fell to nondetectable values. Pressor responses produced by intravenous infusions of Ang II or injections of norepinephrine were blunted on the third day after AV3V ablation. Treatment of these animals with the synthetic AVP analogue desmopressin acetate effectively controlled the hypernatremia and reduced plasma irAng II toward control levels. Additionally, the pressor activity of venous infusions of Ang II was restored to prelesion values (Figure 3), whereas the pressor responsiveness to norepinephrine remained depressed.

From these experiments, we learned that the blunting of the pressor action of Ang II in AV3V-lesioned dogs was an expression of a disorder in the regulation of renal and thirst mechanisms maintaining fluid balance and AVP secretion. In addition, we suggested that removal of the AV3V area produced changes in vascular reactivity by a mechanism that was in part related to hypernatremia and suppression of the corrective osmoreceptor-mediated release of AVP. This interpretation was at variance with conclusions made by other investigators. They believed instead that the reduced pressor responsiveness was due to the elimination of a hypothalamic neuronal pathway at which Ang II acts to stimulate sympathetic vasomotor outflow.

As our understanding of the role of the AV3V region and Ang II pressor reactivity advanced, we were still unclear about the underlying mechanisms. Although decreases in vascular smooth muscle reactivity were not considered by other investigators to account for the reduced pressor responsiveness of AV3V-lesioned animals, we did not think that this was a settled issue. Thus, we proceeded to evaluate the effect of AV3V lesions on vascular reactivity. A study by Brum et al provided the first evidence of an endothelium-dependent mechanism that participated in the depression of vascular responsiveness observed after AV3V lesion. This conclusion was derived from comparisons of vascular relaxation responses in dogs in which lesions of the AV3V either included or spared the OVLT. The importance of this comparison was based on the observation that AV3V lesions that spared the OVLT did not produce an increase in plasma Na+ concentrations (unpublished observations from our laboratory). Isolated rings obtained from a carotid artery of normonatremic AV3V-lesioned dogs showed a potentiation of endothelium-dependent relaxation to acetylcholine. On the other hand, in hypernatremic AV3V-lesioned dogs relaxation responses to acetylcholine were not different from those found in sham-operated dogs. These preliminary data illustrate that central mechanisms contribute to modulation of endothelium-dependent relaxation.

![Figure 3](image3.png)

**Figure 3.** Scatterplot showing relation between plasma Na+ concentration and peak changes in arterial pressure produced by short-term intravenous infusions of angiotensin II before, after anteroventral ventricle (AV3V) lesion, and after treatment with an antidiuretic analogue of vasopressin, DDAVP. Data obtained from Tramposch et al with permission.

![Figure 4](image4.png)

**Figure 4.** Line graphs showing cumulative dose–response curve to acetylcholine in endothelium intact (e+) canine carotid artery rings of dogs 3 days after lesion of anteroventral ventricle area, LH, a group of animals that became hypernatremic after the lesion; LN, dogs that remained normonatremic after the lesion; SH, a group of sham-operated animals. Left graph shows no significant differences between LH and SH endothelium-dependent relaxation. Right graph shows significantly (p<0.05) enhanced endothelium-dependent vasorelaxation of LN group when compared with SH group. Relaxation is expressed as percentage of change of vasoconstriction caused by 40 mM KCL.
mediated vascular responses. The data also suggested that hypernatremia masked the increased activity of relaxant factors produced by the endothelium of AV3V-lesioned dogs (Figure 4). There are no other studies of the effects of AV3V-mediated hypernatremia on endothelium-dependent vascular responsiveness. Moreover, we do not know whether the effects observed in rings from carotid arteries may also occur in the smaller vessels that determine vascular resistance. Nevertheless, the data obtained in these experiments suggest that altered endothelium-dependent vascular reactivity may be one mechanism that contributes to the antihypertensive effects of AV3V lesions. Although the mechanism that accounts for the altered vasoactive functions of the vascular endothelium in conduit arteries of AV3V-lesioned dogs remains to be investigated, the findings agree with the hypothesis that the brain may exert an influence on endothelial function.

**Sodium, the Central Nervous System, and the Endothelium**

As summarized in reviews published elsewhere, the vascular endothelium has many functions. Endothelial cells act to prevent adherence of platelets and blood cells to the vessel wall, synthesize coagulation and growth factors, and participate in the enzymatic processing of neurohormones. Endothelial cells also produce vascular relaxing (EDRF) and constricting factors (EDCF). These endothelial factors modulate the vasoactivity of circulating hormones and neurotransmitters. Lüscher et al. showed that endothelium-dependent contractions produced by either norepinephrine or serotonin in rat aorta are potentiated by exposure to a high salt diet. They interpreted these findings as an indication that salt loading may stimulate the release or production of an EDCF. As reviewed by Vanhoutte, endothelium-dependent relaxations are reduced in a variety of experimental models of hypertension, including those associated with increased salt intake.

Because endothelium-derived factors modulate the prejunctional release of norepinephrine in blood vessels, we repeated experiments in DOC-treated dogs to examine endothelium-dependent relaxing responses 7 days after onset of DOC-induced hypertension. Figure 5 shows the results from experiments done in isometric preparations of isolated carotid artery rings from sham- and DOC-treated dogs. In both groups of animals, acetylcholine induced endothelium-dependent relaxations at doses ranging between 3.16x10^-9 M and 3.16x10^-7 M. However, in animals treated with DOC, relaxation responses to acetylcholine were greater than those obtained in sham dogs. These data suggest a greater sensitivity of the vascular smooth muscle of DOC-treated dogs to EDRF during the stage of hypertension that is associated with increases in sympathetic nerve activity. As indicated by King and Webb, endothelium-mediated compensatory responses may occur in large vessels of animals subjected to various types of experimental hypertension. However, similar findings have not been consistently replicated in resistance vessels. In the rat treated with DOC acetate, salt-enhanced reactivity of the mesenteric vasculature to pressor stimuli is masked by a factor that is released by the endothelium. Because many factors influence vascular reactivity, it is difficult to compare findings between various studies. Although the data obtained in these DOC-treated dogs showed an influence of the endothelium in a large blood vessel, it is possible that a similar change may not occur in either small arteries or resistance vessels.

Little is known of the nature of factors that may influence the vasoactive function of the endothelium. Because the vascular endothelium of organs other than the eye and the liver have been shown not to be innervated, humoral factors are suspected. A natriuretic hormone that acts by dampening the activity of the Na^+K^-ATPase pump may be produced by the brain. Some data suggest the absence of a natriuretic-like factor in rats with AV3V lesions. According to Folkow, this putative natriuretic factor may be a component of the neural circuit that links Na^+ receptors with the overall regulation of sodium and body fluid homeostasis. It is therefore plausible that functional alterations within the brain may modify the natural response of arterial vessels to neurohumoral agents and specifically endothelial-mediated responses. The anatomic location of the vascular endothelium suggests an additional site at which circulat-

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**Figure 5.** Line graph showing cumulative dose-response curve to acetylcholine in endothelium intact (e+) canine carotid artery rings of deoxycorticosterone-treated (DOC) and sham-treated dogs. Relaxation is expressed as percentage of change of vasoconstriction caused by 40 mM KCl. Responses of DOC group are significantly different from Sham group (p<0.05).
ing humoral factors may influence the effect of hemodynamic factors in the release of vasoactive products.

In conclusion, hypertension is a disease of varied etiology in which multifactorial mechanisms contribute to a gradual rise in arterial pressure. Many studies suggest that central neurohormonal influences participate in the initiation of high blood pressure. Lessons learned from physiological studies suggest that the brain plays an important role in the regulation of sodium balance and body fluid volume. But the data reviewed above reveal that the relation among Na⁺, blood volume, and the neurogenic determinants of arterial pressure are complex and interlocking in nature.

On the other hand, it is important to point out that other investigators found no evidence for a role of plasma sodium concentration in the pathogenesis of hypertension. Systematic studies done in Cowley's laboratory⁵²,⁵³ suggest that blood volume expansion and increased cardiac output determined the appearance of hypertension and hypernatremia produced by the constant infusion of Ang II and enhanced salt intake. Their analysis of the hemodynamic determinants of hypertension indicate that concurrent increases in plasma Na⁺ concentrations are subordinate to sodium retention and body fluid expansion and of little significance to the initiation of hypertension.⁵² But in their studies neither the infusion of Ang II nor increased salt intake alone resulted in an elevation of arterial pressure.⁵²,⁵³ Therefore, it is necessary to consider whether both factors were necessary for hypertension to develop. The absence of a compensatory baroreceptor-mediated decrease in vascular resistance during the progressive rise of the blood pressure in dogs given Ang II and salt suggests their aggregate effect on neurohormonal mechanisms that determine arterial pressure. Although volume retention may be a factor that initiates hypertension, this does not belittle the importance of other humoral and neurohormonal factors in contributing to the evolution of high blood pressure. In a previous review of this subject,⁵⁴ we commented that:

Current ideas about angiotensin effects have shifted from its direct vascular excitation to those indirect mechanisms, mediated via nervous and electrolyte changes and effective at decidedly lower angiotensin concentrations than those needed to produce direct vasoconstriction. These effects imply important mutual interactions between neurogenic and hormonal control factors, so organized that, whether the neurogenic or the hormonal factor is the initiator, they will combine to exert a gradually more sustained neurohormonal drive on the cardiovascular system.

It seems to us that the studies reported by Krieger et al.⁵⁵,⁵⁶ are in agreement with this concept.

The preponderance of the evidence obtained both in animal models of hypertension and in hypertensive subjects indicates that increases in plasma Na⁺ concentration play no direct role in the pathogenesis of hypertension. Although our data conform to these previous conclusions, the findings also suggest that changes in plasma Na⁺ concentration may be a marker of an underlying activation of central neural and endocrine mechanisms that participate in the evolution of hypertension. Aviv⁵⁵ has addressed this issue recently. In a Letter to the Editor he endorsed the possibility that increased salt intake in susceptible individuals may cause important trophic changes in vascular smooth muscle because some vasoactive agents can act as a growth factor, while conversely, some growth factors can elicit constrictor responses. That vasoactive agents and adrenergic neurotransmitters have significant trophic and metabolic functions is becoming an accepted tenet as new techniques show the effects of these agents on cell function. It is likely that future research will shed further light on this attractive idea. In addition, we should explore further whether the brain may have a direct influence in regulating the vasoactive function of the endothelium. This mechanism may provide a further linking pathway between peripheral and central mechanisms of cardiovascular control.

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