How Does Salt Raise Blood Pressure?
A Hypothesis

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SUMMARY Existing data in the literature indicate that α2-adrenergic receptor agonists have a profound hypotensive action, that sodium attenuates the affinity of α2-adrenergic receptors for agonists, that the location of these receptors in the central nervous system is mainly at the sites of cardiovascular regulation, and that these sites exert a constant tonic inhibition of sympathetic vasoconstrictor tone. This article proposes the theory that sodium exerts its hypertensive action by decreasing the state of affinity of the α2-adrenergic receptors of the central nervous system for locally occurring agonist neurotransmitters, which results in disinhibition of sympathoinhibitory neurons and leads to the hyperadrenergic state characteristic of salt-induced hypertension.

(Hypertension 8: 83-88, 1986)

KEY WORDS • α2-adrenergic receptors, affinity • central sympathetic nervous system • sympathoinhibitory neurons • disinhibition

The fact that increased consumption of salt promotes the development of hypertension has been established by epidemiological surveys as well as by numerous experimental studies. Furthermore, much research on the permeability of cell membranes has addressed the question of why certain persons tend to retain more sodium than others. However, the actual mechanism by which excessive sodium retention leads to elevation of blood pressure remains unknown. Several theories have been proposed, such as expansion of intravascular fluid volume, alteration of vascular wall structures, and reactivity to pressor substances, but none is wholly satisfactory.

Based on my experimental studies and those of other investigators over the last few years, I have formulated the following hypothesis: Others have suggested that maintenance of blood pressure within a given range is achieved by constant tonic inhibition of sympathetic outflow from the sites of cardiovascular regulation located in the brainstem. It has been demonstrated that these sympathoinhibitory neurons are characterized by a high density of α2-adrenergic receptors, the activation of which produces a hypotensive effect. It has been found in vitro that the sodium ion decreases the affinity of α2-adrenergic receptors for agonists. If this mechanism also is valid in vivo, then loading with sodium chloride may decrease the affinity of α2-adrenergic receptors located in the central nervous system for naturally occurring local agonists, which leads to diminished tonic inhibition of central sympathoinhibitory neurons and, therefore, increased sympathetic outflow to the periphery.

The following is a brief review of the experimental data that support this theory. It presents evidence indicating that 1) sodium excess causes sympathetic overactivity, which is one of the pathogenetic mechanisms of hypertension, 2) the normal function of central catecholaminergic neurons located in the brainstem is to exert a constant tonic inhibition of sympathetic vasoconstrictor tone; and 3) the α2-adrenergic receptor function of these catecholaminergic neurons can be attenuated by the Na+ ion, which decreases the receptors' sensitivity to locally occurring agonist neurotransmitters. The end result is disinhibition of the sympathoinhibitory effect of these neurons and increased sympathetic drive to the periphery. To my knowledge, no experimental or other evidence is incompatible with this hypothesis.

Hypertension, Sodium Excess, and Sympathetic Overactivity

Based on indications that circulating levels of norepinephrine reflect sympathetic neural activity, numerous clinical and experimental studies have reported...
that hypertension is frequently (but not always) associated with sympathetic overactivity. Elevated plasma catecholamine levels have been demonstrated in up to 40% of patients with essential hypertension and were found to be associated with hemodynamic indices of a hyperadrenergic state. A positive correlation between circulating norepinephrine levels and diastolic blood pressure was found in certain subgroups of the essential hypertensive population, such as younger men, in whom the differences from age-matched controls are most apparent. Many investigators have reported this finding, but they have interpreted this hyperadrenergic state as an indicator of anxiety, stressful situations, or suppressed hostility. Increased sympathetic activity has been found to be associated with high sodium intake in experimental animals with deoxycorticosterone acetate (DOCA)-salt hypertension. In accordance with this finding, studies in humans have shown elevated plasma norepinephrine levels after sodium loading, which leads to a rise in blood pressure.

While these studies relied mostly on the norepinephrine levels circulating in the periphery, other studies sought different indices of overactivity in the central sympathetic nervous system. For example, in certain brainstem areas of several experimental models such as spontaneously hypertensive rats (SHR), Dahl salt-sensitive rats, and DOCA-salt rats, the levels of the epinephrine-forming enzyme phenylethanolamine-N-methyltransferase (PNMT) were significantly higher than those occurring in normal controls. Moreover, my colleagues and I found that an inhibitor of PNMT activity, which could cross the blood-brain barrier, could reverse the blood pressure of "sodium-dependent" models of hypertension, such as the DOCA-salt, the one-kidney, one clip renovascular, and the subtotally nephrectomized rat on a high salt diet; however, it did not have a hypertensive action in "renin-dependent" models, such as the two-kidney, one clip renovascular rat.

In short-term experiments using either normal or DOCA-salt rats, we found that a hypertonic saline infusion elicited a sharp rise in both vasopressin and norepinephrine levels. Moreover, the magnitude of blood pressure rise was directly correlated with both norepinephrine and vasopressin levels, and, surprisingly, it was inversely correlated with the change in plasma volume, which reinforced our conviction that sodium-induced hypertension is caused by a pressor mechanism and is not the result of intravascular fluid volume expansion. All of these data, as well as several other corresponding studies, support the view that hypertension induced by sodium excess is due, at least in part, to a neurogenic mechanism mediated through activation of the central sympathetic nervous system. There is also evidence suggesting that vasopressin may participate in the earliest stages of blood pressure rise induced by sodium loading. Thus, its role may be to enhance this sympathetic activation by acting as a neuromodulator.

Regulation of Blood Pressure by Central Catecholaminergic Neurons of the Brainstem

Neural control of blood pressure is exerted by the autonomic nervous system, which regulates cardiac output by way of the sympathetic and vagal innervation of the heart and regulates peripheral vascular resistance by way of the sympathetic nervous system. Major centers for cardiovascular control are the nucleus tractus solitarii (NTS), which is rich in catecholaminergic neurons, and is located near the surface in the dorsal part of the medulla at the end of the fourth ventricle, and the locus ceruleus, which is located near the wall of the fourth ventricle at the level of the pons and whose noradrenergic neurons are activated by the monoamine neurotransmitters norepinephrine and epinephrine.

The NTS is the relay center containing the primary synapse of the baroreceptor afferents, which make contact with interneurons that project to the vasomotor and cardioinhibitory centers of the forebrain. Destruction of the NTS produces hypertension of varying severity or lability, whereas microinjection of norepinephrine into the NTS area was reported to cause a fall in blood pressure. Intravascular fluid volume expansion exerts an inhibitory influence on the locus ceruleus, whereas electrolytic destruction of the locus ceruleus elicits a pressor response. Likewise, anatomical or toxic lesions of noradrenergic neurons in the A1 area, located in the caudal ventrolateral medulla, cause a persistent increase in vascular resistance. Furthermore, microinjection of the inhibitory amino acid γ-aminobutyric acid in the A1 area also produces an increase in blood pressure. These findings are consistent with the view that the main function of noradrenergic neurons in these brainstem regions (i.e., the NTS, A1 area, and locus ceruleus) is the tonic inhibition of sympathetic vasconstrictor tone. Accordingly, disinhibition of catecholaminergic fibers by deafferentation of arterial baroreceptors or by decreased activity of inhibitory catecholaminergic neurons in the brainstem appears to play an important causative role in experimental hypertension.

α-Adrenergic Receptor Function and Blood Pressure Regulation

Subclassification of α-adrenergic receptors into α₁ and α₂ subtypes is carried out by the radioligand binding technique, in which a drug of high specific radioactivity binds in a reversible manner to the receptor recognition site. The choice of drugs is based on their selective affinity or potency in eliciting or inhibiting specific α₁ or α₂ responses. This pharmacological classification appears to be the most valid approach as long as the molecular structure of the receptors remains unknown. Drugs frequently chosen for their high degree of selectivity include the α₂-agonists clonidine and guanabenz, the α₁-antagonists yohimbine and rauwolscine, the α₁-agonist phenylephrine, and the α₂-agonist prazosin. On the basis of this approach, it...
has now been determined that α₂-adrenergic receptors are located both presynaptically (autoreceptors that modulate norepinephrine release) and postsynaptically in various tissues. Ample evidence indicates the existence in the brain tissues of hypotensive α₂-adrenergic receptors that are both presynaptic and postsynaptic. Vascular smooth muscle, on the other hand, was shown to contain the classic postsynaptic α₁-adrenergic receptors as well as postsynaptic α₂-adrenergic receptors, both of which mediate a vasoconstrictor response.

The classic pharmacological response associated with stimulation of presynaptic α₁-adrenergic receptors is inhibition of the release of norepinephrine into central adrenergic and peripheral sympathetic synapses. Physiologically, α₁-adrenergic receptor function can be regulated by the cells to alter responsiveness to stimuli. Cells compensate for increased local concentration of agonist by down-regulation (i.e., decreased receptor number or affinity, or both) and for decreased concentration of agonist or chronic occupancy by antagonist by up-regulation (i.e., increased receptor number or affinity, or both). Desensitization involves uncoupling the α₂-adrenergic receptor from adenylate cyclase and is evidenced by conversion from high to low affinity state. Several in vitro studies that used radioligand binding techniques have shown that α₁-adrenergic receptor sensitivity can also be altered by guanine nucleotides and metal cations. Specifically, the smaller monovalent cations Na⁺ and Li⁺ were shown to inhibit the binding of agonists to α₁-adrenergic receptors, thereby reducing the potency of agonists. Moreover, these same cations that shift α₁-adrenergic receptors to a low affinity state for agonists also increase their affinity for yohimbine, rauwolscine, and other antagonist competitors (i.e., the rank order of affinity of different receptor states for agonists is the obverse of the order of affinity of these states for antagonists). Such bivalent cations as Ca²⁺ and Mg²⁺ have the opposite effect (i.e., they tend to increase the affinity of α₁-adrenergic receptors for agonists).

The same brainstem regions that have been implicated in the regulation of blood pressure by physiological experiments have also been found to have the highest density of α₂-adrenergic receptors in the hindbrain. Using an autoradiographic technique that labeled α₁- and α₂-adrenergic receptors with selective radiolabeled ligands, Young and Kuhar were able to construct a map of the distribution of these receptors throughout the brain. They found a high concentration of α₂-adrenergic receptors in the periventricular areas of the hypothalamus, which, incidentally, is the location of vasopressin-regulating nuclei. In the brainstem, they found the highest concentration of α₂-adrenergic receptors in, among other areas, the NTS, the locus ceruleus and the cells of the A1 area, whereas α₁-adrenergic receptor distribution was low and relatively even throughout the hindbrain.

These central α₁-adrenergic receptors are located presynaptically and postsynaptically and are closely involved in the antihypertensive and bradycardic effects elicited by α₁-agonists. In this context, it is interesting to note that certain strains of rats with decreased catecholamine content in the hypothalamus and brainstem have commensurately increased density of α₁-adrenergic receptors and that hypertension-prone rats, such as the young SHR, were reported to have significantly elevated concentration of α₂-adrenergic receptors in the hypothalamus. Since diminished concentrations of both norepinephrine and epinephrine in these brain areas have been described in SHR, the data suggest up-regulation of the number of receptors in the presence of decreased amounts of agonist. These findings are consistent with the hypothesis that diminished noradrenergic activity and reduced stimulation of central α₁-adrenergic receptor function may be directly related to the rise of blood pressure. Interestingly, Pettinger et al. recently reported that the genetically hypertensive SHR and Dahl salt-sensitive rats may have some defect that also causes a high density of renal α₂-adrenergic receptors, which was thought to be relevant to the mechanism of hypertension in these strains.

Recent reports that in vitro the Na⁺ ion diminishes the affinity of α₁-adrenergic receptors for adrenergic agonists suggested to us that, if this were also true in vivo, the Na⁺ ion, by acting as an inhibitor, could modify the effects of agonists on α₂-adrenergic receptors located in those brain regions presumed to tonically inhibit sympathetic activity. This possibility prompted us to investigate further the effects on blood pressure of NaCl solutions introduced directly into specific areas of the brainstem as well as the effects of NaCl on the responsiveness of peripheral (vascular) α₁-adrenergic receptor function. To this purpose, we designed the following two experiments, both of which gave preliminary results supporting this hypothesis.

In one study, microinjections of hypertonic saline or other equiosmolar electrolytic and nonelectrolytic solutions were administered to the NTS area or to immediately adjacent areas. We found that a hypertonic solution of NaCl produced a significant and lasting pressor response, whereas equiosmotic solutions of LiCl produced sharp, transient hypertensive responses; isotonic NaCl produced a significant, short-lived blood pressure rise; and equiosmotic glucose produced no blood pressure change. Hypertonic NaCl solution introduced into other brainstem regions had no such effect. Pretreatment with the nonspecific α₁-antagonist phentolamine completely abolished all hypertensive responses, whereas an antagonist of the peripheral pressor effect of vasopressin could not. These findings indicated that 1) the hypertensive mechanism activated by these maneuvers was sodium-sensitive and might be briefly responsive to other cations but not to osmotic stimuli or to the mechanical effect of fluid volume, 2) α₁-adrenergic receptors were involved at the level of either the central nervous system or the final effector pathway, and 3) the peripheral vascular pressor action of vasopressin did not contribute to this effect.
The purpose of the second experiment was to study in vivo the influence of sodium on vascular α₂-adrenergic receptors by assessing the early pressor response elicited by parenteral administration of the specific α₂-agonist clonidine to rats. Indeed, prior saline infusion greatly attenuated the pressor effect of clonidine and shifted its dose-response curve downward, which suggests a partial inhibition of the postsynaptic vascular (pressor) α₂-adrenergic receptors.56,57 That this effect of sodium could be obviated by the α₂-blocker yohimbine but remained unaffected by the α₁-blocker prazosin further supports this interpretation. It has been known for some time that the α-adrenergic receptors at medullary cardiovascular sites are very similar to those in the peripheral vasculature and only distinguishable on the basis of differences in accessibility for drugs.58 Therefore, α-adrenergic receptors in the central nervous system would be expected to be influenced by sodium in the same manner as the peripheral ones.

Since central α₂-adrenergic receptors have a vasodepressor function, as evidenced by the hypotensive effect of norepinephrine introduced into certain areas of the brainstem by microinjection59 or by the hypotensive action of pharmacological α₂-agonists such as clonidine, which are even more potent than the naturally occurring ones,60,61 these observations may provide the link between sodium excess and the sympathetically mediated rise in blood pressure. Accordingly, we propose the theory that sodium exerts its hypertensive action in part by decreasing the affinity of central (vasodepressor) α₂-adrenergic receptors for agonist neurotransmitters occurring naturally in those areas of the central nervous system that are presumed to exert a constant tonic sympathoinhibitory action on the peripheral vasculature, and, hence, a constant depressor effect; the resultant sympathetic disinhibition would therefore lead to a hyperadrenergic state with elevation of blood pressure.

An alternative theory proposed by Insel and Motulsky62 suggests that increased intracellular Na⁺ may modulate target organ responses in more than one way; for example, it decreases the affinity of platelet α₂-adrenergic receptors for epinephrine, yet increases the platelet’s response to the agonist (i.e., epinephrine-mediated platelet aggregation). Insel and Motulsky63 applied this theory to other receptors and proposed that, in general, increased Na⁺ concentration causes hypertension by potentiating the response of various pertinent receptors to hypertensive stimuli. Notwithstanding the platelets’ behavior in vitro, there is ample supportive evidence in the literature that Na⁺ decreases the response of other α₂-receptors. However, these authors’ generalization is not necessarily inconsistent with our hypothesis, since it is well recognized that Na⁺ indeed enhances the responsiveness of certain receptors (e.g., α₁-adrenergic and angiotensin receptors) to their respective agonists.41,45,62 Hence, infusions of angiotensin or sympathomimetic amines are far more vasopressor in the face of sodium excess, and such a peripheral pressor mechanism also may contribute to hypertension. It is our belief, however, that a central neurogenic mechanism is much more critical to the pathophysiology of hypertension.

Our theory is consistent with the findings of Chalmers64 and Reis and co-workers,65,66,67 who reached the conclusion that blood pressure is maintained in the normal range by constant tonic inhibition of sympathetic tone by catecholaminergic neurons of the brainstem, as well as with findings of other investigators, mentioned previously,19,51-53 who described in hypertension-prone rats decreased catecholamine content and increased concentration of α₂-adrenergic receptors in brain nuclei involved with blood pressure regulation. A recent report68 that salt loading restricted to the brain by intracerebroventricular infusion of hypertonic saline elevates blood pressure by reducing anterior hypothalamic inhibition of sympathetic vasomotor tone also fits our hypothesis perfectly. Furthermore, since the bivalent cations Ca²⁺ and Mg²⁺ were found to exert the opposite effect on α₂-adrenergic receptors (i.e., to heighten their state of affinity for agonists),69 this hypothesis offers an alternative explanation to recent reports linking deficient dietary calcium intake with hypertension60 and to the long-known hypotensive effect of magnesium.64

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*Hypertension*. 1986;8:83-88
doi: 10.1161/01.HYP.8.1.83

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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