Effect of Sodium on Central α2-Adrenergic Receptors

To the Editor:

I have no quarell with the data presented by Koepke et al., in the April 1988 issue of Hypertension, but I disagree with their interpretation.

The authors found that intracerebroventricular administration of guanabenz produced greater response in spontaneously hypertensive rats (SHR) fed a high salt diet than in SHR fed a normal salt diet and interpreted this as indicative of heightened sensitivity of central α2-adrenergic receptors in these rats. They used the terms responsiveness, sensitivity, affinity, and density of α2-adrenergic receptors interchangeably, as if they all indicated the same function and change concurrently. However, this is not so, as Bmax (density) and Kd (affinity) can move in opposite directions. These studies did not measure either affinity or density—they only measured the magnitude of a final response. If the sympathetic drive of SHR fed a high salt diet is increased, any sympatholytic intervention should produce a greater response. This response is perfectly compatible with my hypothesis, which predicts heightened sympathetic activity but stipulates that sodium causes blunted affinity of α2-adrenergic receptors (i.e., partially inhibits receptor-agonist interaction). However, a high salt diet is indeed associated (in susceptible models) with deficiency in endogenous agonist in certain brain regions, as shown by several studies. This deficiency would favor up-regulation of α2-adrenergic receptor numbers, although the data in the literature are conflicting on this point.

The diminished affinity of α2-adrenergic receptors can be very well overcome by a pharmacological agonist with a very high affinity to these receptors. For example, clonidine was shown to have a higher affinity than natural neurotransmitters for α2-adrenergic receptors. Incidentally, the same interpretation can be used for the data presented by Yang et al., who used clonidine and demonstrated a greater blood pressure fall in SHR fed a high salt diet. The “increased responsiveness” in this setting indicates interference with the mechanism responsible for the blood pressure elevation, namely, the stimulated sympathetic system; it says nothing about the affinity of the α2-adrenergic receptors, although those authors adopted an interpretation similar to that of Koepke et al.

To put this in better perspective, I will use the analogy of a high-renin hypertension, which responds to angiotensin antagonists with a much greater blood pressure fall than does a low-renin hypertension. Does that mean that angiotensin II receptor sensitivity or responsiveness is increased in high-renin states? That would be the interpretation according to the reasoning adopted by Yang et al. and Koepke et al., but it is obviously wrong, as it is well known that angiotensin II receptor sensitivity is decreased in high-renin states. The magnitude of the final response indicates that the predominant mechanism sustaining high blood pressure is angiotensin-mediated, but it offers no information as to the status of the angiotensin II receptors.

Contrary to the authors’ statement, my hypothesis is also compatible with the data of Pettinger et al., who described increased α2-adrenergic receptor density in salt-sensitive SHR and Dahl salt-sensitive rats. Thus, diminished stimulation because of a reduced affinity can lead to up-regulation in receptor numbers.

In summary, the data of Koepke et al. describe greater responses in sympathetically mediated functions in SHR fed a high salt diet. This finding does support the ability of salt to cause sympathetic overactivity in these rats but does not indicate that salt increases central nervous system α2-adrenergic receptor responsiveness or affinity.

I certainly do agree with the final conclusion that “... high dietary sodium intake contributes to the pathophysiology of hypertension by reducing the steady state level of stimulation of central nervous system sympathoinhibitory α2-adrenergic receptors. . . .” This is exactly what my hypothesis states, but it was an unexpected conclusion after all the previously stated arguments to the contrary.

Haralambos Gavras, M.D.
Boston University School of Medicine
Boston, MA 02218

References
Our study indicated that high dietary sodium intake increases the responsiveness of the central nervous system a2-adrenergic receptor control of renal sympathetic nerve activity and urinary sodium excretion in conscious spontaneously hypertensive rats (SHR). This conclusion was based on the findings that 1) for a given intracerebroventricular (i.c.v.) dose of guanabenz (a selective a2-adrenergic receptor agonist), renal sympathetic nerve activity decreased and urinary sodium excretion increased more in conscious SHR on a high rather than a normal sodium intake; 2) i.c.v. administration of rauwolscine (a selective a2-adrenergic receptor agonist) reversed these effects; and 3) surgical renal denervation inhibited the effects of i.c.v. guanabenz administration on urinary sodium excretion in conscious SHR on normal or high sodium intake.

In our study,1 the terms responsiveness and sensitivity were defined functionally. For a given stimulus (i.c.v. dose of guanabenz), a greater change in renal sympathetic nerve activity or urinary sodium excretion in SHR on a high rather than a normal sodium intake reflects a greater responsiveness or sensitivity of central nervous system a2-adrenergic receptors. Guanabenz and rauwolscine are used as a2-adrenergic receptor-selective pharmacological tools to study central nervous system a2-adrenergic receptors in vivo. Thus, a change in responsiveness or sensitivity to a given i.c.v. dose of guanabenz (reversible by rauwolscine) implies an in vivo change in central nervous system a2-adrenergic receptors (e.g., density or affinity). Since we are not able to measure in vivo changes in a2-adrenergic receptor density or affinity using radioligand binding techniques, we must rely on results from in vitro studies. However, the results from in vitro studies do not provide information about in vivo functional significance. In vitro and in vivo studies should be viewed as complementary, not as substitutes for each other.

The in vivo results of our study indicated a greater responsiveness or sensitivity (defined functionally) of central nervous system a2-adrenergic receptors in conscious SHR on a high rather than a normal sodium intake. This increased responsiveness may be caused by an increased density or affinity (defined by in vitro radioligand binding techniques) of central nervous system a2-adrenergic receptors in SHR on high sodium intake. In fact, recent data support this hypothesis. Stemming from their observation that high dietary sodium intake decreases norepinephrine release in the anterior hypothalamus of SHR, Oparil and colleagues2 hypothesized that high dietary sodium intake increases a2-adrenergic receptor density (receptor up-regulation secondary to decreased norepinephrine release) in the anterior hypothalamus of SHR.

These investigators found that high dietary sodium intake in SHR increased a2-adrenergic receptor density in the anterior hypothalamus but had no effect on a2-adrenergic receptor affinity.

Thus, the in vivo functional data of our study1 and the in vitro radioligand binding data of Oparil and colleagues2,3 are complementary. Together, these studies point to the conclusion that high dietary sodium intake increases the responsiveness or sensitivity (defined functionally in vivo and biochemically in vitro) of central nervous system a2-adrenergic receptor control of renal sympathetic nerve activity and urinary sodium excretion.

John P. Koepke, Ph.D.
Washington University School of Medicine
St. Louis, MO 63110

Gerald F. DiBona, M.D.
University of Iowa College of Medicine
Iowa City, IA 52242

References

Individualization of Antihypertensive Therapy

To the Editor:

To our mutual surprise, we discovered in the February 1988 issue of Hypertension the simultaneous publication of two independent investigations performed in our respective groups.1,2 The coincidence encouraged us to follow up on the approach we were using independently—to improve the care of our hypertensive patients by individualizing their therapy through a more precise analysis of the fall in blood pressure induced in each patient by the sequential administration of two or more antihypertensive drugs.1-3 At present, the selection of a drug for an individual hypertensive patient is usually based on trends derived from large-scale randomized clinical trials,4 on various rigid stepped-care programs recommended for current practice,5 or on indices such as age, renin, or race, whose predictive value for the antihypertensive efficacy of a given
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H Gavras

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