Effect of Sodium on Central α2-Adrenergic Receptors

To the Editor:

I have no quarrel with the data presented by Koepke et al.,1 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 indicate 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,2 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.3 This deficiency would favor up-regulation of α2-adrenergic receptor numbers, although the data in the literature are conflicting on this point.4-6 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.7 Incidentally, the same interpretation can be used for the data presented by Yang et al.,8 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.1

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 accord-
Our study indicated that high dietary sodium intake increases the responsiveness of the central nervous system α₂-adrenergic receptor control of renal sympathetic nerve activity and urinary sodium excretion in conscious spontaneously hypertensive rats (SHR). This conclusion was based in part on the findings that 1) for a given intracerebroventricular (i.c.v.) dose of guanabenz (a selective α₂-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 α₂-adrenergic receptor antagonist) 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, the terms responsiveness and sensitivity were defined functionally. For a given stimulus (i.e., 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 α₂-adrenergic receptors. Guanabenz and rauwolscine are used as α₂-adrenergic receptor-selective pharmacological tools to study central nervous system α₂-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 α₂-adrenergic receptors (e.g., density or affinity). Since we are not able to measure in vivo changes in α₂-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 α₂-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 α₂-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 colleagues hypothesized that high dietary sodium intake increases α₂-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 α₂-adrenergic receptor density in the anterior hypothalamus but had no effect on α₂-adrenergic receptor affinity.

Thus, the in vivo functional data of our study and the in vitro radioligand binding data of Oparil and colleagues 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 α₂-adrenergic receptor control of renal sympathetic nerve activity and urinary sodium excretion.

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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,s or on indices such as age, renin, or race, whose predictive value for the antihypertensive efficacy of a given
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