Kidney International, Vol. 34, Suppl. 25 (1988), pp. S-23–S-27

Augmented rise of α_2/β_2 adrenoceptor ratio induced by salt and essential hypertension

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A chronically-high salt intake may be involved in the slow development of "essential hypertension" in susceptible (salt sensitive) individuals [1]. We have previously proposed [2–6] that one important mechanism of salt sensitivity in normotensives leading to hypertension over many years may be an enhanced noradrenergic responsiveness of resistance vessels and of renal proximal tubular cells, with an increase of that part of proximal tubular sodium reabsorption, which is under sympathetic control. We postulated that this enhanced noradrenergic responsiveness may be induced by the high salt diet. Because we had shown enhanced noradrenergic responsiveness in salt sensitive as compared to salt resistant individuals [2], we have measured in the present study α_2 and β_2 adrenoceptors during changes of salt intake in healthy men.

Material and methods

Twenty-four healthy male students, aged 20 to 25 years, were studied three times: 1) during their usual high salt diet containing 200 mmmol per day, 2) after two weeks of moderate salt restriction to 50 mmol per day, and 3) again after two weeks on their usual high sodium diet. Other components of the diet were unchanged. During strictly basal conditions and supine bedrest, blood pressures of at least 720 heart beats during a 90-minute period were collected by an oscillometric method [7], and the mean of all measurements ("basal mean arterial blood pressure average" [8]) was used for assessment of blood pressure response. The diets were prepared and consumed in the Dietary Department of the hospital.

Twenty-four hour urinary samples were used for measurements of sodium potassium, and aldosterone excretion. Blood was drawn after 90 minutes of supine bedrest for the measurements of α_2 adrenoceptors of platelets, of β_2 adrenoceptors of lymphocytes and of plasma catecholamines.

Methods for adrenergic receptor studies were as described by Brodde et al [9]. Binding parameters were calculated using the non-linear parameter optimization as suggested by Rodbard et al [10]. Plasma catecholamines were measured by HPLC [11]. Differences between the different diets were assessed by the Wilcoxon Test.

Results

Figure 1 shows the histograms of blood pressure changes in 62 healthy subjects, 28 with a positive and 34 with a negative family history of hypertension [2–4] studied during changes of sodium intake from 200 to 50 mmol over two weeks. The frequency distribution of blood pressure changes in the hereditary positive subjects is significantly skewed to the left as compared with hereditary negative subjects ($P < 0.01$ U-test of Mann-Whitney). Individual α_2 and β_2 adrenoceptor changes and changes of α_2/β_2 receptor ratios during the high and low salt diets are shown in Figure 2, A through C. There are marked interindividual differences in receptor responses, but overall there is a significant rise of α_2 adrenoceptor density on a high sodium diet ($P < 0.01$) as compared to the low salt diet (Figure 2A, Table 1). In contrast, we observed a significant fall of β_2 adrenoceptors ($P < 0.05$) during the high salt diet (Fig. 2B, Table 1). The α_2/β_2 adrenoceptor ratio also increased significantly ($P < 0.01$) during the high salt intake (Fig. 2C, Table 1). Plasma catecholamines showed a tendency to fall during the high salt diet, which was significant for plasma adrenaline and plasma dopamine (Table 1). There were no correlations between absolute values or changes of plasma catecholamines or of absolute blood pressures and α_2 or β_2 receptor affinities or

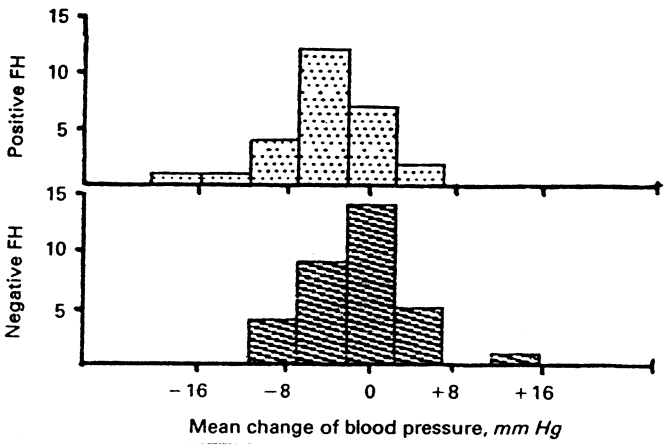


Fig. 1. *Frequency histogram of blood pressure changes during reduction of sodium intake from 200 to 50 mmol over two weeks in 62 normotensive volunteers [2–4] classified according to family history of hypertension.* The frequency distribution is shifted significantly ($P < 0.01$, U-test Mann-Whitney) to the left in subjects with a positive family history of hypertension.

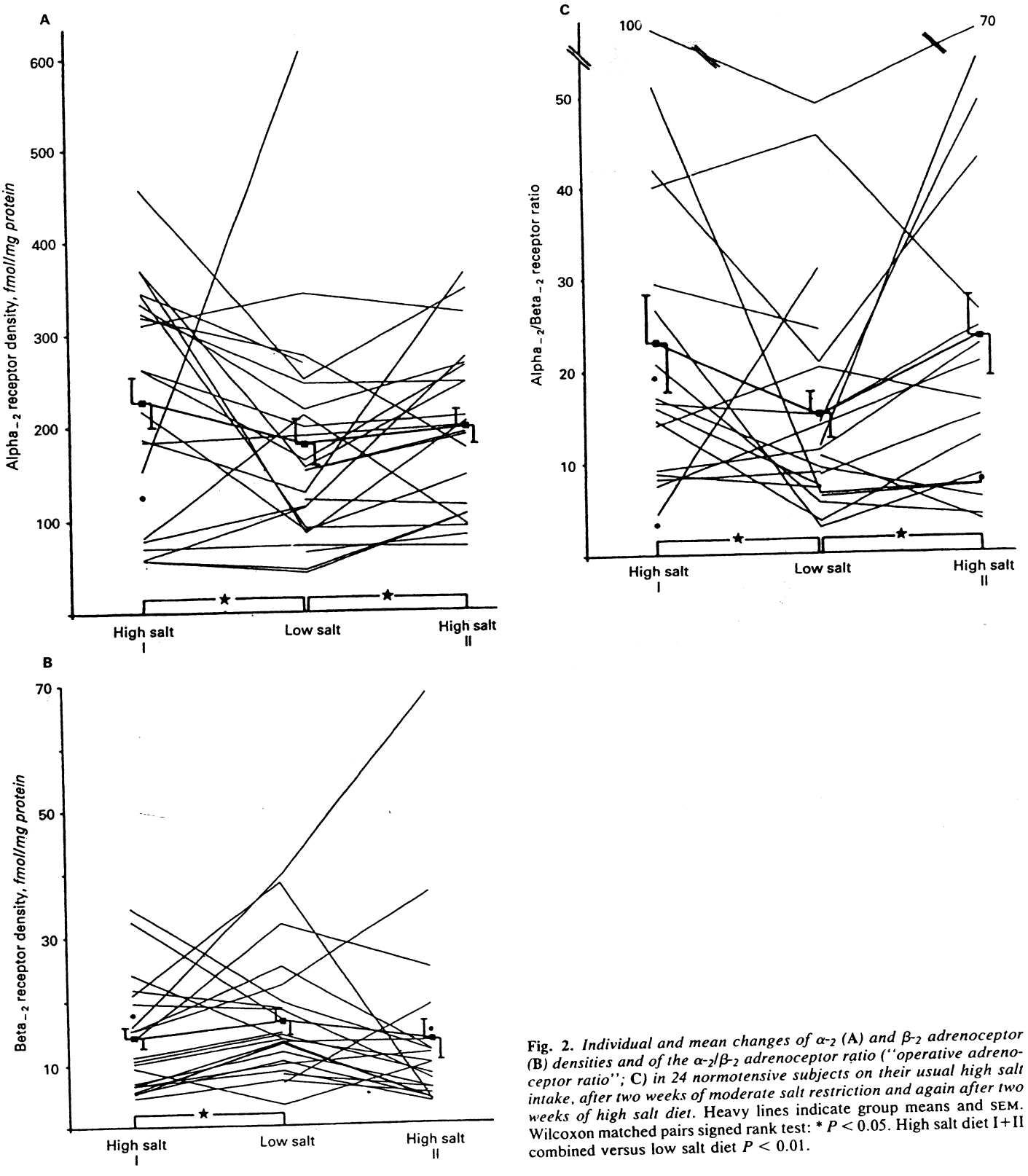
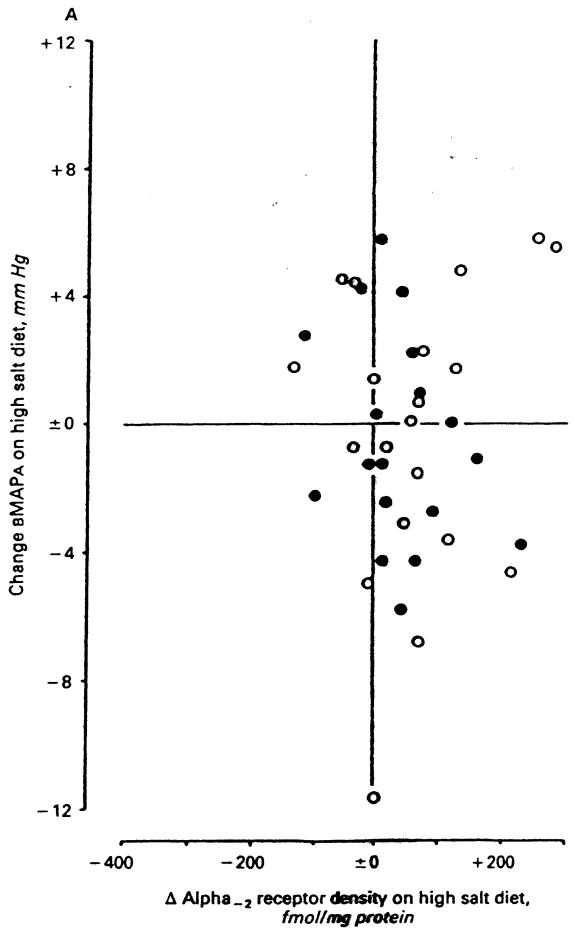


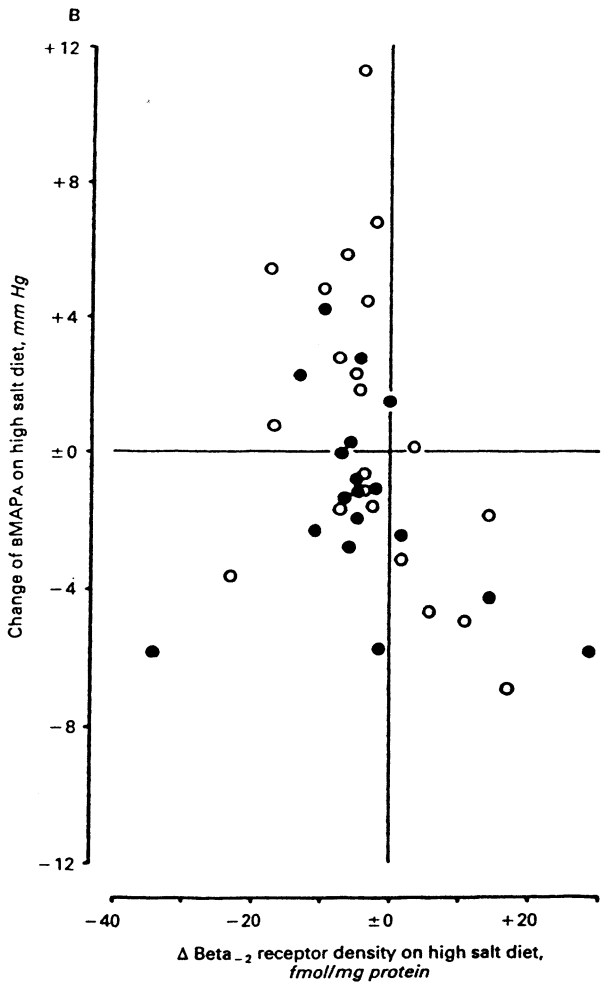
Fig. 2. *Individual and mean changes of α-2 (A) and β-2 adrenoceptor (B) densities and of the α-2/β-2 adrenoceptor ratio ("operative adrenoceptor ratio"; C) in 24 normotensive subjects on their usual high salt intake, after two weeks of moderate salt restriction and again after two weeks of high salt diet.* Heavy lines indicate group means and SEM. Wilcoxon matched pairs signed rank test: * $P < 0.05$. High salt diet I+II combined versus low salt diet $P < 0.01$.

densities, but there was a significant positive correlation between changes of the alpha-2/beta-2 adrenoceptor ratio and individual changes of the basal blood pressure average induced by the high salt diet regardless of the sequence of diets (Fig. 3).

Discussion

The aim of the present study was to investigate whether the link between salt sensitivity and salt resistance to enhanced





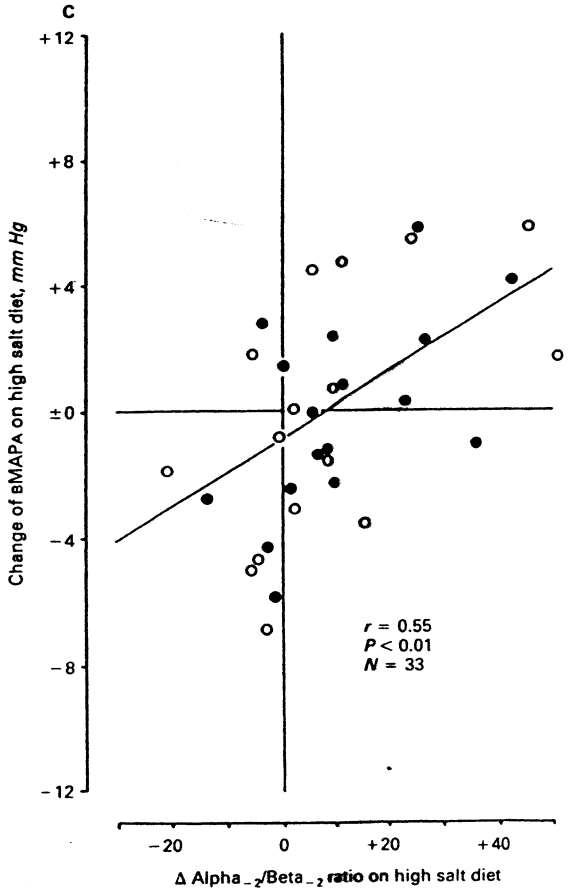


Fig. 3. *Correlation between the change of α-2 (A), of β-2 (B) adrenoceptors and the change α-2/β-2 adrenergic receptor ratio (C) on high salt diet and individual changes of basal mean arterial blood pressure average (bMAPa) in normotensives.* Sequence of the diets: ○ = high salt diet to low salt diet; ● = low salt diet to high salt diet.

Table 1. Mean (SEM) of biochemical measurements and of basal blood pressure average during modification of salt intake in normotensive man ($N = 24$)

	High salt I	Low salt	High salt II
Basal mean blood pressure average *mm Hg*	87.1 (1.43)	86.61 (1.37)	85.79 (1.45)
α_2 density *fmol/mg*	224.9 (26.8)[a]	179.4 (24.6)[a]	194.0 (18.9)[b]
α_2 affinity *nmol/liter*	2.6 (0.26)	2.2 (0.26)[a]	2.4 (0.33)
β_2 density *fmol/mg*	14.03 (1.71)[a]	16.23 (1.89)	13.33 (3.10)[a]
β_2 affinity *nmol/liter*	0.12(0.017)[a]	0.1 (0.017)	0.08 (0.015)
α_2/β_2 ratio	22.7 (5.13)[a]	14.9 (2.6)[a]	23.0 (4.60)[b]
Plasma noradrenaline *pg/ml*	243 (34)	304 (51)	275 (43)
Plasma adrenaline *pg/ml*	42 (7)[a]	54 (9)[b]	34 (5)
Plasma dopamine *pg/ml*	18 (2)[a]	46 (22)	53 (21)
Plasma renin activity *pg AI/ml/hr*	186 (23)[b]	332 (40)	—
Plasma aldosterone *ng/dl*	4.9 (0.6)[b]	7.7 (0.8)	—
24-hr urinary aldosterone *microgram*	7.6 (0.96)[b]	21.5 (2.52)	—
24-hr urinary sodium *mmol*	191.6 (6.66)[c]	47.8 (2.95)[c]	195.6 (16.9)[c]
24-hr urinary potassium *mmol*	69.8 (2.10)	83.2 (3.40)	79.0 (4.90)

Wilcoxon matched pairs test: [a] = $P < 0.05$; [b] = $P < 0.01$; [c] = $P < 0.001$. The superscripts in the last column refer to significances between high salt I and high salt II diets combined versus low salt diet.

noradrenergic sensitivity reported by us previously [2–6] may be caused by differential regulation of adrenoceptors in salt sensitive as compared to salt resistant individuals. The main finding was an upregulation of α_2 adrenoceptors and a downregulation of β_2 adrenoceptors by a high salt diet which initially did not appear to be related to individual changes in blood pressure.

At least the change of β_2 receptors observed during the high salt diet cannot be explained on the basis of the observed changes of plasma adrenaline, as has been suggested by Fraser et al [12], since both β_2 receptors and plasma adrenaline fell concomitantly. We were unable to confirm the upregulation of β_2 adrenoceptors under high salt diet, as reported by Fraser et al [12], in normotensive humans, and we wonder whether or not the dihydroalprenolol used in their study is a suitable ligand for measurement of β_2 receptors [13]. Our results are also in contrast to those of Ashida et al [14] who reported no change of α_2 receptor densities on high salt diet in a small group of normotensives. However, our results are well compatible with work in animals: so Sanchez et al [15] reported a rise of renal α_2 (but not α_1) adrenergic receptors in Wistar Kyoto rats and spontaneous hypertensive rats after a high salt diet. Woodcock et al [16] found a decrease of β_2 adrenoceptor density of mesenteric arteries in DOCA-salt hypertensive rats. Concomitantly with our reports [4–6] of a divergent regulation of α_2 and β_2 adrenoceptors by changes of salt intake, a study on the regulation of alpha and beta adrenergic receptors by triiodothyronine in cultured rat myocardial cells also showed a divergent response of alpha- and beta- adrenoceptors [17], so these reciprocal changes of alpha- and beta- adrenoceptors by different stimuli may possibly represent a more generalized principle [26].

Our results are also compatible with the enhanced blood pressure rise reported by others [18] and us [2] in normotensives on a high salt diet during infusion of exogenous noradrenaline, since our receptor findings would favor enhanced α_2 mediated vasoconstriction [19] and reduced β_2 mediated vasodilation [20]. On the basis of the above cited animal experiments [15, 16], and since adrenoceptor densities of circulating blood cells are at least representative for adrenergic receptors of cardiac tissue [21], we consider it possible that similar changes of α_2 and β_2 adrenergic receptors as described by us on circulating blood cells may have occurred also in tissues involved in blood pressure regulation, such as resistance vessels and renal tubular cells. The α_2 and β_2 adrenoceptors mediate not only opposing effects on resistance vessels, but may also mediate opposing effects on renal tubular handling of sodium [22, 23]. Therefore, we have thought of using the α_2/β_2 adrenergic receptor ratio as a more physiologically relevant parameter for control of vasomotor resistance and, possibly, of renal sodium handling than the absolute α_2 or β_2 adrenoceptor densities alone. To our surprise, this concept was substantiated, since neither the change of α_2 nor of β_2 adrenoceptors but the change of α_2/β_2 receptor ratio correlated ($r = +0.55$; $P < 0.01$) with the observed blood pressure changes: generally, subjects showing a rise of α_2/β_2 receptor ratio during the high salt diet showed a rise of blood pressure regardless of the sequence of the diets (Fig. 3, A through C).

Evaluating the biological significance of the data displayed in figure 3C, one has to consider the complex experimental procedures of deriving α_2/β_2 and the small blood pressure changes induced by variations of salt intake in the healthy man due to the large adaptive capacity of the blood pressure regulating systems. Those subjects with rise of α_2/β_2 receptor ratio (that is, the "operative adrenoceptor ratio") may be prone not only to an increased resistance vessel tone, but possibly also to enhanced sodium retention during a high salt diet as compared to subjects with an unchanged α_2/β_2 receptor ratio. "Defective" regulation of the α_2/β_2 receptor density ratio during high salt intake may, in some way, be genetically determined: subjects with hypertensive antecedents show not only an enhanced α-adrenergic response [2, 18, 24] with enhanced renal sodium reabsorption during mental stress [25], but also as a group are salt sensitive (Fig. 1) [2–5, 8]. Enhanced upregulation of α_2/β_2 ratio by a high salt diet may not only have a hereditary basis, but may be one initial step for the slow rise of blood pressure on a high salt intake in susceptible individuals and may be one important early event in the development of "essential" hypertension.

Acknowledgments

The present study was supported by the Fonds zur Förderung der wissenschaftlichen Forschung, Austria. We should like to thank Mrs. Doris Welter, Department of Neurochemistry, University of Munich, for her expertise in performing the catecholamine measurements.

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