Effect of \( \beta \)-Adrenergic Receptor Blockade on Atrial Natriuretic Peptide in Essential Hypertension

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SUMMARY Plasma levels of atrial natriuretic peptide (ANP) were measured in 32 untreated subjects with essential hypertension and in 31 patients undergoing long-term treatment with \( \beta \)-blockers. Patients receiving \( \beta \)-blockers had significantly higher mean plasma ANP levels (72.0 ± 36.0 [SD] pg/ml) than did untreated hypertensive subjects (39.8 ± 15.8 pg/ml; \( p < 0.01 \)) and healthy normotensive controls (33.9 ± 16.6 pg/ml; \( n = 61, p < 0.01 \)), while the mean plasma ANP concentration in untreated hypertensive subjects was not statistically different from that in control subjects. Administration of atenolol, 50 mg/day, for 4 weeks to 10 untreated subjects resulted in a significant \((p < 0.001)\) rise in plasma ANP levels (from 38.8 ± 9.5 to 68.7 ± 20.6 pg/ml). In 31 patients undergoing long-term treatment with \( \beta \)-blockers, multivariate regression analysis revealed that age, pretreatment mean blood pressure, and plasma concentration of cyclic 3',5'-guanosine monophosphate (cGMP) were significant predictors of plasma ANP levels. These results suggest that \( \beta \)-adrenergic receptor blockade in patients with essential hypertension elevates plasma ANP levels with a concomitant rise in cGMP concentrations, and that increased ANP in plasma may play a role in the compensatory mechanism that operates in response to \( \beta \)-adrenergic receptor blockade.

(Hypertension 10: 221-225, 1987)

KEY WORDS • atrial natriuretic peptide • atrial natriuretic factor • essential hypertension • \( \beta \)-adrenergic blockade • cyclic GMP • catecholamines

A GROWING body of evidence now indicates that atrial natriuretic peptide (ANP) is a circulating hormone in humans.\(^1,2\) Plasma levels of ANP increase in patients with various pathological conditions, including paroxysmal atrial arrhythmias,\(^3,4\) congestive heart failure,\(^5,6\) chronic renal failure,\(^7,8\) and primary aldosteronism.\(^9\) Although a few reports suggest that plasma ANP levels are elevated in patients with essential hypertension (EH),\(^10,11\) whether high blood pressure per se is responsible for elevated plasma ANP levels is unknown. To our knowledge, posttreatment changes in plasma ANP levels in EH patients have not been examined. In the course of such a study, we incidentally found that some EH patients showed an increase in plasma ANP levels after treatment and that these patients had received \( \beta \)-blockers. In the present article, we report the effect of \( \beta \)-blockers on plasma ANP levels in EH patients.

Subjects and Methods
Subjects
Thirty-one EH patients undergoing long-term treatment with \( \beta \)-blockers (treatment range, 1–40 months; mean treatment time, 13.8 months) were studied (Table 1). Twenty-five of the patients had received 50 or 100 mg of atenolol daily, and the remaining six had received 200 mg of acebutolol daily. Thirty-two age-matched untreated subjects with EH and 61 age-matched normotensive healthy subjects served as controls (see Table 1). The diagnosis of EH was made after exclusion of secondary hypertension by routine examinations, including plasma renin activity and aldosterone determinations. Renal arteriography or ad-
renal scintigraphy was performed for the differential diagnosis when indicated. All hypertensive participants were in World Health Organization Class I or II, and none had impaired renal function or any evidence of other diseases except for EH. The mean pretreatment blood pressure in patients receiving β-blockers was not significantly different from that in untreated EH subjects (see Table 1). Normotensive healthy subjects consisted of medical staff and healthy subjects seeking a medical checkup in the Hospital of the Institute for Adult Diseases, Asahi Life Foundation.

In 10 untreated EH subjects (9 men and 1 woman), changes in plasma ANP levels were examined after treatment with atenolol, 50 mg/day, for 4 weeks. Mean blood pressure was decreased significantly (p < 0.001) by this treatment (from 122.7 ± 6.7 to 102.1 ± 9.5 [SD] mm Hg).

Blood samples were collected by venipuncture into heparinized tubes from subjects in the upright position. The subjects were kept in the sitting position for 30 minutes before blood sampling. When plasma levels of cyclic guanosine 3',5'-monophosphate (cGMP) and catecholamines were measured, ethylenediaminetetraacetic acid 2Na salt was used as an anticoagulant. Plasma was quickly separated by centrifugation and stored at −20°C until assayed.

Subjects were fed the recommended diet (NaCl, 7 g/day) and allowed ad libitum water intake.

Assays of Plasma ANP, cGMP, and Catecholamines

Plasma concentrations of ANP were determined by a specific and sensitive radioimmunoassay after separation of ANP from plasma by means of affinity chromatography on anti-ANP-coupled agarose. The details of the radioimmunoassay have been described previously. The recovery of ANP from plasma was 80.7 ± 1.0(SEM)% (n = 37), and the sensitivity of the assay was 12.5 pg/ml. The coefficients of variation averaged 7.2% for intra-assay error and 11.1% for interassay error. Atenolol or acebutolol in an amount of variation averaged 1.6% (epinephrine), 1.2% (norepinephrine), and 2.4% (total dopamine) for intra-assay errors, and 4.8%, 4.2%, and 1.7%, respectively, for interassay errors.

Statistical Analyses

The significance of difference was calculated by Student's t test for paired and unpaired data. For multiple comparisons, Bonferroni's correction was used. Regression lines were obtained by the method of least squares. In patients undergoing long-term treatment with β-blockers, multivariate regression analysis was performed on plasma ANP concentrations, patient characteristics (age and pretreatment and posttreatment mean blood pressure), and plasma levels of cGMP and catecholamines (epinephrine, norepinephrine, and total dopamine).

Results

Figure 1 shows plasma ANP levels in relation to age in control subjects, in untreated EH subjects, and in EH patients undergoing long-term treatment with β-blockers. Some subjects with untreated EH had higher plasma ANP levels than did normotensive controls; however, the mean plasma ANP concentration (39.8 ± 15.8 [SD] pg/ml) was not statistically different from that in normotensive controls (33.9 ± 16.6 pg/ml). On the other hand, the mean plasma ANP concentration in patients receiving β-blockers (72.0 ± 36.0 pg/ml) was significantly higher than that in untreated EH subjects (p < 0.01) or normotensive controls (p < 0.01). When plasma ANP levels were compared with ages of subjects in each group, a significant positive correlation was observed in all three groups (see Figure 1). The slope of the regression line in patients receiving β-blockers was significantly (p < 0.01) greater than that in normotensive controls.

Figure 2 shows changes in plasma ANP levels in 10 untreated EH subjects after the administration of atenolol, 50 mg/day, for 4 weeks. In 9 of 10 subjects, plasma ANP levels rose after the treatment. The mean plasma ANP concentration after the treatment was significantly higher than that in the control period (68.7 ± 20.6 vs 38.8 ± 9.5 pg/ml; p < 0.001).
ANP

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FIGURE 1. Correlations between plasma ANP levels and age in 31 patients receiving β-blockers (●, ————; r = 0.466, p < 0.01), in 32 with untreated essential hypertension (●, ————; r = 0.350, p < 0.05), and in 61 normal controls (○, ————; r = 0.333, p < 0.01). The slope of the regression line in patients receiving β-blockers was significantly steeper than that in normal controls (p < 0.01).

Table 2 shows the result of multivariate regression analysis in EH patients undergoing long-term treatment with β-blockers. Age and pretreatment mean blood pressure were found to be independent and significant predictors of plasma ANP levels (see Figure 1; Figure 3). Significant positive correlations also were observed between plasma ANP and cGMP levels and between plasma cGMP and total dopamine levels (see Figure 3).

Discussion

The present study shows that plasma ANP levels in EH patients undergoing long-term treatment with β-blockers are higher than those in untreated EH subjects and in normotensive controls. Moreover, the administration of atenolol for 4 weeks increased plasma ANP levels in untreated EH subjects. The results indicate that β-adrenergic receptor blockade elevates plasma ANP levels in EH patients. ANP is known to facilitate cGMP accumulation in various tissues, including vascular endothelial and smooth muscle cells. The significant positive correlation between plasma ANP and cGMP levels observed in the present study may indicate that increased ANP in plasma, induced by β-adrenergic receptor blockade, stimulated cGMP production. A close relationship between plasma ANP and cGMP levels has been shown under various experimental conditions.

Several factors should be considered in explaining the observed effect of β-blockers. The major action of β-blockers on the circulatory system is a reduction in...
heart rate and cardiac output. Total peripheral vascular resistance may increase during short-term administration of β-blockers but gradually returns to the pretreatment level during long-term treatment. Although no consistent results have been obtained on the changes in plasma volume, cardiopulmonary volume appears to be unaltered by the administration of β-blockers. If this is the case, the elevated plasma ANP levels associated with β-adrenergic receptor blockade in the present study may be explained by a decrease in cardiac output relative to cardiopulmonary volume, since volume expansion induced by saline loading has been shown to trigger ANP release in humans and in rats. In addition, bradycardia secondary to β-adrenergic receptor blockade may increase the average atrial stretch, thus resulting in the stimulation of ANP secretion. Another possible explanation for the raised plasma ANP levels in patients receiving β-blockers may be a change in sympathetic activity induced by β-adrenergic receptor blockade, which in turn stimulates ANP secretion. β-adrenergic receptor blockade increases plasma catecholamine levels in humans, and β-adrenergic stimulation has been shown to trigger ANP release in vitro. However, the present study failed to demonstrate such a causal relationship between plasma ANP and catecholamine levels.

The effect of β-blockers on plasma ANP levels was seen more clearly in elderly EH patients, as reflected by a significant positive correlation between plasma ANP levels and age (see Table 2) and by a steeper slope of the regression line of plasma ANP levels on age (see Figure 1). One of the most characteristic hemodynamic changes in elderly hypertensive patients is a fall in cardiac output. Therefore, administration of β-blockers to elderly patients may further decrease cardiac output, and the resultant rise in cardiopulmonary volume relative to cardiac output may facilitate ANP release to a greater extent than in younger patients. It may be argued that the changes in plasma ANP levels reflect changes in metabolism or clearance of ANP associated with the decreasing renal function that occurs with advancing age and that may be amplified by β-blocker therapy. However, this possibility appears unlikely, since the main cause of the elevated plasma ANP levels in patients with chronic renal failure is increased ANP secretion due to volume expansion rather than decreased ANP clearance. Thus, increased plasma ANP levels after β-adrenergic receptor blockade may represent a compensatory mechanism that operates in response to relative cardiopulmonary volume expansion. The significant positive correlation between plasma ANP levels and pretreatment mean blood pressure may indicate that elevation of plasma ANP levels after treatment with β-blockers depends on the severity of hypertension. The significant positive correlation between plasma cGMP and total dopamine levels may be explained by the ANP-induced inhibition of dopamine-β-hydroxylase proposed by Racz et al., though the exact mechanism remains unclear.

Whether the increased plasma ANP levels present after β-adrenergic receptor blockade are involved in the antihypertensive mechanism of β-blockers is unknown. Garcia et al. demonstrated that long-term infusion of ANP decreased total peripheral vascular resistance and blood pressure in spontaneously hypertensive rats. In normal men, on the other hand, a hypotensive effect of ANP was apparent only in high dose infusion experiments. Further studies may be necessary to answer this important question.

In conclusion, the present study shows that no gross abnormality exists in ANP secretion in persons with uncomplicated EH and that β-adrenergic receptor blockade in EH patients significantly elevates plasma ANP levels, with a resultant rise in plasma cGMP levels, especially in elderly patients. Increased ANP in plasma may serve as a compensatory mechanism against the hemodynamic changes induced by β-adrenergic receptor blockade.

Acknowledgments

The authors are very grateful to Mr. Yukio Fukuda, Grelan Pharmaceutical Co. Ltd. (Tokyo, Japan), and to Dr. Mitsuaki Isobe for their help in statistical analyses, and to Miss Noriko Yoshida for her secretarial assistance.

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Hypertension. 1987;10:221-225
doi: 10.1161/01.HYP.10.2.221

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/10/2/221

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