NOTE

Plasma Atrial Natriuretic Peptide in States of Altered Thyroid Function

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Abstract

To examine a possible role of atrial natriuretic peptide (ANP) in water and electrolyte disturbances associated with thyroid disorders, plasma ANP levels were studied in patients with hyper- and hypothyroidism. In 5 of the 21 hyperthyroid patients, including two patients with atrial fibrillation and two patients with mild cardiomegaly, the plasma ANP concentration was increased when compared to normal subjects. After treatment with methimazole or propylthiouracil, the plasma ANP concentration fell to normal in 4 patients, while it remained high in one patient who had persistent atrial fibrillation. No significant correlation was found between plasma ANP and the heart rate in untreated hyperthyroid patients. Plasma ANP was within the normal range in all 8 patients with hypothyroidism. During treatment with T₄, the plasma ANP concentration increased in 6 of the 7 patients. Chest X-ray films and ultrasonic echocardiography demonstrated pericardial effusion in 4 of these patients before therapy. A weak but significant correlation was found between the plasma ANP and T₄ concentration, and between plasma ANP and free T₄ in hyper- and hypothyroid patients before and after treatment. These results indicate that abnormalities in ANP dynamics in thyroid disorders may probably be caused by hemodynamic changes resulting from a thyroid hormone excess or deficiency.

Accumulating evidence now indicates that atrial natriuretic peptide (ANP) is a circulating hormone in man and its concentration in plasma changes in various pathologic states. Although the precise mechanism involved in the mediation of ANP secretion in man is unknown, atrial stretch consequent to hemodynamic changes or volume expansion appears to be at least
one of the most important stimuli for ANP release (Sato et al., 1986; Burnett et al., 1986; Bates et al., 1986; Raine et al., 1986). A variety of cardiovascular manifestations are associated with altered states of thyroid function (DeGroot and Leonard, 1970; Skelton and Sonnenblick, 1986). In addition, renal functional changes in thyroid disorders may be clinically self-evident in varied patterns of water and electrolyte derangement (Bradley et al., 1974; Katz et al., 1975). If excessive or deficient secretion of thyroid hormone influences cardiac and renal functions, plasma ANP may be altered in patients with hyper- and hypothyroidism. The present study was undertaken to test this hypothesis by measuring plasma ANP in patients with hyper- and hypothyroidism before and after treatment.

Subjects and Methods

21 patients (9 men and 12 women) with Graves' disease, aged between 18 and 59 yr (35.7±11.3, mean±SD), and 8 patients (a man and 7 women) with hypothyroidism due to Hashimoto's thyroiditis, aged between 31 and 72 yr (49.5±12.5, mean±SD), were studied. All patients in the former group had high serum T4 (18.2±6.3 µg/dl, mean±SD; normal range: 4.5-12.0 µg/dl) and free T4 (5.4±1.9 ng/dl, mean±SD; normal range: 0.7-1.9 ng/dl), while those in the latter group had low serum free T4 (0.22±0.15 ng/dl, mean±SD), and clearly elevated serum TSH concentrations (104±61 µU/ml, mean±SD; normal range: less than 10 µU/ml). Serum sodium was normal in all hyperthyroid and hypothyroid patients (142±3 mEq/l, mean±SD and 141±2 mEq/l, respectively). Hyperthyroid patients were treated initially with 30 mg daily of methimazole or 300 mg daily of propylthiouracil and the doses were reduced according to the serum concentration of T4, free T4, and TSH in each patient. Hyperthyroid patients were treated with daily doses of 0.1-0.15 mg T4. In 18 hyperthyroid patients and in 7 patients with hypothyroidism, plasma ANP was studied again after the treatment for 1.5-12 months, when serum T4, free T4, and TSH returned to normal.

Patients with organic renal diseases were excluded from the study, because plasma ANP is increased in chronic renal failure (Rascher et al., 1985; Hasegawa et al., 1986). 40 healthy subjects (20 men and 20 women), aged between 21 and 70 yr, served as controls. They consisted of students, medical staff and healthy subjects undergoing routine medical examinations.

All study subjects were eating a normal diet and drinking water ad libitum. They were kept in a recumbent position for 30 min before blood collection. Blood was transferred to heparinized tubes and immediately cooled. Plasma was quickly separated by centrifugation and stored at -20°C until assayed.

Plasma concentrations of ANP were determined by a specific and sensitive radioimmunoassay (RIA) after separation of ANP from plasma by means of affinity chromatography on anti-ANP-coupled agarose. The detail of the RIA was described previously (Yamaji et al., 1985). The recovery of ANP from plasma was 80.7±1.0% (mean±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 inter-assay error. Day-to-day variations in plasma ANP, determined by measuring ANP concentrations in 3 to 5 plasma samples obtained from each subject at varying intervals of 1.5-12 months, ranged from 16.2 to 24.8% (18.3±3.4%, mean±SD, n=7). Serum T4, free T4 and TSH were determined by RIA.

Significance of differences was calculated by Student's t-test for paired and unpaired data. Values in the text are expressed as the mean±SD, unless otherwise specified.

Results

Figure 1 shows plasma ANP in 21 patients with Graves' disease. In 5 of the patients, the concentration was increased when compared to normal subjects (37.6±12.2 pg/ml). Of the 5 patients with increased plasma ANP, two had atrial fibrillation and two others mild cardiomegaly (cardio-thoracic ratio: 55% and 54%, respectively), while the remaining one patient had no apparent cardio-vascular manifestation except for sinus tachycardia. After
treatment with methimazole or propylthiouracil, plasma ANP decreased to the normal range in 4 patients. The differences were greater than day-to-day variations in plasma ANP in all patients. Concomitantly, cardiothoracic ratios of the two patients who had cardiomegaly before therapy were reduced to 50% and 48%, respectively, and the normal sinus rhythm was restored in one patient who had had atrial fibrillation. However, the plasma ANP concentration increased in one patient who had persistent atrial fibrillation after the treatment, which may be due to decreased cardiac function judged by a decrease in the ejection fraction. The mean plasma ANP concentration in 21 untreated patients with hyperthyroidism (48.7 ± 41.8 pg/ml) was not significantly different from that in normal subjects. The mean pre-treatment plasma ANP concentration in 18 hyperthyroid patients (51.5 ± 44.5 pg/ml) was not statistically different from the mean plasma ANP in post-treatment periods (34.2 ± 33.7 pg/ml). The plasma ANP concentration is often increased in patients with lone atrial fibrillation (Yamaji et al., 1987; Roy et al., 1987). Excluding the two patients who had atrial fibrillation, the mean pre-treatment plasma ANP concentration in 16 hyperthyroid patients (49.0 ± 46.7 pg/ml) was significantly (p<0.05) higher than the mean post-treatment plasma ANP concentration (32.0 ± 25.5 pg/ml). No significant correlation was found between plasma ANP and the heart rate in untreated hyperthyroid patients, or between plasma ANP and the duration of the hyperthyroidism.
thyroid state in individual patients.

Plasma ANP was within the normal range in all 8 patients with hypothyroidism (Figure 2). The mean plasma ANP concentration in hypothyroid patients (31.5 ± 12.1 pg/ml) was not significantly different from that in normal subjects. When compared to the post-treatment concentration, pre-treatment plasma ANP was higher in 6 of 7 patients, although the mean plasma ANP concentration in the pre-treatment periods (32.2 ± 12.8 pg/ml) was not statistically different from that in the post-treatment periods (50.8 ± 13.8 pg/ml). In 4 of the patients, the differences exceeded the extent of day-to-day variations in plasma ANP levels. In one patient, plasma ANP decreased after treatment, but the explanation for this is unknown at present. Chest X-ray films and ultrasonic echocardiography revealed pericardial effusion in 4 of the 6 patients who responded to the treatment with an increase in plasma ANP. Pericardial effusion disappeared during T4 therapy in all patients.

When plasma ANP in all hyper- and hypothyroid patients before and after treatment was compared with their serum thyroid hormone determined simultaneously, a slight but significant correlation was found between plasma ANP and serum T4 (r = 0.36, p < 0.05), and between plasma ANP and serum free T4 (r = 0.44, p < 0.01).

Discussion

The present study demonstrates that plasma ANP is increased in some patients with hyperthyroidism. In rats, the administration of thyroid hormone has been shown to increase plasma ANP (Kohno et al., 1986a; Ladenson et al., 1986). Gardner et al. (1986) demonstrated that increasing doses of T3 were accompanied by both increased ANP release and increased RNA transcripts of ANP in an in vitro rat neocortical cardiocyte system. In view of these findings, an increase in plasma ANP in some patients with hyperthyroidism may be due to a direct effect of thyroid hormone on cardiomyocytes. However, hyperthyroidism is associated with various hemodynamic changes including increased cardiac output, stroke volume, heart rate; diminished peripheral vascular resistance; widened pulse pressure; and increased circulating blood volume (DeGroot and Leonard, 1970; Skelton and Sonnenblick, 1986). Four of the 5 hyperthyroid patients whose pretreatment plasma ANP was increased had atrial fibrillation or cardiomegaly. Plasma ANP is often increased in patients with lone atrial fibrillation (Yamaji et al., 1987; Roy et al., 1987) and in those with heart disease who have no signs or symptoms of congestive heart failure (Nakaoka et al., 1985). The observed changes in plasma ANP in hyperthyroid patients, therefore, may be ascribed to changes in cardiovascular function, or water and electrolyte metabolism associated with this disorder rather than a direct effect of thyroid hormone on cardiomyocytes. Recently, Kohno et al. (1986b) reported increased plasma ANP in 5 of 6 hyperthyroid patients. Whether their patients had changes in cardiac or renal function is unknown. Of note in this regard is that increased heart rate per se may not be responsible for high plasma ANP in hyperthyroid patients, since no significant correlation was found between plasma ANP and heart rate.

Replacement of thyroid hormone increased plasma ANP in most hypothyroid patients, although their pretreatment plasma ANP was within the normal range. The results generally agree with the recent report by Zimmerman et al. (1987) with an exception that they found significantly lower plasma ANP in untreated hypothyroid patients than in normal subjects. The difference between their study and ours may possibly be due to the age of the patient,
since hypothyroid patients in the present study were older, and plasma ANP is shown to increase with age (Ohashi et al., 1987). However, this seems unlikely because no clear difference in plasma ANP was found among healthy subjects in the 4th, 5th and 6th decades (Nakaoka et al., 1987). Rather, the difference may be due to the small number of controls used in their study. In the present study, pericardial effusion was demonstrated in 4 of the 6 hypothyroid patients who showed an increase in plasma ANP after the replacement of thyroid hormone. If atrial stretch consequent to increased atrial pressure is the main factor in stimulating ANP release from cardiomyocytes, pericardial effusion may decrease ANP secretion by inhibiting atrial stretch. Further, the decreased plasma volume associated with hypothyroidism (Gibson and Harris, 1939) may attenuate ANP secretion, since volume expansion following saline infusion in man increases plasma ANP (Yamaji et al., 1985; Sugawara et al., 1986). Thus, lower plasma ANP in untreated hypothyroid patients may be explained again by hemodynamic changes resulting from thyroid hormone deficiency. Whether decreased plasma ANP may be linked to generalized accumulation of water and sodium in hypothyroidism (Aikawa, 1956) remains unclear at present.

In conclusion, the present study shows that plasma ANP is increased in some patients with hyperthyroidism and that replacement of thyroid hormone increases plasma ANP in most hypothyroid patients. These abnormalities in ANP dynamics in thyroid disorders may probably be caused by the concomitant hemodynamic changes. Whether the increased or decreased plasma ANP observed in patients with thyroid disorders is really of clinical importance in volume homeostasis should be clarified by future studies.

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