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Thyroid Disorders and Brain Natriuretic Peptide

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1. Introduction

The structure of atrial natriuretic peptide (ANP) was first discovered in 1984 (1). In following years, a molecule, which resembled ANP, was isolated from a pig brain (2). This B-type or brain natriuretic peptide (BNP) is a member of the natriuretic peptide family that has physiological effects similar to atrial natriuretic peptide (ANP), including diuretic, natriuretic, and vasorelaxant actions (3,4). Although this peptide is referred to as the brain natriuretic peptide (BNP), it is actually produced in the ventricular myocardium (5). BNP is not a prestored molecule, but if proper stimuli exist it can be produced rapidly through mRNA synthesis. The stimulus triggering the secretion of BNP by the ventricles of the heart is mainly excessive stretching of myocytes rather than the transmural pressure load (6-8). BNP is synthesized both in an inactive N-terminal fragment with 76 amino acids (NTpro-BNP) and an active hormone with 32 amino acids (BNP). ANP and related precursor peptides comprise 98% of all natriuretic peptides in healthy subjects (9).

Like ANP, BNP is induced by pathophysiological conditions of the heart, including hypertrophy, myocardial infarction, and heart failure. BNP levels have been shown to be a good predictor of left ventricular dysfunction and decompensated heart failure, and recently BNP infusion has been approved as an effective treatment for acute heart failure (10,11). Distinct physiological roles of BNP have been elucidated by generation of knockout (KO) mice. While BNP KO mice are no different from control mice with regard to blood pressure, urine volume, and urinary Na+ and K+ excretion, they have more extensive ventricular fibrosis, accompanied by increased transforming growth factor-3 (TGF-3) and collagen mRNA [81]. Studies of cultured cells indicate that BNP inhibits growth of vascular cells, as well as fibroblast proliferation and collagen production by fibroblasts (3,12). Thus, BNP may function more as an autocrine/paracrine inhibitor of cell growth in the heart, while ANP

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functions more as a traditional circulating hormone with pronounced diuretic, natriuretic, and anti-hypertensive effects. (3)

In addition to ventricular myocardium, extracardiac sources of BNP have been detected in tissues at autopsy, including the lungs, kidneys, and adrenal glands, although at much lower levels than ventricular BNP (13). BNP is produced , to a small degree, by the renal glomerular epithelial and mesangial cells (14,15) is a counter-regulatory hormone that physiologically opposes and suppresses the renin-angiotensin aldosterone system (RAAS), endothelin-1 and the sympathetic nervous system (SNS). Endogenous BNP and ANP production maintain renal function and sodium balance when cardiac function acutely deteriorates (16).

Routine BNP testing has recently been introduced as a noninvasive, low-risk test that measures circulating levels of BNP, which are elevated in individuals with both symptomatic and asymptomatic heart failure. The BNP test is used to detect preclinical heart disease or to confirm the cardiac etiology in symptomatic patients. It not only enables the early identification of patients with incipient heart failure but also provides prognostic information based on the magnitude of the increase. Also administration of exogenous intravenous (IV) BNP shown to rapidly improve hemodynamic, volume, neurohormonal, and symptomatic abnormalities in patients with acute decompensated heart failure and to decrease rates of rehospitalization (17,18). Nesiritide IV (human recombinant BNP) is approved for the treatment of acute decompensated CHF. The physiologic effects of nesiritide include veno- and arterial dilatation (without reflex tachycardia), diuresis, and natriuresis (without reduction in renal perfusion or function). Thus, nesiritide increases cardiac index and reduces pulmonary capillary wedge pressure (PCWP) (18). In addition, nesiritide is lusitropic, anti-fibrotic, and inhibits RAAS; thus, nesiritide should stabilize renal function acutely and chronically while improving cardiac function and hemodynamics in CHF patients.

The cardiovascular system is very sensitive to thyroid hormones. Hyperthyroidism and hypothyroidism induce significant changes in cardiac functions. The effects of hyperthyroidism on the heart include hemodynamic changes such as decreased systemic vascular resistance as well as increased cardiac output, heart rate, blood volume, blood pressure and impaired cardiac contractility. It may also lead to atrial arrhythmias (19). These changes result in ventricular stretch and pressure overload, which might cause concomitant rise in BNP concentrations (20). Recent attention has been drawn to the relation of BNP and hyperthyroidism. Studies suggest that plasma BNP and NT-pro-BNP concentrations are frequently increased in hyperthyroidism. This increase is partly due to hyperthyroidism-induced left ventricular dysfunction. Also in vitro animal studies have suggested that T4 and T3 stimulate BNP release from both cultured atrial and ventricular myocytes (21).

There are only a limited number of studies with contradictory results investigating the effect of thyroid function abnormalities on the measurement of BNP. Wei et al. have measured the BNP levels and left ventricular functions of 67 hyperthyroid patients and 32 healthy subjects. The average BNP level was found to be higher in the patients especially the ones with left ventricular dysfunction than the healthy individuals. Nonsignificant correlations between thyroid hormones and BNP levels were identified (19). Biondi et al. demonstrated

an increase of left ventricular mass more specifically, an increase of septal and posterior wall thickness, enhanced resting systolic function and significantly impaired Doppler parameters of diastolic function (22). Smit et al. demonstrated that diastolic dysfunction was impaired in exogenous subclinical hyperthyroidism induced by levothyroxine treatment in 25 differentiated thyroid carcinoma patients (23). Two small studies suggest a beneficial effect of treatment of subclinical hyperthyroidism on cardiac function (24,25). Schultz et al. studied NT-pro-BNP levels in different thyroid function states and found that serum levels of NT-pro-BNP were strongly affected by thyroid function; the higher the thyroid function, the higher the serum levels of NT-pro-BNP. Likewise the treatment of the dysthyroid state resulted in a significant increase in NT-pro-BNP in both overt and subclinical hypothyroid patients and a decrease in both overt and subclinical hyperthyroid patients. In order to evaluate whether those findings were the direct effect of thyroid hormones or were the results of changes in heart function and structure, they compared NT-pro-BNP, thyroid function and cardiac output (CO) or resting pulse rate in a subgroup of patients under study. CO or resting pulse rate did not have any independent effect on NT-pro-BNP levels, whereas , thyroid function had a significant effect on NT-pro-BNP levels (26). Ertugrul et al evaluated the serum BNP levels in 18 overt and 47 subclinical hyperthyroid patients together with 39 subclinical and 13 overt hypothyroid patients. BNP levels were more than five times higher in hyperthyroid than euthyroid control subjects. BNP levels were also higher in subclinical hyperthyroidism than euthyroid control subjects. Free T4 and free T3 concentrations were found to be associated with high serum BNP levels. The BNP level in patients with subclinical or overt hypothyroidism was similar to that of the controls (27). On the other hand, Christ-Crain et al. found that there was no significant difference in NT-proBNP levels of euthyroid and overt hypothyroid, subclinical hypothyroid and subclinical hyperthyroid subjects, and NT-pro-BNP levels were higher in overt hyperthyroidism compared to other groups (9). Kohno et al. have found higher BNP levels in untreated hyperthyroid patients and rats with hyperthyroidism induced by thyroxine than their normal counterparts. Hypothyroid rats had lower plasma BNP concentration than the euthyroid ones. In-vitro effects of T3 and T4 on the release of BNP were investigated in newborn rat atrial and ventricular myocytes in primary culture. T3 and T4 stimulated release of BNP from both cultured atrial and ventricular myocytes in a dose-dependent manner (21). Triiodothyronine also increases BNP gene transcription and amplifies endothelin-dependent BNP gene transcription in rat ventricular myocytes (28). The effect of hyperthyroidism and subclinical hyperthyroidism on the heart may also cause an increase in BNP. At the moment, we do not know which one of these mechanisms is actually responsible for alterations in BNP levels in thyroid dysfunction. There is little known about the effects of endogenous subclinical hyperthyroidism on the heart. Faber et al. demonstrated an increase in cardiac output and a reduction in total peripheral resistance when treating subclinical hypothyroid subjects with L-T4, whereas the opposite is seen on treating subclinical hyperthyroidism with radioiodine (24).

Ertugrul et al studied BNP levels in patients with hyperthyroidism before specific treatment for hyperthyroidism and after euthyroidism was achieved. This study showed that BNP levels were significantly higher in hyperthyroid than euthyroid status of the same patients. It was found that the decrease in BNP levels was positively correlated with the decrease in fT3 and fT4 (29). Kato et al measured serum ANP and BNP levels in 130

patients with thyrotoxicosis and correlated them with serum thyroid hormone levels and with the degree of severity of the heart failure. They reported a significant elevation of BNP and atrial natriuretic peptide levels which returned to normal values after euthyroididsm was established in patients with thyrotoxicosis. It was concluded that both serum thyroid hormones and cardiovascular dysfunction contribute to the increase of serum BNP levels and atrial fibrillation is an independent contributing factor for the increase of BNP (30).

In conclusion, natriuretic peptide levels are altered in different thyroid states with a more pronounced effect in hyperthyroidism compared to hypothyroidism. This seems to reflect distinct atrial and ventricular cardiac dysfunction in thyroid hormone excess or, alternatively, mirrors a direct effect of thyroid hormones on gene expression of natriuretic peptides. As hyperthyroidism results in increased serum levels of pro-ANP, NT-proBNP and BNP levels as typically seen in mild heart failure, hyperthyroidism should be considered in patients presenting with unclear symptoms and mildly elevated natriuretic peptide levels (9). Since the treatment of hyperthyroidism is quite different than the treatment of heart failure, thyroid hormones should be checked in patients with high levels of BNP. Mild elevations in NT-pro-BNP levels should therefore always be accompanied by a thyroid function screening test (26,29).

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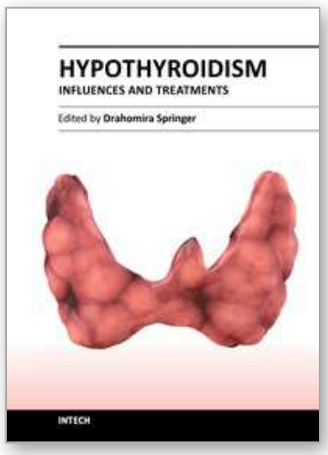

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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