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THE CARDIOVASCULAR EFFECTS OF HYPERTHYROIDISM

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Introduction

In 1786, the cardiovascular manifestations of thyrotoxicosis were recognized by Caleb Parry, who noted, "There is one malady which I have, in five cases, seen coincident with what appeared to be enlargement of the heart — the malady to which I elude is enlargement of the thyroid gland" (Figure 1).[1]

Figure 1. Caleb Hillier Parry; Copyright (1998) Royal Society of Medicine Press, UK.

Thyroid hormone is an important regulator of cardiac gene expression, and many of the cardiac manifestations of thyroid dysfunction are associated with alterations in T_3-mediated gene transcription. As a result, cardiac output, ejection fraction, and heart rate are all found to be increased while isovolemic relaxation time and peripheral vascular resistance are decreased in the hyperthyroid states. Furthermore, thyroid hormone increases blood volume and erythropoietin secretion with subsequent increased preload and cardiac output. However, to understand the alterations in cardiac hemodynamics that accompany hyperthyroidism, it is important to review the underlying mechanisms of thyroid hormone action at the cellular level.

Mechanisms of Action of Thyroid Hormone on the Cardiovascular System

Thyroid hormone causes a wide spectrum of cardiovascular changes due to its effects on the cardiac myocytes and vascular smooth muscle (VSM) cells as well as indirect effects mediated by activation of neuroendocrine systems.

Effects of Thyroid Hormone on Cardiac Myocytes

More than 85% of thyroid hormone is synthesized and released from the thyroid gland in the form of tetraiodothyronine (thyroxine, T_4). T_4 is then converted in target cells to the biologically active form of thyroid hormone triiodothyronine (T_3) by 5′-monodeiodination.[2] The heart, unlike many other cell types, is less efficient at intracellular conversion of T_4 to T_3 and relies mainly on transporting serum T_3 directly. It appears that the cardiac myocyte transports T_3 in marked preference to T_4 through specific transport proteins in the cell membrane.[3]

The intracellular effects of thyroid hormone can be divided into genomic and nongenomic (extra-nuclear) effects.

Genomic Effects. Once inside the myocyte, T_3 binds to four types of thyroid hormone nuclear receptors (TRs): TRα_1, TRα_2, TRβ_1, and TRβ_2. The complex then binds to thyroid hormone response elements (TREs) on myocyte-specific genes, including genes for Ca^{2+}-ATPase, phospholamban, myosin, Beta-adrenergic receptors, adenylate cyclase, GTP-binding proteins, the sodium-calcium exchanger, Na^+/K^+-ATPase, and voltage-gated K^+ channels.[4] Binding of T_3 to TREs can either activate or repress gene expression. Table 1 shows the genes that are either positively or negatively regulated by T_3. These genes encode important structural and regulatory proteins, and the net effect of long-term exposure to high levels of T_3 is an increase in the synthesis of many cardiac proteins associated with cardiac hypertrophy and dysfunction.

Nongenomic (extra-nuclear) Effects. Actions of thyroid hormone that do not require binding to intranu-

Positively regulated	Negatively regulated
Cytochrome P450 IIB6, Cytochrome P450 3B3	Adipocyte fatty acid binding protein
Cytochrome P450 VIIIA1	Phospholipid transporter protein
Cytochrome P450 III A3	Glucose transporter, type 4 (GLUT4)
HDL-binding protein	Cu, Zn-SOD
Cyclo-oxygenase 1 (COX1)	Cardiac muscle myosin heavy chain β-isoform (MHC-β)
Cardiac muscle myosin heavy chain α -isoform (MHC-α)	Tissue inhibitor of metalloproteinase 2(timp2)
Matrix metalloproteinase 2 (MMP2)	Collagen IVα1
L-selectin	Collagen XVIα1
Atrial natriuretic factor	Junction placoglobulin
Retinoic acid receptor α (RARα)	Desmoplakin III
Retinoic acid receptor γ (RARγ)	Erythrocyte adducing alpha subunit
Protein tyrosine phosphatase receptor type-F	Placental growth factor 1
Beta1-adrenergic receptors	Na^{+}-Ca^{++} exchanger
Voltage-gated potassium channels	Cardiac phospholamban
Na^{+}/K^{+}-ATPase	Estrogen-related receptor α
Sacroplasmic reticulum Ca^{++}/ATPase	V-erb-related protein 3, transcription factor COUP2
	Progesterone receptor
	Mineralocortiocid receptor
	Purinoreceptor
	Vascular endothelial growth factor receptor
	Vasopressin V3 receptor
	Sterol regulatory element-binding transcription factor 1
	Adenylyl cyclase catalytic subunits
	Thyroid hormone receptor α1

Table 1. Effect of thyroid hormone on cardiac gene expression.

clear TRs are referred to as nongenomic. These effects of T_3 can occur rapidly and do not involve TR-mediated transcriptional events.[5, 6] T_3-mediated nongenomic effects include effects on membrane ion channels for sodium, potassium, and calcium and effects on actin polymerization, adenine nucleotide translocator 1 in the mitochondrial membrane, and a variety of intracellular signaling pathways in the heart (Figure 2).

Effects of Thyroid Hormone on VSM Cells

VSM cells are physiological targets for the actions of thyroid hormones. Mizuma et al.[7] have recently shown the presence of an iodothyronine deiodinase in human VSM cells, suggesting that these cells can convert T_4 to T_3, promoting modulation of thyroid-dependent events. In the VSM cell, T_3-mediated effects are the result of both genomic and nongenomic actions. Nongenomic actions affect membrane ion channels and endothelial nitric oxide (NO) synthase, increasing local concentrations of NO, which serves to decrease systemic vascular resistance (SVR).[8] Interestingly, exposure of VSM cells isolated from rat aorta to T_3 causes theses cells to relax rapidly, an effect that is independent of cAMP and nitric oxide formation.[9, 10] The full repertoire of target genes for T_3 action in the VSM cell remain unknown; however, it is interesting to speculate that they may be similar to those previously described in the cardiac myocyte.[11]

Neuroendocrine Changes

Various alterations in the neuroendocrine system can accompany thyroid hormone abnormalities. These include alterations in the autonomic nervous system and the renin-angiotensin system (RAS).

The increased heart rate, widened pulse pressure, and increased cardiac output of patients with hyperthyroidism resemble a state of increased adrenergic activity. Theses similarities in clinical manifestations and the therapeutic benefits of beta-blockers, such as propranolol, have led to the suggestion that many of the cardiac manifestations of thyrotoxicosis are caused by increased catecholamine action. In line with this theory, early studies have shown that the density of beta adren-

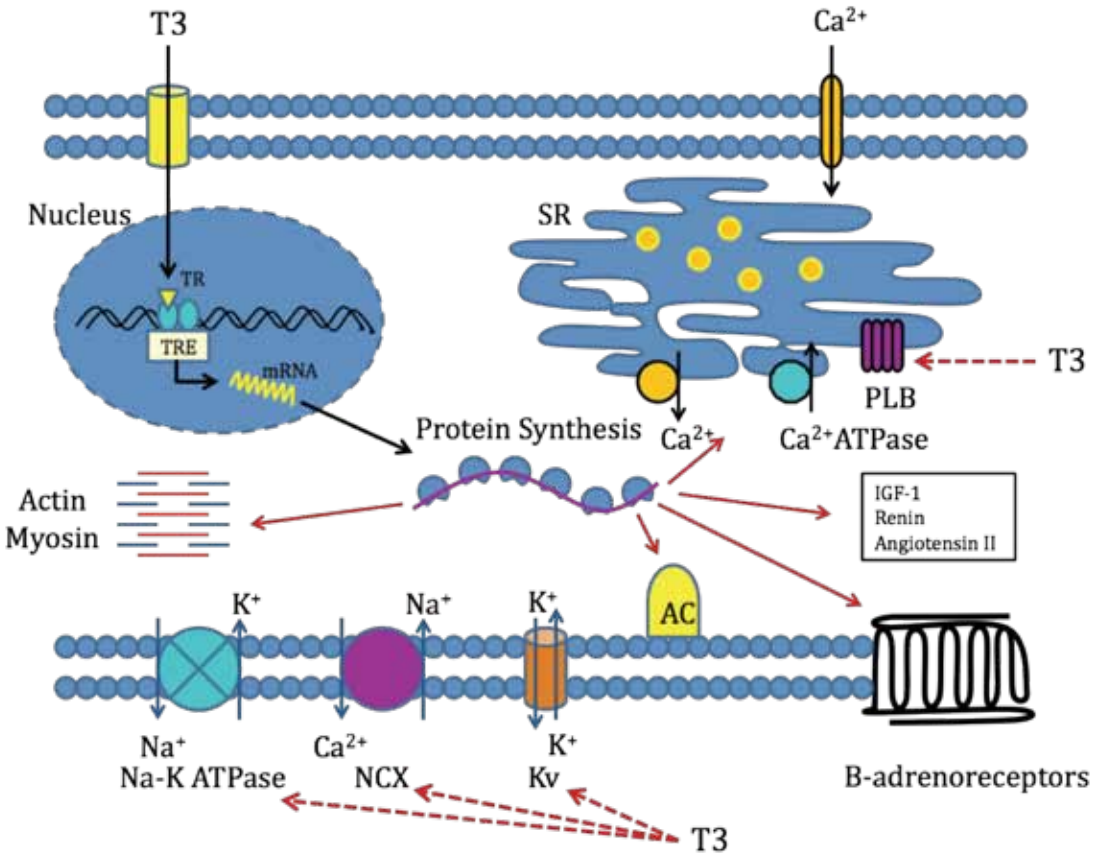

Figure 2. Genomic (solid arrows) and non-genomic (dashed arrows) effects of T_3. AC: Adenylyl cyclase. Kv: Voltage-gated K channels. NCX: Na-Ca exchanger. PLB: Phospholamban. SR: Sacroplasmic reticulum TR: Thyroid hormone receptor. TRE: Thyroid response element.

ergic receptors in the hyperthyroid myocardium and the sensitivity to adrenergic stimulation are increased.[12, 13] However, recent data suggest that despite the increase in beta adrenergic receptor density, the adenylyl cyclase activity is decreased[14] while the circulating catecholamines remain essentially normal,[15] and thus the overall sensitivity of the heart to adrenergic stimulation remains unchanged.[16] This is supported by the fact that administration of a beta adrenergic-receptor antagonist to patients with hyperthyroidism slows the heart rate but does not alter systolic or diastolic contractile performance,[17] strongly suggesting that the positive inotropic effect of T_3 is independent of adrenergic signaling pathways.

The RAS plays an important role in regulating blood pressure. In hyperthyroidism, the RAS is activated as a compensatory response to the reduced systemic arterial resistance and mean arterial pressure. Furthermore, there is evidence that T_3 directly stimulates the synthesis of renin substrate in the liver[18] and enhances the cardiac expression of renin mRNA,[19] leading to increased cardiac levels of renin and angiotensin II independent of the circulating RAS. Moreover, the expression of angiotensin II receptors in the myocardium is increased in the hyperthyroid state.[20] All of the above changes suggest a central role of the myocardial RAS in thyroxine-induced cardiac hypertrophy and the potential therapeutic implications of agents that block this system.

Hemodynamic Effects of Hyperthyroidism

Hyperthyroidism causes stereotypical changes in cardiovascular hemodynamics.[21] It leads to predictable decreases in SVR and increases in resting heart rate, left-ventricular ejection fraction, cardiac contractility and mass, blood volume, cardiac output, and pulmonary artery pressure.

Effects of Hyperthyroidism on Cardiac Output

In patients with hyperthyroidism, cardiac output is 50 to 300% higher than in normal subjects. This is the result of both direct and indirect effects of thyroid hormone on the heart and systemic vasculature. T_3 mediates the expression of structural and regulatory genes in the cardiac myocytes, leading to increased left-ventricular systolic and diastolic contractile function and increased cardiac output.[22] Furthermore, the decrease in SVR and mean arterial pressure stimulates the RAS, which in turn stimulates renal sodium reabsorption and leads to increased plasma volume.

Lastly, thyroid hormone also stimulates erythropoietin secretion,[23] which could expand the red cell volume. The combined effect of these two actions is an increase in blood volume and preload that leads to further increase in cardiac output.

Effects of Hyperthyroidism on Heart Rate and Blood Pressure

Hyperthyroidism leads to an increase in heart rate and predisposes to arrhythmia. Thyroid hormone affects the action potential duration and repolarization currents in the cardiac pacemaker myocytes through both genomic and nongenomic mechanisms, and there is evidence that pacemaker-related genes are transcriptionally regulated by thyroid hormone.[24] A widened pulse pressure is characteristic of hyperthyroidism. Despite the decrease in SVR, recent data suggest that arterial stiffness is increased in hyperthyroidism;[25] thus, hyperthyroidism typically causes an increase in the systolic blood pressure, which can be dramatic in older patients.

Effects of Hyperthyroidism on Pulmonary Arterial Pressure

The association between hyperthyroidism and pulmonary arterial hypertension (PAH) was first reported in an autopsy case.[26] The prevalence of PAH in patients with hyperthyroidism was recently examined and ranged between 35% and 65%.[27-30] Reversibility of PAH after treatment of hyperthyroidism has been observed.[30] Although the effects of thyroid hormones on the myocardium and the SVR are well known, mechanisms underlying PAH associated with hyperthyroidism are not clear. Hemodynamic and autoimmune hypotheses have been proposed.[30]

Therapeutic Implications: Ditpa (3, 5-Diiodothyropropionic Acid); A Thyroid Hormone Analog

Thyroid Hormone in Nonthyroid Related Heart Failure

Due to its positive inotropic and vasodilatory effects, the question naturally arises as to whether or not thyroid hormone might be useful in treating heart failure. In fact, early observations by Hamilton et al. have shown that altered thyroid hormone metabolism occurs in patients with heart failure.[31] The low T_3 syndrome — characterized by reduced serum levels of both total and free T_3, with normal TSH and free T_4 levels, and once believed to be a beneficial adaptive mechanism under conditions of stress — has emerged as a prognostic determinant in patients with heart failure.[32] Moreover, it has been shown that the lower the T_3 concentration, the higher the risk of death in patients with reduced left-ventricular ejection fraction.[33] This has led to clinical trials addressing the efficacy of thyroid hormone replacement therapy in patients with heart failure. The intravenous administration of T_3 in patients with advanced congestive heart failure[34] and the oral administration of T_4 in patients with idiopathic dilated cardiomyopathy[35, 36] had favorable results in terms of improving cardiac performance; however, the potential adverse effects of thyroid hormone, such as increased oxygen demand and tachycardia, have led to the development of selective thyroid hormone analogs with fewer undesirable side effects in patients with heart failure.[37] DITPA, or 3, 5-diiodothyropropionic acid, is a thyroid hormone receptor (TR) agonist that has low metabolic activity[38] compared to thyroid hormone and does not increase heart rate. In other words, DITPA displays an inotropic effect without chronotropic action.

Recently, in a phase II multicenter, randomized, placebo-controlled, double blind trial,[39] patients with New York Heart Association (NYHA) class II to VI heart failure were randomized to DITPA or placebo for 6 months. DITPA was poorly tolerated. Fatigue and gastrointestinal complaints in particular were more frequent in the DITPA group, obscuring the interpretation of congestive heart failure-specific effects, and the hospital review board stopped the study due to concerns about side effects. However, DITPA did increase cardiac index by 18% and decrease SVR by 11%. Interestingly, patients treated with DITPA lost 11 pounds and reduced their total cholesterol levels by 20% and LDL levels by 30% compared to placebo, making it a potential agent for treatment of hyperlipidemia and obesity.

Thyroid hormone in myocardial ischemia. It is suggested that thyroid hormone possesses cardioprotective properties against ischemia and reperfusion injury. Recent research in animal and cell-based models provides substantial evidence that either acute or chronic pretreatment with thyroid hormone before ischemia-reperfusion may be beneficial.[40] Thyroid hormone is now shown to regulate the expression and/or activation of several signaling molecules, which may account for its cardioprotective effect[41] including protein kinase C, mitogen-activated protein kinases (MAPKs), ERK and Akt pro-survival pathways, and small heat-shock proteins.

In animal models, DITPA facilitates arteriolar growth, modifies ventricular modeling, and limits infarct expansion and the decline in ejection fraction in the post-infarcted heart.[42] In combination with captopril, DITPA increased cardiac index in rats with large infarcts more than captopril alone.[43] These data and

others[44, 45] indicate that DITPA improved the function of the surviving myocytes, expanding the rationale for its therapeutic potential.

Summary

Thyroid hormone has profound effects on cardiac muscle, the conducting system, the peripheral circulation, and the sympathetic nervous system that predictably alter cardiovascular hemodynamics in patients with hyperthyroidism. These physiological effects can be modulated by age, the rapidity of onset and severity of hyperthyroidism, and by concomitant medications. Thyroid hormones (principally T_3) act by modifying gene transcription to alter rates of myocardial protein synthesis. In addition, nongenomic modes of action of T_3 have also been identified. The identification of tissue-specific pathways of thyroid hormone action is being translated into novel therapies. Thyroid hormone analogs (agonists and antagonists) have already been shown to be clinically valuable for a variety of conditions, including hypercholesterolemia, obesity, and heart failure. Clinical trials are in progress to expand the therapeutic approaches of small molecules that bind to thyroid hormone receptors to improve a variety of cardiovascular diseases.

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