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Signaling Mechanisms in Thyroid Hormone-Induced Cardiac Hypertrophy

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Abstract

Cardiac hypertrophy is a significant independent risk factor for increased mortality, comprising of maladaptive changes in cellular, molecular and metabolic processes that ultimately lead to heart failure. However, cardiac hypertrophy represents a continuum from physiological to compensatory to pathological hypertrophy, so that treatment modalities aimed to shift hypertrophy towards the physiological phenotype would represent an attractive therapeutic strategy. Many of the physiological changes caused by thyroid hormone (TH) treatment may provide direct benefit to the failing heart. Recent experimental studies have shown that TH rapidly activates pro-survival PKB/Akt-mTOR signaling pathways, thus providing cytoprotection and increasing synthesis of normal contractile proteins and metabolic enzymes. TH induces a normal physiological phenotype by binding to nuclear TH receptors that regulate expression of specific genes which promote cell survival and enhance contractile function. Physiological cardiac growth occurs with a coordinated angiogenic response that normalizes myocardial perfusion during hypertrophy, and recent studies support a significant role for TH and its endothelial cell surface integrin receptors and nuclear receptors in neovascularization during TH-induced hypertrophy. The present review examines these molecular mechanisms and intracellular signaling pathways activated in thyroid hormone-induced cardiac hypertrophy that support its therapeutic potential in the treatment of heart disease.

Keywords

physiological hypertrophy; heart failure; protein translation; apoptosis; neovascularization

1. Introduction

Hypertrophy of the human heart is a clinical diagnosis defined by an increase in myocardial mass that has been described as the single most important independent risk factor for increased mortality (Vakili et al. 2001; Levy et al. 1990). On the other hand, not all cardiac hypertrophy is associated with depressed contractile function, and this has been designated as “compensatory” or adaptive hypertrophy when increased ventricular wall thickness can normalize wall stress and preserve systolic function, as might occur during initial phases of hypertensive disease. Numerous clinical studies have documented the progression of compensated cardiac hypertrophy with normal contractile function to depressed cardiac function (described as “decompensation”) ultimately resulting in heart failure, a highly lethal disease with eight-year mortality (American Heart Association, Heart Disease & Stroke

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Statistics, 2009). In contrast to this description of "pathological" hypertrophy, increased myocardial mass can also occur without adverse functional consequences in certain conditioned athletes and has been defined as "physiological" hypertrophy. Recent reviews have put into perspective the molecular and cellular basis for the continuum between physiological and pathological cardiac hypertrophy (Dorn 2007; Dorn & Force 2005). Understanding the molecular and biochemical changes that occur in physiological and pathological cardiac hypertrophy may direct the development of therapeutic strategies to treat patients with heart failure. Therefore, the induction of physiological hypertrophic responses including increased synthesis of normal contractile proteins and mitochondria, normalization of metabolic pathways and chamber geometry, reduction of fibrosis, and neovascularization in proportion with myocardial growth, could confer benefit to the pathologically hypertrophied heart. The observation that thyroid hormone (TH) or its analogues activate many of the beneficial aspects of physiological hypertrophy has raised the possibility of their therapeutic utility in the treatment of the post-infarcted heart or in heart failure. This topic has been the subject of several recent reviews (Dillmann 2009; Galli et al. 2009; Pantos et al. 2008; 2009a).

2. TH-induced physiological cardiac hypertrophy

Cardiac growth in response to thyroid hormones (L-thyroxine, T4; and 3,5,3′-tri-iodo-L-thyronine, T3) has been defined as physiological hypertrophy. At the basic cellular level, hypertrophy involves the enlargement of the cardiac myocyte; however, at the organ level, hypertrophic growth requires the proportional proliferative growth of other cell types within the heart including those of the vasculature. Thus, to elicit a physiological growth response, thyroid hormones must stimulate cellular proliferation as well as cardiomyocyte enlargement in a manner that produces normal myofibrillar assembly. Early studies showed that hypertrophy of the heart in response to TH resulted from increased rates of protein synthesis due to increases in translationally active ribosomes, a process that reflects an increase in "efficiency" of the translational machinery, and to a greater "capacity" of protein translation that involves increased cellular content of active ribosomes and mRNAs, requiring transcriptional activation by TH (reviewed by Morgan et al. 1987). Furthermore, thyroid hormones regulate expression of specific genes activated in normal maturational growth, and prevent the expression of the "fetal" gene program characteristic of pathological hypertrophy (reviewed by Dillmann 2002; Klein & Ojamaa 2001). Thus, the effects of TH on cellular processes are diverse and complex, are cell type specific and involve multiple regulatory mechanisms. It is this diversity of actions of THs that has attracted attention in the development of these molecules as potential therapeutic agents.

3. Signaling pathways activated in cardiac hypertrophy

There is substantial evidence that stimuli associated with pathological or maladaptive cardiomyocyte hypertrophy involve activation of heterotrimeric G protein-coupled receptors (GPCR) signaling primarily through Gαq and include agonists such as angiotensin II, endothelin-1 and catecholamines (reviewed by Clerk et al. 2007; Dorn & Force 2005; Molkentin & Dorn 2001). In contrast, physiological or adaptive hypertrophy appears to be mediated by activation of phosphatidylinositol 3′ kinase (PI3K-Class IA p110α-isoform) and signaling through protein kinase B, PKB/Akt, in response to ligands acting principally via membrane receptor tyrosine kinases, such as IGF-1 and insulin (McMullen et al. 2004; reviewed by Oudit et al. 2004 and Naga Prasad et al. 2003); (Figure A shows schematic representation of these signaling events). Shioi et al. (2000) first showed that PI3K determined heart size using transgenic mice with targeted overexpression of a constitutively active p110α isoform of PI3K (caPI3Kα) resulting in increased heart size; conversely, overexpression of a catalytically inactive PI3Kα (dnPI3Kα) molecule resulted in smaller hearts with no observable myocyte necrosis, apoptosis, interstitial fibrosis or contractile dysfunction. In

response to pressure overload, the smaller hearts of dnPI3Kα transgenic mice hypertrophied to a similar extent as wildtype hearts; however, in response to exercise training (swimming), the dnPI3Kα mutant protein was able to significantly blunt the hypertrophic response in these mice, thus supporting a role for PI3Kα in mediating physiological but not pathological hypertrophy (McMullen et al. 2003). Further evidence supporting a role for the PI3K/Akt pathway in regulating cardiac hypertrophy came from cardiac-specific inactivation of a phosphatase (PTEN, phosphatase and tensin homolog on chromosome 10) that negatively regulates the PI3K/Akt pathway by dephosphorylating 3′-phosphorylated phosphoinositides. Thus, hearts of transgenic mice expressing an inactive PTEN protein showed significant hypertrophy (Crackower et al. 2002).

The changes in heart size elicited by PI3K activation are mediated by the immediate downstream effector kinase, PKB/Akt, that was shown to be activated in cardiomyocytes of the caPI3Kα transgenic mice and inhibited in the dnPI3Kα mice (Shioi et al. 2000). Furthermore, studies in transgenic mice with cardiac-restricted overexpression of constitutively active PKB/Akt lead to a significant increase in heart size, thus supporting a role for PKB/Akt in the regulation of cardiac growth (Condorelli et al. 2002; Shioi et al. 2002). PKB/Akt mediates the hypertrophic response by regulating several downstream targets including glycogen synthase kinase-3β (GSK-3β) (Antos et al. 2002; Michael et al. 2004) which is a negative regulator of cell growth (reviewed in Murphy & Steenbergen, 2005), and mammalian target of rapamycin (mTOR), a master modulator of protein synthesis (reviewed by Wang & Proud, 2006). Rapamycin, an inhibitor of mTOR activity, attenuates pressure overload hypertrophy induced by aortic constriction, and is partially effective in regressing established hypertrophy (McMullen et al. 2004). Downstream targets of mTOR are the S6 kinases (p70/85 and p54/56), the translation initiation factor binding protein (4E-BP1) and elongation factor (eEF2) kinase. 4E-BP1 plays a key regulatory role in the initiation of protein translation by binding to and inhibiting eukaryotic initiation factor 4E (eIF4E) initiation complex formation. Activation of mTOR results in phosphorylation of 4E-BP1 and eEF2 kinase that relieves their inhibitory effect on eIF4E and eEF2, respectively, thus enabling translation to proceed (reviewed by Tee & Blenis 2005). The S6 kinases (i.e., $p70^{S6K}$) are also important regulators of protein translation by virtue of their ability to phosphorylate the 40S ribosomal subunit protein S6, which enables the translation of mRNAs containing a 5′ terminal oligopyrimidine (TOP) track that are important in ribosome biogenesis (Jefferies et al. 1997).

4. Signaling mechanisms in TH-induced physiological cardiac hypertrophy

The well characterized actions of thyroid hormones on gene expression fail to adequately explain the observed effects of TH on cardiomyocyte hypertrophy. Evidence has accumulated to unequivocally show that receptors for thyroid hormone (TRs) not only function as transcriptionally active proteins, but they also participate in cytoplasmic-initiated signaling processes resulting in unique biological responses as illustrated in Figure A & B (reviewed by Davis et al. 2008; Furuya et al. 2009; Moeller et al. 2006). TRs are derived from two genes that are alternatively spliced to give rise to four T3-binding receptor isoforms, of which TRα1 and TRβ1 are predominant in the cardiomyocyte with TRα1 expressed in both nuclear and cytosolic compartments (Kinugawa et al. 2005; Kenessey et al. 2006). Simoncini et al. (2000) were first to report T3-dependent TR-mediated activation of phosphatidylinositol 3′-kinase (PI3K) activity in human endothelial cells, and to subsequently publish that direct physical interaction of TRα1 with the p85α regulatory subunit of PI3K resulted in Akt phosphorylation and activation of endothelial nitric oxide synthase (Hiroi et al. 2006). Similar TH-dependent TR-mediated PI3K activation has been described in other cell types including human fibroblasts (Cao et al. 2005), pituitary cells (Storey et al. 2006) and cardiomyocytes (Kenessey & Ojamaa 2006). In experimental animal studies, Kuzman et al (2005) showed increased phosphorylation of Akt, S6 kinase ($p70^{S6K}$) and mTOR in hypertrophied hearts of

thyroxine treated rats. In light of these novel observations, extranuclear signaling activities of TH and its receptors offers a potential mechanism by which this hormone induces cardiomyocyte hypertrophy independent of its regulatory effects on gene expression.

In studies of cultured primary rat cardiomyocytes, we showed that wortmannin, a specific PI3K inhibitor, blocked T3-stimulated protein synthesis as measured by reduced [^{3}H]-leucine incorporation into cellular protein, and prevented T3-induced myocyte hypertrophy (Kenessey & Ojamaa 2006). This response was initiated by T3-dependent activation of PI3K through a direct protein-protein interaction of cytosolic TRα1 and PI3K (Figure A). Furthermore, we have shown that TRα1 and PI3K are present in plasma membrane lipid raft fractions that are enriched in caveolin-3, a scaffold protein of caveolae, and that a complex of TRα1-PI3K-caveolin-3 co-immunoprecipitated from purified cardiomyocyte plasma membranes, suggesting their localization to caveolae (Kenessey & Ojamaa, unpublished data). A downstream target of PI3K and dependent on its enzymatic product, L-α-phophatidylinositol-3,4,5-triphopsphate (PIP3), is the phosphoinositide-dependent kinase, PDK1, and its target, PKB/Akt (Shioi et al. 2002; reviewed by Tee & Blenis 2005). T3 treatment resulted in Akt phosphorylation, and subsequent phosphorylation of mTOR in a time frame consistent with its location downstream of Akt in the signaling pathway. Two downstream targets of mTOR, 4E-BP1 and S6 kinases, are important regulators of protein translation, and their regulation by phosphorylation enables protein synthesis to proceed. We showed that T3 treatment of cardiomyocytes resulted in phosphorylation of S6K ($p70^{S6K}$), followed by sustained phosphorylation of S6 ribosomal protein, and increased phosphorylation of 4E-BP1. These effects were blocked by inhibitors of PI3K and mTOR, further supporting a role for the PI3K-Akt-mTOR signaling pathway in T3-induced cardiomyocyte hypertrophy.

5. Other growth factors in TH-induced cardiac hypertrophy

Is there a role for other growth factors in mediating thyroid hormone-induced physiological cardiac hypertrophy, including those known to produce pathological hypertrophy such as angiotensin II, endothelin and catecholamines? As discussed above, myocyte hypertrophy initiated by these diverse stimuli results from the activation of partially overlapping signaling pathways that lead to an increase in protein synthesis. Several reports have suggested that the rennin-angiotensin-system (RAS) contributes to cardiac hypertrophy in hyperthyroidism, with increased expression and activity of renin and angiotensin II in cardiac tissue of TH-treated animals (Kobori et al. 1997; 1999). Treatment with angiotensin receptor (AT1R) antagonists or angiotensin converting enzyme (ACE) inhibitors has been shown to attenuate TH-induced cardiac hypertrophy (Hu et al. 2003; Kobori et al. 1997; Pantos et al. 2005). Whether these effects are attributable to direct actions of TH and RAS in the myocardium or to hemodynamic changes known to occur in hyperthyroidism remain unclear. A recent study has provided evidence that TH-induced cardiomyocyte hypertrophy through Akt-mTOR mechanism can be inhibited by AT1R blockade (Diniz et al. 2009). However, it remains to be reconciled how TH signaling through AT1R –Gq linked pathways (known to induce pathological hypertrophy) can induce a physiological hypertrophic phenotype.

6. TH-regulated transcription maintains physiological cardiac phenotype

As illustrated in Figure A, GPCR agonists that induce pathological hypertrophy also activate the PI3K-Akt signaling pathway; however, the activated PI3K isoform (p110γ) differs from the isoform (p100α) activated by growth factors mediating physiological hypertrophy. PI3K-p110γ is activated by recruitment to the plasma membrane by βγ subunits of activated Gq protein, whereas p110α is principally activated by binding to ligand-activated growth factor receptors. Intracellular signaling initiated by these distinct types of stimuli that ultimately result in either physiological or pathological hypertrophy converge at the Akt-mTOR junction to

increase protein synthesis. Therefore, the mechanisms by which increased protein synthesis result in distinct forms of hypertrophy (adaptive/physiological or maladaptive/pathological) must necessarily involve stimulus-dependent regulation of gene expression, producing unique cardiac phenotypes. In this regard, thyroid hormones acting through nuclear receptors are perhaps the only known stimuli positioned to simultaneously regulate cardiac gene expression that translates into a normal phenotype and to induce cardiomyocyte hypertrophy by increasing protein synthesis.

TH regulation of cell phenotype can be classified into several modes of TH action: (1) effects mediated through TH receptors (TRα1, TRβ1) localized in the nucleus that interact with specific DNA elements on T3-responsive genes (historically defined as genomic action), or (2) effects initiated by T3-binding to cytosolic TRs with activation of intracellular signaling pathways including PI3K-Akt-mTOR, or (3) effects that are independent of TRs and initiated by TH binding to plasma membrane receptors (i.e., integrin αVβ3), resulting in an intracellular signaling response. These genomic and non-genomic activities of TH have been the topic of recent reviews (Davis et al. 2008; Moeller et al. 2006). All modes of TH action, whether initiated in the nucleus, cytosol or plasma membrane have the potential to influence gene expression. Recent studies focusing on cytosolic TR-initiated actions of TH showed that activation of the PI3K-Akt-mTOR pathway was necessary for TH induction of genes encoding hypoxia inducible factor (HIF-1α) and calcineurin inhibitor protein, ZAKI-4α (also known as modulatory calcineurin-interacting protein, MCIP2) (Cao et al. 2005; Moeller et al. 2005). HIF is a key mediator of angiogenesis and metabolic adaptation to hypoxia by increasing the expression of genes involved in glycolysis, glucose transport, cell survival, antioxidant enzymes and mitochondrial function (reviewed by Loor & Schumacker 2008). Whether other TH-induced cardiac genes are regulated in a non-genomic PI3K-dependent manner remains to be determined.

Bergh et al. (2005) have recently identified integrin αVβ3 as a cell surface receptor for TH. Binding of L-thyroxine (T4) or T3 (with lower affinity) resulted in rapid phosphorylation of mitogen-activated protein kinase (MAPK/ERK1/2), and its subsequent nuclear translocation and phosphorylation of TRβ1, thereby increasing TRβ1 transcriptional activity (Davis et al. 2000). Whether TH signaling initiates at integrins on cardiomyocytes or on other cardiac cell types such as endothelial cells has not been investigated. Integrins are a class of receptors that physically connect the intracellular sarcomeric contractile machinery to extracellular matrix proteins at specific plasma membrane sites comprising of both structural and signaling proteins, that play a significant role in mediating mechanical stress-induced cardiac hypertrophy (reviewed by Brancaccio et al. 2006; Samarel, 2005). It may, therefore, be interesting to consider a role for TH acting via integrin signaling to downstream targets such as Akt/GSK3β and ERK1/2, in modulating the hypertrophic and cell survival responses to hemodynamic overload.

The physiological cardiac phenotype induced by TH is mediated principally through its actions on specific genes by binding to nuclear TRs (reviewed by Klein & Ojamaa 2001; Dillmann 2002 & 2009). These T3-responsive genes encode both structural and regulatory proteins including myofibrillar proteins, such as the myosin heavy chains (MHC α and β), and the sarcoplasmic reticulum proteins, calcium-activated ATPase (SERCA2) and phospholamban. The increase in diastolic and systolic cardiac function observed with hyperthyroidism can be largely explained by changes in expression of these proteins (Kiss et al. 1994; Ladenson et al. 1992; Mintz et al. 1991; Rohrer et al. 1991). TH regulation of collagen gene expression in cardiac fibroblasts is likely responsible for the absence of fibrosis in TH-induced myocardial hypertrophy (Yao & Eghbali 1992). Other TH-responsive genes such as those of the adrenergic receptor complex including β-adrenergic receptors, guanine-nucleotide regulatory proteins, and adenylyl cyclases, contribute to increased adrenergic activity of the heart with

hyperthyroidism resulting in increased heart rate, widened pulse pressure and increased cardiac output (Hoit et al. 1997; Ojamaa et al. 2000). Genes encoding several plasma-membrane ion transporters such as Na^+/K^+-ATPase, Na^+/Ca^{2+} exchanger, and voltage-gated K^+ channels are regulated by TH, leading to increases in inotropy and chronotropy (Gick et al. 1990; Gloss et al. 2001; Ojamaa et al. 1999; Reed et al. 2000). De et al. (2004) used a limited cDNA microarray analysis (588 genes) to study differentially expressed genes in TH-induced hypertrophied rat hearts. The results confirmed previously documented TH-regulated genes, but also identified TH regulation of genes involved in glucose and lipid metabolism. Recently, studies of microRNAs have shown that a cardiac-specific microRNA (miR-208) encoded by an intron of the αMHC gene is required for cardiomyocyte hypertrophy and its expression is regulated by TH (van Rooij et al. 2007). Hearts of miR-208 knockout mice resemble hyperthyroid hearts with physiological hypertrophy, absence of fibrosis and reduced expression of βMHC. These studies implicate miR-208 in the TH-signaling pathway and provide a novel mechanism by which TH regulates cardiac function and hypertrophy (reviewed by van Rooij & Olson 2007).

7. TH-induced neovascularization in cardiac hypertrophy

Physiological cardiac hypertrophy requires proportional increases in myocardial capillary density, whereas pathological hypertrophy arising from heart diseases such as aortic stenosis, dilated or ischemic cardiomyopathy has been shown to be associated with decreased capillarity (Karch et al. 2005; Rakusan et al. 1992). Therefore, in physiological or compensatory cardiac hypertrophy, growth promoting signals must simultaneously induce hypertrophy and angiogenic growth factor expression to maintain the balance between myocyte growth and coronary angiogenesis. This has been clearly illustrated in a transgenic mouse model of Akt-induced myocardial hypertrophy in which enhanced angiogenesis was associated with mTOR-dependent induction of myocardial vascular endothelial growth factor (VEGF) and angiopoietin-2 expression during the compensatory phase of hypertrophy; whereas inhibition of angiogenesis resulted in an accelerated conversion from compensatory hypertrophy to heart failure (Shiojima et al. 2005; reviewed by Shiojima & Walsh 2006). Thus, induction of angiogenic growth factors such as VEGF is an important component in compensatory or physiological hypertrophy, and several angiogenic transcription factors including GATA4 and hypoxia-inducible factor (HIF-1α) have been reported to be activated by hypertrophic stimuli including thyroid hormone (Heineke et al. 2007; Ma et al. 2004; Moeller et al. 2005; Molkentin et al. 1994; Sano et al. 2007). Early anatomical studies documented a coordinated angiogenic response to TH-induced myocardial growth in experimental animal models, suggesting that formation of new capillaries and arterioles served to normalize myocardial perfusion during hypertrophy (Chilian et al. 1985; Tomanek & Busch 1998). Recent studies have elucidated potential molecular mechanisms underlying TH-induced angiogenesis. Using a chick chorioallantoic membrane model of angiogenesis, Davis et al. (2004) showed that the proangiogenic effect of T4 was initiated at the endothelial cell membrane and was dependent on increased fibroblast growth factor (FGF2) expression and secretion. These authors subsequently reported the identification of integrin αVβ3 as the endothelial cell surface receptor for T4 and the initiation site for T4-induced activation of ERK1/2 signaling and induction of angiogenesis (Bergh et al. 2005). A potential role for nuclear TRs in regulating coronary angiogenesis has also been recently proposed. Studying transgenic mouse models, Makino et al. (2009) reported that cardiac capillary density was significantly reduced in TRβ deficient mice but not in TRα KO mice or cardiomyocyte-specific TRβ KO mice, suggesting that TRβ expression in endothelial cells plays a role in angiogenesis. These authors showed that coronary endothelial cells (EC) isolated from TRβ KO mice had reduced ability to form capillary networks than EC from either wildtype or TRα KO mice. Furthermore, in a pressure-overload model, T3 administration restored capillary density in the ventricular myocardium, normalized TRβ levels, induced coronary endothelial cell KDR/Flk1 (VEGF receptor)

expression, and significantly increased coronary vascular conductance. Taken together, these data support a significant role for TH and its endothelial cell surface integrin receptors and nuclear TRs in neovascularization during TH-induced physiological hypertrophy.

8. TH protects cardiomyocytes from cell death during hypertrophy

Cardiac myocyte death is an irreversible cellular event occurring during stress-induced hypertrophy that can lead to decompensation and heart failure (reviewed by Diwan & Dorn 2006). In contrast, stimuli that promote physiological or adaptive hypertrophy signal principally through the PI3K and PKB/Akt pathway that is consistently associated with increased rates of protein synthesis and with cytoprotection (Matsui & Rosenzweig 2005). Cytoprotection occurs in part as a result of inhibition of cell death mediators, thus preventing apoptosis which is a highly regulated process involving either an extrinsic death receptor pathway or an intrinsic mitochondrial pathway that culminates in the degradation of proteins and cleavage of DNA. Recent studies have shown that activation of prosurvival kinases of the PI3K/Akt and ERK1/2 signaling pathways can protect the heart against ischemia reperfusion injury (reviewed by Hausenloy & Yellon 2004). Kuzman et al. (2005) showed that thyroid hormone treatment of cardiomyocytes cultured in serum-depleted conditions prevented cell apoptosis through an Akt-mediated mechanism. These authors subsequently showed that T3 treatment following myocardial infarction in experimental animals reduced cardiomyocyte apoptosis in the infarct border area which was associated with activation of the Akt signaling pathway (Chen et al. 2008). Using a Langendorff-rat heart model of ischemia reperfusion injury, Pantos et al. (2009) showed that T3 treatment during the reperfusion period significantly enhanced the recovery of function and reduced myocyte apoptosis. These data support an anti-apoptotic function of TH that may be important in preventing adverse cellular responses during TH-induced growth of the heart.

9. Therapeutic potential of TH treatment of patients with pathological hypertrophy or heart failure

If the beneficial characteristics of physiological hypertrophy were imposed on the maladaptive hypertrophied heart, then progression to heart failure may be averted. Konhilas et al. (2006) tested this hypothesis using exercise as the physiological growth stimulus, and found that the severity of the hypertrophic cardiomyopathy was significantly reduced. Since exercise may not be appropriate for heart failure patients, other more suitable molecular targets are necessary. TH treatment stimulates physiological cardiac hypertrophy with many molecular features that could be beneficial to the decompensated hypertrophied heart. In experimental animal models of myocardial ischemia, treatment strategies with TH or thyroid hormone analogues have shown improved contractile function, increased capillarity, and reduced cardiomyocyte apoptosis (reviewed by Pantos et al. 2008). The human experience with TH treatment strategies has also shown promise. Recently, a randomized, placebo-controlled trial using short-term treatment (3 days) with T3 replacement therapy in patients with chronic heart failure and low-T3 syndrome showed significant increases in stroke volume and left-ventricular end-diastolic volume with significant improvements in the neurohumoral profile including plasma levels of noradrenaline, B-type natriuretic peptide and aldosterone (Pingitore et al. 2008). Studies using longer-term treatment with L-T4 treatment of patients with idiopathic dilated cardiomyopathy showed improvement in cardiac contractility, exercise performance and circulatory function (Moruzzi et al. 1996). Emerging experimental and clinical evidence support a critical role of TH in maintaining normal cardiovascular function, and thus the potential therapeutic utility of TH (L-T3, L-T4 or thyroid analogues) in the treatment of decompensated “pathological” cardiac hypertrophy or heart failure has taken on renewed significance (reviewed by Galli et al. 2009).

10. Conclusions

Thyroid hormone treatment induces physiological cardiomyocyte hypertrophy by activation of intracellular signaling pathways which preserve cell survival, maintain normal myocyte protein expression, reduce fibrosis and promote neovascularization proportional to organ growth. These diverse pleiotropic actions of TH may provide the basis for its therapeutic utility in the setting of congestive heart failure or following myocardial ischemic injury.

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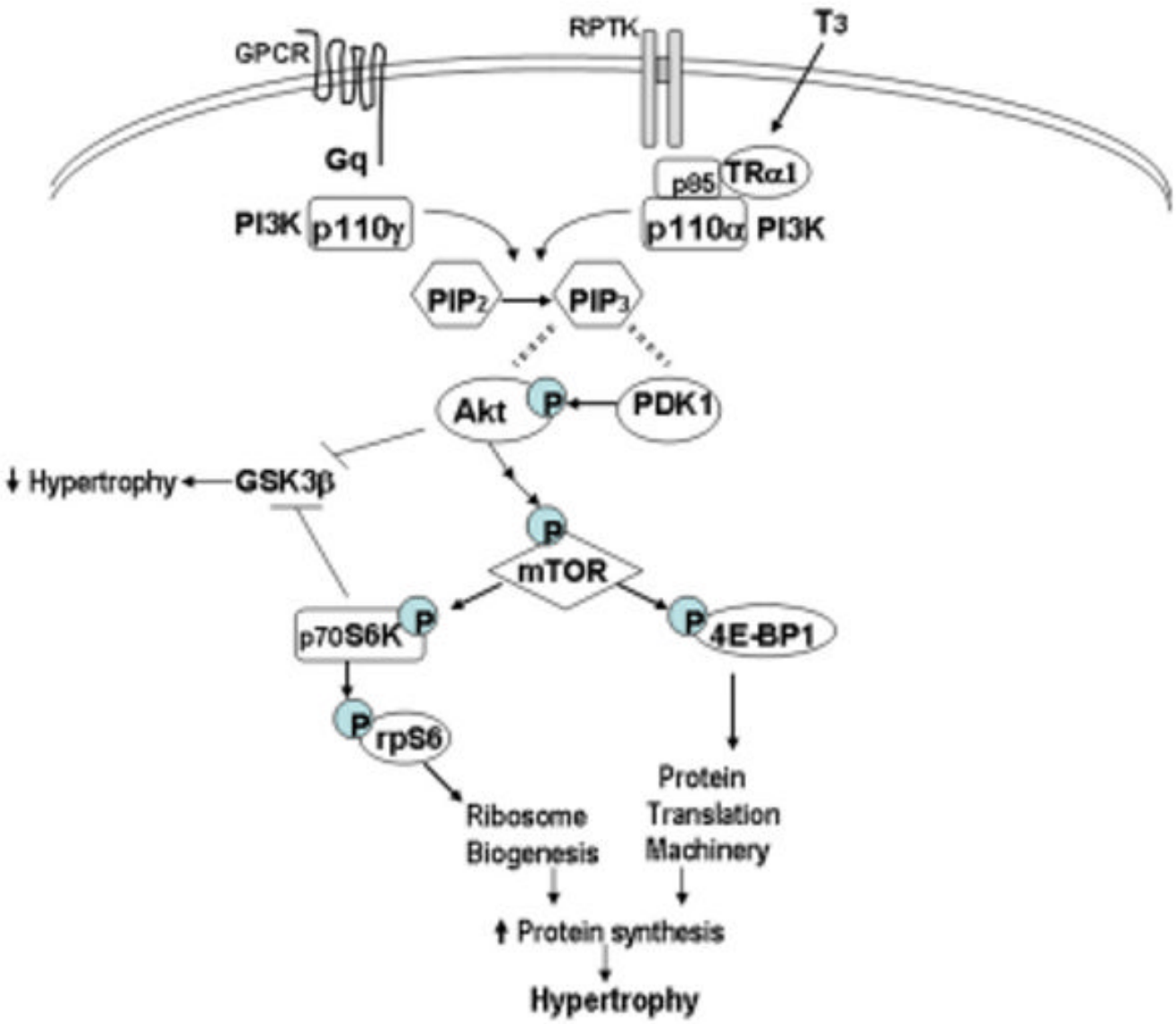

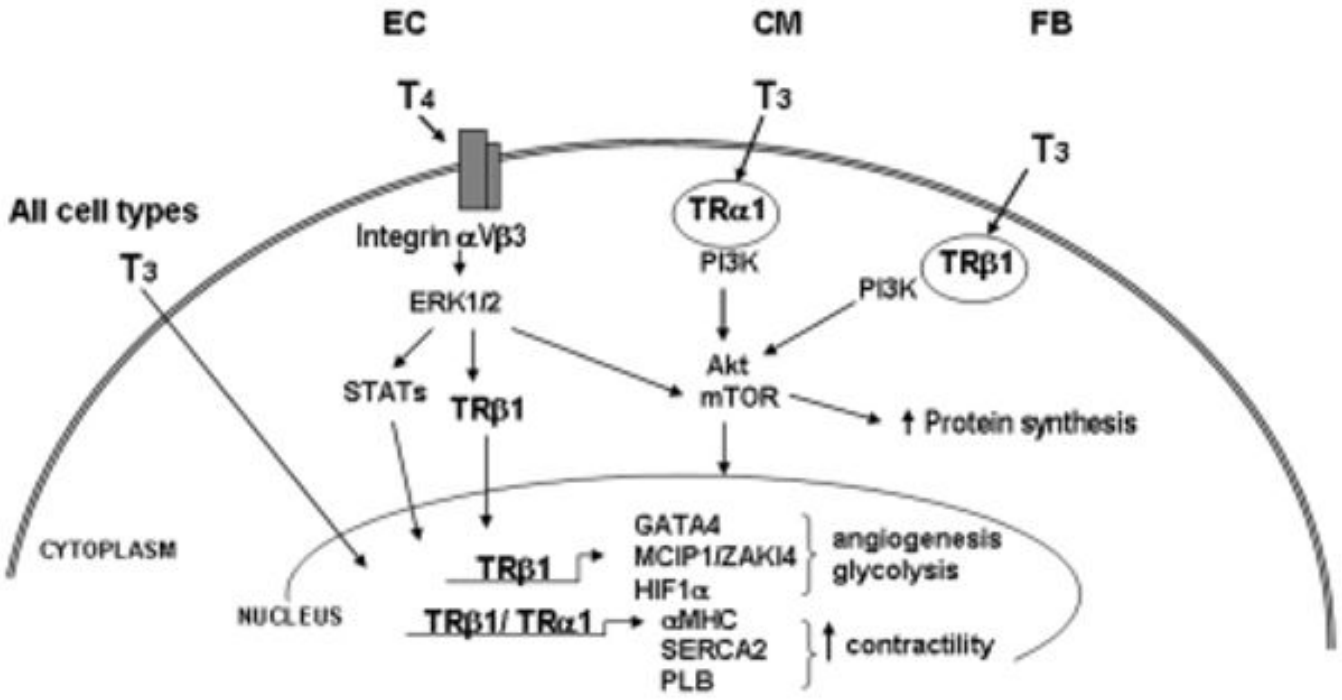

Figure. Schematic representation of thyroid hormone signaling in cardiac hypertrophy

(A) In physiological hypertrophy, T3 binding to cytoplasmic TRα1 or growth factor binding to receptor protein tyrosine kinases (RPTK) activates PI3K isoform p110α through direct interactions with the p85 subunit of PI3K. p110α phosphorylates phosphatidylinositol PIP2 at the 3′ position to produce PIP3, which serves to bind phosphatidylinositol-dependent kinase (PDK1) and Akt, allowing PDK1 to phosphorylate Akt. Activation of Akt then leads to activation of mTOR (mammalian target of rapamycin) which regulates protein synthesis through downstream targets including S6 kinase (p70S6K) and initiation factor eIF4E binding protein (4E-BP1), resulting in increased rates of protein translation and ribosome biosynthesis, leading to cardiomyocyte hypertrophy. Akt and S6K also phosphorylate and inhibit glycogen synthase kinase (GSK3β), an inhibitor of protein synthesis, thereby promoting cardiac hypertrophy. In contrast, pathological hypertrophic agonists (i.e., angiotensin, catecholamines) acting through G-protein coupled receptors (GPCR) and Gq, activate the Akt/mTOR pathway by associating with the p110γ isoform of PI3K.

(B) Reported effects of thyroid hormones (T3, L-tri-iodothyronine; T4, L-thyroxine) on various cell types including endothelial cells (EC), cardiomyocytes (CM) and fibroblasts (FB). T3 activation of the PI3K/Akt/mTOR signal transduction pathway as been shown to be initiated by binding to cytoplasmic thyroid hormone receptors (TRα1 and TRβ1), resulting in increased protein synthesis and activation of a hypertrophic gene program. In endothelial cells, T4 has been reported to bind to a plasma membrane integrin receptor (αVβ3) and to activate the mitogen-activated protein kinase (ERK1/2) signaling pathway, leading to TRβ1 phosphorylation and/or translocation to the nucleus where its transcriptional activity is enhanced. Furthermore, T3 can enter the nucleus directly in virtually all cells and bind to nuclear TRs that regulate expression of target genes that increase cardiac contractility, stimulate angiogenesis, regulate cell metabolism and provide cytoprotection. (MCIP, inhibitor of calcineurin; HIF, hypoxia-inducible factor; MHC, myosin heavy chain; PLB, phospholamban; SERCA2, sarcoplasmic reticulum calcium ATPase; GATA4, transcription factor).