Cardiac Thyroid Hormone Metabolism and Heart Failure

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Keywords

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Abstract

The heart is a principal target of thyroid hormone, and a reduction of cardiac thyroid hormone signaling is thought to play a role in pathological ventricular remodeling and the development of heart failure. Studies in various rodent models of heart disease have identified increased activity of cardiac type III deiodinase as a possible cause of diminished levels and action of thyroid hormone. Recent data indicate novel mechanisms underlying the induction of this thyroid hormone-degrading enzyme in the heart as well as post-transcriptional regulation of its expression by microRNAs. In addition, the relevance of diminished thyroid hormone signaling for cardiac remodeling is suggested to include miRNA-mediated effects on pathological signaling pathways. These and other recent studies are reviewed and discussed in the context of other processes and factors that have been implicated in the reduction of cardiac thyroid hormone signaling in heart failure.

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Apart from the rapid changes in cardiac output that are governed by the autonomic nervous system, the heart itself has a remarkable capacity to adapt to long-term changes in demand. Postnatal growth, exercise training, pregnancy, and increased levels of circulating thyroid hormones all result in a higher hemodynamic load to which the heart responds with cardiomyocyte hypertrophy [1]. The resulting increase in ventricular mass normalizes wall stress, maintaining adequate cardiac output and contractile efficiency. However, when the chronic hemodynamic overload is the result of hypertension, aortic stenosis, valvular disease, cardiac ischemia or loss of functional tissue due to myocardial infarction (MI), pathological remodeling ensues, resulting in progressive contractile dysfunction and chronic heart failure. An estimated 23 million people worldwide are affected by this condition, presenting a major burden on the healthcare system and society [2]. Although various therapeutic interventions may alleviate the symptoms, there is as yet no effective cure.

A large number of signal transduction pathways and factors have been identified that play a role in conveying the mechanical and (neuro-)hormonal stimuli that drive

physiological and/or pathological cardiac remodeling [1, 3]. Stimulation and repression of gene expression are the result of direct transcriptional effects as well as regulation of translation efficiency by microRNAs (miRNAs) [4, 5]. In the case of pathological remodeling, the maladaptive changes in gene expression result in cardiomyocyte dysfunction, apoptosis, fibrosis, and capillary rarefaction. A reduction of the levels of plasma thyroid hormone (TH) is one of the hormonal changes associated with advanced heart failure, as it is with other critical illnesses [6, 7]. This is considered to play a role in the progression of the disease, because virtually every aspect of cardiac contractility, energy metabolism, and myocyte shape, as well as angiogenesis and fibrosis, are to some degree regulated by this hormone [6, 8–11]. Unexpectedly, cardiac-specific inactivation of TH by type III deiodinase (DIO3) was found in various rodent models of heart failure, suggesting an additional mechanism by which reduced TH action may play a role in this disease, particularly also in the early stages of pathological remodeling [12].

In this brief review, we first present a summary of the essential aspects of TH metabolism and action pertaining to the heart, followed by a discussion of recent data concerning the possible causes and consequences of altered cardiac TH metabolism in pathological remodeling, particularly following MI. Although there is a large body of data indicating involvement of altered TH action in human heart disease [6, 8–11], changes in cardiac TH metabolism as a contributing factor have to the best of our knowledge not been reported yet. The reviewed literature therefore concerns rodent studies, unless otherwise indicated. The processes, pathways, and factors addressed in the text are depicted schematically in Figure 1.

Tissue TH Homeostasis

The thyroid primarily synthesizes and secretes the pro-hormone 3,5,3',5'-tetraiodothyronine (T4) and in smaller amounts 3,5,3'-triiodothyronine (T3), which is the high-affinity ligand of the nuclear thyroid hormone receptors (TR) that mediate most of the effects of TH on gene expression [13].

Cellular Uptake of TH

Cellular uptake of TH is mediated by members of the monocarboxylate transporter family, i.e., MCT8 and MCT10, and the organic anion transporter family, i.e., OATP1C1 [14–18]. Whereas expression of OATP1C1 is restricted to the central nervous system in rodents, both

MCT are expressed in the mouse heart, with MCT8 to a higher level than MCT10 [19]. The relative importance of either transporter for cardiac TH uptake is not known, but results from MCT knockout models for other tissues suggest that MCT8 is the principal TH transporter [20]. The minimal metabolism of T4 in rodent hearts [21] furthermore indicates the importance of T3 uptake. Effects of cardiac remodeling on protein expression of TH transporters have not been reported, but in a rat model of diabetic cardiomyopathy mRNA levels of MCT8 were found to be upregulated, while those of MCT10 were downregulated [22].

TH Deiodination

Conversion of T4 to T3 requires removal of 1 iodine atom from the outer ring of T4 and this is mediated by deiodinases type I and II, DIO1 and DIO2, respectively (reviewed in [23]). DIO1 has a much lower affinity for T4 than DIO2 and is primarily expressed in the liver and kidney. DIO2 is more widely expressed and its activity is a source of plasma T3, but also cellular T3 in various tissues, although this does not include the rodent heart [21, 24]. Studies using a mouse model in which both deiodinases were knocked out showed that compensatory thyroidal T3 secretion is able to maintain serum T3 homeostasis [25]. However, these studies also showed unique and critical roles of DIO1 and DIO2 activity in iodide conservation and tissue-specific T3 production, respectively [25]. DIO3 catalyzes the removal of an inner-ring iodine, converting T3 to the inactive metabolite 3,3'-diiodothyronine (T2), and, with lower affinity, T4 to the inactive metabolite 3,3',5'-triiodothyronine or reverse T3 (rT3). DIO3 is expressed in the placenta and in most fetal tissues.

Differential Expression of Deiodinases

Tissue-specific timing of DIO3 and DIO2 expression appears to play an essential role in the regulation of cellular proliferation and differentiation at different stages of development [23]. Shortly after birth, DIO3 expression drops to low or undetectable levels in most tissues, including the heart. Substantial expression in the healthy adult is primarily limited to the skin and brain, but coordinated transient expression of DIO3 and DIO2 is an aspect of tissue regeneration, for instance in liver and skeletal muscle [26–28]. Reduction of tissue T3 levels by DIO3 promotes cell proliferation in regenerating tissue, while subsequent expression of DIO2 increases T3 to drive differentiation. Perhaps not surprising, DIO3 plays a similar role in tumorigenesis, with

Fig. 1. Schematic summary of some of the processes and factors involved in the homeostasis and action of T3 in cardiomyocytes. Dashed lines indicate possible, but not yet confirmed interactions. The monocarboxylate transporters MCT8 and MCT10 mediate the uptake of both T4 and T3, and T4 may be converted to T3 by deiodinase type 2 (DIO2). The T3 receptor (TR) mediates transcriptional effects that include proteins involved in calcium homeostasis (SERCA2a, PLN) and contraction (MHCα, MHCβ) as well as miRNAs that may modulate other signal transduction routes. Cytosolic TR mediates a stimulatory effect of T3 on a sig-

naling cascade involved in physiological hypertrophy (PI3K/p85, Akt, mTOR). Deiodinase type 3 (DIO3) inactivates T3. Expression of DIO3 from the genomic DLK1-DIO3 imprinted region is stimulated by proliferative signals and signaling cascades involved in pathological hypertrophy (sonic hedgehog [SHH], GLI; transforming growth factor β [TGFβ], SMAD; hypoxia-inducible factor-1α [HIF1α] and MAPK). Expression of DIO3 is limited by miR-214 and possibly by miR-21 acting through GRHL. See text for details.

high activities found in a number of different cancers and DIO3 is consequently also classified as an oncofetal protein [29, 30].

Differential expression of DIO2 and DIO3 can contribute to cellular T3 homeostasis under conditions of low or high plasma TH levels in various tissues [23]. Whether this also plays a role in the heart is uncertain. Although DIO2 activity remained undetectable in hypothyroid right ventricular (RV) myocardium of the rat [24], the low DIO2 activity found in mouse and rat left ventricular (LV) tissue increased up to 5 fold in severe hypothyroidism [31]. However, ventricular DIO2 activity remained low compared to other tissues expressing DIO2, and

whether cardiac T3 levels were actually affected was not examined in that study.

Altered deiodinase expression is also an aspect of changes in the set point of systemic TH homeostasis in response to starvation and severe illness. The reduction of circulating TH levels involves both downregulation of the hypothalamus-pituitary-thyroid axis and altered peripheral TH metabolism, including induction of DIO3 activity [32, 33]. This so-called nonthyroidal illness syndrome is considered adaptive, given the overall stimulatory effect of TH on metabolism and energy turnover. Induction of cardiac DIO3 activity as a result of caloric restriction or noncardiac illness has not been reported.

TH Action

The principal mode of action of TH in modulating gene expression is transcriptional regulation of responsive genes mediated by TR, usually acting as heterodimers with the ubiquitously expressed retinoid X receptor (RXR) [13]. Examples of positively regulated cardiac genes are the fast myosin heavy chain MHC α (Myh6), the voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3) and the sarcoplasmic reticulum Ca²⁺-ATPase (SERCA2a). Only few cardiac genes are negatively regulated by T3, e.g., the slow myosin heavy gene MHC β (Myh7) and the SERCA2a inhibitor phospholamban (PLN) [11, 34]. The responsiveness of these cardiac genes is most evident during the postnatal rise of T3 in rodents when SERCA2a expression increases, MHC β is almost completely replaced by MHC α , and PLN expression decreases, resulting in marked enhancement of cardiac performance [4].

TH and the Fetal Gene Program

The T3-dependent changes in gene expression mentioned above are part of the transition from the fetal to the adult cardiac gene program and the concomitant physiological hypertrophy. The partial reversal of this transition that is seen in the chronically overloaded heart – and to some extent also in the hypothyroid heart – is indicative of the possible involvement of reduced T3 action in pathological remodeling. The relevance of the recapitulation of the fetal gene program in cardiac remodeling has been a matter of debate. An adaptive role is suggested by the shift to the energetically more efficient MHC β isoform, as well the reduction of SERCA2a activity, which will result in reduced energy turnover associated with contraction in the stressed myocardium [1, 35]. Nevertheless, it has conclusively been shown that the reduction of SERCA2a expression and activity is a pivotal aspect of contractile dysfunction and failure [36, 37]. In addition, only modest re-expression of the fetal gene program was observed in models of physiological hypertrophy [1]. The prevailing view is that the re-expression of the fetal gene program is perhaps initially an adaptive response, but ultimately a maladaptive one, also because the extent of the expression of this program is associated with the progressive decline in cardiac function in both animal models and humans [38, 39].

TH Receptors and Nongenomic Actions

Changes in expression of nuclear TR and its co-factors can obviously contribute to altered T3 signaling [13], but the importance for cardiac remodeling is not clear. TR α 1

is the predominant receptor in cardiomyocytes [40–42] and a study using a mouse model of LV pressure overload showed that cardiac function improved after TR expression was increased using viral transduction [43]. In line with this, reduced levels of TR α 1 were found following MI in mice [44]. However, no changes were found in this model by others [45], whereas a marked increase in TR α 1 expression was found in a mouse model of dilated cardiomyopathy [46].

TH and its metabolites may also exert nongenomic actions at the level of the plasma membrane, or through TR located in the cytoplasm [40, 47]. Particularly relevant for the present discussion is the observation that T3-liganded TR α 1, located in the cytosol, binds the p85 α regulatory subunit of phosphoinositide 3-kinase (PI3K), activating the (PI3K [p110 α])-Akt-mTOR pathway [48]. In cardiomyocytes, this plays a role in T3-induced ventricular hypertrophy, which is perhaps not surprising since this pathway also mediates physiological cardiac growth induced by insulin-like growth factor 1 acting through its membrane receptor [1].

Deiodinase Expression in Pathological Cardiac Remodeling

As already mentioned, involvement of impaired TH signaling in cardiac pathological remodeling is suggested by similar changes in the expression of some of the TH-regulated cardiac genes in hypothyroidism and in heart failure. Induction of DIO3 activity in the failing heart as a possible cause of a local hypothyroid condition was first observed in a rat model of pathological RV hypertrophy induced by pulmonary arterial hypertension [24]. The ventricle-specific expression of DIO3 correlated with the extent of the changes in gene expression characteristic of pathological remodeling and was associated with a reduction of tissue T3 levels [24, 49, 50]. Induction of cardiac DIO3 activity has since been found in rodent models of LV pathological remodeling induced by aortic stenosis [51], MI [45, 52], isoproterenol [53], and diabetes mellitus [22]. DIO3 activity in the mouse model of MI was already maximal at 1 week after MI surgery and remained high for at least 8 weeks [45]. A contribution to the observed DIO3 activity of non-cardiomyocytes in ventricular remodeling, particularly inflammatory cells [33], cannot be excluded, but immunohistochemical analyses localized DIO3 expression only to cardiomyocytes [45, 50]. The re-expression of DIO3 was seen in an estimated 20% of cardiomyocytes

throughout the spared, remodeling myocardium [45]. In both the pulmonary arterial hypertension model and the model for post-MI LV remodeling, the increase in DIO3 activity was associated with a ventricle-specific 50% reduction in tissue T3 levels.

DIO3 Expression and T3-Dependent Transcriptional Activity

In vivo determination of T3-dependent transcription in the failing left or right ventricle conclusively showed a cardiomyocyte-specific reduction to a level similar to that seen in overt hypothyroidism [45, 50]. Although a contribution to this effect of altered levels of TR or its co-factors cannot be excluded, the increase in cardiac DIO3 activity and associated reduction of cellular T3 levels in these different models appear to be the principal cause of the local hypothyroid condition of the failing right or left ventricle. In contrast, Wang et al. [46] found increased DIO2 activity and a 2.5-fold increase in LV T3 levels in a mouse model of dilated cardiomyopathy induced by a cardiac troponin T (cTNT) mutation. They furthermore showed that LV remodeling depended on increased T3 signaling through the PI3K (p110 α)-AKT and p38 MAPK pathways, the latter being a factor in pathological hypertrophy. The large increase in T3 levels in this model is remarkable, since even cardiac-specific DIO2 overexpression only marginally increased cardiac T3 levels in mice [51, 54]. This is most likely related to the limited capacity for uptake of T4 in rodent myocardium [21], suggesting that increased expression of both DIO2 and transporters with higher affinity for T4 are unique aspects of this particular model of LV remodeling.

Regulation of DIO3 Expression in Pathological Cardiac Remodeling

Signaling pathways and factors that have been implicated in the activation of cardiac DIO3 expression include transforming growth factor β /SMAD, MAPK (p38, ERK), sonic hedgehog/GLI, and hypoxia-inducible factor-1 α , as reviewed by Pol et al. [12]. However, none of these have as yet been conclusively shown to be involved in the re-expression of DIO3 in the failing heart. The heterogeneous expression of DIO3 throughout the myocardium, as for instance seen in the mouse MI model, implies activation of specific signaling cascades in some cells, but not in others. The resulting dilution when analyzing tissue homogenates may explain the difficulty in identifying DIO3-regulating pathways.

Regulation of Deiodinase Expression by miRNAs

The importance of miRNAs in the regulation of cardiac gene expression is now well established [5]. These highly regulated, short noncoding RNAs reduce the efficiency of translation of specific target mRNAs, or in some cases induce their degradation. Upregulation of a specific protein can consequently be the result of a decrease of one or more miRNAs targeting its mRNA, or the result of an increase of other miRNAs that suppress the expression of a transcriptional inhibitor of its gene. With respect to deiodinase expression, Dio1 mRNA has been shown to be targeted by miR-224, possibly playing a role in tissue hypothyroidism in renal cancer [55], and miR-214 has been shown to target Dio3 mRNA [56]. However, upregulation of this miRNA in the post-MI heart precludes a role in the increased expression of DIO3 [56, 57]. Nevertheless, the observed co-expression of miR-214 and DIO3, together with the increase in cardiac miR-214 expression in hypothyroidism, suggests that it may play role in limiting the expression of DIO3 and the associated negative effects of tissue hypothyroidism [56]. Such a role is in line with the reported improvement of post-MI survival in a miR-214 knockout mouse model [57].

Di Girolamo et al. [58] recently showed that miR-21 stimulates DIO3 expression in basal cell carcinomas by targeting the tumor suppressor grainyhead-like 3 (GRHL3), which they identified as a powerful inhibitor of DIO3 transcription. Upregulation of cardiac miR-21 plays an important role in the development of heart failure in several models, as it stimulates fibroblast survival, interstitial fibrosis, and myocyte hypertrophy [59]. GRHL3 is present in the developing mouse heart [60], but levels in the adult animal are not known. Nevertheless, the unexpected link between miR-21 and DIO3 expression warrants analysis of GRHL3 expression in models of ventricular remodeling.

DIO3 Expression and Cardiomyocyte Proliferation

A global analysis of cardiac miRNA expression in the mouse model of post-MI remodeling and DIO3 expression revealed an unexpected upregulation of a large miRNA cluster located in the DLK1-DIO3 genomic region [61]. DIO3 is located at the most distal part of the delta-like homologue 1 (DLK1)-DIO3 genomic imprinted region on mouse chromosome 12F1, which includes, next to DIO3, the protein-coding genes DLK1 and retrotransposon-like gene 1 (RTL1), as well as the non-coding RNA sequences Gtl2 (MEG3), Rian (MEG8), MIRG, and numerous miRNAs [62]. Activation of the DLK1-DIO3 region is an aspect of increased pluripotency and

proliferative activity in stem cells and various tumors [63, 64], with a predicted role for many of these miRNAs in regulating the associated signaling pathways [65]. Because like DIO3, the expression of the induced miRNAs in the MI model was localized to cardiomyocytes, it was suggested that a proliferative response was initiated in the stressed cardiomyocytes in the remodeling LV following MI, rather than for instance in the small population of cardiac progenitor cells [61]. Although cardiomyocyte proliferation, also in response to injury, is possible in the mouse heart up until postnatal day 7, this capacity is subsequently lost completely [66]. The present data therefore suggest that at least in the context of post-MI remodeling, induction of DIO3 expression may also be an integral part of the program that drives cardiomyocyte proliferation in fetal and early post-natal life. Re-activation of this program by proliferative signals is apparently possible, but it cannot be completed in the terminally differentiated adult cardiomyocyte.

Relevance of DIO3 Activity in Pathological Cardiac Remodeling

As mentioned in the introduction, a reduction of cardiac T3 signaling will at least contribute to a wide range of changes in gene expression and cardiomyocyte function that characterize pathological ventricular remodeling [6, 8–11]. Apart from direct transcriptional regulation of T3-responsive genes, indirect effects can be mediated by T3-regulated miRNAs, although to date only 2 cardiac miRNAs have been analyzed in detail. A complex and not fully resolved network involves the miRNAs that are located in introns of the T3-regulated genes *Myh6* (miR-208a) and *Myh7* (miR-208b). Like their host genes, miR-208a expression is stimulated by T3, while miR-208b is repressed [67–69]. Unexpectedly, upregulation of *Myh7* expression was shown to depend on the expression of miR-208a, involving downregulation of a TR accessory protein (THRAP1) [70]. Moreover, miR-208a appears to play a pivotal role in various aspects of pathological hypertrophy and is considered a target for therapy [70, 71].

TH Regulation of Cardiac miRNAs

A recent analysis of miRNA expression levels in hearts of hypothyroid mice that were treated for 3 days with T3 revealed a miRNA signature of 52 significantly regulated miRNAs, including miR-208a and -b [69]. Target analyses predicted that most of the newly identified T3-responsive miRNAs suppress critical components of signal

transduction pathways involved in pathological cardiac hypertrophy, and only some target factors that would lead to enhanced signaling involved in physiological cardiac hypertrophy. These *in silico* results need to be confirmed, but the suggested miRNA brake on pathological pathways imposed by T3 would help to explain why a chronic increase in hemodynamic load in mild hyperthyroidism typically leads to physiological ventricular hypertrophy, without adverse remodeling [1]. Conversely, tissue hypothyroidism in the overloaded ventricle would be expected to enhance pathological signaling. This is in line with the notion that reduction of cardiac T3 levels is an ultimately maladaptive response, a notion that is based on the attenuation of pathological remodeling by increasing cardiac T3 levels. This was for instance shown in a model of pressure overload by overexpression of DIO2 [51], and by T3 treatment in models of post-MI remodeling and diabetic cardiomyopathy [72, 73].

Conclusion

Although the reviewed data suggesting a role of increased DIO3 activity in impairment of T3 signaling and maladaptive remodeling are compelling, proof of a causal relationship is still lacking. One study addressed this question using DIO3 knockout mice in a model of pathological hypertrophy induced by isoproterenol [53]. Reduced survival in the DIO3 knockout animals compared to the wild-type animals suggested that the induction of DIO3 is in fact an adaptive response. Interpretation of these data is, however, complicated by the presence of a restrictive cardiomyopathy with fibrosis and contractile dysfunction in the DIO3 knockout mouse [53]. Analysis of pathological remodeling using a cardiomyocyte-specific, conditional DIO3 knockout model is therefore needed. This model has now been developed [D. Salvatore, pers. commun.] and will first be used to determine the role of DIO3 activity in the impairment of TH signaling in post-MI remodeling.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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