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Cardioprotection and thyroid hormones

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Abstract The evolution of cardiac disease after an acute ischemic event depends on a complex and dynamic network of mechanisms alternating from ischemic damage due to acute coronary occlusion to reperfusion injury due to the adverse effects of coronary revascularization till post-ischemic remodeling. Cardioprotection is a new purpose of the therapeutic interventions in cardiology with the goal to reduce infarct size and thus prevent the progression toward heart failure after an acute ischemic event. In a complex biological system such as the human one, an effective cardioprotective strategy should diachronically target the network of cross-talking pathways underlying the disease progression. Thyroid system is strictly interconnected with heart homeostasis, and recent studies highlighted its role in cardioprotection, in particular through the preservation of mitochondrial function and morphology, the antifibrotic and proangiogenetic effect and also to the potential induction of cell regeneration and growth. The objective of this review was to highlight the cardioprotective role of triiodothyronine in the complexity of post-ischemic disease evolution.

Keywords Cardioprotection · Thyroid hormone · Acute myocardial infarction · Heart failure

Abbreviations

HF	Heart failure
CV	Cardiovascular
TH	Thyroid hormone
ATP	Adenosine triphosphate
H^+	Hydrogen ions
PKC	Protein kinase C
ERK	Extracellular signal-regulated kinases
AKT	Protein kinase B
ROS	Reactive oxygen species
I/R	Ischemic/reperfusion
BCL-2	B cell lymphoma-2
PTP	Permeability transition pore
PTPO	Opening of the PTP
L-T3S	Low T3 syndrome
AMI	Acute myocardial infarction
T3	Triiodothyronine
rT3	Reverse T3
TRs	TH-specific receptors
p38MAPK	p38 mitogen-activated protein kinases
HSP	Heat-shock protein
p53	Tumor suppressor protein
PI3K	Phosphoinositide 3-kinase
T4	Tiroxine
MMPs	Metalloproteinases
TIMPs	Tissue inhibitors of MMPs
TGF	Transforming growth factor
bFGF	Fibroblastic growth factor
VEGF	Vascular endothelial growth factor
HIF-1α	Hypoxia-inducible factor 1 alpha
mTOR	Mammalian target of rapamycin
MHC	Myosin heavy chain

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Introduction

In the last decades, treatment of ischemic cardiac events shot down drastically the rate of mortality for cardiac events. This was mainly linked to the effort to reopen occluded coronary artery vessel as fast as possible from the onset of pain, initially by intravenous thrombolytic agents and then by primary percutaneous transluminal coronary angioplasty and implantation of coronary stents [1], associated with antiplatelet therapeutics, that help to maintain vessel patency. Nonetheless, the incidence of post-ischemic heart failure (HF) remains a remarkable clinical and prognostic issue, increasing the risk of both cardiac and overall death [2, 3]. According to 2020 World Health Organization projections, cardiovascular (CV) disease and their complications, in particular post-ischemic HF, will be the most important cause of death and morbidity, with high costs to worldwide healthcare systems. Such projection strengthens the need to develop new strategies for multiple preventive and therapeutic interventions targeted at promoting myocyte protection against acute and chronic ischemic bouts. Therefore, cardioprotection is definitely the new target of therapeutic intervention in cardiology to minimize irreversible ischemic damage and favor functional recovery of the ischemic-damaged myocardium. The mechanisms favoring myocyte survival programs are complex and multifactorial and involve different and frequently cross-talking pathways. This postulates the need to take into account the actions of the large number of components to understand the complex dynamic network of cardioprotection [4] (Fig. 1). Among all the components of cardioprotection, the thyroid system may play a determinant role due to its effects to maintain cardiac homeostasis, the regulating effect on different intracellular pathways involved in cardioprotection, the effects on mitochondrial function and the potential effects on myocyte regeneration and differentiation. This review is focused on the role of thyroid hormones (TH) on cardioprotection, starting from the complexity of cardioprotection.

Cardioprotection: a dynamic complex network

Extensive experimental literature highlighted the multiple and intermingled factors involved in myocyte survival that give characterize cardioprotection as a complex dynamic network. According to Heusch, cardioprotective mechanisms appear as a highly concerted spatiotemporal program in which the abrupt occlusion of a coronary artery is the "primum movens" of the ischemic myocardial damage [5].

Cardioprotection in the acute phase of ischemic heart disease

Ischemic cell death is the consequence of the depletion of adenosine triphosphate (ATP) due to cessation of aerobic metabolism and oxidative phosphorylation and a shift to anaerobic metabolism, which induces depletion of glycogen store, intracellular accumulation of hydrogen ions (H^+) and cellular acidosis [6, 7]. Irreversible myocyte damage occurs in a few hours in the presence of occluded vessel, and importantly, its extent is influenced by the presence of collateral circulation, by the presence of ischemic conditioning due to preexistent coronary stenosis and by the individual need for oxygen and nutrients [8]. The following step of myocardial damage is the reperfusion through coronary angioplasty and stenting [6]. In the pathophysiology of the reperfusion injury, the mechanism of calcium overload offers an example of the fine tuning of the biological systems intended as networks of cooperating units, whose function is strictly dependent each other. Indeed, at reperfusion, extracellular washout of accumulated H + ions establishes a large gradient greatly favoring the influx of sodium via the Na/H exchanger in order to correct rapidly occurring intracellular acidosis. The increased intracellular sodium concentration strongly stimulates the reverse action of the Na^+/Ca^{2+} exchanger pump, especially when acidotic inhibition of this pump is relieved, resulting in even greater elevations of intracellular calcium concentration [6, 9].

Other examples of such complex and strictly integrated phenomena are the molecular mechanisms of cytoprotection. These systems include stimulation of heat-shock proteins, activation of protein kinase C (PKC), extracellular signal-regulated kinases (ERK) and protein kinase B (Akt) pathways, inhibition of apoptosis, mechanisms of cell growth and angiogenesis including increased expression of the vascular endothelial growth factors and mechanisms of metabolic adaptation such as the stimulation of glucose metabolism.

An emerging mechanism of cardioprotection implies regulation of mitochondrial function and biogenesis. Actually, mitochondria are integrally involved in regulating myocardial calcium flux, myocyte cell death and remodeling events, reactive oxygen species (ROS) generation and antioxidant response, and in furnishing cardioprotective responses to physiological insults [10]. Not surprisingly, mitochondrial dysfunctions are critical determinants for myocyte loss during the acute ischemic stage, as well as during the progression of cardiac disease [10–13]. During ischemic/reperfusion (I/R) damage to the mitochondrial outer membrane along with activation of the proapoptotic B-cell lymphoma-2 (Bcl-2) proteins leads to

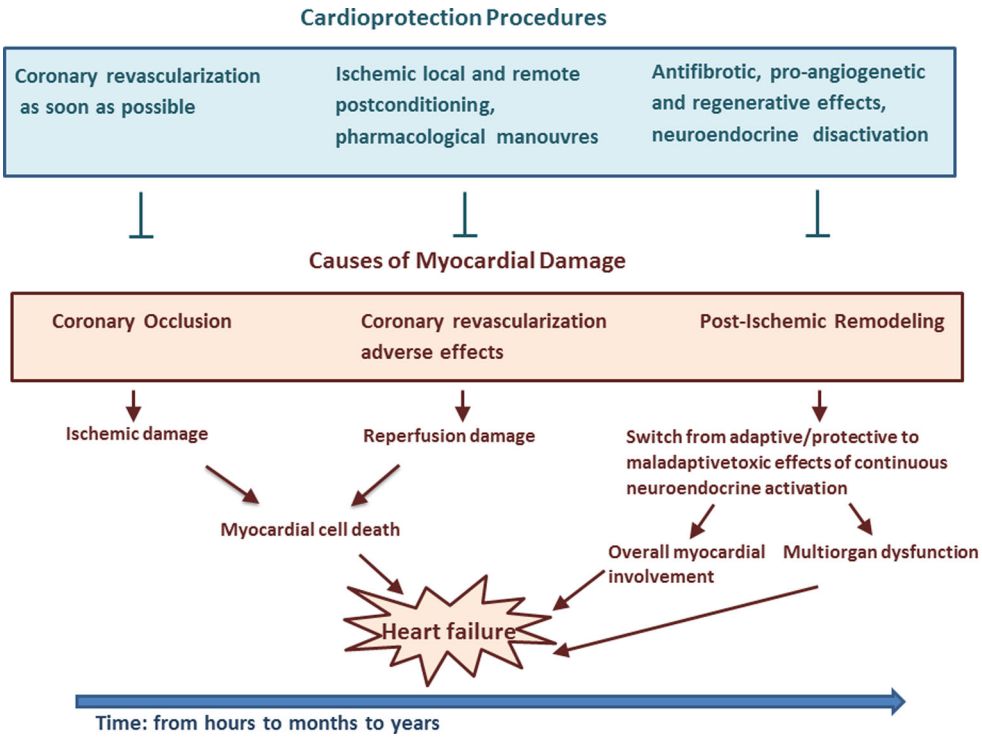

Fig. 1 Schematic representation of the dynamic and complex network of the post-ischemic myocardial damage and cardioprotection. The cause of damage and the corresponding mechanisms changes along the time from acute step, coronary occlusion and revascularization of the culprit vessel, to the chronic phase, post-ischemic remodeling. All these factors and mechanisms, strictly intertwisted with each other, share the final result that is the heart failure syndrome. Therefore, cardioprotection procedures cannot disregard the dynamic complexity of the mechanisms leading to heart failure, and a multiple approach should be applied in order to protect heart in the different phases of myocardial damage

mitochondrial outer membrane permeabilization, release of cytochrome *c*, caspase activation and apoptosis [14]. Massive oxidative stress can lead to a sudden increase in inner mitochondrial membrane permeability that is attributable to the opening of the so-called permeability transition pore (PTP). Opening of the PTP (PTPO) is accompanied by release of ROS and calcium [15, 16]; this can propagate the damage to neighboring mitochondria and culminate in activation of calcium-dependent proteases (calpains) and lipases, inducing necrotic cell death [17, 18]. As such, in recent years scientific efforts have focused on mitochondria as a target for cardioprotection in ischemic heart disease and cardiomyopathy.

Cardioprotection in the chronic phase of ischemic heart disease

Following acute phase of myocardial infarction, post-ischemic remodeling process is another dynamic mechanism influencing myocyte function and survival. Post-ischemic LV remodeling is the final result of molecular, subcellular, cellular and interstitial processes which involve changes in cardiomyocytes, extracellular matrix and vasculature (microcirculation) affecting the infarct region, acute myocardial infarction (AMI) border and remote regions [19]. This is a dynamic process, lasting several months from the AMI phase, causing thinning of the infarct area, infarct expansion at the site of the necrotic border zone, and hypertrophy and fibrosis of the remote zone likely occurring as a direct response to increased wall stress [20]. In the pathophysiology of HF, the activation of the neuroendocrine system, gathering sympathetic autonomic nervous, renin–angiotensin–aldosterone and natriuretic peptides, as well as inflammatory system, is initially protective and adaptive to hemodynamic changes induced by reduced cardiac output. However, due to their continuous activation, their protective mechanisms become first less effective, conferring resistance to myocardial hypoxic injury, and then maladaptive and dangerous for the entire body and heart, contributing to myocardial damage and progression of the disease [21–23].

Thyroid system in acute myocardial infarction

Low triiodothyronine (T3) syndrome (L-T3S) is the more frequent mild alteration of TH metabolism in AMI occurring in almost 22 % of patients [24]. Low circulating T3 levels associated with a corresponding increase in reverse T3 (rT3), the inactive T3 metabolite, occur rapidly within 12 h from the onset of symptoms, reaching the nadir by 72 h. Greater T3 down-regulation has been observed in patients with left ventricular dysfunction, larger myocardial infarction and intense proinflammatory and stress response [25, 26]. Further increased levels of rT3 were associated with negative outcome resulting as an independent predictor of short-term and long-term mortality [27].

L-T3S occurs also in the experimental I/S setting [28], inducing several histological, molecular and structural abnormalities within the myocardium, which can be reversed after normalization of TH metabolic profile [29]. Although a low T3 state has been generally interpreted as a merely adaptive mechanism finalized to reduce catabolic processes of illness and thus having beneficial effects through the reduction in metabolic demand, the experimental and clinical data rebut this hypothesis, suggesting an effective role in cardioprotection [30].

Thyroid system and cardioprotection

Several elements sustain the hypothesis that TH system plays an effective role in the complex scenario of cardioprotection. These can be recapitulated in the following points:

1. TH exerts a regulating function in tissue differentiation during the transition from fetal to postnatal growth, during which THs induce transcriptional programming leading to the typical gene expression profile of the adult heart
2. TH regulates cardiovascular homeostasis directly through genomic and non-genomic actions and indirectly by THs regulating effects on other systemic pathways
3. TH orchestrates function of several intracellular signals
4. TH is well-known regulators of mitochondrial biogenesis and function
5. TH has antifibrotic, proangiogenetic and regenerative effect in the heart.

The regulation of the intracellular signaling, mitochondrial activity and the regenerative processes induced by TH are strictly intertwisted and depend on transcriptional and non-transcriptional actions of THs. The genomic effects of TH on the heart are mediated by TH-specific receptors (TRs), TRα (TRα1 and TRα2) and TRβ (TRβ1 and TRβ2) which bind to TH response elements in the promoter region of some genes [31]. Among the TRs, TRα1 may represent an important molecular effector of TH-induced cardioprotection since it is the most common isoform in the heart, and it binds T3 with high affinity and regulates important genes related to cell protection differentiation and growth [32]. This role appears to have a dual action which is dependent on its liganded or unliganded (with repressive action) state and on the concentration of circulating THs [33]. When T3 s is low, TRα1 receptor is highly expressed and in the unliganded state acts as a repressor of TH-positive-regulated genes, whereas the rise of T3 results in the conversion of TRα1 into the liganded state, triggering cell differentiation [34]. In the context of post-ischemic myocardial damage, overexpression of nuclear TRα1 in cardiomyocytes can result in pathological or physiological growth in the absence or presence of T3 [32]. Further, the inhibition of TRα1 with debutyl-dronedarone abolishes the beneficial effect of acute T3 treatment on ischemia/reperfusion injury [35]. Similarly, TRα1 inhibition induced after AMI has been associated with marked activation of the noxious p38 MAPK signaling, potentially causing apoptosis and low proliferative activity [36, 37].

Thyroid system and intracellular signaling

The cardioprotective effect of TH is mediated by regulation of prosurvival pathways, including activation of the PI3K/AKT and PKC signaling cascade [38–40]; enhancement of HSP70 and HSP27 expression, phosphorylation and translocation [41, 42]; and also suppression of p38MAPK [43].

In particular, it was found that T3 treatment for 3 days after AMI reduced myocyte apoptosis in the border area, possibly via Akt signaling [39]. The antiapoptotic effect of T3 was also reported by Pantos et al. [42] in an ischemia/reperfusion model with decreased p38 MAPK activation. In a recent study, TH was found to have a dose-dependent effect on Akt phosphorylation, which may be of physiological relevance [38]. Mild activation of Akt caused by the replacement dose of TH resulted in favorable effects, while further induction of Akt signaling by higher doses of TH was accompanied by increased mortality and ERK activation, some of the most well-studied kinases in relation to pathological remodeling [44]. This study may be of important therapeutic relevance because it shows that, in the case of L-T3S, TH replacement therapy may be sufficient to restore cardiac function, while excessive TH doses may be detrimental rather than beneficial.

In addition, Pantos et al. [42] showed that a preemptive 2-week T4 administration increased heat-shock protein (HSP) 70 expression and decreased p38 MAPK activation in response to ischemia, changes that closely resemble ischemic preconditioning. The same treatment also led to increase in the basal expression and phosphorylation of HSP27, and earlier and sustained redistribution of HSP27 from the cytosol–membrane to the cytoskeleton–nucleus cellular fraction [43]. Such changes might help to protect myocardium against ischemic insult, resulting in the improvement of post-ischemic functional recovery.

Thyroid hormone: the effect on mitochondria

THs are well-known modulators of mitochondrial biogenesis, function and Ca^{2+} cycling [45–47]. Changes in thyroid status are associated with bioenergetic remodeling of

cardiac mitochondria and great alterations in the biochemistry of cardiac muscle, with consequences on its structure and contractility [46].

Further, in a rat model of I/R, specific changes in mitochondrial proteomic profiling have been observed in relation to different post I/R circulating T3 level [48]. Retention of physiological T3 concentration in the early post-ischemic setting is associated with the upregulation of proteins with functional relevance in rescue of the mitochondrial integrity and mitochondrial quality control and in optimization of substrate utilization. These differences, along with the better recovery of post I/R cardiac function and mitochondrial activity in the presence of maintained T3 plasma level, prompted the authors to speculate that a condition of L-T3S in the early setting of the post I/R wound healing might affect mitochondrial function and contribute to adverse remodeling [48]. Accordingly, in the same experimental models of post-ischemic model of L-T3S, T3 administration at physiological or near physiological dose rescued mitochondrial function which was related to reduced cardiomyocyte loss in the peri-infarct zone and better preserved cardiac performance [49]. The proposed underlying mechanisms were related to the upregulation of mitochondrial biogenesis and to the activation of the cardioprotective mitochondrial channel mitoK^{+}-ATP [28]. More recently, correction of the post-ischemic low T3 syndrome has been shown to downregulate the mitochondrial-targeted noxious effect of tumor suppressor protein (p53) possibly through the upregulation of the miRNA 30a [28]. The main mitochondrial-targeted post I/R noxious pathways and T3-mediated cardioprotective effects are summarized in Fig. 2.

Thyroid hormone: the antifibrotic cardiac effect

The target of cardioprotection cannot be limited only on cardiomyocytes, but also on the other cells composing the myocardium that include fibroblasts and endothelial cells, that play a pivotal role to preserve architecture and function of the myocardium and which are involved in the chronic pathophysiological evolution of heart failure. Interstitial remodeling is associated with synthesis and deposition of collagen along with deregulation of a family of matrix proteases, matrix metalloproteinases (MMPs) and the tissue inhibitors of MMPs (TIMPs) [50]. Their effect is dependent on degrading certain extracellular matrix components, regulation of cell proliferation, migration, differentiation and apoptosis [51, 52]. It is generally documented that MMPs increase whereas TIMPs reduce their activity following MI. However, a temporal and spatial factor of MMPs and TIMPs activation is to be taken into account where MMP-1, 2, 3, 7 and 9 can be activated early and MMP-8, 13 and 14 late after acute MI [53]. Further TIMPs 1–3 expression is reduced in both remote and border infarcted zone, whereas TIMP-4 is unchanged in the remote but decreased in the border infarcted zone [54]. TH treatment with both T3 and T4 has been associated with a reduction in interstitial fibrosis in animal models of ischemic and non-ischemic heart failure, and this effect can be related partially to the influence of TH on MMPs and TIMPs activity [55, 56]. T3-induced cardiac hypertrophy was not associated with fibrosis but with an increase in MMP-2 and TIMP-2 expression [57]. Similarly, cardiac hypertrophy induced with T3 in rats has been associated with a reduction in collagen I and III with an increase in MMP-1 activity and a decrease in TIMP-l and 4 expression [58]. More recently, a tendency toward increased MMP-2 expression and TIMPs) −1 to −4 expression was also observed in long-term T4-treated MI rats, in which a reduction in collagen deposition in the LV non-infarcted area has been also documented [55]. The antifibrotic effect of T3 is further suggested by the evidence that early T3 replacement after ischemia/reperfusion in rat decreased the activation of the profibrotic TGF-α1 signaling while inducing the expression of the antifibrotic miRNA-29c, 30c and 133, and this effect was associated with the reduction in the scar size and with the maintenance of cardiac performance [59].

Thyroid hormone: the proangiogenetic effect

Chronic hypothyroidism is associated with rarefaction of coronary microvasculature with the consequence of impaired vasodilation. This alteration is reversed by T3 administration that promotes remodeling of coronary resistance vessels, consisting of proliferation of vascular smooth muscle cells, pericytes and endothelial cells. [60, 61]. The proangiogenetic effect induced by T3 involves different molecular mechanisms and starts as non-genomic action through the interaction with integrin αVβ3 at the level of plasma membrane of endothelial cells [62]. The transduction of the TH signal is further mediated by mitogen-activated protein kinase ERK1/2 with the consequent transcription of proangiogenetic genes, such as basic fibroblastic growth factor (bFGF) and vascular endothelial growth factor (VEGF) [63]. Further, another molecular circuit involved in the T3 proangiogenetic action occurs via the expression of hypoxia-inducible factor 1 alpha (HIF-1α) through the interaction of TH with cytoplasmic TRβ and the activation of P13K signaling [64, 65]. T3-induced angiogenesis has been documented in several experimental physiological and pathological rat models of cardiovascular disease, including ischemia, hypertension and diabetic cardiomyopathy [55, 56, 66]. In a rat model of post-ischemic HF, correction of the low T3 state with T3 supplementation favored a better maintained capillary density

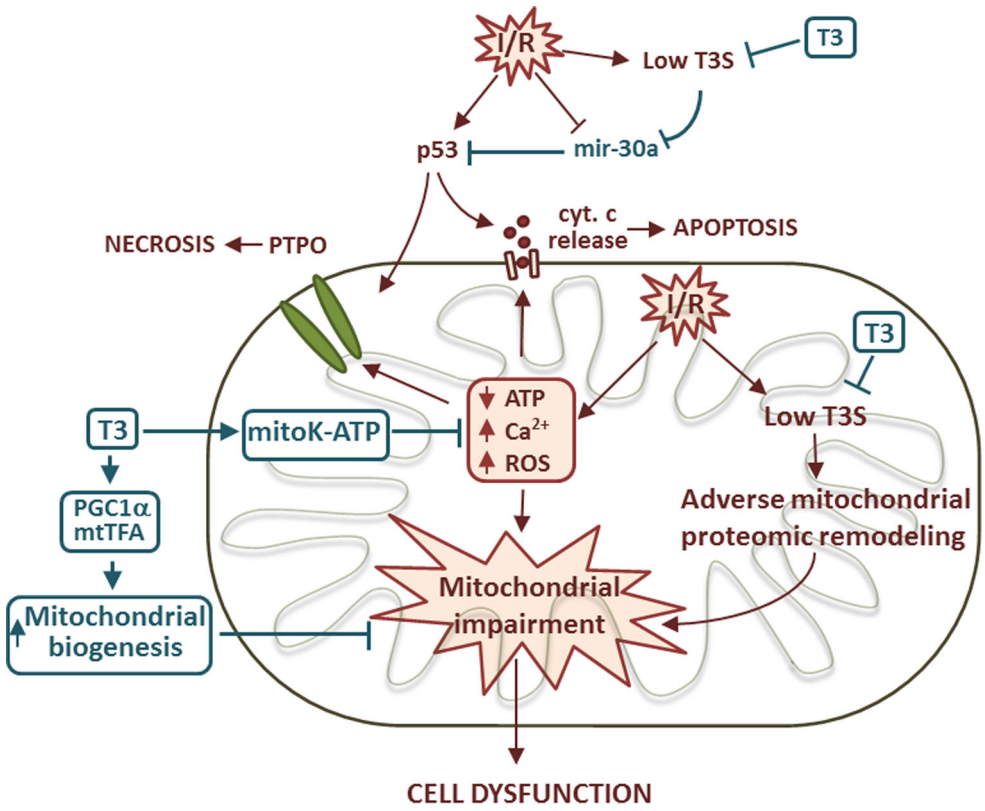

Fig. 2 Main mitochondrial-targeted noxious and cardioprotective mechanisms following cardiac I/R. I/R injury leads to ATP depletion followed by calcium overload and accumulation of reactive oxygen species (ROS), the driving pathways of cell death. p53 upregulation further favors mitochondrial-dependent apoptosis and necrosis of the injured cardiomyocytes. I/R also prompts the adverse remodeling of mitochondrial proteome, which enhances the mitochondrial impairment responsible for cell dysfunction. These noxious cascades are particularly severe in the presence of a post-ischemic low T3 state (L-T3S). L-T3S correction is associated with the activation of several cardioprotective pathways including: (1) opening of the protective mitoK^{+}-ATP channel (mitoK-ATP); (2) favoring mitochondrial biogenesis through the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) and mitochondrial transcription factor A (mtTFA); (3) reducing the post-I/R level of p53 possibly through the upregulation of its target miRNA 30a. Deleterious effects of I/R are indicated in *dark pink*, and cardioprotective pathways are evidenced in *cyan*

in the border zone in association with HIF-1α stabilization and TRα1 upregulation [27].

Thyroid hormones and the regenerative cardiac processes

As mentioned above, the mechanisms continuously activated during heart failure evolution change their action from adaptive and protective to maladaptive and toxic for the myocardium. Among these, we can include fetal recapitulation, that consists in the increase in β and decrease in α myosin heavy chains, decreased SERCA/PLB ratio, and also in the preference of glucose metabolism over fatty acids [67]. Although the pathophysiological relevance of fetal recapitulation is still uncertain, one argument in favor of its adaptive role may be that it lowers energy expenditure of the myocardium in response to hypoxia and ischemia reperfusion injury [68, 69]. A fascinating hypothesis is that TH may be a regulator of the dedifferentiation/redifferentiation process of myocytes through TRα1 action [34]. In this context, the role of TRα1 is noteworthy. In fact, the overexpression of unliganded TRα1 in neonatal cardiomyocytes was associated with increased β myosin isoform expression and impaired calcium handling and contraction [70, 71]. Further, inhibition of T3 binding to TRα1 abolished cardiac embryonic cells differentiation [72]. Another evidence of the role of this receptor in myocyte redifferentiation process is the stress response to phenylephrine, which has a growth effect mediated by ERK and mTOR signaling [73]. Following phenylephrine administration and in the absence of TH, there was a switch of myosin isoform to a fetal pattern associated with a redistribution of TRα1 with increased accumulation at the nuclear levels at the expense of the cytosolic levels [72]. This TRα1 response was abolished by inhibition of mTOR signaling with the consequence of cell atrophy [74]. With regard to myosin isoform gene switching, a complex network of miRNA-208a and b and miRNA 499 preside over

cardiac hypertrophy mechanisms [75]. miR-208a is a cardiac-specific miRNA encoded by the α-MHC gene. Deregulation of TH signaling in cardiac disease leads to α-MHC/miRNA-208a inhibition, while in vitro treatment with THs significantly upregulates α-MHC/miRNA- 208a expression and reduces β-MHC/miRNA-208b expression, as well as miRNA-499 [76]. These data suggest that physiological TH concentrations are necessary to guarantee adequate miRNA levels and to avoid fetal myosin isoform switching.

THiRST study

TH replacement therapy in ST elevation myocardial infarction (THiRST) study is a phase II, randomized, double-blind, placebo-controlled study, consisting in the administration of T3 in patients with AMI, treated with primary angioplasty, and with evidence of free T3 levels below the lower reference limit (<2.2 pg/mL) or decrease in free T3 plasma levels >20 % with respect to the admission levels in the first 24 h. The maximum daily dosage was 15 mcg/m^2b.s./die to be assumed as drops three times during the day. Patients were treated for a maximum treatment period of 6 months. The initial object of the study was to assess whether T3 replacement therapy reduced infarct size, regional wall motion abnormalities and improved systolic and diastolic myocardial function. Preliminary unpublished results on 30 patients treated with and without T3 therapy showed the absence of minor or major side effects induced by T3 treatment. In particular, no arrhythmias were induced and heart rate did not increase, but rather decreased at follow-up in T3-treated patients. Further cardiac magnetic resonance showed that there was a significant reduction in the global extent of necrosis, whereas regional systolic function tendentially improved.

Conclusions

Cardioprotection should be regarded as a complex dynamic network in which coronary occlusion, myocardial reperfusion and post-ischemic remodeling can be viewed as a pathophysiological continuum of myocardial injury. Numerous metabolic, molecular and hormonal mechanisms contribute to this phenomenon; they are strictly integrated to each other and act at distinct time periods, both in the acute and the chronic phase, with different times of action and with potential different effects, from protective to maladaptive or toxic, depending on the context in which they work, the time of activation and the interaction among them. It is also notable that the evolution of post-ischemic heart failure starts as a regional disease; subsequently, the infarcted area evolves through an organ disorder and thus becomes a systemic disease in its progression [77]. Therefore, the network of information stemming from all the factors playing a role in cardioprotection cannot ignore the concept of complexity applied to the human biological systems. This can be compared to a nonlinear, dynamic and intertwisted network in which small changes can result in large effects and big changes may result in none or small effects. In this complex dynamic network, TH system may be a newly identified player orchestrating the different molecular, tissue and cellular elements involved.

Compliance with ethical standards

Conflict of interest The authors of the paper "Cardioprotection and Thyroid Hormones," Alessandro Pingitore, Giuseppina Nicolini, Claudia Kusmic, Giorgio Iervasi, Paolo Grigolini and Simona Forini declare that they have no conflict of interest.

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