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Review

Thyroid hormone as a therapeutic option for treating ischaemic heart disease: From early reperfusion to late remodelling

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ABSTRACT

Thyroid hormone (TH), apart from its "classical" actions on cardiac contractility and heart rhythm, appears to regulate various intracellular signalling pathways related to response to stress and cardiac remodelling. There is now accumulating experimental and clinical evidence showing a beneficial effect of TH on limiting myocardial ischaemic injury, preventing/reversing post infarction cardiac remodelling and improving cardiac hemodynamics. Thyroid analogs have already been developed and may allow TH use in clinical practice. However, the efficacy of TH in the treatment of cardiac diseases is now awaiting to be tested in large clinical trials.

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1. Introduction

Although several genes encoding important regulatory and structural proteins in the myocardium are thyroid hormone responsive, thyroid hormone (TH) has attracted little attention in relation to heart diseases. Two dogmas have dominated the field; TH is detrimental to ischaemic myocardium due to acceleration of heart rhythm and "low T3 state", which accompanies heart diseases, has a protective role and needs no treatment. However, accumulating experimental and clinical evidence shows that low levels of triiodothyronine (T3) in heart failure are associated with increased mortality and morbidity (Pantos et al., 2007a; Pingitore et al., 2006;

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Pingitore et al., 2005). Furthermore, a cardioprotective effect of TH has been demonstrated in cells, animals and even in humans (Kuzman et al., 2005; Pantos et al., 2002; Ranasinghe et al., 2006; Zinman et al., 2006). The molecular basis of these novel effects is now beginning to be identified in the hope of developing new therapeutic strategies to treat cardiac diseases. With this evidence in mind, this review highlights important issues in this new field of research.

2. TH modulates ischaemic injury

TH could potentially have detrimental effects on the ischaemic myocardium due to acceleration of heart rate. However, there are several lines of evidence supporting a cardioprotective role of TH. Acute and long-term TH treatment is shown to protect the myocardium from ischaemia–reperfusion injury. Thus, early studies in animal models of ischaemia–reperfusion and in patients undergoing GABG showed that administration of TH at the reperfusion phase could result in marked improvement of postischaemic left ventricular function (Dyke et al., 1993; Dyke et al., 1991; Holland et al., 1992; Kadletz et al., 1994; Klemperer et al., 1995; Novitzky et al., 1989; Novitsky et al., 1991; Ranasinghe et al., 2006). Furthermore, thyroid hormone effect on cardiac function was associated with less myocardial injury with significant reduction of apoptosis and LDH and troponin release (Pantos et al., 2009a; Ranasinghe et al., 2006; Fig. 1).

Thyroid hormone pretreatment was also shown to confer protection from subsequent lethal ischaemia, in a similar pattern as ischaemic preconditioning (Buser et al., 1990; Klemperer et al., 1995; Kuzman et al., 2005; Liu et al., 1998; Pantos et al., 2003a; Pantos et al., 2006a; Pantos et al., 2003b; Pantos et al., 2002; Pantos et al., 2001; Spinale, 1999; Walker et al., 1995; Zinman et al., 2006).

3. TH-induced cardioprotection: potential underlying mechanisms

3.1. The role of stress kinase intracellular signalling

Complex intracellular kinase signalling underlies the response of the cell to stress with sustained activation of the so called pro-death signalling pathways p38 MAPK or JNKs to have detrimental effect while activation of the pro-survival ERK or PI3K/Akt signalling to be protective (Bogoyevitch et al., 1996; Pantos et al., 2006b). A delicate balance between pro-survival and pro-death signalling seems to exist and determine cell fate after an ischaemic insult (Pantos et al., 2006b). Thus, pharmacological interventions targeting stress kinase signalling pathways may be new therapeutic modalities for combating ischaemic heart disease.

TH is shown to activate pro-survival PI3K/Akt signalling pathway in cardiac cells and in the myocardium and confer protection to subsequent lethal ischaemia (Kuzman et al., 2005). Furthermore, TH is shown specifically to suppress the ischaemia–reperfusion induced activation of the pro-death p38MAPK signalling pathway (Pantos et al., 2009a; Pantos et al., 2002).

3.2. The role of redox-regulated signalling

TH seems to induce cardioprotection via activation of redox-regulated signalling pathways. This is supported by the fact that cardiac protection after TH administration in rats, coincided with the completion of mitochondrial biogenesis, mildly increased MDA levels (an index of oxidative stress) and induction of redox-regulated cardioprotective molecules, such as HSP70 (Pantos et al., 2006a). Here, it should be noted that similar mechanisms have been proposed for the TH mediated protection against ischaemia and reperfusion injury in other tissues (Fernandez et al., 2007).

3.3. The role of cytoskeleton — small heat shock proteins

Small heat shock proteins are thought to be important regulatory molecules for cytoskeleton integrity. Interestingly, interventions which accelerate translocation of these proteins to cytoskeleton upon ischaemia such as ischaemic preconditioning are shown to confer protection from ischaemic injury (Eaton et al., 2001; Sakamoto et al., 2000). Furthermore, increased phospho-HSP27 levels in the myocardium have been associated with the observed increased tolerance of the diabetic and the post-infarcted heart to ischaemia and reperfusion injury (Chen et al., 2005; Pantos et al., 2007b). Hormones like insulin appear to induce cardioprotection via activation of p38MAPK/HSP27 signalling pathway (Li et al., 2008). TH is shown to preserve cytoskeletal integrity in cultured cardiomyocytes subjected to simulated ischaemia (Zinman et al., 2006). Furthermore, in animal models, TH pretreatment was found to increase the phospho-HSP27 levels in the myocardium while accelerating the translocation of this protein to the cytoskeleton upon ischaemia, indicating a critical role of HSP 27 in TH mediated cardioprotection (Pantos et al., 2003a).

4. TH and postischaemic remodelling

Viable myocardium undergoes several changes in the course of cardiac remodelling following myocardial infarction aiming to adapt the heart to hemodynamic compromise. However, this response appears to be maladaptive; although the development of cardiac hypertrophy may be beneficial by normalizing wall stress, the expression of contractile proteins is switched to fetal pattern (pathological hypertrophy). Thus, it is likely that interventions which can activate signalling pathways that promote “physiological” hypertrophy may favorably remodel the post-infarcted myocardium. Among the most important regulators of physiological growth is TH, which serves an important role during development by promoting tissue differentiation.

Recent experimental studies provide substantial evidence showing that TH administration early or late in the course of myocardial infarction can prevent/reverse cardiac remodelling (Pantos et al., 2007c; Pantos et al., 2008a; Pantos et al., 2009b). Thus, left ventricular EF% was significantly improved after short and long-term TH administration beginning immediately after infarction. Furthermore, contractile indices, independent of loading conditions, such as $+dp/dt$ and $-dp/dt$, were also improved. Similarly, TH administration improved cardiac function in hearts with old MI (Pantos et al., 2009b).

5. TH improves cardiac function by regulating the expression of contractile proteins

TH administration early or late after myocardial infarction was shown to improve contractile function by altering the expression of contractile proteins in the myocardium. Thus, TH administration immediately after infarction, prevented the induction of β-MHC in the viable myocardium of the post-infarcted hearts. Furthermore, the ratio of SERCA/PLB was significantly increased after TH treatment (Ojamaa et al., 2000; Pantos et al., 2007c). Similarly, TH treatment reversed the fetal pattern of myosin isoform expression in hearts from animals with old myocardial infarction (Pantos et al., 2009b).

There is accumulating evidence showing that novel signalling pathways such as PKC or HSP 70 may also be involved in the regulation of cardiac contractility. In fact, PKC isoforms α and ε can control cardiac contractility through myofilament phosphorylation (Hambleton et al., 2006; Scruggs et al., 2006). Furthermore, pharmacological and gene therapy-based inhibition of PKCα enhances cardiac contractility and attenuates heart failure (Hambleton et al., 2006), while overexpression of PKCε results in cardiac dysfunction. HSP70 seems also to be crucial for the response to stress

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