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Review Article
Inhibitory Effects of Thyroid Hormones on Mitochondrial Oxidative Stress: A Systematic Review

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Abstract
Oxidative stress condition which is due to increased cellular free radicals has a main role in cell injury. Although free radicals are generated in normal metabolism, they may also be produced in excessive amounts during pathological conditions such as oxygen toxicity, drug overdose, chemical toxicity, ischemic-hypoxic injury and so on. The main parts of free radicals are Reactive Oxygen Species (ROS) which are mainly generated in cellular respiration. Increase in amount of ROS in pathological conditions can disturb mitochondrial function and make cellular damage. Thyroid hormones can act as a cytoprotective and antioxidant by inducing and activating some defense mechanisms against increased free radicals and mitochondrial oxidative stress. To review and categorize underlying mechanisms for the inhibitory effects of thyroid hormones on mitochondrial oxidative stress, Medline, Scopus and Web of science were searched for *in vitro*, *in vivo*, animal and human studies reporting antioxidant and cytoprotective effect of thyroid hormones in oxidative stress. After excluding duplicate, irrelevant and old articles the studies which had eligible criteria from 1980-2015 were included. Fifty one studies were included and evaluated in our study. It was found that thyroid hormones can induce cytoprotective and mitochondrial antioxidant effects through three mechanisms, consisting of increased activity and expression of uncoupling proteins, increased activity of mitoKATP channels, and increased activity and expression of antioxidant enzymes. Thyroid hormones have antioxidant effects through different mechanisms. More studies are needed to determine probable further mechanisms for thyroid hormones antioxidant effects and to confirm tissue hypothyroidism in oxidative stress.

Key words: Antioxidant enzymes, cytoprotection, mitochondria, oxidative stress, systematic review, thyroid hormones

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INTRODUCTION

Cell injury by free radicals, particularly Reactive Oxygen Species (ROS) is one of the main mechanisms for cell damages. Free radicals are atoms or molecules having single unpaired electron in the outer orbital. Energy created by this unstable configuration may lead to chemical reaction with cellular key molecules (carbohydrate, lipids, proteins and nucleic acids which are the main components of cells) initiating autocatalytic reactions. Free radicals are generated during normal metabolism and in most pathological conditions such as oxygen toxicity, ionization radiation, ultraviolet light, drugs, chemicals, toxins, reperfusion after ischemic injury (Droge, 2002; Hensely *et al*., 2000; Li and Jackson, 2002; Salvemini and Cuzzocrea, 2002). The ROS are molecules derived from oxygen and produced in some normal cellular activities such as cellular respiration, however, they may be generated in excessive amounts in pathological conditions and make harmful effects on the cells. Superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}HO$) are the principal ROS involved in the cell injury (Droge, 2002). In a review study, Saeidnia and Abdollahi (2013) thoroughly demonstrated the role of ROS in cellular damage and Oxidative Stress Related Diseases (OSRDs). The cells can control the ROS concentration by some defense mechanisms to prevent damage. When there is ROS overproduction or ineffective cellular defense, free radicals accumulate and their concentration increases. The result is an excess of free radicals, leading to a pathologic condition called oxidative stress. In other words, oxidative stress is an accumulation of oxygen derived free radicals, which have an important role in a wide variety of pathologic processes and diseases, including cancer, Alzheimer's disease, aging and so on (Abdollahi *et al*., 2014). Free radicals are degraded by: (1) Intracellular enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase, (2) Endogenous or exogenous antioxidants such as vitamin A, vitamin C, vitamin E, cysteine, glutathione, selenium, ceruloplasmin and transferrin and (3) Spontaneous decay. Superoxide anion (O_2^-) is a precursor for most ROS. In dismutation reaction superoxide anion is converted to hydrogen peroxide (H_2O_2) by SOD. After that, the majority of hydrogen peroxide is reduced to water and a small amount converted to hydroxyl radical ($^{\cdot}HO$). Electron transportation in cellular respiration is the main process to generate ROS in the most tissues. In this process, some electrons may leak and reduce oxygen molecules which result in producing ROS (Turrens, 2003). It is very important to know, superoxide formation is related to two factors: (1) Concentration of electron donors and (2) Concentration of oxygen (Szewczyk *et al*., 2009).

It is clear that any factor which can inhibit or control oxidative stress may have antioxidant and cytoprotective effects. With due attention to the important role of thyroid hormones in the cell biology, the protective effects of these hormones on the oxidative stress condition have been studied in the recent years. The role of thyroid hormones as an oxidant or antioxidant is controversial. Some studies indicated thyroid hormone-induced oxidative stress (Venditti and di Meo, 2006), whereas in a recent animal research by Abdolghaffari *et al*. (2015), the cardioprotective effects of triiodothyronine against phosphine-induced cardiac and mitochondrial toxicity have been confirmed. They administrated T_3 at 3 doses (1, 2 and 3 μg kg^{-1}) in a rat model of aluminum phosphate induced cardiotoxicity and found that T_3 at the dose of 3 μg kg^{-1} significantly improved ECG and oxidative stress parameters (Abdolghaffari *et al*., 2015). There are some other studies showing the antioxidant and cytoprotective effects of thyroid hormones in oxidative stress condition (De Castro *et al*., 2014; Forini *et al*., 2011, 2015; Mourouzis *et al*., 2013; Pantos and Cokkinos, 2010; Pantos *et al*., 2010a, b, 2011a, b, 2007, 2009). In contrary conditions, these questions arise: What is the role of thyroid hormones in oxidative stress condition? Do thyroid hormones have antioxidant and cytoprotective effects? What are the mechanisms for these effects?

In trying to make a clearance on such controversies and the answer to the above questions, in this review article, the antioxidant effects of thyroid hormones and mechanisms related to these effects have been criticized.

METHODS

This study was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al*., 2009).

Eligibility criteria, information sources and search protocol: In this study, electronic search was performed on Medline, Scopus and Web of science. All *in vitro, in vivo*, animal and human studies reporting antioxidant and cytoprotective effects of thyroid hormones in oxidative stress were included. Additional studies were identified through other sources and the records screened with titles and abstracts. After excluding duplicate, irrelevant and old articles, the studies which showed the antioxidant effects of T_3 and described the mechanisms of these effects from 1980-2015 were evaluated.

Study selection and quality assessment: Assessment of the studies was based on their title or abstract and those studies which had the eligibility criteria were selected for full text review.

Data collection, data items and synthesis of results: Data were collected and classified according to the thyroid hormones inhibitory effects on mitochondrial oxidative stress. Free radicals, oxidative stress, antioxidant enzymes and the mechanisms of the thyroid hormones on oxidative stress were discussed. The mechanisms of the thyroid hormones inhibitory effect on mitochondrial oxidative stress were categorized and discussed in three sections based on the data and the results of the selected articles.

RESULTS

Study selection and characteristics: Our initial search through database identified 138 published articles; on the other side, we had 19 additional records through other sources. After removing duplicate articles, 152 articles remained. Titles and abstracts were reviewed and 87 papers were excluded. The full texts of the remaining 65 articles were assessed for eligibility. Nine papers had old data, two papers had duplicated data and three papers were irrelevant that all of them were excluded. Finally 51 articles were included. Figure 1 shows the flow chart of study selection.

Results of studies: In our full data extraction, the main mechanisms for the inhibitory effects of thyroid hormones on mitochondrial oxidative stress can be categorized and summarized as follows: (1) Increased activity and expression of uncoupling proteins, (2) Increased activity of mitoKATP channels (ATP-sensitive potassium channels) and (3) Increased activity and expression of antioxidant enzymes.

Increased activity and expression of uncoupling proteins: Uncoupling proteins are located in the mitochondrial inner membranes and have a major duty in cellular physiology. These proteins are effective in maintaining the proton (H^+) gradient on both sides of the inner membrane and transport proton (H^+) from inter-membrane space to the mitochondrial matrix. In other words uncoupling proteins (UCPs) are the number of mitochondrial anion carrier proteins which transport anion from the mitochondrial matrix to inter-membrane space and proton from inter-membrane space to the mitochondrial matrix (Nedergaard *et al*., 2005). This class of mitochondrial proteins has five known types including UCP1, UCP2, UCP3, UCP4 and UCP5. The amounts and expression of uncoupling proteins are regulated by numerous factors such as thyroid hormones, norepinephrine, epinephrine and leptin (Gong *et al*., 1997).

It looks each UCP has a particular function and the expression of UCPs varies in different tissues according to necessity. For example, UCP1 called thermogenin is responsible for non–shivering thermogenesis and it is more expressed in Brown Adipose Tissue (BAT), whereas, UCP2 are further expressed in muscle cells and they are responsible for the elimination of ROS in oxidative stress condition (Arsenijevic *et al*., 2000).

It should be noted that cellular respiration is always associated with the production of small amounts of ROS (Raha and Robinson, 2000). Increased ROS amounts are very harmful to cells. There are some mechanisms for eliminating

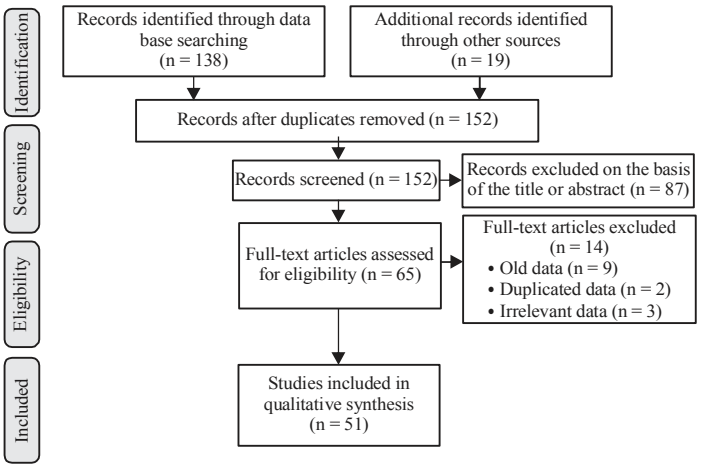

Fig. 1: Flow chart of study selection

and controlling ROS amounts to prevent cells from ROS adverse effects. Mild uncoupling is one of these mechanisms. Mild uncoupling is done by UCPs that transport anions and cations and is mediated by thyroid hormones in mitochondria (Skulachev, 1996, 1998; Starkov, 1997).

As mentioned, UCPs transport proton from mitochondrial inter-membrane space to mitochondrial matrix and transport anions vice versa. By this mechanism, UCPs reduce concentration of ROS and protect cells from lipid peroxidation (Nedergaard *et al*., 2005; Ricquier and Bouillaud, 2000).

The UCPs have a main role in the proton-leak process in mitochondria. There are 2 kinds of proton-leak in mitochondria: (1) Basal, it occurs in all tissues and there is no known regulatory mechanism for it and (2) Inducible, this kind of proton-leak process is done by UCPs and carefully regulated by known regulatory mechanism of Brand *et al*. (1999). Negre-Salvayre *et al*. (1997) showed the role of UCPs particularly UCP2 in reduction of ROS and prevention of oxidative stress damages. One year later, Skulachev (1998) showed that mild uncoupling is a defense mechanism in cellular respiration and UCPs act as an antioxidant. Vidal-Puig *et al*. (2000) represented that proton-leak was reduced and ROS production was increased in UCP3 knockout mice. Some studies demonstrated UCP2 and UCP3 are more effective as an antioxidant in ROS controlling than the other UCPs (Arsenijevic *et al*., 2000; Negre-Salvayre *et al*., 1997; Vidal-Puig *et al*., 2000). Dulloo and Samec (2001) showed UCP1 has a damper effect on ROS productions. Ramsden *et al*., 2012 found UCP4 and UCP5 reduced superoxide anion formation in neurons of Parkinson's patients. In this way they showed neuroprotective effects of UCPs against neurotoxins and ROS. The UCPs can restrict harmful effects of ROS on macrophage and prevent cellular degeneration (Rousset *et al*., 2004). The specificities of the known five types of UCPs are shown in Table 1.

Regulation of mitochondrial DNA transcription is one of the important effects of thyroid hormones. Considering this effect, thyroid hormone can influence mitochondrial RNAs and protein concentration (Cioffi *et al*., 2013; Wrutniak-Cabello *et al*., 2001). In a study, in hypothyroid rats, mtRNA concentration raised after T_3 administration. Hypothyroidism was induced in rats by tapazol, for 4-5 weeks and after that T_3 was administrated at a dose 20 μg/100 g/day. Steady concentration of mtRNA in hepatocytes was 2-8 times higher after administration of T_3 in comparison with when T_3 was not administrated, whereas there was no significant change in mitochondrial rRNA concentration (Mutvei *et al*., 1989).

Tri-idothyronine can induce increasing of uncoupling proteins. In some animal studies, UCP2 and UCP3 expression was increased by T_3 administration in cardiomyocytes and skeletal muscle cells (Gong *et al*., 1997; Lanni *et al*., 1999, 1997; Silvestri *et al*., 2005).

The UCPs (particularly UCP2 and UCP3) act as an antioxidant in oxidative stress condition and are effective in reduction of free radicals. In addition, expression and function of UCPs are increased by thyroid hormones. So thyroid hormones are critical in regulating and controlling free radicals in oxidative stress condition (Lanni *et al*., 2003). It is very important to know, in spite of increased expression and function of UCPs of thyroid hormones, ATP production increases. In an animal study on rat, after T_3 administration, despite high UCPs expression ATP generation was increased during oxidative stress (Short *et al*., 2001). Summary of studies related to the antioxidant effects of UCPs and thyroid hormones is shown in Table 2.

Increased activity of mitoK_{ATP} channels: Potassium channels are a class of ion channels which exist in almost all human cells. They are classified according to their functions and site of action. There are 4 potassium channel classes: (1) Calcium-activated potassium channel, (2) Inwardly

Table 1: Specificities of UCPs

Type of UCPs	Other name	Greatest tissue expression	Main function
UCP1	Thermogenin	Brown adipose tissue	Heat generation
UCP2	-	Muscular cells	Control of mitochondrial ROS
UCP3	-	Muscular cells	Control of mitochondrial ROS
UCP4	SLC25A27	Brain tissue	Control of mitochondrial ROS
UCP5	SLC25A15	Brain tissue	Control of mitochondrial ROS

UCP1: Uncoupling protein 1, UCP2: Uncoupling protein 2, UCP3: Uncoupling protein 3, UCP4: Uncoupling protein 4, UCP5: Uncoupling protein 5, ROS: Reactive oxygen species

Table 2: Effects of uncoupling proteins and thyroid hormones on ROS and oxidative stress

Study	Year of publication	Model	Extracted data
Negre-Salvayre *et al.* (1997)	1997	Animal study	UCP2→ ↓ROS
Arsenijevic *et al.* (2000)	2000	Animal study	UCP2→ ↓ROS
Vidal-Puig *et al.* (2000)	2000	Animal study	UCP3→ ↓ROS
Dulloo and Samec (2001)	2001	Review article	UCP1→ ↓ROS
Rousset *et al.* (2004)	2004	Review article	UCP3→ ↓ROS
Ramsden *et al.* (2012)	2012	Review article	USP4 and UCP5→ ↓ROS
Ricquier and Bouillaud (2000)	2000	Topical review	Mechanism of ↓ROS by UCPs
Nedergaard *et al.* (2005)	2005	Meeting article	
Skulachev (1996)	1996	Research article	Mild uncoupling by THs→ ↓ROS
Starkov (1997)	1997	Review paper	
Skulachev (1998)	1998	Review article	
Lanni *et al.* (2003)	2003	Minireview	THs controlling oxidative stress
Abdolghaffari *et al.* (2015)	2015	Animal study	
Gong *et al.* (1997)	1997	Animal study	T_3 → ↑UCP3 expression
Lanni *et al.* (1997, 1999)	1997		T_3 → ↑UCP2 expression
	1999		T_3 → ↑UCP3 expression
Short *et al.* (2001)	2001		T_3 → ↑UCPs expression
Silvestri *et al.* (2005)	2005		T_3 → ↑UCP2 and UCP3 expression
Mutvei *et al.* (1989)	1989	Animal study	T_3→ ↑mtRNA concentration

UCP: Uncoupling protein, UCP1: Uncoupling protein 1, UCP2: Uncoupling protein 2, UCP3: Uncoupling protein 3, UCP4: Uncoupling protein 4, UCP5: Uncoupling protein 5, ROS: Reactive oxygen species, TH: Thyroid hormone, T_3: Triiodothyronine, mtRNA: Mitochondrial RNA

rectifying potassium channel, (3) Tandem pore domain potassium channel and (4) Voltage-gated potassium channel (Jessell, 2000; Littleton and Ganetzky, 2000). Inwardly rectifying potassium channels have 7 subfamilies (Kir-1-Kir-7) and mitochondrial ATP-sensitive potassium channel is one of them (Kubo *et al.*, 2005; Suzuki *et al.*, 1997; Zhou *et al.*, 1999). The ATP-sensitive potassium channels were first identified in myocardial cells by a Japanese research group (Noma, 1983). This class of potassium channels regulates cellular and intracellular organelles membrane potassium concentration and has an important function in cellular biologic activities consisting of cell metabolism, apoptosis and gene expression. According to function and site of action, this class is categorized into three subclasses: (1) Sarcolemmal ($sarcK_{ATP}$), (2) Mitochondrial ($mitoK_{ATP}$) and (3) Nuclear ($nuclK_{ATP}$) (Zhuo *et al.*, 2005). The $MitoK_{ATP}$ channels were first identified in liver cell mitochondria by Inoue *et al.* (1991). After that, these subclasses of potassium channels were identified in mitochondria of heart, brain, kidney, musculoskeletal and other human cells, respectively (Bajgar *et al.*, 2001; Cancherini *et al.*, 2003; Debska *et al.*, 2002, 2001).

The cytoprotective effect of $mitoK_{ATP}$ channels in neural and cardiovascular damages has been shown in several studies (Busija *et al.*, 2008; Szewczyk *et al.*, 2009). The cardioprotective effect of $mitoK_{ATP}$ channels in ischemic-hypoxic conditions play an important role against oxidative stress. Activation of these channels in ischemic damages can protect cardiomyocytes against further injuries. In this process, $sarcK_{ATP}$ and $mitoK_{ATP}$ have a dominant role (Liu *et al.*, 1998; Zhuo *et al.*, 2005).

Ordinarily, mitochondrial function decreases at the beginning of the cellular energy crisis. This is due to mitochondrial internal membrane potential disturbances and trans-membrane ion transport imbalance which may lead to free radicals overproduction (Zhuo *et al.*, 2005). In this condition, $mitoK_{ATP}$ channels are activated and help the cell to

regulate membrane potential, intracellular Ca^{+2} concentration and ATP production, as well as reduction of free radical concentration (Xu *et al*., 2001).

Akao *et al*. (2001) showed the role of mitoK_{ATP} channels against cell death in oxidative stress. They emphasized mitoK_{ATP} channels have an important function in preserving mitochondrial integrity. Ardehali *et al*. (2005) showed that mitochondrial ATP-binding cassette protein 1 (mABC1) has a beneficial effect on cell protection against oxidative stress by activation of mitoK_{ATP}.

It seems, K_{ATP} channels have an important activity in ischemic preconditioning (IPC). With knockout of sarcK_{ATP} genes, myocardial damage was increased in ischemic condition (Suzuki *et al*., 2002). Preconditioning phenomenon was first described by Murry *et al*. (1986). In this phenomenon, after short term ischemia-hypoxia episodes, myocardial cells prepare to deal with prolonged ischemia attacks. The IPC leads to a decrease in the size of infarction and reduces the risk of arrhythmias (Cohen *et al*., 2000; Kloner, 1998; Murry *et al*., 1986). Increased ROS concentration is a trigger to open the K_{ATP} channels in IPC. In other words, when the ROS concentration is rising, K_{ATP} channels will be opened to reduce the ROS amounts and their harmful effects (Zhang *et al*., 2001).

There are three hypotheses regarding cardioprotective effects of the K_{ATP} channels: (1) Decrease in the mitochondrial Ca^{+2}uptake, (2) Swelling of the mitochondrial matrix and increase in ATP synthesis and (3) Decrease in ROS levels (Ardehali *et al*., 2005). These three hypotheses are shown in Fig. 2. Diazoxide and pinacidil effects on decreasing mitochondrial Ca^{2+} uptake is due to activation of mitoK_{ATP} channels. These effects are reversible by a channel blocker such as 5-HD (Holmuhamedov *et al*., 1999). Murata *et al*. (2001) showed reduction of mitochondrial calcium overload is a consequence of partial mitochondrial membrane depolarization by mitoK_{ATP} channels. They presented this process is a significant mechanism of cardioprotective effect of mitoK_{ATP} channels. Opening of mitoK_{ATP} channels leads to mitochondrial matrix swelling and this process results in electron transport chain activation and generating more ATP, which helps myocardial recovery (Grover and Garlid, 2000; Halestrap, 1989; O'Rourke, 2000). In other words, mitochondrial matrix expansion results in improving fatty acid oxidation, cellular respiration and ATP production. Increased ATP production following mitoK_{ATP} channel activation was shown in the other studies (Kowaltowski *et al*., 2001).

Reactive oxygen species production has increased in the early IPC period and leads to mitoK_{ATP} channel activation. Opening of mitoK_{ATP} channels has an important role in the reduction of ROS concentration in both early and delayed phases of IPC and it results in preventing further myocardial damages (Forbes *et al*., 2001; O'Rourke, 2004; Ozcan *et al*., 2002; Hoek *et al*., 1998). Likewise, it can be noted that opening of mitoK_{ATP} channels has an important task in decreasing oxidative stress damages. This process is complementary for mild uncoupling to reduce mitochondrial ROS concentration (Skulachev, 1996). Heinen *et al*. (2007) and Kulawiak *et al*. (2008) confirmed that opening of mitoK_{ATP} channels in oxidative stress leads to reduction of ROS concentration.

The effect of thyroid hormones on potassium channels has been studied previously. These channels can be more activated in the presence of thyroid hormones. Sakaguchi *et al*. (1996) considered the effects of T_3 on cardiac electrophysiology in guinea pig. They found that inward rectifier potassium channels become more active with T_3 administration. In addition, thyroid hormones have a regulatory effect on mRNA expression of potassium channels. Abe *et al*. (1998) indicated this effect of thyroid hormones on cardiomyocytes of rat in 1998 and Nishiyam *et al*. (1998) confirmed the regulatory effects of thyroid hormones on potassium channels isolated cardiomyocytes from euthyroid rat and exposed these cells to H_2O_2 and found that with T_3 administration mitoK_{ATP} channels were becoming more active and the effect of H_2O_2 as a free radical was decreased on

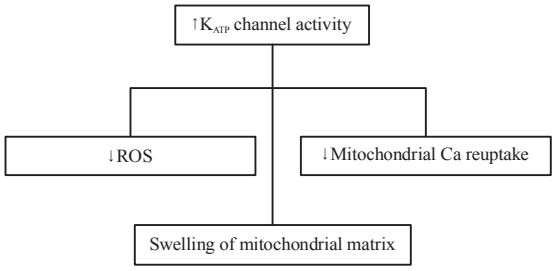

Fig. 2: Three hypotheses for cytoprotective efffects of K_{ATP} channels

Table 3: Cytoprotective effects of thyroid hormones via increased activity of mitoK$_{ATP}$ channels

Study	Year of publication	Model	Extracted data
Busija *et al.* (2008)	2008	Review article	Cytoprotective effects of mitoK$_{ATP}$
Szewczyk *et al.* (2009)	2009	Critical review	
Liu *et al.* (1998)	1998	*In vitro*	Cardioprotective effects of mitoK$_{ATP}$ in ischemic damage
Holmuhamedov *et al.* (1999)	1999	*In vitro*	
Zhuo *et al.* (2005)	2005	Review article	
Xu *et al.* (2001)	2001	*In vitro*	Cytoprotective mechanisms of mitoK$_{ATP}$
Murata *et al.* (2001)	2001	*In vitro*	
Akao *et al.* (2001)	2001	*In vitro*	↑mitoK$_{ATP}$ activity → ↑mitochondrial integrity → ↓ apoptosis
Ardehali *et al.* (2005)	2005	*In vitro*	mABC1 → ↑ mitoK$_{ATP}$ activity → ↓ oxidative stress
Zhang *et al.* (2001)	2001	*In vitro*	↑ mitoK$_{ATP}$ activity → ↓ROS
Heinen *et al.* (2007)	2007	*In vitro*	
Kulawiak *et al.* (2008)	2008	*In vitro*	
Ardehali (2004)	2004	Review article	3 hypotheses for cardioprotective effect of K$_{ATP}$ channel
Halestrap (1989)	1989	*In vitro/in vivo*	↑ mitoK$_{ATP}$activity → matrix swelling → ↑ATP generation
Grover and Garlid (2000)	2000	Review article	
O'Rourke (2000)	2000	Review article	
Kowaltowski *et al.* (2001)	2001	*In vitro*	
Hoek *et al.* (1998)	1998	*In vitro*	↑ mitoK$_{ATP}$ activity → ↓ROS → ↓myocardial damages
Forbes *et al.* (2001)	2001	*In vitro/in vivo*	
Ozcan *et al.* (2002)	2002	*In vitro*	
O'Rourke (2004)	2004	Review article	
Sakaguchi *et al.* (1996)	1996	*In vitro*	T_3→ ↑K$_{ATP}$ channels activity
Forini *et al.* (2011)	2011	Animal study	T_3→ ↑ mitoK$_{ATP}$ activity
Abe *et al.* (1998)	1998	Animal study	THs → ↑K$_{ATP}$ channels mRNA expression
Nishiyama *et al.* (1998)	1998	Animal study	
Forini *et al.* (2014)	2014	Animal study	T_3→↓mitochondrial damages in ischemic condition
De Castro *et al.* (2014)	2014	Animal study	THs → ↓ROS
Forini *et al.* (2015)	2015	Animal study	T_3 → ↓ oxidative stress

MitoK$_{ATP}$: Mitochondrial ATP-sensitive potassium channel, mABC1: Mitochondrial ATP-binding cassette protein 1, ROS: Reactive oxygen species, K $_{ATP}$ channel: ATP-sensitive potassium channel, ATP: Adenosine triphosphate, T_3: Triiodothyronine, TH: Thyroid hormone

cardiomyocyte (Forini *et al.*, 2011). In the other study, Forini *et al.* (2014) considered the cardioprotective effects of T_3 in ischemic condition. They showed T_3 treatment can prevent further mitochondrial disturbance and damage in ischemic cases. Forini *et al.* (2015) thoroughly described T_3 cardioprotective effects, particularly on the oxidative stress condition in a review article. De Castro *et al.*, (2014) showed the effects of thyroid hormones on reduction of ROS concentration and also control of oxidative stress in infected rat myocardium. Summary of studies related to the antioxidant effects of mitoK$_{ATP}$ channels and thyroid hormones is shown in Table 3.

Increased activity and expression of antioxidant enzymes: One of the important mechanisms for reducing the amounts of free radicals is increased activity and expression of the enzymes catalyzing free radicals to low risk or harmless products. Superoxide dismutase (SOD), catalase and glutathione peroxidase are the most important antioxidant enzymes which catalyze free radicals.

Superoxide dismutase (SOD): Superoxide dismutase enzymes are a group of enzymes catalyzing the dismutation reaction of superoxide (O_2^-) to oxygen or hydrogen peroxide (H_2O_2). Superoxide anion (O_2^-) is a byproduct of oxygen metabolism. If the effects of superoxide are not controlled, it can be harmful to cells. For this reason, superoxide dismutase enzymes have an important cytoprotective activity against harmful effects of superoxide. Large amounts of hydrogen peroxide are harmful to cells, but these harmful effects are much less than superoxide effects and hydrogen peroxide is immediately degraded by some enzymes such as catalase.

The SOD has a critical activity in living cells exposed to oxygen. Dismutation reactions by SOD are described below:

$$SOD+O_2\text{-}\rightarrow SOD+O_2$$
$$SOD+O_2\text{-}+2H^+\rightarrow SOD+H_2O_2$$

Enzymatic activity of SOD was first identified by McCord and Fridovich (1968). Before that time, SODs had known as metalloproteins with unknown function. SOD enzymes have a polypeptide structure that in their active sites has metals such as copper, zinc, manganese, iron or nickel as a co-factor. They are classified according to their metal and protein fold: (1) Copper and zinc type (Cu/Zn type), which binds both copper and zinc, (2) Iron or manganese type (Fe or Mn type), which binds either iron or manganese and (3) Nickel type (Ni type), which binds nickel. All of them are exist in the human cells. In oxidative stress condition, the activity and concentration of SODs increases and they play their antioxidant activity by reducing superoxide concentration.

Catalase: Catalase is one of the important enzymes in all living cells exposed to oxygen. Catalase acts as a cytoprotective agent against ROS in oxidative stress condition. This enzyme catalyzes oxygen peroxide to oxygen and water:

$$2H_2O_2\rightarrow 2H_2O+O_2$$

Catalase is a tetramer with 4 polypeptide chains that each one has 500 aminoacids. The H_2O_2 is a byproduct of oxygen metabolism, which can be harmful to cells in oxidative stress condition. For this reason, it should be rapidly converted to harmless products.

Glutathione peroxidase (GPx): Glutathione peroxidase is a general name for an enzyme group having peroxidase activity. They protect cells from oxidative damages. There are 8 known isoenzymes for GPx named GPx-1-GPx-8. GPx catalyzes the hydrogen peroxide to harmless products in this reaction:

$$2GSH+H_2O_2\rightarrow GS\text{-}SG+2H_2O.$$

If GPx activity is decreased, hydrogen peroxide concentration will be raised and results in lipid and hydrogen peroxidation (Arthur, 2000; Meyer *et al*., 1994; Yu and Chung, 2006).

It appears that thyroid hormones can increase expression and activity of antioxidant enzymes. Das and Chainy (2001) studied T_3 effects on oxidative stress parameters in mitochondria of rat liver cells and found H_2O_2 concentration which had risen in hypothyroid state, returned to normal value after T_3 administration. They also showed catalase activity was reduced in hypothyroidism, but it was increased and returned to normal value after T_3 treatment. In another study on adult rat brain, it was shown antioxidant enzyme activity is influenced by thyroid state. In this way, they indicated antioxidant activities in mitochondria are under the thyroid hormones control and regulation of antioxidant activities and ROS balance are dependent on the normal thyroid function (Das and Chainy, 2004). Choudhury *et al*. (2003) showed T_3 administration to PTU-treated rats (hypothyroid rat) resulted in a rise in the level of catalase activity. In a research study on a normal (euthyroid) fish Anabas testudineus, short term effect of T_3 on the enzymes catalyzing ROS was tested. They showed 30 min after T_3 injection at a dose of 200 ng in euthyroid fish, lipid peroxidation products such as malondealdehyde were decreased. Triiodothyronine *in vitro* with concentration of 10^{-6} M could increase catalase, glutathione peroxidase and glutathione reductase activities as well as glutathione level. They suggest short term administration of T_3 has a rapid regulatory effect on the removal of ROS (Sreejith and Oommen, 2006). In a human study done by Naazeri *et al*. (2014) increased catalase and SOD activities were considered in hyperthyroid state, however, they believe this increased enzyme activity is in response to increased ROS due to hyperthyroid state. Summary of studies related to antioxidant enzymes and thyroid hormones is shown in Table 4.

Table 4: Effects of thyroid hormones on antioxidant enzymes

Study	Year of publication	Model	Extracted data
Das and Chainy (2001)	2001	Animal study	$T_3 \rightarrow \uparrow$catalase activity in hypothyroidism
Choudhury *et al.* (2003)	2003	Animal study	
Das and Chainy (2004)	2004	Animal study	Antioxidant enzymes activity of adult rat brain are influenced by thyroid states
Sreejith and Oommen (2006)	2006	*In vivo*	$T_3 \rightarrow \uparrow$SOD, catalase and GTx activity
		In vivo	$T_3 \rightarrow \uparrow$ catalase, Gtx and GR

T_3: Triiodothyronine, ROS: Reactive oxygen species, SOD: Superoxide dismutase, GTx: Glutathione peroxidase, GR: Glutathione reductase

DISCUSSION

As a result of our study, there are numerous studies addressing antioxidant effects of thyroid hormones and underling mechanisms. Thyroid hormones can have a major role in oxidative stress condition as an antioxidant and cytoprotective agent. It appears cytoprotective effects of thyroid hormones are not only in hypothyroid state, but in euthyroid cases (Sreejith and Oommen, 2006). In euthyroid oxidative stress condition, we may have a tissue hypothyroidism worsening the condition and the positive effects of thyroid hormone administration in this situation are due to improving the tissue hypothyroidism and reduction of ROS concentration. The inhibitory effects of thyroid hormones on mitochondrial oxidative stress are through three mechanisms showed and summarized in Fig. 3.

Uncoupling proteins: One of the significant defense factors of cell to counteract mitochondrial free radicals is uncoupling protein's activity (Arsenijevic *et al.*, 2000; Dulloo and Samec, 2001; Negre-Salvayre *et al.*, 1997; Ramsden *et al.*, 2012; Rousset *et al.*, 2004; Vidal-Puig *et al.*, 2000). As mentioned UCPs transfer protons from mitochondrial intermembrane space to mitochondrial matrix and by this way UCPs can reduce free radicals concentration, when ROS are overloaded during pathological conditions (Nedergaard *et al.*, 2005; Ricquier and Bouillaud, 2000). Thyroid hormones have a critical role in controlling UCPs function and mild uncoupling process (Skulachev, 1996, 1998, Starkov, 1997). In mild uncoupling the activity of UCPs is promoted to decrease ROS concentration, but ATP generation is not disturbed. In other words, the balance between uncoupling process and ATP generation, carried out by thyroid hormones to restore normal cellular function. There are some questions regarding this situation that may guide to further researches: Is there any tissue or cellular hypothyroidism in critical cellular conditions? Do cells need more thyroid hormone to restore their function in critical condition? If there is a cellular hypothyroidism, is it due to decreased thyroid hormones or decreased tissue response to thyroid hormones?

MitoK_{ATP} channels: Potassium ATP sensitive channels are a class of ion channels having a critical role in cellular function. Increased mitoK_{ATP} channel activity during pathological conditions can lead to decreased mitochondrial calcium overload and ROS concentration. In this way cellular apoptosis and oxidative stress may be decreased. On the other side opening of mitoK_{ATP} channels result in swelling of mitochondrial matrix and increases ATP generation (Ardehali, 2004; Kowaltowski *et al.*, 2001; Murata *et al.*, 2001; Xu *et al.*,2001). So, mitoK_{ATP} channel activity has a fundamental role in restoring mitochondrial function during pathological processes (Ardehali, 2004; Szewczyk *et al.*, 2009). Numerous studies showed mitoK_{ATP} channel activity is under the control of thyroid hormones (Abe *et al.*, 1998; Forini *et al.*, 2011; Nishiyama *et al.*, 1998; Sakaguchi *et al.*, 1996). Undoubtedly, the function of these channels is disturbed in hypothyroidism, but ambiguity in this regard, is what was discussed in relation to the uncoupling proteins and cellular hypothyroidism. Evaluation of mitoK_{ATP} channels functions in different pathologic conditions and the role of thyroid hormones in these conditions are issues requiring further studies.

Antioxidant enzymes: The effect of thyroid hormones on antioxidant enzymes is a controversial topic. The activity of catalase is obviously increased by thyroid hormones in both hypothyroidism and euthyroidism (Choudhury *et al.*, 2003; Das and Chainy, 2001, 2004; Sreejith and Oommen, 2006). The SOD activity was raised after T_3 administration in some studies (Sreejith and Oommen, 2006); however, it was decreased in some other studies after T_3 administration (Abdolghaffari *et al.*,2015). In other words, the effect of thyroid hormones on SOD activity in oxidative stress needs to be more studied in further studies. In relation to GTx the issue is similar to SOD.

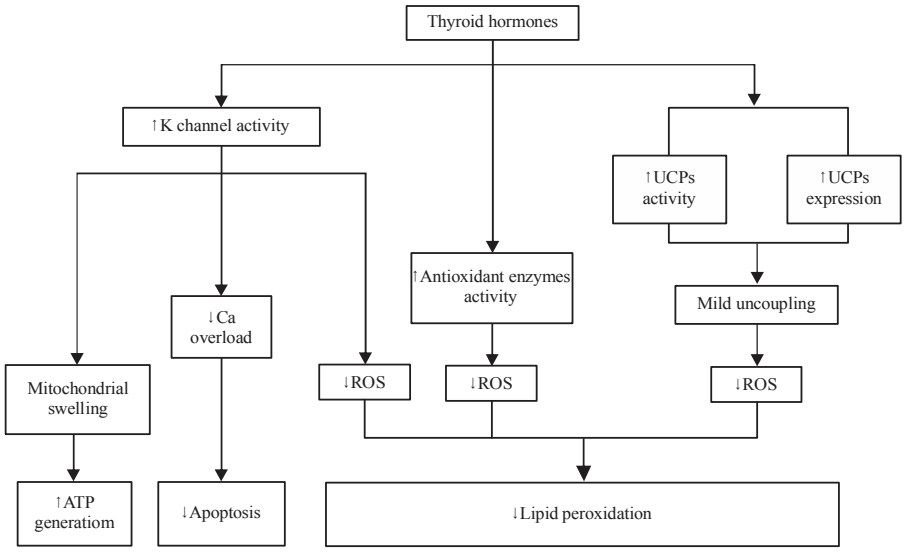

Fig. 3: Antioxidant effects of thyroid hormones

CONCLUSION

All these considerations, let us to place great emphasis on the thyroid hormone effects of oxidative stress, however, there are some questions in this regard which should be answered and need further studies for investigation. For instance, we certainly believe that thyroid hormone by having such effects can be helpful in reducing cardiotoxicity of compounds that act through oxidative stress such as phosphides in the human level. It can also conclude that by use of in-silico phannaco-toxicology system, there will be possible to develop medicines better than thyroid hormones for other oxidative stress diseases. Without a doubt, the role of thyroid hormones in cell biology and body physiology is very important and this role should be further studied during pathological state such as oxidative stress especially in ICU patients.

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