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Role of Thyroid Hormones in Insulin Resistance and Diabetes

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Abstract: Several recent studies suggest that thyroid hormones role is not completely understood in insulin resistance as well as in the development of type 2 diabetes mellitus. Through the perturbation of gene expression linked to glucose metabolism both hyper- and hypothyroidism may cause impaired glucose utilization in skeletal muscle or overproduction of hepatic glucose, thus contributing to the induction of insulin resistance. The complex crosstalk between immune cells and skeletal muscle cells and adipose tissue, the ability of macrophages to release thyroid hormones, the ability of T_3 to induce M2 macrophage polarization, the proinflammatory role of thyroid hormones and the antinflammatory effects of insulin all represent important events where thyroid hormone interference may lead to insulin resistance. The crosstalk between thyroid hormones and insulin in the modulation of oxidative status, and also to some extent in the antagonistic effects on several aspects of mitochondrial activities, could represent novel downstream targets for future therapeutic strategies in the treatment of insulin resistance and type 2 diabetes.

Keywords: Diabetes, hormone crosstalk, hyperthyroidism, hypothyroidism, inflammation, insulin resistance, oxidative stress, thyroid hormones.

INTRODUCTION

The two thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), are synthesized by the thyroid gland and are potent modulators of metabolism, growth and development [1]. They stimulate various physiological activities essential for the development and maintenance of tissues and organs such as the heart, skeletal muscle, brain and bones; generally thyroid hormones increase both metabolic rates and oxygen consumption and thus the rate of ATP turnover. The major form of thyroid hormone secreted from thyroid gland is T_4 whereas T_3 is produced mainly in target tissues by deiodination of T_4, but it is T_3 that elicits most actions of thyroid hormones [2]. T_3 is a pleiotropic hormone able to stimulate many essential aspects of carbohydrate metabolism, including (i) enhancement of insulin-dependent entry of glucose into cells; (ii) increased gluconeogenesis and glycogenolysis; (iii) increased thermogenesis and metabolism; and (iv) stimulation of the heart rate contributing to the regulation of systemic vascular resistance [3-5]. But T_3 is also involved in several disorders including cardiovascular diseases, chronic liver disease and diabetes [6-8]. Most biological effects of T_3 are mediated by hormone binding to the specific nuclear Thyroid Receptor (TR) proteins TRα and TRβ, which are hormone-activated transcription factors that act by modulating the expression of a large number of target genes that display thyroid hormone response elements [9-11]. TR proteins are encoded by two genes; *Thyroid Hormone Receptor Alpha* (*THRA*) located on chromosome 17 supplies TRα1 together with two isoforms unable to bind T_3 (TRα2 and TRα3), whereas *Thyroid Hormone Receptor Beta* (*THRB*) located on chromosome 3 is responsible for expression of the three active β-isoforms TRβ1, TRβ2 and TRβ3. None of these nuclear receptors bind T_4. The physiological responses produced *via* TRs are known as genomic effects, and like all hormone responses coupled to protein synthesis it takes a long time for the effects to manifest, typically more than one hour. However, it is well known that thyroid hormones also can act through extranuclear or nongenomic mechanisms; in this context the biological response can be very fast (seconds or minutes). Both T_3 and T_4 are able to bind to specific receptor sites located on the external part of the αvβ3 integrin present in the plasma membrane of target cells [12]. Through mechanisms still partially unknown, the nongenomic actions of thyroid hormones rapidly activate transduction pathways involving cytoplasmic kinases such as Mitogen-Activated Protein Kinase (MAPK) or Phosphatidylinositol 3-Kinase (PI3K) [13-16]; these early factors can modulate various downstream responses, and may actually end up triggering nuclear effects such as gene transcription and cell proliferation [17, 18]. Nongenomic effects of thyroid hormones have been observed in nerve cells, where the hormones can modulate the activity of several receptor channels for the major

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neurotransmitters; in heart tissue thyroid hormones increase the activity of sarcoplasmic reticulum Ca^{2+}-ATPase, Na^{+},K^{+}-ATPase and some voltage-gated potassium channels (K_v1.5, K_v4.2, K_v4.3), while a negative effect is seen for Na^{+}/Ca^{2+} exchanger, Ca^{2+}-channels and other K^{+}-channels (K_v1.2, K_v1.4) [12]. In immune system cells thyroid hormones non-genomically stimulate various biological responses, including a potentiation of the effects of lipopolysaccharide or cytokines such as interferon-γ, as well as the induction of Signal Transducer and Activator of Transcription proteins STAT-1 and STAT-3, leading to activation of the mammalian Target Of Rapamycin (mTOR) pathway [19]. Recently several authors have reported an enigmatic and apparently widespread crosstalk between thyroid hormones and insulin, the latter representing the most important hypoglycemic hormone [20-22]. Insulin interacts with target cells through binding to the transmembrane insulin receptor in the plasma membrane; this receptor contains two extracellular α-subunits able to bind the hormone and two transmembrane β-subunits with intracellular tyrosine kinase activity. After the insulin binding to α-subunits, the auto-phosphorylation of the β-subunits determines receptor activation, that in turn activates by phosphorylation the downstream insulin receptor substrate (IRS) proteins, which through activation of PI3K can stimulate the MAPK pathway involved in cell differentiation, proliferation and cell death. Alternatively PI3K may activate Akt signaling implicated in cell growth and protein synthesis, and also in phosphorylation of Glycogen Synthase Kinase-3β with subsequent increase in glycogen synthesis and glucose uptake [23, 24]. In insulin resistance in type 2 diabetes mellitus, which is associated with several complications such as nephropathy, retinopathy, neuropathy and increased cardiovascular risk, the ability of insulin to promote its normal signaling is markedly decreased, but the mechanisms leading to perturbation of signal transduction are not clear [25]. However, among the different factors involved in insulin resistance, key roles are played by lipid accumulation, oxidative stress and inflammation [26-28]. Taken together these processes determine the activation of stress-sensitive kinases including Protein Kinase Cθ, the Inhibitor of Nuclear Factor κB subunits (IKKβ) and c-Jun N-terminal Kinase 1, which in turn can inhibit insulin signaling [29, 30].

THYROID DISEASES AND TYPE 2 DIABETES

In diabetes elevated blood glucose levels are positively coupled with a higher prevalence of thyroid disorders. Several studies indicate the development of thyroid disorders in type 2 diabetic patients, with hypothyroidism being the most common disorder; however, both hyperthyroidism and hypothyroidism have been found to be associated with the presence of carbohydrate metabolism disorders [4, 20]. The high plasmatic levels of thyroid hormones found in hyperthyroidism cause an enhancement of metabolic rates, with a subsequent increase in insulin production in order to favor glucose uptake, but these conditions are also positively coupled to increased insulin degradation and insulin resistance [31]. In liver thyroid hormones stimulate the endogenous production of glucose through the increase in gluconeogenesis and glycogenolysis, that in turn seems responsible for the decrease of liver sensitivity to insulin [32]. In the liver the ability of thyroid hormones to induce or decrease gene expression linked to gluconeogenesis and glycogenolysis, and to stimulate the expression of the GLUT-2 glucose transporter, are considered direct effects, whereas TH-dependent enhancement activity of hypothalamic and parasympatic nervous system effects on liver usually are classified as indirect effects [20, 33]. Direct effects of thyroid hormones on glucose homeostasis are also reported for peripheral tissue such as muscle and fat tissue, where the hormones can stimulate the expression of GLUT-1 and GLUT-4, β2-adrenergic receptor, Phosphoglycerate Kinase, Hypoxia-Inducible Factor-1, Peroxisome Proliferate Activated Receptor gamma (PPAR-γ) Coactivator-1-α and Uncoupling Protein 3 [20].

Hyperthyroidism reduces the insulin-secretory capacity of pancreatic β cells, whereas hypothyroidism can modify carbohydrate metabolism and thus stimulate the development of glucose intolerance and type 2 diabetes mellitus [34-36]. These effects are probably important since they can interfere with β cell sensitivity to glucose, the initial event of glucose-stimulated insulin secretion [37]. For this function it is necessary for β cells to maintain a normal expression of GLUT2 and glucokinase levels, and T_3 can modulate both GLUT2 and glucokinase expression in the pancreatic islets [38].

Hyperthyroidism also appears to be linked to increased glucose uptake in skeletal muscle where, as a consequence of muscle insulin resistance, glucose is processed mainly by glycolysis that generates lactic acid which is released in circulation and returns to the liver determining an increase of hepatic glucose production [32]. In addition peripheral insulin resistance can be due to hyperthyroidism-induced proinflammatory mediator secretion (IL-6, TNFα and several other adipokines) by adipocytes [39, 40]. Also hypothyroidism can be considered a risk factor for insulin resistance; at low thyroid hormone levels a decrease in intestinal glucose uptake and adrenergic activity has been reported, as well as a reduction of liver and muscle gluconeogenesis and glycogenolysis and of insulin secretion [32]. Thyroid hormones can also interfere with insulin pancreatic secretion: it has been reported that, in hypothyroidism, glucose-induced insulin secretion in β-cells is reduced, whereas in hyperthyroidism β-cells response to glucose is increased [36]. Neonatal hypothyroidism is positively coupled to an increased mass of β-cells as well as to development of glucose intolerance [41]. Moreover, neonatal β-cells showing thyroid hormone receptors are insensitive to glucose-induced insulin secretion; their exposure to thyroid hormone determines the activation of the transcription factor MAFA that stimulates β-cells maturation and insulin secretion, suggesting that thyroid hormone may be considered a physiological regulator of β-cells functions [42]. However, the effects of thyroid hormone on pancreatic β cells have so far been little investigated. It is known that T_3 increases proinsulin mRNA expression through a mechanism which depends on the stimulation of PI3K and the inactivation of Glycogen Synthase Kinase-3β, that in turn is responsible for the increase in Pancreatic and Duodenal Homeobox-1 (PDX-1), the most important transcriptional factor for proinsulin gene expression [43]. T_3 stimulates pancreatic ductal cells that are considered β cells precursors toward the progression into mature β cells, and T_3 can also act as a mitogenic, pro-survival factor for pancreatic β cells through a mechanism that seems to involve MAPK/ERK activation,

suggesting that the hormone can be considered an important factor to define new strategies to counteract diabetes [44].

The relationship between thyroid hormones and insulin resistance has also been reported through the analysis of T_3/rT_3 (reverse T_3) ratio, an important marker of peripheral T_3 metabolism which is significantly increased in insulin resistance [45]. A considerable increase in thyroid hormones levels, even if within the normal range, is positively associated with both insulin resistance and the early events of the development of type 2 diabetes [46]. In patients with subclinical hypothyroidism, T_4 treatment induces an improvement of insulin sensitivity and a decrease in plasma glucose levels [47]. Conversely, insulin can interfere with thyroid functionality by promoting mitogenic effects on thyroid cell cultures; such effects seem to play a key role for the increase in thyroid volume and thyroid nodule formation [48]. Moreover, Insulin-like Growth Factor Binding Protein-3 can interfere with the TRα1 and inhibit T_3 responsive gene transcription [49].

The crosstalk between thyroid hormones and insulin during insulin resistance has also been found for other tissues. Adipose tissue can modulate insulin sensitivity of skeletal muscle by the release of factors such as adipokines, but at same time also the muscle can affect adipose tissue by the production of several myokines, and interestingly both hypothyroidism and hyperthyroidism can interfere with the normal adipocyte-myocyte crosstalk thus contributing to the insulin resistance [40]. Changes in the concentrations of thyroid hormones observed in obese and/or diabetic patients may in part be explained by an imbalance in the normal crosstalk between adipose tissue and thyroid function, which in this way contributes to insulin resistance [50]. Recently, Lin and Sun [51] have shown for 3T3-L1 adipocytes that T_3 is essential to increase insulin-stimulated translocation of GLUT4, as well as to the glucose uptake through a signaling mechanism that includes Akt phosphorylation and the translocation to the plasma membrane of Vesicle-Associated Membrane Protein 2 (VAMP2).

In skeletal muscle cells such as L-6 myoblast thyroid hormones can genomically stimulate the expression of glucose transporters and promote an increase of glucose uptake; however, T_3 can also act by a non-genomic mechanism since it is able to induce after short time (30 min) an increase in insulin-dependent GLUT4-mediated glucose uptake, without interfering with other transporters such as GLUT1 and GLUT3 [52]. Recently we have shown that in L6 myoblasts T_4 can inhibit the Insulin Growth Factor-1 (IGF-1)-induced glucose uptake and proliferation by the involvement of αvβ3 integrin, through interference with downstream effectors such as PIK-kinase and ERK1/2 kinases [53]. Interestingly, it has been reported that in thyroidectomized rats treated with T_3 (0.3 to 100 μg/100 g body weight) the hormone rapidly (within 30 min) increases GLUT4 mRNA and protein expression and restores GLUT4 trafficking to the plasma membrane. These findings suggest that T_3 exerts a rapid post-transcriptional effects on GLUT4, an effect that is essential to the induction of T_3-induced insulin glucose uptake [54]. In skeletal muscle Akt and Rho GTPase Rac1 can be considered important regulators of insulin-stimulated glucose uptake, both of them being downregulated in insulin resistance [55]. Gordon *et al.* [56] have shown that in L-6 muscle cells T_3 stimulates glucose uptake through a nongenomic mechanism that includes the phosphorylation of the insulin receptor β and PI3K activation in a manner similar to that caused by insulin. The ability of T_3 to induce glucose uptake has also been reported in chick embryo heart cells and rat thymocytes, and in all these cases the hormone increases the V_{max} of glucose transport without interfering with the K_d through a mechanism independent of newly synthesized proteins [57,58]. In muscle tissue insulin resistance involves the accumulation of triglycerides, diacylglycerols and ceramides within skeletal muscle fibers; these lipids and lipid metabolites can stimulates serine kinases that impair insulin signaling and generate skeletal muscle insulin-resistance [59]. Several authors have shown that the cell membrane-permeant ceramide analog C2-ceramide inhibits Akt activation and GLUT4 translocation in response to insulin without affecting upstream effectors such as IRS-1 and PI3K, suggesting that ceramide could cause insulin resistance through altering intracellular GLUT4 sorting [60]. But also contradictory data have been observed for ceramide, which in fact has been reported to stimulate glucose uptake under some conditions (S. Incerpi, unpublished data).

THYROID HORMONES AND INSULIN RESISTANCE: ROLE OF THE IMMUNE RESPONSE

In obese mice the infiltration of macrophages into the adipose tissue, and the subsequent release of proinflammatory cytokines such as Tumor Necrosis Factor α (TNFα), Interleukin 1-β (IL-1β) and IL-6, is directly associated with insulin resistance, suggesting that the activity of such cells of the innate immune system have a significant role [61]. Chemokines released from adipose tissue in obese animals can activate monocytes and stimulate the release of proinflammatory adipokines [62]. The physiological crosstalk between skeletal muscle and immune cells is very important for muscle performance, since immune cells through the phagocytosis of microbes and antigens and the release of cytokines and other specific growth factors contribute to muscle repair after injury [63]. In this context the phenotypic modification of macrophages, that can shift from classic activated M1 or proinflammatory macrophages able to produce inducible Nitric Oxide Synthase (iNOS), TNFα, IL1β and IL6 to alternative activated macrophages, also called M2, usually antinflammatory cells, represent a central point in muscle regeneration [64]. Interestingly an increased number of M1 macrophages in several muscle diseases (myopathies) has been reported also in case of skeletal muscle insulin resistance [65-67]. It is now widely accepted that thyroid hormones act as modulators of the immune response: immune functions, such as chemotaxis, phagocytosis, generation of Reactive Oxygen Species (ROS), and cytokine synthesis and release, are altered in hypo- and hyper-thyroid conditions, even though for many immune cells no clear correlation has been found between altered levels of T_3 or T_4 and effects on the immune responses. Thyroid hormones can induce important responses related to the immune function, such as ROS production and cell migration in THP-1 monocytes, in the short time range characteristic for nongenomic actions [68]. In hypothyroidism, the proinflammatory response of macrophages is stimulated, whereas in hyperthyroidism it is de-

creased. In particular, in hyperthyroid rats the phagocytic activity and hydrogen peroxide release by macrophages are inhibited, whereas in hypothyroidism phagocytosis and ROS levels are enhanced [68]. Immune cells such as lymphocytes, monocytes granulocytes and mast cells produce and release T_3, and interestingly the hormone concentration in such cells can be regulated through thyroid hormones [69], and measurements have shown that the TSH-dependent T_3 content in immune cells can be very considerable during physiological as well as pathophysiological conditions [70]. Recently, Perrotta *et al.* [71] reported that T_3 modulates macrophage maturation and the functions able to promote the differentiation of bone marrow-derived monocytes into unpolarized macrophages and their shift to M1 proinflammatory macrophages. Analogously insulin can modulate several monocyte/macrophage functions, such as inhibition of proinflammatory response, stimulation of the release of antinflammatory molecules, and improved chemotaxis, phagocytosis and killing activities [72]. Taken together these data suggest that insulin can mimic the activity of antinflammatory hormones and counteract the toxic effects of high blood glucose in several immune cells [73]. Several reports have shown that the activated M2 macrophages are required to maintain the physiological insulin sensitivity [74, 75]. In this context it has been observed that deletion of the PPAR-γ gene in mice macrophages determines a strong decrease in M2 macrophages in whole body, and also induces skeletal as well as liver insulin resistance [76]. Ikeda *et al*. [77] demonstrated that exercise enhances insulin sensitivity in skeletal muscle partly through the accumulation of M2 macrophages and their ability to activate GLUT4 trafficking to the plasma membrane in the target cells, suggesting that such antinflammatory cells can be considered positive modulators of physiological insulin sensitivity in skeletal muscle.

THYROID HORMONES AND INSULIN RESISTANCE: ROLE OF OXIDATIVE STRESS

Oxidative stress, an altered balance between the production of free radicals and antioxidant defences, plays a role in many different pathological processes [78], but the link between the oxidative stress and energy crisis, generally considered part of the metabolic syndrome, is common also for conditions such as ageing and obesity [79]. Among the different sources of free radicals, ROS produced through the overactivity of the respiratory redox chain in the mitochondria represents the principal amount of ROS generation in aerobic cells [80]. In physiological conditions the excess of ROS is counteracted by both enzymatic and nonenzymatic antioxidant mechanisms [81]. It has been suggested that in skeletal muscle an excessive mitochondrial release of hydrogen peroxide and superoxide anion as well as the overstimulation of the NADPH oxidase plays an important role in insulin resistance [82]. Recent studies have shown that these major ROS types can stimulate downstream targets such as p38 MAPK, Jun Kinase, GSK-3, IKKβ and other serine kinases which are associated with the inhibition of insulin-dependent glucose transport activity [28]. Since mitochondria are intracellular targets for T_3, the crosstalk between T_3 and mitochondria during the development of diabetic diseases [4, 83] must be taken into consideration. Iwen et al. [84] recently reviewed the connection between thyroid hormones and the metabolic syndrome; they concluded that for all components of the metabolic syndrome there was a major influence of thyroid hormones. It is well known that T_3 may act on mitochondria activities both through indirect (by interaction with nuclear receptors) and direct mechanisms (binding to specific mitochondrial receptors) [85]. Skeletal muscle mitochondria are very responsive to T_3 effects; the hormone stimulates several different genes that are involved in functions such as mRNA transcription and maturation, protein degradation, cellular metabolism, oxidative metabolism and signal transduction [86]. Actually most of these T_3 effects could turn out to be due to its deiodinated derivative 3,5-diiodo-L-thyronine (T_2); in fact it has been found that T_2 formation is responsible for many of the effects of thyroid hormones in mitochondria [87]. T_2 binds directly to a specific site on subunit V_a of cytochrome *c* oxidase (Complex IV) at the inner mitochondrial membrane, so far the only known binding site target of T_2 [88]. In hepatic cells, T_3 upregulates the expression of Nuclear Respiratory Factors 1 and 2, a transcriptional factor involved in mitochondria biogenesis and PPAR-γ Coactivator-1-α, a transcriptional coactivator of NFR-1 [89]. Moreover it has been reported that T_3 modulates mitochondria biogenesis in skeletal muscle through the activation of AMP-activated protein kinase, which is also involved in the influx of fatty acid into mitochondria and in the subsequent β oxidation signaling promotion as well as GLUT4 translocation [90]. T_3 upregulates several uncoupling proteins such as UCP1 that is most expressed in brown adipose tissue, UCP2 (ubiquitously) and UCP3, which is abundantly expressed in skeletal muscle. The expression and activity of UCPs induced by T_3 can be considered very important since the unhindered passage of electrons through the respiratory chain reduces the possibility of ROS generation [86]. Taken together these observations suggest that T_3-induced UCPs systems may be considered among the nonenzymatic antioxidant mechanisms promoted by T_3 [86]. However, in several tissues such as heart, liver, skeletal muscle, hippocampus, cerebellum and medulla, the effects of hyper- or hypothyroidism on the activity or abundance of antioxidant enzymes such as Superoxide Dismutase, Glutathione Peroxidase and Catalase, and on the oxidative status of the cells, are very contradictory, apparently depending very much on hormonal dosage and administration, as well as on the strategy of thyroid gland inhibition. In fact hypothyroidism seems not to modify, reduce or increase oxidative stress, whereas hyperthyroidism in some systems induces oxidative stress, but in other seems to reduce oxidant generation [90]. However, it is possible to propose thyroid hormones as hormones able to induce ROS generation depending on the metabolic status of mitochondria [91]. In type 2 diabetes mellitus patients several studies have shown mitochondria dysfunction and/or a marked decrease in mitochondrial numbers; however it is not very easy to define whether these effects are the cause or consequence of skeletal muscle insulin resistance [92, 93]. Mitochondria also represent a target for insulin, and in skeletal muscle mitochondria the hormone upregulates the expression of several genes including NADH dehydrogenase I, cytocrome *c* oxidase subunits, ATP5G1 subunits of ATP synthase and UCP2. However, the hormone can also decrease protein catabolism as well as increase enzyme activities [94, 95]. Insulin can also act as an antioxidant hormone, being able to

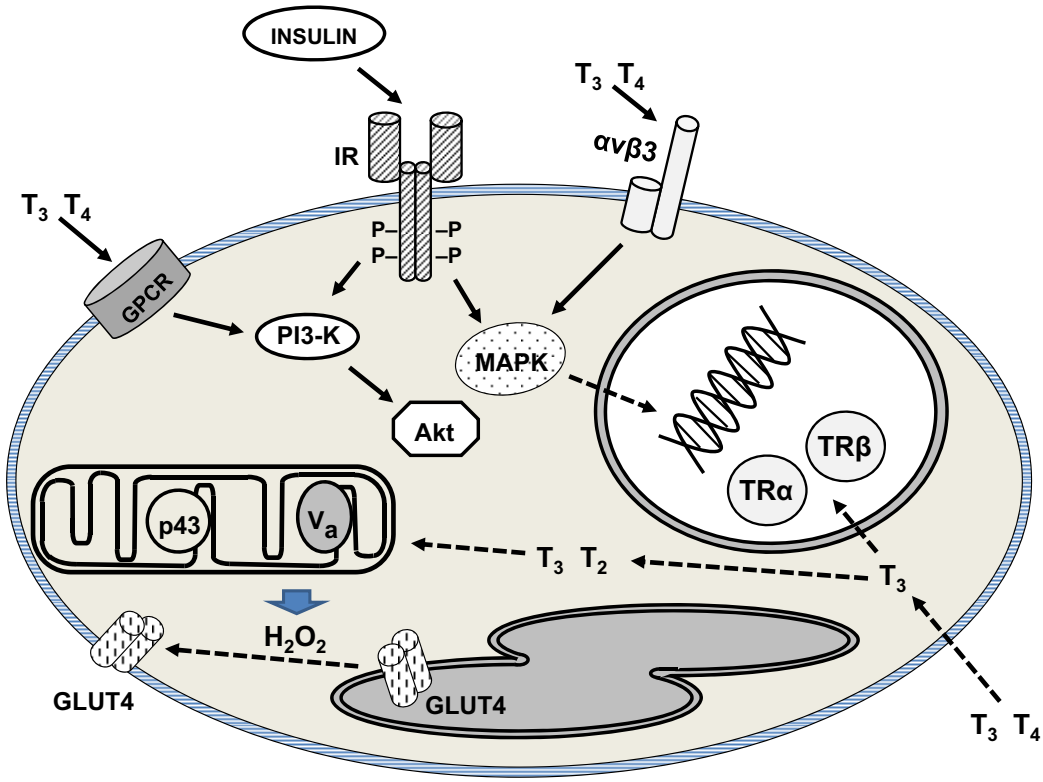

Fig. (1). A schematic representation of the receptors potentially involved in the cross-talk between insulin and thyroid hormones. The situation is particularly complicated for thyroid hormones where several receptors may be involved. T_3 and T_4 can enter cells using amino acid transport systems, but only T_3 binds to the receptors TRα and TRβ; these are normally called nuclear receptors, although they in fact move between cytosol and the nucleus, and binding of T_3 may occur both inside and outside the nucleus (not shown here). Different deiodinases transform T_4 into T_3 and subsequently to T_2 [107], and both T_3 and T_2 have specific binding sites in mitochondria. However, T_3 and T_4 also use receptors located at the plasma membrane: the integrin αvβ3 which activates the MAPK signaling pathway, and a G-protein coupled receptor that activates PI3K and Akt [108]. Interestingly these two pathways are also activated by insulin, suggesting a direct mechanistic link between thyroid hormones and insulin resistance.

promote the scavenging of various types of ROS, in part by the induction of several antioxidant factors such as glutathione, catalase, superoxide dismutase and nitric oxide synthase, which can attenuate the potentially dangerous effects of ROS on DNA, lipid peroxidation and protein modification. Many of these insulin antioxidant effects seem to be linked to the crosstalk between transcriptional factors such as nuclear factor erythroid 2-related factor (Nrf2) and nuclear factor κB (NFκB) that are involved in the transcription of antioxidant enzymes [96]. However, the relationship between insulin and its antioxidative activities is rather complicated also because many effects seem coupled to the concentration levels of the hormone; in fact at high concentration insulin can actually promote oxidative stress [97, 98]. In addition evidence suggests that insulin oxidative and antioxidative effects depend on tissue specificities [96]. At the same time, also the relationship between mitochondrial activities and insulin sensitivity appears influenced by several factors, including the tissue and cell type selected and the targets of mitochondria selected, and in this context it is not yet understood whether mitochondrial defects are the causes or the consequence of insulin peripheral resistance [99]. In fact, the inhibition of oxidative phosphorylation or β-oxidation, and at the same time also the inhibition of complex I or complex IV of the respiratory chain, can elicit opposite responses to insulin sensitivity, depending on the cell type selected [100]. It should be mentioned that also resistance to thyroid hormone by itself is associated with raised energy expenditure and muscle mitochondrial uncoupling [101]. However, the mechanism by which lipid accumulation (in particular triacylglycerol, diacylglycerol and ceramides) coupled to mitochondrial dysfunction can promote insulin resistance seems now better defined; in fact lipid metabolites stimulate several isoforms of Protein Kinase C, Jun kinase and/or IKKβ, that in turn can interfere with insulin-induced IRS-1 phosphorylation and the subsequent activation of downstream effectors such as PI3K and GLUT4 [102, 103]. Thyroid hormones stimulated fatty acid oxidation (FAO) in a variety of tissues in a receptor-dependent, but transcriptional-independent manner. Recently the details of the molecular mechanisms behind thyroid hormone effects on specific mitochondrial-targeted FAO pathways have been reviewed by Sayre and Lechleiter [104]. It has long been known that a shortened mitochondrial isoform of thyroid hormone receptor TRα known as p43 is located in the mitochondria, but not in the nucleus. Apparently thyroid hormone signaling to regulate mitochondrial fatty acid metabolism depends on both full-length and shortened–length receptors, but also in this case the details are still missing. Mice on a high fat diet do not become insulin resistant if the lack the TRα receptor [105], but it is not yet known whether the p43 receptor form is involved in this effect. Finally, it should be

remembered that the connection between insulin resistance and mitochondria is not well understood at all; a very recent study reported that increased mitochondrial efficiency actually preceded the development of high-fat-induced insulin resistance in skeletal muscle cells, in contrast to what has been generally assumed [106].

CONCLUSIONS

In this review we have summarized recent reports concerning the relationship between of thyroid hormones, hypo- and hypothyroidism, and insulin resistance. Taken together these observations suggest a strong association between thyroid hormone-induced effects on glucose metabolism, immune cells functions, and the oxidative status in the development of insulin resistance and diabetes. Thyroid hormones have a large impact on glucose metabolism and can act as insulin agonist or antagonist, depending on the tissues and cells studied; this suggests the existence of one or more complex signaling pathways shared by insulin and thyroid hormones (Fig. **1**). The relationship between thyroid hormones and insulin appears very complex with respect to the role of immune system cells, and also for the importance of oxidative stress in the induction of insulin resistance. The ability of thyroid hormones to modulate several macrophage activities can be considered an important target in order to define a new strategy to modulate the crosstalk between thyroid hormones and skeletal muscle during insulin resistance. In this context the activation of several antinflammatory mechanisms [72] represents another step where thyroid hormones and insulin seem to interact, but neither the mechanisms involved nor their specific function to counteract peripheral insulin resistance are well understood. However, the thyroid hormone-induced oxidative stress in combination with the capacity of insulin to activate antioxidant responses, and also the interference with mitochondrial activities, together form a very promising scenario to define future strategies to counteract insulin resistance and diabetes; in particular because our knowledge of antioxidant defences and the phenomenon of oxidative stress has improved very much in the last decade.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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