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Chapter 10

Thyroid Hormone and Energy Expenditure

Einav Yehuda-Shnaidman, Bella Kalderon and Jacob Bar-Tana

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1. Introduction

One of the most pronounced effects of Thyroid Hormone (TH, Triiodothyronine (T3), Tetraiodothyronine (T4)) is modulation of metabolic efficiency, energy expenditure and calorigenesis. Thus, hypothyroidism results in decreased energy expenditure and basal metabolic rate accompanied by weight gain and cold intolerance, while hyperthyroidism results in hypermetabolism, weight loss despite increased energy intake, intolerance to heat, loss of lean mass, bone resorption and tachycardia. TH role in modulating metabolic efficiency has been realized for over a century but its cellular mode-of-action remained to be resolved.

2. Mode-of-action of TH in modulating metabolic efficiency

The first description of TH-induced calorigenesis dates to 1895 (1). That initial report has been followed by exhaustive data focusing on the phenomenology of TH action as reflected by hyper- and hypothyroidsm. Thus, high levels of TH in mammals increase oxygen consumption and heat production, resulting in pronounced body weight loss, while low levels of TH are associated with a decrease in metabolic rate and the oxidation of energy substrates (glucose, fatty acids and amino acids), resulting in pronounced increase in body weight (2-6). Although it was widely accepted that TH stimulates calorigenesis by affecting respiration, its cellular mode-of-action remained to be resolved. Hence, exhaustive attempts were made by the scientific community throughout the twentieth century to verify the mechanism(s) involved in modulating metabolic efficiency by TH. Studies by Lardy and Feldott (7) and Hess and Martius (8) have pointed out during the 1950s, that the respiratory control ratio of isolated mitochondria was robustly decreased in the presence of added T4. TH was thus claimed to have direct action at the mitochondrial level by inducing 'mitochondrial uncoupling', namely, dissociating mitochondrial phosphorylation from its substrate oxidation driver. However, the high T4 doses used in those studies implied possible non-physiological activity rather than authentic TH-induced calorigenesis. Later

evidence in support of 'mitochondrial uncoupling' has however indicated increase in oxygen consumption and mitochondrial proton permeability of isolated liver mitochondria derived from hyperthyroid rats, with concomitant decrease in mitochondrial phosphate potential and inner mitochondrial membrane (IMM) potential (9, 10). These observations were further corroborated by increase in liver oxidizing capacity of hyperthyroid rats accompanied by decrease in phosphate and cytosolic redox potential (11), while opposite effects were reported in livers of hypothyroid rats (12). Similarly, hepatocytes isolated from T3-treated rats show higher oxygen consumption and lower IMM potential as compared with non-treated control (13-16). Also, a decrease in IMM potential has been reported in TH-treated human lymphocytes or those derived from hyperthyroid patients (17). Overall, these findings suggested that TH indeed induces mitochondrial uncoupling, and that mitochondrial uncoupling may account for the cellular mode-of-action of TH in modulating metabolic efficiency *in vivo*.

Concomitantly with the proposed mitochondrial paradigm of TH, others have proposed non-mitochondrial activity of TH in modulating metabolic efficiency. Thus, TH was claimed to induce "futile substrate cycles", namely, opposing energy-requiring metabolic pathways that proceed simultaneously without generating net products, e.g. glycolysis accompanied by gluconeogenesis, lipolysis with lipogenesis (18, 19), Na+/K+ ATPase with concomitant Na+/K+ leakage (13), or glycerol-3- phosphate/NADH mitochondrial shuttling (20). However, these proposed mechanisms could account for only a small fraction (about 15%) of the total increase in oxygen consumption induced by TH (13, 21), resulting in a mitochondrial paradigm consensus for TH-induced calorigenesis. Yet, the concerned mitochondrial targets still remained enigmatic.

3. Nuclear / mitochondrial targets of TH

TH effects in the mitochondrial context may consist of long-term effects that are dependent upon gene expression, and short-term effects that are refractory to inhibitors of protein synthesis. An important finding reported by Tata et al (2), indicated that the calorigenic activity of TH was abrogated by actinomycin D, implying that TH-induced mitochondrial uncoupling is mediated by modulating nuclear gene expression of respective mitochondrial and/or extra-mitochondrial proteins. These results were followed by extensive studies ((22, 23) and others) that resulted in discovering the nuclear TH receptors (THR) of the superfamily of nuclear receptors, acting as target for TH in modulating nuclear gene expression. THR are encoded by two distinct tissue-dependent genes coding for splice variants of the THRα (brain, bone, heart) and THRβ (liver, brain, heart) isoforms. THR homodimers or heterodimers with other members of the superfamily of nuclear receptors (e.g., retinoic X receptor (RXR)) may interact with TH-response elements (TRE) in the promoters of TH-responsive genes, resulting in transcriptional activation or suppression as function of transcriptional co-activators or co-suppressors recruited by TH/THR to the transcriptional complex of respective promoters. Indeed, TH binding to nuclear THR results in direct transcriptional activation of the expression of genes coding for components of mitochondrial oxidative phosphorylation (i.e. βF1-adenosine triphosphatase, adenine

nucleotide translocase (ANT), cytochrome c1) (24, 25), or genes coding for intermediate factors that are indirectly involved in promoting the nuclear expression of mitochondrial components (i.e. nuclear respiratory factors 1 and -2, peroxisome proliferator-activated receptor-γ coactivator-1) (26), or in stimulating mitochondrial DNA replication (27). Hence, TH-induced mitochondrial uncoupling was believed to be accounted for by TH-induced gene expression of respective protein targets that modulate mitochondrial oxidative phosphorylation. In pursuing putative proteins involved in TH-induced mitochondrial uncoupling, a number of candidates have been suggested. These included the adenine nucleotide translocase, proteins that are involved in phosphatidylglycerol and cardiolipin synthesis (28), and in particular the mitochondrial uncoupling proteins (UCPs).

4. Mitochondrial uncoupling proteins (UCPs)

With the discovery of UCPs, extensive efforts were invested in verifying their putative role in mediating the calorigenic effect of TH. In fact, the UCP-coding genes have TREs in their promoters and their expression level is increased by TH treatment, implying their putative role in mediating TH-induced calorigenesis (40). UCP1 (29) mediates proton leak in brown adipose tissue IMM (30), resulting in uncoupling fuel oxidation from ATP synthesis and in dissipating IMM potential as heat. The adaptive thermogenic response of UCP1 is driven by the sympathetic nervous system in response to cold temperature or high-energy cafeteria diet, and could apparently serve as target for TH in modulating total body energy expenditure. Indeed, recent findings by Lopez et al (31) have indicated that TH treatment results in suppressing hypothalamic AMP-activated protein kinase (AMPK) activity, resulting in SNS-induced thermogenic response of brown adipose fat. However, UCP1 is specifically expressed in brown adipose tissue, which is sparse in adult humans. While recent findings point to some brown adipose islets in adult humans (32-37), their putative impact on total body energy expenditure still remains to be resolved. Hence, other proteins that share sequence homology with UCP1(38), including the ubiquitously expressed UCP2, and in particular the UCP3 that is expressed in skeletal muscle, were pursued for their role in mediating TH-induced calorigenesis (39). However, the following observations may indicate that UCP2 and UCP3 may not account for TH-induced mitochondrial uncoupling (41). Thus, findings suggest that UCP2/3 do not contribute to adaptive thermogenesis (42), but may have a role in ROS signaling (43) and/or in exporting fatty acid anions from the mitochondrial matrix (44). Also, the expression of liver UCP2/3 proteins is restricted to Kupffer cells, implying that the uncoupling effect of TH in liver parenchymal cells is not due to UCPs. Most importantly, UCP3 knock-out mice are lean and show normal response to TH (45), leaving unresolved the specific proteins that may mediate TH metabolic effects in the mitochondrial context.

5. Mitochondrial permeability transition pore (PTP)

In analogy to UCPs, mitochondria consist of Permeability Transition Pores (PTP) (46-50) located at the contact sites of the inner (IMM) and outer (OMM) mitochondrial membranes. The molecular composition and structure of mitochondrial PTP still remains to be resolved. The current model of PTP consists of the integral proteins ANT (in the IMM), the voltage-

dependent anion channel (VDAC, in the OMM), cyclophylin D (CypD, in the mitochondrial matrix) and the Bcl2 family of proteins (in the OMM). PTP gating may present itself in definitive or transient modes, differing in reversibility and synchronization (51, 52). Definitive synchronized PTP gating is induced by intramitochondrial Ca^{+2} load (53), and is enhanced by oxidative stress, depletion of adenine nucleotides, increased inorganic phosphate, increased matrix pH, and depolarization of the IMM (54-56). This opening/gating mode results in high-conductance PTP (HC-PTP), extensive depolarization of the IMM (~70% decrease in IMM potential), rapid passage of ions and solutes of less than 1500 Da across the IMM, and mitochondrial swelling. These may lead to rupture of the OMM, release of mitochondrial proapoptotic proteins (such as cytochrome c, apoptotic intrinsic factor), followed by programmed cell death/apoptosis (57). Alternatively, spontaneous, non-synchronized, transient/flickering PTP gating due to cyclic opening and closure of individual PTP channels may result in reversible and limited depolarization of the IMM (~30% decrease in IMM potential), moderate decrease in proton motive force, and passage of solutes of less than 300 Da, accompanied by mitochondrial contraction rather than swelling (58-63). Most importantly, in contrast to the irreversible proapoptotic depolarization inflicted by definitive PTP gating, transient low conductance PTP (LC-PTP) gating is innocuous and reversible, leading to mild mitochondrial uncoupling. These findings may indicate that LC-PTP may serve as mitochondrial target of TH in inducing physiological mitochondrial uncoupling and calorigenesis.

6. Mitochondrial PTP gating by TH

In testing the role played by PTP gating in TH action, a straightforward approach would be to examine whether TH-induced uncoupling is inhibited by the PTP specific inhibitor, cyclosporin A (CSA). CSA acts as a potent inhibitor of PTP gating due to its binding to CypD, resulting in interfering with CypD interaction with PTP-ANT (64, 65). Indeed, TH-induced lowering of mitochondrial membrane potential and proton gradient followed by mitochondrial swelling are all eliminated by added CSA, pointing to PTP involvement in TH mitochondrial activity (66, 67). In addition, liver mitochondria of hypothyroid rats show decrease in mitochondrial Ca^{+2} efflux, swelling and protein release, being restored by TH treatment (68-70). Furthermore, TH treatment of Jurkat cells induces induce LC-PTP gating (71), implying that mitochondrial PTP may serve as target for TH in inducing mitochondrial uncoupling. However, as described below, TH activity in gating PTP is not accounted for by modulating gene expression of structural components of mitochondrial PTP.

Adenine Nucleotide Translocase (ANT): ANT is a central player in oxidative phosphorylation due to its primary function in translocating adenine-nucleotides via the IMM. ANT function in the PTP context has been verified by its direct association with CypD and VDAC (72), as well as by PTP gating being activated and inhibited by the ANT ligands Atractylate and Bongrekic acid, respectively (73). Moreover, ANT/CypD/VDAC- reconstituted liposomes show PTP characteristics in terms of sensitivity to Ca^{+2}, CSA and ANT ligands ((74, 75) but see also (76)). Also, over-expression of ANT isoforms (ANT1, ANT3) promotes apoptosis, being inhibited by CSA (77, 78). Moreover, ANT expression levels affect

mitochondrial IMM potential, with high ANT levels resulting in IMM depolarization and mitochondrial proton leak (71, 77, 79). Hence, in light of ANT structural and regulatory functions in the PTP context, and since the expression level of ANT2, the only ANT isoform expressed in liver, is increased in hyperthyroidism and decreased by hypothyroidism (80), TH-induced ANT expression could apparently account for liver TH-induced LC-PTP gating. However, over-expression of ANT2 in HeLa cell line or in rat primary hepatocytes resulted in extensive mitochondrial depolarization that was not inhibited by CSA (71), implying the formation of PTP-nonrelated ANT channels (81), or of CSA-insensitive PTP (82). Lack of an obligatory linkage between PTP and ANT conforms to other findings pointing to PTP gating by proapoptotic ligands in liver cells or isolated mitochondria that lack ANT (76).

Cyclophilin D (CypD): CypD is a member of the family of peptidyl-prolyl cis-trans isomerases (PPIase) (83). The CypD protein contains a mitochondrial-targeting sequence that directs it specifically to the mitochondrial matrix. The link between CypD and PTP has been verified by CypD direct association with ANT (72) as well as by CSA inhibition of PTP gating due to its interaction and inhibition of CypD activity (64, 65, 84). Moreover, PTP opening by Ca^{+2} and oxidative stress was enhanced in isolated mitochondria of neurons over-expressing CypD (85), while CSA-sensitive PTP opening was abrogated in isolated mitochondria of CypD knock-out mice (86). These CypD characteristics may indicate that CypD could apparently serve as protein target of TH in inducing PTP opening and mitochondrial uncoupling. Indeed, liver mitochondria of hyperthyroid rats show increased expression of CypD as well as its PPIase enzymatic activity (71), while opposite effects prevailed in liver mitochondria isolated from hypothyroid rats. However, over-expression of CypD in HeLa cell line, or in rat primary hepatocytes, resulted in mitochondrial hyperpolarization rather than PTP opening (71, 87). Moreover, over-expressed CypD was found to desensitize cells to apoptotic stimuli or to protect cells from mitochondrial depolarization and apoptosis induced by over-expression of ANT1 (77, 78). Hence, TH-induced CypD expression may not account for TH-induced PTP gating and calorigenesis. CypD induction by TH may reflect TH activity in inducing peptidyl-prolyl cis-trans isomerase activity and protein folding rather than PTP opening (88).

Voltage Dependent Anion Channel (VDAC): VDAC is a highly abundant protein of the OMM. Its primary function consists of exchanging anions between the cytosol and the inter-membrane mitochondrial space (89). Previous findings have indicated its putative role in gating mitochondrial PTP (90-94). However, its expression level is not changed by *in vivo* TH treatment (71), excluding VDAC from being a molecular target of TH in inducing mitochondrial uncoupling.

7. Modulation of Bcl2-family proteins by TH

The family of Bcl2 proteins consists of more than 20 proteins that were extensively studied in terms of their role in cell death (95). The Bcl2 family is grouped into two main subfamilies: proapoptotic proteins (e.g. Bax, Bak, and others) and anti-apoptotic proteins (e.g. Bcl2), which promote or inhibit PTP gating, respectively (95-97). Bcl2-family proteins

may directly interact with PTP components such as ANT (98-100) or VDAC (101), and when over-expressed or added to isolated mitochondria may specifically induce (e.g. Bax and Bak) (102-104) or antagonize (e.g. Bcl2) (105) PTP gating. Similarly, depletion of proapoptotic Bax or Bak results in failure of PTP gating (98, 105, 106), whereas Bcl2 inactivation results in definitive PTP gating triggered by oxidative stress (107). Thus, mitochondrial Bcl2-family proteins and their respective heterodimers (e.g., Bax/Bcl2, Bad/Bcl2) may apparently serve as candidate targets of TH in inducing mitochondrial uncoupling (108-110). Indeed, TH-induced PTP gating is accompanied by increase in mitochondrial Bax and Bak, together with decrease in mitochondrial Bcl2 content, whereas hypothyroidism results in opposite effects that are reversed by TH (71). Modulation of the mitochondrial content of Bcl2 proteins by TH is due to their specific translocation in/out of mitochondria, rather than reflecting modulation of their expression and total cellular content. Amplifying the ratio of mitochondrial pro- vs. anti-apoptotic proteins, results in robust decrease in mitochondrial Bax/Bcl2 heterodimer with concomitant increase in free Bax, leading to PTP gating by free mitochondrial Bax (111). Indeed, over-expression of Bcl2 protects against TH-induced mitochondrial PTP gating (71), implying that depletion of mitochondrial Bcl2 by TH may account for TH-induced mitochondrial uncoupling.

8. Extra-mitochondrial upstream signals that induce TH-induced PTP gating mediated by Bcl2-family proteins

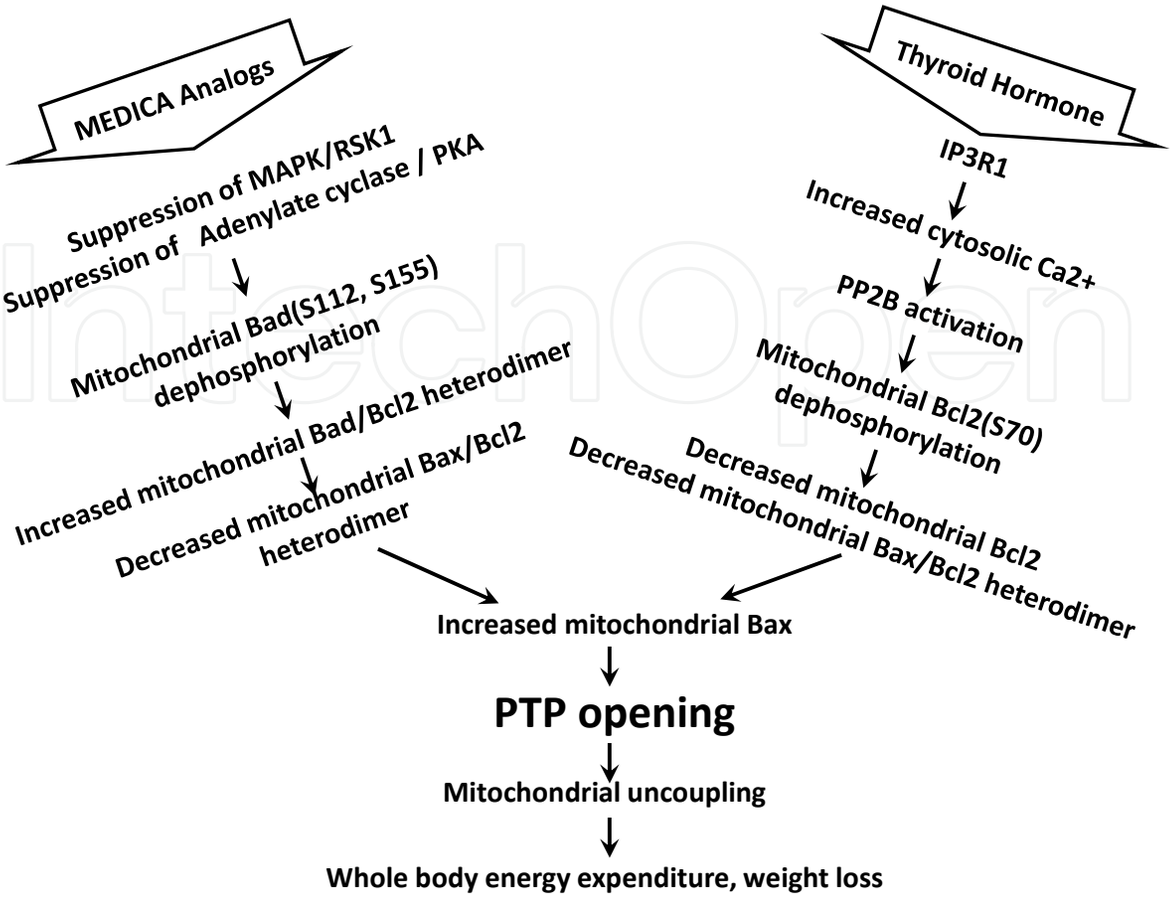
Since Bcl2-Bax hetrodimerization may depend on Bcl2(S70) phosphorylation state (112), mitochondrial Bcl2 depletion by T3 was further verified in terms of Bcl2(S70) phosphorylation profile. Indeed, concomitantly with decrease in mitochondrial Bcl2, T3 treatment results in decreased phosphorylation of monomeric mitochondrial Bcl2(S70) as well as of Bcl2(S70)-Bax heterodimer (113), indicating that mitochondrial Bcl2 depletion may reflect Bcl2(S70) dephosphorylation by TH. In pursuing kinases (e.g. PKA, PKC) or phosphatases (e.g. PP2A, PP2B/Calcineurin) reported to be involved in Bcl2(S70) phosphorylation (112, 114), neither PKA, PKC nor PP2A were found to mediate phosphorylation/dephosphorylation of Bcl2(S70) by TH (113). In contrast, dephosphorylation of Bcl2(S70) and the depletion of mitochondrial Bcl2 protein by T3 are both reversed by the FK506 inhibitor of PP2B, indicating that the TH effect may be mediated by activation of PP2B (113). Furthermore, added FK506 blocksT3-induced opening of PTP, indicating that dephosphorylation of Bcl2(S70) and its mitochondrial depletion by T3-activated PP2B may account for mitochondrial PTP opening by TH. Since TH-induced PP2B activation was not accompanied by increase in PP2B expression, PP2B activation was further pursued by searching for TH-induced increase in cytosolic Ca^{+2} (113). Indeed, Ca^{+2} -activated PP2B has previously been reported to bind and dephosphorylate Bcl2(S70) (115, 116). Most importantly, T3 treatment resulted in pronounced increase in Ca^{+2}, while Ca^{+2} chelation by BAPTA resulted in abrogating LC-PTP gating by TH, indicating that TH-induced PP2B activity involved mobilization of intracellular Ca^{+2} (113). Indeed, T3-induced mobilization of intracellular Ca^{+2} has recently been reported to mediate a variety of non-genomic effects of TH (117, 118).

The dynamic equilibrium between cytosolic Ca^{+2} ($[Ca^{+2}]c$) and endoplasmic reticulum (ER) Ca^{+2} ($[Ca^{+2}]ER$) is maintained by an interplay between the inositol 1,4,5-trisphosphate receptor (IP3R1) and the sarcoplasmic Ca^{+2} ATPase (SERCA) that catalyzes ER Ca^{+2} efflux and influx, respectively (119). IP3R1 is activated by binding of the IP3 ligand and may further be modulated by its phosphorylation by PKA, PKC or CaMKII, its dephosphorylation by PP2B, or by its association with one or more of about 50 proteins, including FKBP12 or Bcl2 (120, 121). The putative role played by IP3R1 in TH-induced PTP gating was evaluated by verifying the effect of TH in cells lacking IP3R1 (113). Thus, PTP opening, dephosphorylation of mitochondrial Bcl2(S70) and depletion of mitochondrial Bcl2 are all abrogated in cells lacking IP3R1, indicating that IP3R1 is indeed required for TH-induced mitochondrial uncoupling. Similarly, T3 is ineffective in increasing $[Ca^{+2}]c$ upon inhibition of IP3R1 by 2APB, indicating a specific requirement for IP3R1 activity in modulating $[Ca^{+2}]c$ by TH. Furthermore, T3-induced gating of IP3R1 is accounted for by both, increase in IP3R1 expression and protein levels, complemented by IP3R1 truncation into channel-only isoforms. Truncated IP3R1 isoforms have been reported to serve as channel-only peptides capable of carrying out $[Ca^{+2}]ER$ efflux in the absence of added IP3 (122-126). IP3R1 truncation by TH may reflect TH activation of IP3R1 proteases that remain to be further verified. The IP3R1 / PP2B crosstalk in mediating TH-induced PTP gating is supported by constitutive PP2B-induced PTP gating under conditions of suppressing IP3R1 expression by siRNA (127). Hence, PP2B is acting downstream to TH-induced IP3R1, and is obligatory as well as sufficient in mediating PTP by $[Ca^{+2}]c$.

Over all, TH-induced expression of the IP3R1 channel accompanied by its truncation is proposed to result in $[Ca^{+2}]ER$ efflux, increase in $[Ca^{+2}]c$ and $[Ca^{+2}]c$-activated PP2B, followed by dephosphorylation of mitochondrial Bcl2(S70) with concomitant decrease in mitochondrial Bcl2 protein levels and increase in mitochondrial free Bax (Scheme 1). The decrease in mitochondrial Bcl2 and/or the respective increase in mitochondrial free Bax may initiate and promote variable PTP gating, resulting in physiological LC-PTP–induced calorigenesis. LC-PTP gating may drift to HC-PTP–induced apoptosis as function of additional prevailing conditions that may affect mitochondrial permeability transition.

9. Thyromimetic agents and energy expenditure

Increase in energy expenditure by TH has long been considered for treating obesity. Indeed, treating obesity by thyroid extracts was quite popular throughout the 20th century and well into the 1970s, being later abandoned due to severe side effects consisting of cardiac dysrhythmias, bone resorption / osteoporosis, electrolyte disturbances, and loss of lean body mass (128). Thus, a final ruling warning against the use of thyroid preparations for the treatment of obesity of euthyroid subjects has been issued by the FDA on 1978. Similarly to TH, treating obesity by uncoupling of mitochondrial oxidative phosphorylation by 2,4-dinitrophenol (DNP) has been introduced on 1933, but abandoned on 1938 due to fatal hyperthermia (129).



Scheme 1. PTP-induced calorigenesis by Thyroid Hormone and MEDICA Analogs

These early attempts were followed by rational drug design of synthetic structural analogs of TH that may avoid the lethal chronotropic cardiac effects of TH, while maintaining the beneficial effects of TH in the context of diseases of the Metabolic Syndrome (130, 131). Most efforts in that direction were invested in designing thyromimetics that selectively target the liver TH-receptor isoforms (THRβ) while avoiding the heart isoforms (THRα). Tissue selectivity has been further pursued by designing thyromimetics that undergo selective hepatic uptake. These efforts have mainly resulted in thyromimetics effective in treating dyslipidemia, due to increased expression of hepatic LDL-receptors together with CYP7A1 / 7-alpha-cholesterol hydroxylase, resulting in enhancing hepatic uptake of LDL-cholesterol and its conversion into bile. Liver-specific thyromimetics were further found to induce the expression of the hepatic scavenger receptor SR-B1 that mediates reverse cholesterol transport. However, in contrast to the advances made in designing hypolipidemic thyromimetics, the efficacy of thyromimetics in treating obesity and obesity-induced diabetes type 2 still remains to be verified. Moreover, the use of thyromimetics for treating diseases of the Metabolic Syndrome involves potential harmful risks due to: a. The partial selectivity of thyromimetics for hepatic THRβ, resulting in positive chronotropic effects as well as enhanced bone and muscle catabolism induced by high-dose. Hence, the safety of hypolipidemic thyromimetics still remains to be verified in subjects suffering from congestive heart failure or coronary heart disease. b. Since THRβ regulates the feedback loop

of hypothalamic TSH, thyromimetics may suppress the production of endogenous TH, resulting in combined hypo- and hyperthyroidsm. These limitations, combined with our present view of the mode-of-action of TH in the mitochondrial context, may however point to an alternative strategy, namely synthesizing thyromimetics that may directly target mitochondrial PTP while avoiding the TH/THR transduction pathway altogether.

Long chain fatty acids (LCFA) have long been shown to induce mitochondrial uncoupling due to their protonophoric activity (81, 132) and/or PTP gating ((51, 133), and ref therein), implying a potential mitochondrial thyromimetic activity. However, the uncoupling activity of LCFA is confounded by their dual role as putative uncouplers of oxidative phosphorylation and as substrates for oxidation or esterification. MEDICA analogs consist of long chain dioic acids (HOOC-C(α')-C(β')-(CH2)n-C(β)-C(α)-COOH (n=10-14)) that are substituted in the $\alpha\alpha'$ or $\beta\beta'$ carbons (134). MEDICA analogs may be thioesterified endogenously into their respective mono acyl-CoA thioesters (135), however, they are not esterified into lipids nor β-oxidized, thus dissociating between the substrate role and the putative uncoupling activity of natural LCFA.

Similarly to TH, MEDICA analogs induce calorigenesis in animal models *in vivo*. Thus, treatment of rats with MEDICA analogs results in an increase in oxygen consumption accompanied by a decrease in liver mitochondrial phosphate potential and cytosolic redox potential, reflecting mitochondrial uncoupling *in vivo* (136). Furthermore, treatment of obese leptin receptor-deficient rats (*e.g.* Zucker, cp/cp) with MEDICA analogs results in increased oxygen consumption and food consumption together with weight loss, implying increased total body energy expenditure (137, 138). Also, the non-protonophoric mitochondrial activity of MEDICA analogs is similar to that of TH (71), in terms of promoting CSA-sensitive decrease in phosphate and redox potentials with concomitant increase in oxygen consumption in cultured cells as well as *in vivo* (11, 16, 67, 139, 140), indicating that both MEDICA analogs and TH do converge onto LC/HC-PTP gating (11, 71). Indeed, similarly to TH, PTP gating by MEDICA analogs is mediated by modulating the profile of mitochondrial Bcl2-family proteins, resulting in decrease in mitochondrial Bcl2-Bax heterodimer with concomitant increase in mitochondrial free Bax (71, 113). However, different transduction pathways are involved in modulating the mitochondrial content of free Bax by TH or MEDICA analogs. Thus, dissociation of the Bcl2-Bax heterodimer by TH is driven by dephosphorylation of Bcl2(Ser-70) by T3-activated PP2B (113), whereas dissociation of the Bcl2/Bax heterodimer by MEDICA analogs is driven by dephosphorylation of Bad(Ser-112, Ser-155) (141). The decrease in phosphorylated Bad(Ser-112, Ser-155) results in its decreased binding to14-3-3 followed by its increased binding to mitochondrial Bcl2, resulting in Bax displacement and PTP gating (142, 143). Decrease in phosphorylated Bad by MEDICA analogs is due to suppression of the Raf1/MAPK/RSK1 and the adenylate cyclase/PKA transduction pathways, and their respective downstream targets Bad(Ser-112) and Bad(Ser-155) (141). Hence, the TH and MEDICA transduction pathways converge at their downstream Bax target but diverge upstream of the Bcl2/Bax heterodimer (Scheme 1). LC-PTP gating by MEDICA analogs may account for their thyromimetic calorigenic activity in *vivo*.

10. Conclusion

Energy expenditure by TH has long been realized to be accounted for by uncoupling of mitochondrial oxidative phosphorylation. However, the mode-of-action of TH in promoting mitochondrial uncoupling remained elusive. Mitochondrial uncoupling by TH is transduced by TH-induced gating of mitochondrial PTP due to modulating its Bcl2-family proteins. This mode-of-action underscores the physiological aspects of mitochondrial PTP in modulating metabolic rate, in contrast to most previous studies that analyzed mitochondrial PTP in its apoptotic context. TH-induced gating of mitochondrial PTP may offer a whole new dimension of developing novel anti-obesity drugs that promote weight loss by targeting mitochondrial PTP.

Author details

Einav Yehuda-Shnaidman, Bella Kalderon and Jacob Bar-Tana
Human Nutrition and Metabolism, Hebrew University Medical School, Jerusalem, Israel

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