

Stimulation of Thermogenesis via Beta-Adrenergic and Thyroid Hormone Receptors Agonists in Obesity Treatment – Possible Reasons for Therapy Resistance

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Abstract

The worldwide epidemic of obesity and the limited effectiveness of the available treatments led to a renewed interest in developing therapeutic approaches which would reduce obesity by increasing energy expenditure. Knowledge of the mechanism involved in the regulation of thermogenesis in mammals has led to the belief that compounds activating adrenergic receptors beta and/or thyroid hormone receptors may be effective in obesity treatment. However, the translation of the results obtained in the in vitro and in animal studies on humans occurred to be not as direct and effective as expected. This mini-review discusses the potential role of thermogenesis impairment in development of human obesity as well as possible limitations in the application of thermogenic compounds in obesity treatment.

Key words

Obesity treatment; Thermogenesis; Adrenergic receptors beta; Thyroid hormone receptors.

Introduction

The imbalance between energy intake and expenditure accompanied by the collapse of mechanisms protecting against the excessive accumulation of energy reserves are considered to be the main causes of obesity [1]. Accordingly, available treatments of obesity are aimed at decreasing calorie intake and/or increasing energy expenditure. However, long-term effects of various non-invasive methods including diets and pharmacotherapy with drugs reducing intestinal ingestion are unsatisfactory. Therefore, bariatric surgery, albeit expensive and potentially harmful, seems to be most effective [2]. Such situation has led to a renewed interest in developing therapeutic approaches which would reduce obesity by increasing energy expenditure. In this mini-review the potential role of thermogenesis impairment in development of human obesity as well as possible limitations in the application of thermogenic compounds, namely agonists of the adrenergic receptors beta and thyroid hormone receptors, in obesity treatment are discussed.

Brown Adipose Tissue in Human Energy Expenditure

In small mammals and in human newborns, non-shivering (adaptive) thermogenesis in brown adipose tissue (BAT) is the most important regulatory mechanism for maintaining body temperature. Energy produced in the BAT mitochondria, due to the oxidation of lipolysis-derived fatty acids, is not used to produce high-energy bonds of adenosine-5'-triphosphate (ATP), but is released as heat, mostly thanks to uncoupling protein 1 (UCP1) [3].

It was believed that in humans, age progression is accompanied by a complete atrophy of BAT; however, novel methods of imaging led to the identification of BAT stores in several areas of the adult human body, as well as of cells reminding brown adipocytes dispersed within the visceral white adipose tissue (WAT) also known as beige/brite adipocytes [4].

The prevalence and activity of BAT differ between individuals and are inversely related to age, body mass index (BMI) and the total fat content [5]. BAT activity may vary even in the same subject, depending

on cold exposure which is the most powerful and physiological stimulus for its activation. Activity of the cold-stimulated human BAT measured by the uptake of fatty acids and glucose (per gram of tissue) can be higher than in insulin-stimulated skeletal muscle [6]. Apart from its contribution to cold-induced thermogenesis, recent human studies demonstrated that BAT also participates in diet-induced thermogenesis, which may constitute up to 10% of whole body energy expenditure [7]. Therefore, stimulation of thermogenesis in brown adipocytes seems to be an attractive therapeutic pathway in treatment of obesity and related metabolic disorders.

Regulation of Adaptive Thermogenesis

The function of brown adipocytes is under strict neurohormonal control. In organisms exposed to cold, stimuli from the Paraventricular nucleus and from the preoptic area of hypothalamus lead to the increased noradrenaline release from the sympathetic nerve fibers in the vicinity of BAT. Such β -adrenergic signaling, executed by the activation of the β 1 adrenergic receptor (ADRB1), predominantly results in the proliferation of brown adipocytes, while signaling executed by the β 2 and β 3 adrenergic receptors (ADRB2 and ADRB3, respectively), results mainly in the activation of lipolysis (in WAT and in BAT) and of thermogenesis (in BAT) [8]. Chronic sympathetic stimulation, observed in patients with catecholamines secreting tumors, leads to the induction of UCP-1 positive brown-like (beige) adipocytes in WAT, and subsequently – to increased energy expenditure due to intense thermogenesis as well as to body fat reduction caused by the

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increased lipolysis and glycogenolysis [9].

The adrenergic system interacts with thyroid hormones (TH) in controlling the non-shivering thermogenesis to counteract environmental stress. While adrenergic stimulation provides the means for rapid responses, triiodothyronine (T3) increases the capacity of cells to respond to catecholamines and maintains a metabolic rate appropriate for the availability and mobilisation of fatty acids from fat stores to ensure adrenergic responses [10]. Apart from the influence on ADRB density, T3 may also potentiate adrenergic stimulation *via* other mechanisms including enhancing the intracellular accumulation of cyclic adenosine monophosphate (cAMP) [11]. In turn, cold-induced noradrenergic stimulation of brown adipocytes results in the local activation of the type 2 5'-iodothyronine deiodinase, which catalyzes the conversion of the prohormone – thyroxine (T4) to T3. Subsequently, T3 acting by its nuclear receptors (TRs) bound to the thyroid hormone-response elements present in the regulatory regions of various genes, including the genes for uncoupling proteins, increases their expression. Catecholamines may also potentiate the activity of T3 by increasing the retention of TRs in the nucleus or by increasing the recognition of DNA sequences through protein kinase A-mediated phosphorylation of TRs [12].

Knowledge of the mechanisms involved in regulation of thermogenesis in adipose tissue suggests two potential strategies for its pharmacological activation in treatment of obesity. The first strategy is based on adrenergic receptors beta (ADRBs) activation, while the second – on stimulation of thyroid hormone receptors (TRs).

Adrenergic Receptors Beta as Targets for Obesity Treatment

ADRBs are members of the G protein-coupled receptor family that after activation induce the adenylyl cyclase leading to the increase in intracellular cAMP levels. cAMP acts as a second messenger activating protein kinase A that subsequently results in the phosphorylation of multiple targets [13]. In adipose tissue, this process may result in adipocytes proliferation and induction of nonshivering thermogenesis (BAT) as well as in the mobilization of stored fatty acids for lipolysis (WAT). There is mounting evidence coming from animal models and from genetic studies that the dysfunction of ADRBs may play a role in the development of obesity.

Animal studies

Adipocytes from genetically obese (ob/ob) mice display an impaired response to beta-adrenergic stimulation due to significantly reduced expression of all ADRBs isoforms in BAT and WAT [14]. Crucial role of ADRBs in mediating thermogenesis and lipolysis was confirmed by experiments performed on mice with the combined targeted disruption of the three ADRBs (TKO mice) which have increased susceptibility to cold-induced hypothermia as well as to diet-induced obesity [15,16]. Animals with selective knockout of the *adrb1* easily develop hypothermia due to the severely disturbed cold-induced and diet-induced thermogenesis and when placed on a high-fat diet – gain significantly more weight than wild type controls and develop features of the metabolic syndrome that include: impaired glucose tolerance, hypercholesterolemia, and hypertriglyceridemia [17]. Although targeted disruption of the *adrb2* gene does not impair cold- and diet-induced thermogenesis in mice and seems to have no influence on body weight, adiposity and lipids metabolism, it impairs glucose homeostasis possibly by accelerating hepatic glucose production and insulin secretion [18]. Similarly, mice with *adrb3* knockout, due to the normal

function of the ADRB1, are able to maintain core body temperature in cold but their resting metabolic rate is lower compared to wild-type controls that predispose them to obesity [19].

Genetic studies

There is also indirect evidence from genetic studies that ADRBs receptors might participate in the regulation of body weight in humans, because certain polymorphisms in their genes were associated with metabolic complications and increased weight gain (Table 1).

The *ADRB2* gene (encoding ADRB2) is located on chromosome 5q31-32 and composed of one exon, spanning 2 kb of DNA. This gene contains several single nucleotide polymorphisms (SNPs) both in the encoding sequence as well as within the 5'-untranslated region (UTR) that were found to be associated with obesity. *In vitro* studies showed that despite having no influence on ligand binding or adenylyl cyclase activity, the A285G (rs1042713, causing Arg16Gly substitution) and C318G (rs1042714, causing Gln27Glu substitution) SNPs, located in the extracellular N-terminus of *ADRB2*, determine the efficacy of the agonist-promoted receptor down-regulation. While the 285G variant enhances, the 318G is not only associated with a strong resistance to the down-regulation, but also encodes the protein that is less susceptible to degradation [20]. Creation of double mutants let to assess the combined effect of these two SNPs and showed that in the 285G/318G combination, the presence of the 285G variant determines the biological effect and the protein is more susceptible to agonist-promoted down regulation, while the 285A/318G mutant is completely resistant to this process. The strong linkage disequilibrium between these two polymorphisms and their interaction may partially explain the discrepancies between the genetic studies regarding their association with obesity. The 318C allele was associated with higher risk of weight gain in inactive French and Swedish men as well as in Spanish women [21-23]. However, subsequent studies did not manage to replicate this association [24] or even pointed to the opposite variant as the causative one in Caucasians [25].

In turn, the 285G allele (alone as well as in combination with 318G) was found to be associated with weight gain and blood pressure elevation in Japanese [24-26] although previous study carried in the same population denied this association [27].

The T allele of the *ADRB2* C730T SNP (rs1800888, causing Thr164Ile substitution) located in the fourth membrane-spanning domain impairs both receptor affinity towards agonists as well as its interaction with G protein resulting in lower adenylyl cyclase activity [28]. In some populations this variant was not only directly associated with obesity [29], but also considered as a predisposing one, since it might determine exercise capacity [30].

Another functional SNP in *ADRB2* vicinity is a T-47C change (rs1042711, causing Arg19Cys substitution) located in 5'-leader cistron (a peptide encoded by a short open reading frame 102 bp upstream the *ADRB2* coding block). The -47C variant results in lower *ADRB2* expression on protein level and its impaired ability to activate adenylyl cyclase [31]. A combination of -47C/285A/318C (Cys19/Arg16/Gln27) was found to be a risk-haplotype for hypertension and obesity [32]. However, the interpretation of most case-control studies regarding the association between *ADRB2* SNPs with obesity is difficult due to several reasons, including ethnic and gender-associated differences as well as the lack of haplotypes analysis and inadequate understanding of how the combination of different variants affect the receptor function, not to mention the gene-gene interactions. It is also worth mentioning that recent meta-analysis did not confirm the association of the *ADRB2* variants with obesity [33].

Gene	Polymorphism (rs)	Base substitution	Amino acids substitution	Variant	Functional consequences	Reference
ADRB1 (10q24-26)	rs1801252	A231G	Ser49Gly	231G	↑ receptor down regulation	[38]
	rs1801253	G1251C	Gly389Arg	1251C	↑ interaction with G protein	[39]
					↑ response to antagonists	[40]
ADRB2 (5q31-32)	rs1042711	T-47C	Arg19Cys	-47C	↓ ADRB2 expression	[31]
					↓ interaction with G protein	[31]
	rs1042713	A285G	Arg16Gly	285G	↑ receptor down regulation	[20]
	rs1042714	C318G	Gln27Glu	318G	↓ receptor down regulation	[20]
					↓ receptor degradation	[20]
	rs1800888	C730T	Thr164Ile	730T	↓ affinity towards ligands	[28]
					↓ interaction with G protein	[28]
ADRB3 (8p12)	rs4994	T190C	Trp64Arg	190C	↓ response to agonists lipolysis ↓	[34,36]

↑ - increased, ↓ - decreased

Table 1: Obesity-associated functional polymorphisms in genes encoding adrenergic receptors beta(ADRB).

Among the various polymorphisms identified in the *ADRB3* gene (encoding ADRB3, located on chromosome 8p12 and composed of two exons spanning 1.4 kb and 0.7 kb of DNA, respectively), the rs4994 T190C SNP causing amino acids substitution (Trp64Arg) in the first intracellular loop of the receptor was the most frequently studied in the context of its relationship with obesity. In initial *in vitro* studies, the presence of the 190C allele was associated with lower receptor response to agonists as well as with impaired catecholamine-stimulated lipolysis. However, other researchers did not observe any differences in the receptor function between carriers of particular alleles [34]. In some case-control studies, carriers of the 190C allele showed tendency to lower metabolic rate, abdominal obesity and insulin resistance compared to the individuals homozygous for the 190T variant. Yet, the results of further studies were not so univocal, probably due to the heterogeneity of the studied populations. A large meta-analysis involving results of 97 case control-studies and over 44 000 individuals suggested association of the 190C allele with BMI in East Asians but not in Caucasians [35].

The T190C polymorphism (rs4994) remains in strong linkage disequilibrium with two synonymous SNPs: G1856T (rs4997) and G3139C (rs4998) constructing the two major haplotypes: 190T-1856G-3139G – named a “Trp haplotype” and 190C-1856T-3139C – named an “Arg haplotype”. The *in vitro* studies analyzing influence of these haplotypes on ADRB3 function showed that adipocytes possessing the “Arg haplotype” present lower lipolytic activity in response to catecholamines [36].

Among SNPs identified in the *ADRB1* gene (encoding ADRB1, located on chromosome 10q24-26 and composed of one exon 2.4 kb long) two of them, A231G (rs1801252 causing Ser49Gly substitution) and G1251C (rs1801253, causing Gly389Arg substitution), have been most commonly studied due to their high (more than 10%) frequency in different populations [37].

The A231G SNP is localized in the extracellular N-terminus of the receptor, near the first transmembrane-spanning domain. Although functional studies found no differences between the 231A and 231G alleles in ligands binding affinity, and in the basal and stimulated adenylyl cyclase activity, the 231G variant was associated with the enhanced long-term agonist-promoted down-regulation of the receptor [38]. In a case-control association study, the 231G variant was found to be associated with higher BMI in type 2 diabetic patients [24]. It was proposed that the reduced signaling *via* ADRB1 in 231G positive individuals may be associated with attenuated lipolysis and therefore with the increase in BMI. However other studies did not confirm this association [37].

The G1251C SNP is located in the vicinity of the seventh transmembrane-spanning domain and may influence receptor coupling to Gs. In functional studies, the 1251C allele was associated with higher basal and isoproterenol-stimulated adenylyl cyclase activity but also with greater response to beta adrenergic antagonist (metoprolol) [38-40]. However, in experiments performed in human adipocytes there was no difference between the two variants in the cells lipolytic sensitivity and maximum lipolytic capacity [41]. In some cohort studies, the 1251C allele was associated with higher BMI due to the enhanced adiposity [42], while other researchers did not confirm this association [43]. Interestingly, in a longitudinal study assessing risk of obesity over 24-year observation period, a significant interaction between the *ADRB1* 1251G (Gly389) and *ADRB2* 285G (*Gly16*) alleles in creating a risk of the weight gain in men was observed. This association could be explained by a cumulative effect of the lower activity of ADRB1 and lower ADRB2 density. In woman, the *ADRB1* 1251G homozygosity was associated with obesity when interacted with *ADRB3* 190C variant, probably due to the combined effect of reduced functionality of the *ADRB1* 1251G allele and reduced sensitivity of the *ADRB3* 190C variant [44].

In summary, given the (i) ethnic heterogeneity, (ii) inadequate number of study participants (iii) linkage disequilibria between the studied variants and (iv) complex interactions among the genes encoding ADRBs, it is often difficult to draw firm conclusions from most case-control studies regarding associations of polymorphisms within these genes and obesity. The reliable meta-analysis was performed only for the *ADRB3* T190C (Trp64Arg) SNP and on the basis of its results, one can conclude that the 190C (Arg64) is an obesity-predisposing allele in Asian populations. However, pathophysiological mechanisms linking this polymorphism with increased adiposity are less clear since results of the functional studies regarding its influence on receptor activity are unequivocal.

ADRBs ligands in treatment of obesity

Given their crucial role in mediating cold-induced thermogenesis, ADRBs seemed to be promising targets for obesity treatment. However, in this case imitating of physiology was more difficult than expected. While mild cold exposure in humans leads to the activation of a sympathetic response only in certain organs (BAT and peripheral vessels), systemic administration of nonselective β-adrenergic receptors agonists (ephedrine or isoprenaline) leads to the general adrenergic response and increases energy consumption by a number of organs, including the heart, liver and skeletal muscle, but exerts little effect on thermogenesis in brown adipocytes [6,45]. Doses of ephedrine that are effective in stimulation of BAT in rodents are unacceptable

in humans because of their cardiovascular effects. Similarly, despite its unquestionable role in mediating cold-induced thermogenesis clinical application of norepinephrine is limited due to its adverse effects on the cardiovascular system. Interestingly, while stimulation of ADRB1 and ADRB2 by isoprenaline does not activate BAT in humans, their blockade by the administration of propranolol decreases glucose uptake in BAT in patients in thermoneutral conditions [46]. The possible explanation of this phenomenon is that high concentrations of sympathomimetics in the postsynaptic areas required for the effective stimulation of brown adipocytes cannot be achieved by their systemic administration.

Therefore, novel selective agonists of ADRBs have been developed in attempt to stimulate brown adipocytes proliferation and activation. The *in vitro* studies performed on human multipotent adipocyte-derived stem cells suggest that activation of ADRB3 receptors by a selective agonist (CL-316243) leads to the increased UCP1 mRNA synthesis and differentiation towards brown adipocytes [19]. In rodents, ADRB3 ligands induce intense thermogenic and lipolytic response that results in the loss of fat mass without affecting the lean body mass and in the subsequent improvement of glucose control [47]. Moreover, acting in hypothalamus, CL-316243 occurred to be effective in reducing food intake in mice *via* leptin-independent mechanism and despite increased hypothalamic expression of the orexigenic neuropeptides [48]. Despite promising data from the *in vitro* and from animal studies, these agents occurred to have limited efficacy in humans, probably due to the (i) lower number of ADRB3 in human adipose tissue than in transfected cell-lines used for the *in vitro* experiments, (ii) poor selectivity of the compounds for the human ADRB3, and (iii) different contribution of white and brown adipocytes in rodents and in humans [49]. The lower expression of ADRB3 in adipose tissues of obese subjects may constitute another reason of low efficacy of these compounds in obesity treatment [50].

Therefore, one can conclude that identifying highly selective agonists that are able to selectively stimulate the low numbers of ADRB3 in human tissues is challenge and is additionally compounded by pharmacodynamic differences between rodents and humans.

Thyroid Hormone Receptors as Targets for Obesity Treatment

Thyroid hormone receptors (TRs) belong to the nuclear hormone receptor superfamily and act as ligand-dependent transcription factors regulating expression of target genes. Two genes *THRA* (located on chromosome 17q12-22, containing 11 exons) and *THRB* (on chromosome 3p22-24, containing 17 exons) encode TR α and TR β respectively. Both of them exist in several isoforms due to the alternative splicing or use of alternative promoters. The isoforms have tissue- and organ specific localisation, with TR α 1 being a predominant isoform in the brain, bone, heart and intestine, TR α 2 – a variant receptor that lacks a functional hormone-binding site and antagonizes TR α 1 action, TR β 1 dominating in liver, kidney and thyroid and TR β 2 being a chief form involved in the regulation of the hypothalamus-pituitary axis and in the neurosensory development [51]. Both TR α 1 and TR β 1 are also expressed in human adipose tissue [50,52] and there is data coming from the observational, animal and genetic studies suggesting that they could constitute potential targets for obesity treatment.

Observational studies

Weight gain and increased adiposity are typical features of hypothyroidism and cross-sectional analyses adjusted for age, BMI and

total body fat confirmed independent and inverse association of free thyroxin (fT4) level with volume of the visceral fat stores [53]. There are also studies suggesting that thyroid status may influence not only general adiposity but also distribution of adipose tissue pointing at inverse correlation between the fT4 levels and visceral adiposity and at the positive correlation of TSH with the amount of subcutaneous fat [54]. This phenomenon can be partially explained by the differences in the TRs expression between the visceral and subcutaneous tissues as well as between obese and slim individuals [50]. The decreased expression of TRs in adipose tissues of obese individuals is also suggested as a potential mechanism of a relative resistance to thyroid hormone that manifests itself by the increased fT3 serum levels [52] and correlates positively with the increase in weight [55]. Another explanation for the elevation of fT3 (and thyroid stimulating hormone – TSH) in obese individuals is the regulatory action of leptin – an adipokine secreted by the adipose tissue that can promote expression of the thyrotropin releasing hormone (TRH) gene in the hypothalamus and increase peripheral conversion of T4 to T3 *via* stimulation of deiodinases. Finally, it is also postulated that thyroid function abnormalities observed in obese individuals may constitute an adaptive process aimed at the increase of the resting energy expenditure [56].

Animal studies

The metabolic phenotype of mice with targeted disruptions of *thra* is very variable, depending on the mutation. The *thra* *-/-* mice are cold intolerant and have higher energy expenditure in room temperature. Despite the increased appetite, they are leaner than the wild type animals. Interestingly these differences disappear in thermoneutral conditions, suggesting that exposition to cold results in *thra* *-/-* mice in activation of facultative thermogenesis pathway (increased sympathetic activation) that is more energy demanding and associated with relative resistance to diet-induced obesity [57]. Animals with frame shift *thra* mutations (TR α 1-P398H and TR α 1-L400R), resulting in reduced T3 affinity and/or decreased binding to the cofactors, have reduced cold-induced thermogenesis. In contrast, TR α 1-R384C mice (with decreased receptor affinity towards T3) are hyperphagic and resistant to obesity due to a centrally induced hypermetabolism caused by apo-TRh1 (binding DNA without binding T3). In turn TR α 1-P453H mice (with impaired receptor binding capacity) demonstrate increased body fat and insulin resistance [58].

In analogous experiments with *thrb* *-/-* mice, no major disturbances in body weight regulation and cold-induced thermogenesis have been observed, while in mice with targeted *thrb* mutations severe growth retardation is accompanied by an impaired weight gain. It is suggested that high T3 levels lead in these animals to the increased activation of TR α 1 [59].

Genetic studies

Heterozygous mutations within genes encoding TRs, causing reduced receptor affinity towards T3 or impaired interaction with transcription cofactors, lead to the development of resistance to thyroid hormone (RTH) syndromes [58]. The clinical picture of RTH may vary depending on the affected TR isoform and on the type of the mutation which can be inherited or occur *de novo* only in some organs and tissues [60]. Although over 170 different mutations in *THRB* have been described to date, in general the RTH β , caused by heterozygous mutations in the ligand-binding domain of *THRB*, is characterized by high serum TH levels with nonsuppressed TSH leading to goiter, tachycardia, hyperphagia and raised energy expenditure [58]. It is speculated that hyperphagia and increased resting energy expenditure

observed in patients with classical RTH β is mediated by elevated TH acting centrally on TR α [61].

Patients with mutations in the *THRA* region unique for TR α 1, causing a very rare RTH α has normal body temperature, but lower basal metabolic rate and tendency to gain weight with age [62].

A recent study suggest that two SNPs (rs12939700 C1890A and rs1568400 A-635G) located in the critical regions of *THRA* involved in the regulation of splicing may contribute to the development of obesity [63]. In high cardiovascular risk cohort carriers of the rs12939700 A allele had higher weight and higher prevalence of obesity than CC homozygotes. In turn, in general population and in the longitudinal study, individuals homozygous for the G variant of the A-635G SNP had significantly higher baseline BMI as well as higher increase in weight and in waist circumference after the 6-year follow-up. What is interesting, the analysis of this SNP in high cardiovascular risk patients showed a gene-diet interaction: only the individuals with GG genotype and a high intake of saturated fats showed a significant association with increased BMI. None out of several other SNPs identified in *THRA* and *THRB* was associated with obesity [64].

TRs ligands in treatment of obesity

In animal model of obesity (ob/ob mouse), the administration of exogenous T3 decreases body weight and body fat without a significant change in body protein content [65]. There is a lack of well-designed prospective studies regarding the use of thyroid hormones in euthyroid obese patients. Available studies were conducted on relatively small number of patients and the effect of hormone therapy on the weight loss was not consistent [66]. Use of thyroid hormones in supraphysiological doses is associated with serious cardiological complications and osteoporosis and these effects are traditionally associated with the activation of TR α receptors. Therefore, a number of selective TR β agonists are being tested for their efficacy in obesity treatment. The use of selective TR β ligands has been linked to metabolic improvement in animal models of diet-induced obesity, nonalcoholic liver disease, and genetic hypercholesterolemia. GC-1, an agonist with 10-fold higher affinity towards TR β compared to TR α , was found to accelerate metabolic rate and reduce fat mass in rats without causing heart hypertrophy and bone mass loss [67]. The treatment of rats with another TR β selective agonist GC-24 partially prevented the metabolic alterations (e.g. hyperinsulinemia and hypertriglyceridemia) associated with a hypercaloric diet by increasing energy expenditure in BAT [68]. However, this effect was more pronounced in initially normal-weight than in obese animals [69]. Another TR β selective agonist KB-141 increased metabolic rate and lowered plasma cholesterol levels without tachycardia in lean rats. Moreover, its administration to obese Zucker fa/fa rats improved glucose tolerance and insulin sensitivity suggesting that selective TR β activation may be a useful strategy to attenuate features of the metabolic syndrome [70].

Clinical trials with the use of selective TR β ligands proved their efficiency in improving the lipid profile, while no significant effect on weight loss was noted, suggesting that the regulation of basal metabolic rate in humans is also dependent on TR α signaling [71]. This theory is supported by the experiments performed on hypothyroid mice, in which the treatment with the selective TR β agonist (GC-1) alone failed to restore proper thermogenic function. It is suggested that TR α mediates in synergism between T3 and the adrenergic pathway, while induction of UCP1 expression depends on TR β activation [72]. TR α (as it was mentioned above) seems to be also important in T3-dependent central regulation of satiety [73]. New TR α selective agonists are being

studied in order to improve our understanding of the role of this isoform in thermogenesis and other T3 regulated processes [74]. The effectiveness of these compounds, however, may be limited due to the decreased expression of *THRA* and *THRB* genes in adipose tissues of obese individuals [50,52].

Final Remarks and Conclusions

The worldwide epidemic of obesity creates a need of developing new non-invasive methods of its treatment. Given the promising results of the *in vitro* and animal studies, the activation of thermogenesis in adipose tissue *via* adrenergic beta receptors and/or thyroid hormone receptor ligands seems to be an attractive therapeutic approach. However, the results of studies regarding the use of these compounds in the treatment of obesity in humans are largely disappointing. Among the probable causes of these discrepancies one should list: (i) differences in the mechanisms regulating thermogenesis and in its role in the body's energy expenditure in humans and rodents, (ii) genetic variations (polymorphisms and mutations) that may impair the function of the target receptors (ADRBs and TRs), and (iii) a decreased expression of ADRBs and TRs in adipose tissues of obese individuals that can significantly reduce the effectiveness of the therapy.

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