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REVIEW

Thyroid hormone metabolites and analogues

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Abstract

Several metabolic products that derive from L-thyroxine (T4) and 3,3′5-L-triiodothyronine (T3), the main thyroid hormones secreted by the thyroid gland, possess biologic activities. Among these metabolites or derivatives showing physiological actions some have received greater attention: diiodothyronines, iodothyronamines, acetic acid analogues. It is known that increased thyroid hormone (T3 and T4) levels can improve serum lipid profiles and reduce body fat. These positive effects are, however, counterbalanced by adverse effects on the heart, muscle and bone, limiting their use. In addition to the naturally occurring metabolites, thyroid hormone analogues have been developed that either have selective effects on specific tissues or bind selectively to thyroid hormone receptor (TR) isoform. Among these GC-1, KB141, KB2115, and DITPA were deeply investigated and displayed promising therapeutic results in the potential treatment of conditions such as dyslipidemias and obesity. In this review, we summarize the current knowledge of metabolites and analogues of T4 and T3 with reference to their possible clinical application in the treatment of human diseases.

Introduction

The major product generated within the thyroid as precursor is 3,5,3′,5′-tetraiodo-L-thyronine (T4), which is formed at three so-called "hormonogenic sites" on thyroglobulin polypeptide chain. T4 is considered a precursor of the active hormone, although it possesses some biological activities. 3,5,3′-triiodo-L-thyronine (T3) is now universally considered the active form of the thyroid hormones. In addition, there are many metabolic products that derive from T4 and T3 and that possess a variety of biological activity. Many biochemical pathways, such as sulfation, deiodination, decarboxylation, deamination, and *N*-acetylation are involved in the formation of naturally occurring compounds, defined metabolites or derivatives. Recently, among metabolites showing biological activities diiodothyronines, iodothyronamines, acetic acid analogues have received more attention.

One of the most widely recognized effects of thyroid hormones (TH), in particular T3 in adult mammals is its influence over energy metabolism, also known as the "calorigenic effect". Indeed, it is universally accepted that TH are unique in their ability to stimulate calorigenesis/thermogenesis by affecting cellular respiration with a concomitant reduction in metabolic efficiency. These effects are due to a transcriptional modulation of specific genes, which are mediated via nuclear formation of complexes between T3 and nuclear thyroid hormone receptor (TR) proteins, and the subsequent occupancy of regulatory complexes (composed of TR and other nucleoproteins) at thyroid hormone response elements on hormone-responsive genes. The metabolic effects of TH are mainly mediated by the β isoform of the nuclear recepors. It is known that increased thyroid hormone levels can improve serum lipid profiles and reduce fat but, these positive effects are counterbalanced by the induction of a thyrotoxic state and in particular a harmful effects on the heart, muscle and bone. Thus, attempts to use thyroid hormones for cholesterol-lowering and weight loss purposes have so far been limited.

Because of this in recent years, analogues have been developed that either have selective effects on liver vs. heart or bind selectively to TRβ rather than to TRα. Thus far, several tissue-specific and TR isoform–specific compounds have been developed that are geared, in principle, toward

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the potential treatment of conditions, such as dyslipidemia and obesity. Among these: GC-1 ((3,5-dimethyl-4[(40-hydroxy-30-isopropylbenzyl)-phenoxy] acetic acid), KB141 (2-[3,5-dichloro-4-(4-hydroxy-3-propan-2-ylphenoxy) phenyl] acetic acid), KB2115 (Eprotirome, 3-(3,5-dibromo-4-(4-hydroxy-3-(1-methylethyl)-phenoxy)-phenyl)-amino-3-oxopropanoic acid), and 3,5-diiodothyropropionic acid (DITPA) were investigated and displayed promising therapeutic results. However, although the encouraging results (in particular in the treatment of experimentally-induced obesity, in dyslipidemia and liver diseases) significant adverse effects have been noted and have limited their use [1].

In this review, we summarize our current understanding of metabolites and analogues of TH with reference to their possible clinical application in the treatment of some diseases, such as fatty liver disease, insulin-resistance, metabolic syndrome, abnormalities of the nervous system, and cancer.

GC-1

One of the most studied analogues of TH that possesses the beneficial metabolic properties of T3 is GC-1. The GC-1 was designed and synthesized by Chiellini et al. [2]. GC-1 resulted a thyroid hormone analog that has a high affinity for the TRs and is selective in both binding and activation function for TRβ over TRα.

Immediately after the synthesis of GC-1, many studies demonstrated its beneficial effects mainly on dyslipidemias and obesity with no undesirable effects mainly on the heart.

One of the first studies aimed at evaluating the effects of GC-1 "in vivo" was in the year 2000. In this investigation GC-1 was administered to hypothyroid mice and hypercholesteremic rats, and its effect was compared with that of equimolar doses of T3 [3]. The results, showing the cholesterol- and triglyceride-lowering capacity of GC-1, were encouraging. A very relevant finding from this study was that no harmful effects were found on heart weight, heart rate, and mRNAs coding for proteins related to cardiac contraction, such as myosin heavy chain α (MHCα), MHCβ, and sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2). Later, the same authors carried out a study of the effects of GC-1 on metabolic rate and cholesterol level in rats and primates. They showed that GC-1 had the capacity to lower cholesterol and to stimulate metabolic rate without inducing tachycardia. GC-1 decreased serum HDL in treated mice, increased the expression of HDL receptor SR-B1, stimulates the activity of cholesterol 7b-hydroxylase and increased the fecal excretion of bile acids. Thus, GC-1 may regulate key steps in the reverse cholesterol transport pathway without increasing heart rate [4]. In a more recent study, the authors investigated the capacity of T_3 and the thyroid hormone receptor-β selective agonists GC-1 and KB2115 of reducing serum cholesterol in mice devoid of functional LDLRs (LDL receptors). The results demonstrated that the positive effects of the analogs were due to the induction of Cyp7a1 expression and to the stimulation of the conversion and excretion of cholesterol as bile acids. Based on this LDLR-independent mechanism, the authors claimed that thyromimetics such as GC-1 and KB2115 may represent promising cholesterol-lowering treatment of diseases, such as homozygous familial hypercholesterolemia, (a rare genetic disorder caused by a complete lack of functional LDLRs) for which there are limited treatment options, because most therapeutics are only minimally effective [5].

In addition, recently Goncalves et al. [6] showed that GC1 recovers the reduced tolerance to exercise in hypothyroid rats. Unlike T4, GC-1 also administered in supraphysiological doses (10 × T4) does not alter effort to tolerance test nor does it modify diameter of cardiomyocytes. Thus, the authors of these findings suggest that GC-1 combined with exercise may safely treat hypercholesterolemia and/or obesity.

KB141 and KB2115

Studies using synthetic analogues continued with other molecules. One of these was the KB141. KB141, binds with 14-fold greater affinity to TRβ than TRα, and there has been reported to be a 10-fold difference between its ability to induce a heart rate increase and its cholesterol-lowering activity [7]. Grover et al. [8] examined the effect of TRβ activation on metabolic rate and heart rate (HR) with either $TR\alpha1^{-/-}$ mice or the selective TRβ agonist KB141 in mice, rats, and monkeys [8]. They compared the results with those obtained with T3. T3 had a greater effect on increasing HR in wild type (WT) than in $TR\alpha1^{-/-}$ mice. In addition, T3 increased metabolic rate in both WT and $TR\alpha1^{-/-}$ mice, but the effect in the $TR\alpha1^{-/-}$ mice at the highest dose was half that of the WT mice. Thus, metabolic stimulation was likely due to both TRβ and TRα. KB141 increased metabolic rate both WT and in $TR\alpha1^{-/-}$ mice and reduced both cholesterol level and stimulated metabolism in rats without increasing HR. In primates, KB-141 caused significant cholesterol, lipoprotein (a), and body-weight reduction (up to 7% after 1 week) with no effect on HR. The authors conclude that TRβ-selective agonists may constitute a previously uncharacterized class of drugs to treat obesity, hypercholesterolemia, and elevated lipoprotein. Nevertheless, KB141 has not been pursued for human use [7].

Recently, a novel THR-selective analogue has been identified, KB2115 (Eprotirome) [9]. KB2115 has modestly higher affinity for TRβ than for TRα and has minimal non-hepatic tissue uptake. KB2115 like GC-1 was able to markedly reduce serum cholesterol in mice devoid of functional LDLRs [5] and to prevent, in high-fat diet rats, the development of hepatic steatosis [10]. A clinical trial, in which Eprotirome was given in combination with statin therapy, has shown that it strongly lowers the serum cholesterol levels without adverse extrahepatic thyromimetic effects [11]. Despite these encouraging results, clinical trials were discontinued because long-term studies in dogs resulted in cartilage damage [12] and eprotirome showed the potential to induce liver injury by increasing in transaminase and conjugated bilirubin concentrations [13]. Recently, other TRβ selective agonist MGL-3196 have been developed with none of the side effect of thyroid hormone axis. Results from human studies showed that doses from 50 to 200 mg of MGL-3196 per day induced a reduction in serum lipids, including LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B, and triglycerides [14].

DITPA

Another important TH analogue is the DITPA. It binds with similar affinity to both TR isoforms with relatively low affinity [15]. In humans, DITPA has been studied in the context of heart failure [16, 17]. In fact, when administered in a pilot trial in patients with congestive heart failure, DITPA increased cardiac index, decreased systemic vascular resistance, serum cholesterol, low-density lipoprotein cholesterol and body weight. As some studies have shown that the cellular uptake of DIPTA is monocarboxylate trasporter 8 (MCT8) independent [18], it was used in the treatment of patients with mutations in MCT8 gene responsible for Allan–Herndon–Dudley syndrome (AHDS). In fact, the administration of DITPA to MCT8 KO and control mice results in similar tissue availability and DITPA is able to, at least partially, restore the abnormal expression levels of several well-known T3-responsive genes and deiodinase activity in the liver and brain of hypothyroid control and MCT8 KO mice in a dose-dependent way [18]. Furthermore, the administration of the lowest dose DITPA to MCT8 KO mice has only minor effects on TH markers in the brain, whereas it already normalizes the hypermetabolic state [19]. In line with the preclinical data, treatment of four AHDS patients with increasing doses of DITPA normalized the high serum T3 levels in all four patients. However, several markers of peripheral TH action, including heart rate and body weight showed variable responses among the patients [20]. No effects were observed on neuropsychological functioning. It is yet unclear to what extent DITPA rescues brain development in human AHDS subjects should administration be started early after birth.

Metabolites

Recently, evidence has been provided that some TH metabolites, for a long time considered inactive products of the metabolism of thyroid hormones, possess biological activities. The endogenous occurring compounds that received marked attention were 3-Iodothyronamine (3-T1AM), 3,5-Diiodo-L-Thyronine (T2), ReverseT3 (rT3), Triiodothyroacetic acid (Triac), and Tetraiodothyroacetic acid (Tetrac).

3-T1AM

After demonstrating a rapid effect of T4 on adrenergic nerves, MB Dratman was the first to hypothesize that thyroxamines (including some thyronamines) could be metabolites of T4 formed by activating enzymes involved in the formation of biogenic amines such the amino acids-decarboxylase [21]. Recently the enzyme responsible of these transformations was identified as ornithine decarboxylase [22]. A previous study of the same group had provided evidence of extrathyroidal formation of 3-iodothyronamine in humans [23].

The first manuscript that reported remarkable biological effects of the 3-T1AM was published in 2004 by Scanlan et al. [24]. In this study on rats the authors showed a powerful and rapid action of 3-T1AM on thermoregulation, energy homeostasis and metabolism. These remarkable effects were contrary to the thermogenic and metabolic actions of T3. This generated considerable interest in the scientific community and motivated studies aimed to demonstrate the physiological role of this molecule and its possible therapeutic use. Conflicting results can be found in the literature on the concentration of 3-T1AM in blood and tissue, but seem concordant that it concentrates in some organs, such as liver, brain, and muscle [25]. Most of the effects of 3-T1AM have been obtained on rodents and “in vitro” models and also because of supra-physiological concentrations used, remains to be shown that some results obtained “in vitro” and on animal models is then possible to reproduce in humans. With regard to the beneficial effects of 3-T1AM they relate specifically to actions on metabolism, liver (or hepatocytes), adipose tissue, nervous system and cancer.

Mariotti et al., have demonstrated that “in vivo” 3-T1AM administration produces significant transcriptional effects, more evident in adipose tissue than in liver of rats. These effects might contribute to explain the increased lipid metabolism and the reduced fat mass, suggesting the use of 3-T1AM as a lipolytic agent and gain importance in view of a possible clinical use in obesity and dyslipidemia [26]. Studies on nervous system “in vivo” models showed that 3-T1AM improved learning capacity, decreased pain threshold to hot stimuli, enhanced curiosity and raised plasma glycaemia in a dose-dependent way, without modifying T3 and T4 brain concentrations. This feature might have important implications for the treatment of neurodegenerative-induced memory disorders [27]. Many studies have also explored the effect of 3-T1AM on cancer cells, demonstrating that this metabolite is able to reduce growth and viability of these cells. These findings support the potential for use of this compound for its anti-proliferative properties in cancer cells [28].

T2

A study aimed to show a possible presence of mitochondrial specific binding sites for T3 reported that these sites had the capacity to bind a diiodothyronine such as the 3–3′-diiodo-L-thyronine [29]. Soon after Horst et al. analyzed the effects of a series of thyronines on the oxygen consumption in isolated perfused rat liver. Surprisingly, they showed that 3,5-diiodo-L-thyronine (T2) had the greatest capacity to stimulate liver oxygen consumption [30]. T2 is an endogenous metabolite of thyroid hormones. Over the last decades, T2 has received marked attention as it was demonstrated to be a biologically active compound. Several studies indicated that T2 exhibits important biological effects in different tissues such as liver, skeletal muscle, heart and brown adipose tissue (BAT) [31–33]. Although the formation of T2 has not been experimentally demonstrated, the most plausible pathway for T2 is an unknown peripheral enzymatic process, probably utilizing T3 as its precursor. Indeed, we have demonstrated that already after 12 h of administration of T3 in rats the serum concentration of T2 resulted increased [34]. The same results have been obtained in patients receiving T4 supplements [35]. A great body of evidence has reported that T2 is able to mimic some of T3’s effects on the metabolism [36]. The accumulated evidence suggests that the actions of T2 do not simply mimic those of T3 but instead are specific actions exerted through mechanisms that mostly are independent of those actuated by T3 and do not involve TRs [37]. However, some studies have highlighted that T2 binds to the long form of TR in tilapia stimulating its growth. In this species, therefore, it is possible that T2 operates a transcriptional activity mediated by TR [38].

It has been shown that T2 administration to hypothyroid rats increases their resting metabolic rate [34], cold tolerance [39], and their ability to use lipids as metabolic substrates [40, 41]. In addition, chronic administration of T2 to rats fed a high fat diet (HFD) was able to prevents body weight gain, liver adiposity, hypercholesterolemia and hypertriglyceridemia, concomitantly preserving muscle glucose uptake and insulin sensitivity [42–45]. The dose of 25 μg/100 g body weight (for 4 week) used in these experiments did not altered hypothalamus-pituitary-thyroid axis [37, 42, 43]. Administering the same dose of T2 to HFD-overweight rats significantly reduces pre-existing hepatic fat accumulation and hyperlipidemia, through its ability to stimulate hepatic mitochondrial fatty acid oxidation [46]. Notably, T2 directly activates SIRT1, leading to the deacetylation of PGC1α and activation of its transcriptional activity to induce expression of the genes involved in fatty acid oxidation. “In vitro” study also shows that T2 in steatotic hepatocytes reduced the lipid content and lipid droplet diameter by modulating the activities and localization of lipases [47]. In addition to the stimulation of pathways of lipid oxidation, “in vivo” studies, using a validated rat model of fatty liver, show that T2 prevent the pathways leading to lipid storage in lipid droplets (LDs), promote the processes of lipid mobilization from LDs and secretion as VLDL, confirming its anti-steatotic ability [48]. More recently, Iannucci et al., using a metabolomic approach, showed that T2 like T3 had lipolytic effects in the liver mediated by autophagy and increased fatty acid oxidation, although the metabolic profiles of two compounds confirmed that there may be some differences in the mechanism (s) and magnitude of their metabolic effects. Interestingly, although both T2 and T3 decreased hepatic fat content, only T2 was able to rescue the impairment in AKT and MAPK/ERK pathways caused by HFD [49].

It was also showed that T2 enhances glucose-induced insulin secretion in both rat β-cells and human islet cells [50]. In addition, “in vivo” studies on adipose tissues show that T2, besides activating BAT thermogenesis [51], is able to promote the browning of white adipose tissue in overweight rats. These results indicate that the browning may be another mechanism by which T2 exerts its beneficial effects on overweight and fat mass [52, 53]. Furthermore, T2, when simultaneously administered to rats exposed to HFD, rapidly (within a day) promotes visceral adipose lipolysis through HSL activation. Long-term treatment with T2 produced effects on adipocyte morphology (already measurable after 2 weeks and persistent at 4 weeks of treatment), tissue vascularization, and the protein profile [54]. At the gastrocnemius muscle level and without inducing sarcopenia, T2 prevents the HFD-induced IMCL accumulation as well as the derangement in insulin signaling, mainly by inducing a structural and biochemical shift toward glycolitic type II myofiber [45]. Recent studies have shown that the T2-shift toward glycolitic myofiber is accompanied by a co-adaptation of mitochondrial structural and functional features [55].

Ample evidence suggests that mitochondria are the principal target of T2. Indeed, the ability of T2 to stimulate not only liver oxidative capacity and to increase FoF1-ATP synthase expression and activity, but also skeletal muscle mitochondrial uncoupling underlies this hormone's effect on the increased resting metabolic rate [56–59]. Recent studies of effect of T2 on individual electron transport chain complexes, their organization in supercomplexes and their relationship whith mitochondrial oxidative capacity show that T2, by influencing the kinetic properties of specific mitochondrial respiratory pathways, promotes a rapid response of the organelle to variations in energy demand [41]. In addition, T2 may preserve liver mitochondrial integrity by inducing protective repair mechanisms against mtDNA oxidative stress [60].

In a case study, T2 supplementation led to an increase of resting metabolic rate and a body weight reduction without undesirable side effects [61].

All these data provide stronger rationales and tools for using T2 to treat human metabolic disorders. However, further studies are being conducted to fully explore its beneficial therapeutic application.

Triac and Tetrac

As described above, the deiodinases regulate the bioavailability of T3 in targets cells but other metabolic pathways exist that modify the iodothyronines skeleton. The other pathways include decarboxylation of the alanine side chain, resulting in iodothyronamines [22, 24], and subsequent oxidative deamination resulting in the formation of iodothyroacetic acid derivatives [62]. The mechanism by which iodothyronines are converted to iodothyroacetic acid metabolites is complex and has not been fully elucidated. Some of these metabolites, such as Triac and Tetrac, have been found to exert biological effects. The most noteworthy ones are those related to prevention of abnormal brain development, resistance to TH in patients harboring TRβ mutations, transporter defect and to cancer. Several studies showed that Triac regulates thyroid activity by inhibiting TSH production and secretion [63]. In addition to its effect on HPT axis, it has been reported that the thyromimetic effect of Triac, at an equal TSH suppressive dose, are at least as potent as those of T4 in most peripheral organ such as liver and skeletal muscle [64, 65].

Kersseboom et al. have shown that "in vitro" studies the cellular uptake of Triac is MCT8-independent [66] and that the administration of Triac in Pax8 KO mice was able to prevent abnormal brain development. This prevention was shown by an almost normal Purkinje cell morphology, myelination and parvalbumin expression in the cerebral cortex [66]. These effects were also observed in MCT8/OATP1C1 dKO mice. These findings further confirm that MCT8 is not required for this response [66]. The positive results obtained by Triac on brain development have also been supported by studies in chicken in which MCT8 was silenced [67], and in a zebrafish model lacking MCT8 [68]. As MCT8 is not required for Triac action, Triac has the therapeutic potential in the treatment of patients with specific defects in TH signaling [69], such as patients harboring mutations in TRβ (resistance to thyroid hormone (RTH) [70] and in patients with AHDS, which is characterized by severe intellectual and motor disability. Several studies have supported the therapeutic efficacy of Triac and its less rapidly metabolized precursor Tetrac in AHDS. Tetrac treatment normalize the serum TH pattern of MCT8 KO mice that is similar to that of AHDS [71]. The putative role of Triac as a therapy for AHDS patients is currently under investigation in a prospective interventional cohort study, the Triac Trial (NTCO2060474) [72]. Further studies on Tetrac are needed to determine its efficacy and utilization in humans [72]. The possible effects of Triac and Tetrac on cancer cells have been carried out because they act at integrin (αvβ3), receptors of plasma membrane that are heightened in these cells. Both metabolites show anti-proliferative effects in cancer cells [36]. As Tetrac has the capacity to bind nuclear TR with a high affinity, some studies have been carried out by chemical modification of Tetrac in a nanoparticulate drug to minimize its access to the nucleus when it is internalized by the cells [73]. The actions are anti-proliferative, pro-apoptotic and anti-angiogenic by multiple mechanisms. The actions of Triac on cancer cells has not been fully investigated and further studies are needed to assess its possible anticancer agent [74].

In addition to biological activities above mentioned, it has been reported that Triac inhibits expression and secretion of leptin in both white and brown adipocytes with a potency similar to that of T3 [75]. Very recently, it has been shown that Triac exhibits shows anti-inflammatory properties in a mouse model of hepatitis [76].

rT3

Inner ring deiodination at the 5 position of T4 generates rT3, a thyroid hormone analogue that via nongenomic actions influences some cellular events. Several years ago, it was shown that rT3 like T4 was able to restore the levels of filamentous actin (F-actin) into cerebellar cells of hypothyroid neonate rats in which rT_3 initiates actine polymerization in astrocytes and is at least 100-fold more potent than T3 [77]. Recently, Domingues et al. [78] provided evidences that rT3 restores neurochemical parameters induced by congenital hypothyroidism in rat hippocampus and that rT_3 actions are initiated by interaction of the hormone with the integrin αvβ3 receptor. Heterodimeric integrin αvβ3 is overexpressed in a number of types of cancer and T4 has been shown to stimulate their

Table 1 Beneficial effects exerted by TH metabolites and analogues

Analogues		Beneficial effects	References
GC-1	↓	Total or LDL-cholesterol levels Triglyceride levels	[3–5]
	↑	Tolerance to exercise	[6]
KB141	↓	Cholesterol levels Lipoprotein levels Body weight	[8]
KB2115	↓	Total or LDL-cholesterol levels Hepatic steatosis	[5, 10]
DITPA	↑	Cardiac index	[15, 16]
	↓	Systemic vascular resistance Cholesterol levels Lipoprotein levels Body weight	[15, 16]
	↑	TH signaling in resistance to thyroid hormone and Allan–Herndon–Dudley syndrome	[17]
Metabolites			
3-T1 AM	↑	Anti-Amnestic and learning capacity Lypolitic effect	[25, 26]
	↓	Thermoregulation Growth and viability of cancer cells	[23, 27]
3,5-T2	↑	Resting metabolic rate	[33, 60]
	↓	Body weight gain Cholesterol and triglycerides levels Hepatic steatosis Insulin resistance Blood glucose	[41, 42, 45, 47–49, 52]
	↑	Browning of white adipose tissue Mitochondrial DNA repair	[51, 59]
Triac	↑	Brain development Anti-proliferative, pro-apoptotic and anti-angiogenic effect in cancer cells	[35, 65–67, 73]
	↑	TH signaling in resistance to thyroid hormone and Allan–Herndon–Dudley syndrome	[68, 69, 71]
	↓	Inflammation Expression and secretion leptin	[74, 75]
Tetrac	↑	Anti-proliferative effect in cancer cells Brain development	[35, 70, 72]
rT3	↑	Brain development	[76, 77]
	↓	Neuronal damage	[80]

proliferation really via αvβ3 [36]. Lin et al. [79] showed that also rT3 caused increases of proliferation in vitro of human breast cancer and glioblastoma cells and concluded that rT3 may be a host factor supporting cancer growth. These conclusions are supported by observation that in the non-thyroidal illness syndrome (NTIS) that may be associated with advanced cancers circulating rT3 levels may be increased [80]. On the other hand, in contrast to these adverse effects on cancer cell, rT3 shows beneficial effect in some case of neuronal damage. Recent studies have shown that rT3 attenuates the damage in post-ischemic brain after reperfusion injury [81] and support the possible therapeutic use of this agent in reducing neuronal damage and improving stroke outcome.

Conclusion

It is evident that some metabolites and analogues of TH are able to affect some interesting metabolic/physiological pathways involved in mechanisms that underlie some relevant diseases. In fact, many of these influence lipid metabolism offering interesting perspectives for deeper investigations on their use as therapeutic agents useful to counteract some disease states such as obesity, hypercholesterolemia, hypertriglyceridemia, insulin resistance. In addition, in the last decades, numerous studies have highlighted the positive effect that these compounds have on the etiology and progression of diseases related to the nervous system and the cancer (summarized in Table 1). However, although encouraging, these findings must be investigated more thoroughly before affirming that they are promising candidates for clinical application.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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