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Neuroprotective effects of thyroid hormones and their metabolites

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Abstract:

Background: Classical thyroid hormones have an established necessary role in the normal development of the central nervous system and recently, they have also been considered as decisive factors influencing cognitive functions in adult brain and involved in the development of Alzheimer's disease. The picture summarizing thyroid hormone effects on adult brain, however, does not only include classical thyroid hormones but also the products of their peripheral metabolism. These latter have been considered as inactive breakdown products for long but recently were proved to produce significant biological effects.

Objective: In this review article we present recent evidence supporting the hypothesis that thyroid hormones exert a neuroprotective effect in brain areas involved in learning and memory. Moreover, we summarized the evidence that suggests that non-classical thyroid hormones produce significant neurological effects in the adult brain. Also, we discuss the possible role of thyroid hormones in the cognitive impairment typical of Alzheimer's disease.

Methods: A comprehensive review of the literature on the current knowledge on the effects of classical and non-classical thyroid hormones in adult brain and their role in Alzheimer's disease was performed.

Results: The available literature suggests that both classical and non-classical thyroid hormone act as neuroprotective agents in brain areas related to learning and memory. Their role in these areas support the idea that they may be involved in the development of Alzheimer's disease.

Conclusion: Thyroid hormones produce significant neurological effects, act as neuroprotective agents and might be considered as future diagnostic and therapeutic tools for Alzheimer's disease.

Keywords: thyroid hormone, 3-iodothyronamine, neuroprotection, memory, hippocampus, dementia.

1. INTRODUCTION

With this review we aim to summarize the effects produced by thyroid hormones (TH) and their metabolites in the adult brain with a special focus on the modulation of learning and memory in both physiological and pathological conditions.

The first part of this paper provides the reader with the necessary background to understand the production, metabolism and modes of action of TH. The second part deals with the neuroprotective role and neurological effects of classical TH and their metabolites.

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1.1Thyroid hormones: synthesis and transport to tissues.

The thyroid gland is involved in the production of the so-called classical thyroid hormones (TH) that include the two main iodothyronines: 3,5,3',5'-tetraiodo-L-thyronine (T_4) and 3,5,3'-triiodo-L-thyronine (T_3). The definition of classical TH has been used to differentiate T_4 and T_3 from the products of peripheral TH metabolism (apart from T_3). TH metabolites, that have been for long thought to represent only TH breakdown products, have been recently proven to produce relevant biological effects[1].

The synthesis of TH by the thyroid gland is a very complex process whose biochemical details go beyond the scope of this review, however, the main steps will be briefly exposed. The initial passages in thyroid hormones synthesis consist in iodide uptake, that is operated by the thyroidal sodium-iodide symporter, and its oxidation, mediated by thyroid peroxidase. Once oxidized, the iodide is incorporated into the protein thyroglobulin (Tg) at the level of tyrosine residues producing either monoiodotyrosine (MIT) or diiodotyrosine (DIT). The coupling of MIT and DIT or of

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two DITs, mediated by the thyroid peroxidase, leads to the formation of T_3 and T_4 respectively. TH are still part of Tg molecule (stored in the thyroid colloid) and, they are released once Tg undergoes cleavage. This process occurs in the fagolysosome formed after the pinocytosis of the colloid in thyroidal cells[2].

The efficient synthesis of thyroid hormones in the thyroid gland requires the combined expression of a number of thyroid cell-specific proteins and the transduction of the effects induced by thyroid-stimulating hormone (TSH), synthesized by the pituitary gland. This process leads to the daily appropriate synthesis of 110 nmol/l (85 μg) of T_4 and of very small amount of T_3 by the thyroid gland. The T_4 is synthesized entirely within the thyroid gland; on the contrary, only 20% of T_3 present in the circulation is secreted directly by the thyroid gland itself. The remaining T_3 derives from the peripheral 5'-monodeiodination of T_4. Given T_3 higher affinity for TH, T_3 was thought to be the active form of T_4[3–5]. The deiodinase activity and thyroid gland TH synthesis act with the hypothalamic-pituitary axis in a tight-regulated fashion so that TH levels appropriately meet the requirements of peripheral tissues.

Due to their chemical structure, classical iodothyronines are poorly soluble in water and, therefore, have to bind reversibly to plasma proteins to be transported to peripheral tissues. Indeed, only 0,03% of total T_4 and 0,3% of total T_3 in serum is circulating in their free form.

Three are the main proteins that bind TH in the serum; thyroid binding protein (TBG), transthyretin (TTR or thyroxine-binding pre-albumin) and human serum albumin (HAS). A small amount (between 3 to 6%) of plasma TH are bound to lipoproteins; however, their physiological significance in TH binding is still under evaluation.

TH binding proteins can be seen as a reservoir and a buffering system that guarantees a constant supply of TH to tissue. This, in turn, protects the organism against the abrupt changes of plasma TH levels that can occur as a result of altered production, degradation or increased urinary loss. In addition, they also may play a role in targeting TH delivery to specific tissues. However, it has to be underscored that the portion of TH that is available to the tissues and that undergoes deiodination and degradation is the one that is present in the unbound form.

In order to produce their effect on nuclear and cytoplasmatic receptors, TH have to cross cell plasma membrane. Since 1950s [6,7] and for twenty years, it was believed that the passage of TH through the cell membrane occurred through passive diffusion. This misbelieve was based on the fact that TH have a lipophilic skeleton and should, therefore be able to cross the cell membrane without the need of transporters. The first report that suggested the presence of an energy-dependent mechanisms for the entry of TH in the intracellular space was that of Christensen et al in 1954 [8]. However, this work escaped attention and several later reports strongly advocated that TH diffuse passively through the plasma membrane to reach their intracellular targets [6,7]. The first two groups that addressed the possibility of a plasma membrane transport for TH were the group of Rao and Breuer in Germany [9] and the group of Hennemann in the Netherlands [10]. Afterwards, several groups have demonstrated that TH passage in the intracellular space requires a saturable and stereospecific uptake [11–13]. Even though, during the last decades, several studies on the kinetics of TH passage through cell membrane suggested the presence of specific transporters, only recently, such transporters have been identified at the molecular level. In addition, their importance has been highlighted by the identification of a neurological syndrome associated with genetic mutation of one of them, Allan-Herndon-Dudley syndrome. This disease is characterized by severe neurological involvement and reduced cerebro-spinal fluid (CSF) T4 concentration[14–16] in children.

TH transporters all belong to the solute-carrier gene (SLC) gene family and include Na+/taurocholate-cotransporting polypeptide (NTCP), several members of the Na+-independent organic anion-transporting polypeptide (OATP) family, two members of the monocarboxylate transporters (MCT) and large neutral amino acid transporters (LAT) [17–21]. Apart from MCT8, all transporters are also involved in the translocation of other substance, mainly steroids and amino acids whose concentrations in the tissue exceed by far TH concentrations.

1.2 Thyroid hormone peripheral metabolism

Once inside the cell, TH undergo to tissue-specific metabolism[22]. This includes deiodination, a process that leads to the formation of T_3 and other deiodinated thyronines. Conjugation with sulphate or glucuronic acid, that increases iodothyroinine solubility in bile and urine and, therefore also increases their clearance. Deamination and decarboxylation lead to the formation of acetic acid-TH analogs and thyronamines. Among these processes, deiodination is the one that is mainly involved in the regulation of TH tissue availability[5,23]. Indeed, they modulate T_3 concentration and TH receptor (TR) saturation removing specific iodine molecule from plasma T_4 and T_3. If the removal concerns the phenolic ring (5'-deiodination or outer ring deiodination) the net effect is the activation of T_4 into T_3, whereas, if the deiodination occurs at the level of the tyrosil ring (5-deiodination or inner ring deiodination), then, it produces 3,3',5'-triiodothyronine (rT_3)[24]. Deiodinase type I (DI) ,II (DII) and III (DIII) have in common the presence of a selenocysteine residue which is present at the catalityc domain of the enzyme structure but those enzymes have different roles in TH metabolism. Indeed, DI can function as either an outer or inner ring iodothyronine deiodinase; DII only acts as an outer ring deiodinase; whereas, DIII catalyses inner ring deiodination[24,25]. In addition, as it can be seen in Table 1 their affinity to TH is significantly different, with DII and

DIII Km (that inversely correlates with affinity) in the nanomolar range and DI one in the micromolar range.

DI was the first selenocysteine deiodinase to be discovered (by biochemical assays and cloning). It performs in an equally effective manner, inner and outer ring deiodination[25], and TH sulfatation facilitates the inactivation of T_3 and T_4 operated by this enzyme[26,27].

Table 1. Characteristics of deiodinases I, II and III.

	DEIODINASES		
Characteristics:	D1	D2	D3
Molecular weight (monomer, Da)	29,000	30,500	31,500
Preferred substrates (deiodination location)	rT3 (5'), T3S(5)	T4, rT3	T3, T4
Km (M)	10^{-7}, 10^{-6}	10^{-9}	10^{-9}
Tissues where there is high activity	Liver, kidney	CNS, pituitary, brown adipose tissue, placenta	Placenta, CNS, hemangiomas

Even though DI has been demonstrated to be a transmembrane protein, its specific location is still controversial. Some reports suggested that it is present at the plasma membrane and, potentially, this could represent a good location with regard to accessibility to circulating TH [28]. In addition, the plasma membrane location may explain why, apparently, DI has a very limited contribution in the intranuclear levels of T_3 when compared to DII[29,30]. On the other hand, other body of evidence may indicate that, as it happens for DII, DI is expressed in the endothelial reticulum with the catalytic subunit in the cytosolic space[31,32]. The limited contribution of DI to nuclear T_3 may then be explained by the fact that DII has a 1000-fold lower Km for T_4 than DI in the context of normal free T_4 concentrations in humans and thus could have a major role in extrathyroidal intracellular T_3 production[33].

With regard to its enzymatic properties, DI-mediated deiodination follows a ping-pong kinetics with two substrates: iodothyronines and an endogenous intracellular cofactor that has not been identified yet and with which propylthiouracil (a drug used to manage hyperthyroidism) competes, thus, inhibiting irreversibly DI[34–36]. Northern and Reverse transcription polymerase chain reaction (RT-PCR) analysis demonstrated that DI is present in human liver, kidney, thyroid, in pituitary gland and in circulating mononuclear cells but is notably absent from the CNS[37,38].

DII is the most recent cloned of the three deiodinase, it is an obligate outer ring selenodeiodinase that is, therefore, involved in the activation of T_4 to T_3 and in the conversion of rT_3 to 3,5-diiodo-thyronine (T_2)[25]. rT_3 also represent an excellent substrate for DII, although it is less affine than T_4[39]. Contrary to DI, DII intracellular location has been demonstrated to be in the endothelial reticulum where it is an integral membrane protein with its catalytic component in the cytosol[28]. With regard to its tissue distribution and local activity, it has to be highlighted that DII is known to be particularly important in the brain since it is involved in the production of more than 75% of nuclear T_3 in rodent cerebral cortex[40]. In the cortex DII mRNA is predominantly expressed in the glial cells, in addition, its activity is increase in tanycytes, a subclass of ependymal cell that are believed to be involved in the transfer of molecules from the CSF to the CNS[41–43] Moreover, DII mRNA or DII activity were found in human thyroid, heart, skeletal muscles, placenta, kidney and pancreas[39,44,45].

DIII is involved in inner ring deiodination and converts thyroid hormones into their biologically inactive counterparts[46]. It metabolizes T_4, T_3 and T_2 and does not recognizes as substrates the sulfated iodothyronines [47]. It seems likely that DIII contributes to TH homeostasis protecting tissues from the excess of TH. The most striking evidence of this role in TH homeostasis was identified during embryogenesis; indeed, as it was demonstrated in several foetal and neonatal animal models, its expression is strictly regulated in a tissue-specific pattern. This suggests that DIII is critical to coordinate thyroid hormone effects during a period (embryogenesis) when excess or reduced levels of TH may be detrimental. DIII has been identified in foetal liver but its expression appears to decrease during gestation and to disappear at the end of it [48]. In addition, with in situ hybridization in rats, it has been discovered that DIII mRNA is highly expressed in neurons located in areas of the brain that have been implicated in the processes of learning and memory (e.g. pyramidal and granule cells in the hippocampus); moreover, these areas represent locations with the highest concentration of TH receptors in the CNS[49–51]. Also, in Xaenopus laevis DIII has a pivotal role in retina differentiation[52].

As already mentioned TH can also undergo decarboxylation and oxidative deamination at the level of their alanine side chain. These processes occur in the liver and in peripheral tissues[53–55]. Their role in the generation of specific TH metabolites will be considered in the next sections.

Collectively, the data that has been presented suggest that TH transport and peripheral metabolism are complex processes that influences TH levels at which tissues are exposed and may, in turn, play a role in regulating TH peripheral activity.

1.3 Transport of thyroid hormones to the CNS

TH can reach the brain through two main pathways (Fig 1). They can cross the blood-brain barrier (BBB) and reach cells close to brain capillaries or they can be translocated through

the choroid plexus (CP) into the CSF in the cerebral ventricles[56].

The BBB is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid. It is made up by capillary endothelial cells and astrocyte processes named astrocytic feet (or "glia limitans") and it owes its permeability to the presence of tight junctions between endothelial cells in CNS vessels that selectively permit solute passage from blood to brain[57,58].

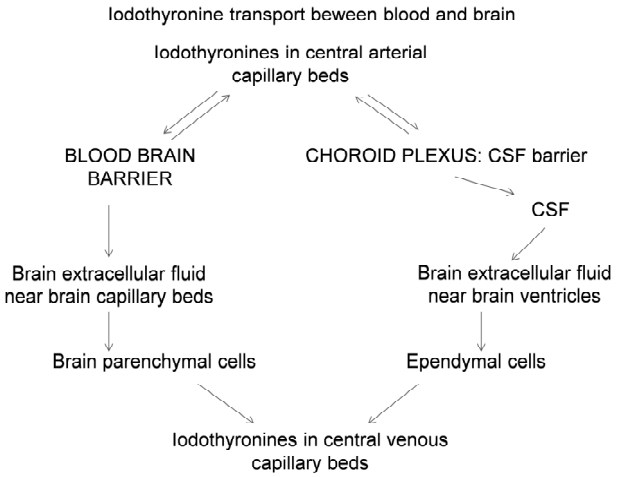

Figure 1 Iodothyroinine transport between blood and brain.

With regard to the CP, it is a structure that is part of the blood-cerebrospinal fluid barrier alongside with the arachnoid membrane that is located at the cerebral blood-CSF boundary[59].

The CP is a complex structure composed by several capillaries which are in strict contact with a layer of ependymal epithelium that is differentiated in a secretory fashion. The capillaries of the CP functional units are fenestrated and have no tight junction as their counterpart in the BBB; indeed, the barrier in this structure is represented by ependymal cells that regulate the passage of solutes. These modified cells have microvilli at the CSF-facing surface that may facilitate the secretion process, ultimately leading to the formation of the CSF. CPs are part of the brain ventricular system that is composed by four cavities lined by ependymal cells and containing CSF: two lateral ventricles connected to a third ventricle though the Monro foramina and a fourth ventricle in connection to the third one through the cerebral acqueduct and to the subarachnoidal space via the Magendie and the Luschka apertures. CPs in human brain are present in all the parts of the ventricular system apart from the cerebral acqueduct, the frontal and the occipital horn of the lateral ventricles. CSF is secret by CPs at a rate of 0.3 to 0.4 ml/min and its total volume is estimated to be approximately 100 to 150 ml in normal adults, suggesting that CSF is replaced three or four time each day. The composition of the CSF is tightly regulated and it is different from that of plasma. It contains 0.3% plasma proteins (15-40 mg/dL)[60], 60-80% of plasma glucose and has an osmolarity of 295 mOsm/L [61]. CSF flows through the ventricles, exits the ventricular system to reach the subarachnoid space where it is absorbed at the level of the arachnoid villi by a valve-like process that leads to the one-way flow to the venous sinuses. These latter are connected to the systemic circulation[59].

Several studies in the 1970s and 1980s demonstrated that both T_4 and T_3 can cross the blood brain barrier and the choroid plexus in a saturable manner[62,63] suggesting the presence of specific transporters. Namely OATP1A2, OATP2B1 [64,65], OATP-F [66]and LAT1 [67,68] are expressed in blood vessels and MCT8 [16]and OATP3A1 [69] in the choroid plexus.

Similarly to serum, in the CSF TH are bound to proteins, in this case TTR is the only protein implied in TH binding. CP is the tissue that has the highest concentration of TTR mRNA per gram tissue weight[70,71]. It has also to be mentioned that the amino acid sequence of TTR across all vertebrates is highly conserved[72], and this may suggest that the transport of TH in the brain has started to become pivotal after the formation of the part of the cortex involved in higher functions. Soprano et al in 1985[73] discovered that TTR synthesis in the CP was fundamental for the movement of T_4 into the CSF while it was not necessary for the passage of T_3. Moreover, in 1992 Kohrle's group demonstrated that TTR-T_4 complexes present in the blood are not transported across the CPs, suggesting that the TH transport requires TTR to be synthesized in the CP[74,75]. Another interesting point that has to be raised comes from comparative studies on TTR among mammalian and non-mammalian animals. In mammals TTR has a higher affinity for T_4 than for T_3 and this is in contrast with all the evidences coming from studies in fish, reptile and birds that express a TTR with a higher affinity for T3[76]. We do not know yet what could have been the selection process for the change of TTR affinity. TTR preferential affinity for T4 may represent, in mammalian brain, an additional level of regulation of TH brain levels. Indeed, it would be necessary that deiodinases expressed in specific region in the brain activate the pro-hormone T_4 into its active form, therefore, regulating locally the production of T_3.

Once TH reach brain tissue, they have to be internalized by cells in order to reach their intranuclear receptors. With regard to cell transporters necessary for TH translocation in the intracellular space, LAT1, LAT2 and MCT8 are expressed in neuronal and glial cells and are necessary for T_3 and T_4 uptake [77,78]. On the whole, as already mentioned, it is estimated that about 80% of cerebral T_3 is produced locally [79]. The cellular distribution of deiodinases is peculiar and may indicate the presence of an additional level of control on TH brain levels. Indeed, under physiological

conditions DII is only expressed in glial cells and is not present in neurons, on the contrary, DIII is expressed in neurons. DII mRNA has not only been found in glial cell bodies but also in cell processes which are closely connected to neurons and the synapses they form. In addition, astrocytes can also have access to the portion of TH that reaches the brain via the BBB. These evidences may indicate that glial cells regulate T_3 levels in the brain and their availability for neurons. On the contrary, neurons are mainly involved in the inactivation of T_3, adding another level of regulation of TH brain availability. Furthermore, deiodinase activity is temporally and spatially regulated to guarantee the correct modulation of critical brain processes either during development or adult life.

As a consequence of the complexity of TH metabolism and distribution, the interstitial concentrations of TH in the central nervous system may significantly differ from the serum ones [80], and are related more closely to those in the CSF.

1.4 General mechanisms of action of thyroid hormones

TH are involved in the regulation of cell functions through two mechanisms: genomic, that implicate the interaction with nuclear receptors and non-genomic ones, that, on the contrary, depend on the binding of plasma membrane and intracellular receptors.

Nuclear TR have been cloned for the first time in 1986[81,82] and, in the following years, were found to belong to a larger superfamily of receptors that included also receptors for retinoic acid, vitamin D, steroid hormones, peroxisomal proliferator receptors. The TR A and TR B are the genes that encode α and β TR isoforms respectively. Through alternative splicing they give rise to a variety of proteins. Only four of these are functional receptors, namely TRα1, β1, β2, and β3; whereas, the others do not bind TH[83]. Functional TH receptors produce their effects, once bound to TH, through the interaction with specific DNA sequences that are known as TH response elements located in the regulatory regions of a wide variety of target genes[84–86].

TRα1 and TRβ1 are expressed in almost all tissues with few significant differences in their abundances. TR α1 is highly expressed in the brain, with nearly all neurons expressing this isoform[87]. TRα2 expression is limited to the anterior pituitary, the hypothalamus and cochlea. Moreover, differences have also been detected in the timing of expression of these isoforms during development[84,88].

With regard to TH non-nuclear receptors, their existence has been postulated by the 1960s and 1970s[89], however, after the identification of nuclear TR most work focused on genomic pathways of action of TH. More recently, the extra-nuclear mode of action has been acknowledged on the basis of a variety of evidences including the rapid onset of some of some of TH responses, the maintenance of those effects even after blocking transcription and the involvement of plasma membrane signaling pathways. However, it has to be underlined that the variety of non-nuclear receptors that can be activated by TH and the molecular mechanisms that mediate their action have still to be defined thoroughly.

One of the putative non-genomic TH receptors is the integrin αVβ3 which is expressed at the plasma membrane[90,91]. Its interaction with TH induces the binding to laminin and the subsequent activation of intracellular signaling pathways that mediate actin cytoskeleton remodeling. The TH have also been demonstrated to stimulate the activity of Na+/H+ exchanger type 1 (NHE-1), a phosphor-glycoprotein that has a housekeeping role in the control of intracellular pH and cell volume and is involved in regulatory events triggered by several growth-stimulating signals[92].

Furthermore, TH can stimulate phosphatidyl-inositol 3-kinase and Rac activity that in turn where involved in the stimulation of voltage-activated potassium channels[88].

Other TR have been found in the cytoplasm; among these proteins there is the reduced nicotinamide adenine dinucleotide phosphate-dependent cytosolic T3-binding protein that is also known as μ-cristallin (CRYM), that seem to be involved in the regulation of TH concentrations at the level of the extranuclear space[93]. From a clinical point of view it has to be underscored that mutations of CRYM have been associated with pathological alterations of the inner ear development[94].

Moreover, a truncated form of TRα that lacks the DNA-binding domain has been shown to be imported into the mitochondrial inner membrane in a T_3-dependent mode and to stimulate oxidative phosphorylation[88].

Overall, the new evidences support the presence of non-nuclear receptors that may mediate rapid TH effects and suggest the need to better characterize the non-genomic signaling pathways.

The previous subsections provided the reader with the necessary background to evaluate the effects of TH and their metabolites on brain function and the possibility that they act as neuroprotective agents. Evidences supporting a neuroprotective role for TH and their metabolites will be presented in the next sections.

2.Thyroid hormone and TH metabolite effect on the adult brain and implications in neurological disorders

2.1 Classical thyroid hormone effects on adult brain

The acknowledgment of TH importance during brain development, comes from an extensive literature that demonstrated that limited TH availability throughout foetal and neonatal periods results clinically in irreversible and severe neurological consequences, including mental retardation, deafness-mutism and motor dysfunction[95]. Experimental models supported this finding, suggesting that

even mild TH insufficiency during brain development results in significant and irreversible neurological impairment. Subsequent evaluations shed light on the effects that TH may produce during neurodevelopment and that could underlie their importance during this specific stage. In particular, TH increase post-mitotic survival of neuronal progenitors[96], regulate neuronal migration, arborisation and myelination[97–100] and affect neurogenic precursor proliferation[101]. TH also act on olygodendrocytes and astrocytes, regulating the proliferation of the precursors of the first ones[102] and the morphology and maturation of developing astrocytes[103,104].

TH effects on the brain, however, are not restricted to the foetal and neonatal period. The concept that adult brain is able to buffer TH alterations without significant side-effects has been challenged by the evidence, coming from both clinical studies and animal models, that thyroidal dysfunction has also an impact on adult brain functioning. Adult-onset hypothyroidism has been associated with clinical alterations involving several cognitive areas; indeed hypothyroid patients show psychotic behavior, hallucinations, confusion and significant learning and memory impairment[105,106].

Many groups have recently devoted a great effort in order to dissect the putative mechanisms involved in the alterations seen in memory domain in hypothyroidism. Several behavioral studies reported that adult-onset hypothyroidism in rodents induces learning and memory impairment. In particular the identified alterations did not involve only short-term and long-term forms of memory but also the acquisition phase of the different behavioral tests used[107,108]. This data is further corroborated by the evidence that thyroid hormone deficiency is able to produce electrophysiological and biochemical alterations in the hippocampus, an area that plays a key role in memory processes. Alzoubi et al.[109] demonstrated that hypothyroidism in adult rats dampened the expression of long-term potentiation after high frequency stimulation (HFS) in the CA1 of the hippocampus. This finding is associated with a significant reduction of CAMKII activity that is normally seen after HFS and that is thought to be involved in long-term potentiation (LTP), one of the electrophysiological correlates of memory, at the molecular level[110]. Also, hypothyroid rats showed reduced RNA and protein levels of neurogranin, another key factor in LTP expression. Gerges et al.[111] and Dong et al[110,112] showed that the levels of calcineurin are reduced in hypothyroidism. In a subsequent study, Alzoubi et al[113] demonstrated that also PCREB, pMAKp42/p44, BDNF and CAMKIV levels were reduced in the hippocampus of hypothyroid rats. Interestingly both the electrophysiological and the biochemical alterations identified were completely reverted by the restoration of euthyroid status.

Another process that has been investigated and that might be involved in TH effects on learning and memory is hippocampal adult neurogenesis. With adult neurogenesis, we refer to the generation of neuronal progenitors and their anatomical and functional integration in the adult specific brain network. The subgranular zone (SGZ) in the dentate gyrus of the hippocampus is one of the very few areas in the brain that exhibits neurogenesis into adulthood. Adult neurogenesis in rat hippocampus was firstly described by Altmand and Das[114] in the 1965 and was subsequently demonstrated also in humans in 1998[115]. However, its functional role in hippocampal circuitry has been questioned for long. Evidences coming from rodent models suggest that adult hippocampal neurogenesis is important for cognitive function. New neurons have been demonstrated to play a fundamental role in memory pattern separation (a process involved in memory formation). Moreover, they integrate in the circuitry of old granule cells that mediate memory pattern completion (a mechanism involved in memory storage and retrieval)[116–118]. It could be speculated that the effects produced by TH on cognition may imply their ability to also modulate neurogenesis at the level of the SGZ in the hippocampus.

TH modulate several aspects of neurogenesis in the hippocampus, acting on post-mitotic progenitors[119,120].

In rodents, hypothyroidism is associated with decreased rate of production of neuroblasts[121], decreased survival of adult granule cell progenitors and increased apoptotic rate in the internal compartment of the SGZ[122,123]. These effect are completely reverted by TH administration and restoration of euthyroid status. In addition, TRalpha 1 knock-out does not affect progenitor proliferation, indeed TRalpha 1, the receptor that mediated most of brain effects of TH[87,124] on adult neurons, is not expressed in neuronal progenitors but is highly expressed in immature neurons[119].

Moreover, TH have been proven to affect cholinergic function in the brain. One of the first theories of physiopathology of AD suggests that cholinergic function is disrupted early in the course of the disease and that it contributes to cognitive dysfunction[125].

Either chronic or subchronic T4 administration was proven to enhance the ability to learn a spatial task; this effect was significantly associated with increased cholinergic activity in frontal cortex an hippocampus in rats[126].

Moreover, on intact synaptosomes isolated from adult rat cerebral cortex, T_3 stimulates Ca^{2+}-dependent cholinergic transmission [127]. In a recent study, Fu et al. [128] demonstrated that T_4 administration in aged mice (24 month old) restored impaired spatial memory evaluated through the Morris water maze and, in parallel, increased hippocampal levels of acetylcholine. Moreover, TH were also proven to be neuroprotective in the setting of ischemia. During brain hypoperfusion several processes are involved in the induction of neuronal injury, in particular glutamate excessive release from neurons and glial cells and the subsequent increased intraneuronal calcium levels play a fundamental role[129]. *In vitro* studies proved that TH

induce an increase in glutamate uptake by astrocytes by genomic and non-genomic mechanisms. Namely they increased glutamate transporter 1 (GLT1) and glutamate aspartate transporter (GLAST) mRNA and protein levels in astrocytes genomically[130] and the modulation of N-methyl-d-aspartate (NMDA)-evoked currents in neurons, preventing glutamate-induced death[131]. In rodent models, repeated daily T_4 administration increased postischemia neuronal survival[132].

We presented recent data suggesting a possible neuroprotective role of classical TH in areas of the brain and neurotransmitter systems that functionally mediate cognitive function and specifically learning and memory. The data also support the hypothesis that TH produce significant behavioral, electrophysiological and molecular modifications in the hippocampus, an area that is crucially involved in memory.

2.2Classical TH role in Alzheimer's disease

The body of evidence that was discussed in the previous section supports the hypothesis that TH may be involved in the biochemical and electrophysiological alterations identified in the hippocampus that may underlie cognitive dysfunction seen in hypothyroid conditions. Moreover, the possibility to revert those alterations with TH treatment may suggest a possible neuroprotective role of TH in areas involved in learning and memory.

Given the role of TH deficiency in memory dysfunction, it is not surprising that TH have been considered also as decisive factors involved in the development of dementia [133–141]. Dementia is a syndrome that is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Dementia clinical manifestations vary depending on the specific location of brain pathology. In Alzheimer's disease (AD), the most common form of dementia, pathological modifications begin in the entorhinal cortex, spread to the hippocampus, and then diffuse to posterior temporal and parietal neocortex, eventually causing a relatively diffuse degeneration throughout the cerebral cortex[142]. As a result, AD primarily presents as memory loss and is associated only later in the course of the disease with aphasia or other disturbances of language[143].

TH abnormalities have been demonstrated to occur in 36% of patients with dementia. It has also been suggested that subtle abnormalities in thyroid function may play a role in AD. Indeed, euthyroid patients with AD showed a significant reduction in plasma T_3 levels vs control patients [144] and increased TSH was a risk factor for dementia in the elderly [135]. Biochemical analysis performed in AD patients reported reduced T_3 in the frontal cortex [140] and reduced TRH in the hippocampus [141,145]; however, the interpretation of these findings may be complicated by chemical reactions occurring post-mortem. There are a number of mechanisms that have been proposed to explain the observed association between TH and an increase risk to develop AD. As already mentioned, TH have been demonstrated to influence cholinergic signaling in both developing and adult animals. These effects may play a role in AD development; indeed, biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters, especially acetylcholine. Finally, evidence coming from both in vivo and in vitro studies has shown that TH regulate the expression of the amyloid precursor protein (APP) gene. The APP plays a pivotal role in AD pathology. Indeed neuritic plaques, that represent the pathological hallmark of AD pathology, contain Aβ amyloid that derives from APP proteolytic cleavage operated by β and γ secretases. It has been demonstrated that T_3 repress APP promoter and regulate also APP protein processing and subsequent secretion[146,147], reducing the amount of neurotoxic Aβ species in AD brains. Moreover, in an *in vivo* study it has been demonstrated that hypothyroidism is associated with an enhanced production of APP protein in mouse brains[148]. Fu et al demonstrated in a beta amyloid induced AD model that T_4 administration prevented cognitive impairment typical of the model, improving significantly memory function[149].

To clarify the association existing between TH and AD risk, serum hormonal levels may not be reliable. Indeed, due to TH transport to the brain and local metabolism, cerebrospinal fluid (CSF) TH concentrations may represent more accurately brain TH levels.

Reduced T_3 and increased rT_3 were described in AD patients [136], while increased T_4 with unchanged T_3 was reported in another investigation performed both in AD and in other forms of dementia [137]. More recently, a significant positive association has been identified between rT_3/T_3 ratio and clinical deterioration in AD patients, suggesting that the reduction of active metabolites of T_4 acts in AD progression[138].

The evidence presented above may suggest that in AD brains a significant alteration of classical TH metabolism occurs and might play a role in the development and the progression of cognitive impairment. This might open the possibility to find another therapeutic approach to AD that contemplate the restoration of correct TH local metabolism.

2.3. TH metabolites and their role in the brain

2.3.1 3,3',5'-Triiodothyronine (rT3)

rT3 is a product of 5-deiodination operated by either DI or DIII. rT3 can act as an actin polymerization inducer in astrocytes and has been demonstrated to revert the alterations in neuronal and astrocytic cytoskeleton seen in rodent models of hypothyroidism[150,151]. The presence of an appropriate organization of the cytoskeleton is also fundamental during brain development. In particular, it plays

a pivotal role in migration of granule cells in the cerebellum. Granule cells are sensible to TH action and rT3 was demonstrated to directly regulate F-actin polymerization in cerebellar neuronal cells and to regulate their migration to their specific destination[152]. These effects do not occur via a genomic pathway; indeed, they were demonstrated to be mediated by TRΔα1, a native TR isoform that lacks the nuclear signal and is located in the extranuclear compartment of neurons and astrocytes[153].

2.3.2 3,5-diiodo-thyronine (T_2)

3,5-diiodo-thyronine (T_2) derives from the deiodination of classic TH and has been extensively studied for the metabolic effects that in part seem to mimic those produced by T3[154].

With regard to its effect on brain function, T_2 is effective in inducing short-term modification of intracellular calcium concentrations and nitric oxide release in pituitary GH3 cells. In particular, it increases intracellular Ca^{2+} by facilitating its efflux from mitochondria via mt-NCX[155].

In addition, a recent study[156] demonstrated in a mouse model of stroke that T_2 is able to reduce infarct size as well as edema formation. This new finding might open the way to new neuroprotective approaches to reduce the fatal consequences of ischemic brain stroke.

2.3.3 Thyronamines and synthetic analogues

Thyronamines (Fig.2) are a class of endogenous signaling compounds that differ from thyronines only for the absence of the carboxylate group in the alanine side chain.

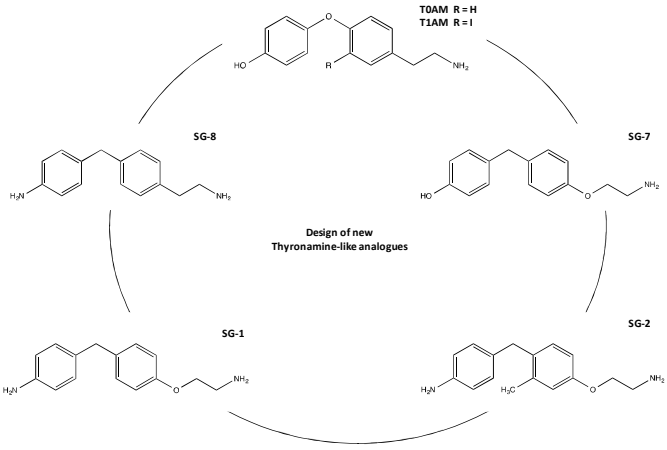

Figure 2. Structures of endogenous thyronamines ad new synthetic thyronamine-like analogues.

So far, only the mono (3-iodothyronamine, T_1AM) and deiodinated (thyronamine, T_0AM) forms have been detected in vivo using a liquid chromatography tandem mass spectrometry method in virtually every tissue in mice (C57Bl/6), in brain of several other rodent species and in human sera, thyroid, skeletal muscle, adipose tissue and prostate (reviewed by Hoefig et al. in 2016[157]).

The exact metabolic pathway leading to thyronamine production in every tissue has not been disclosed completely yet. In a recently published paper, it was demonstrated that in the everted gut sac model, T_1AM may derive from T_4 after three deiodinating passages and a decarboxylation mediated by deiodinases and ornithine carboxylase respectively[158].

T_1AM was firstly identified by Scanlan et al.[159] in rodent brain, and, later studies demonstrated that this thyronamine produces relevant neurological effects closely mirroring those produced by classical TH [160]. In particular, T_1AM, has been proposed as a novel memory enhancer; indeed, when administered i.c.v., it improved learning and memory in mice in the passive avoidance test [161]. Although some of the effects of TH can be mediated by T_1AM, this derivative was shown to interact mainly with the trace amine associated receptor 1 ($TAAR_1$) without any action on nuclear TH receptors[159]. This could explain the fact that when administered in vivo at concentrations that have shown neurological effects, T_1AM had scarce effects on cardiovascular function and energy expenditure (two main areas where TH produce significant activity).

Moreover, it has to be underscored that T_1AM produces protective effects on acute stroke [162], in particular, preconditioning with T_1AM reduced brain infarct size in a mouse model of focal ischemia.

In addition, a recent study[163] suggested that not only T_1AM but also its metabolite 3-iodothyroacetic acid (TA_1) may be involved in learning and memory. With regard to TA_1 production, in vivo administration of exogenous T_1AM showed that oxidative deamination, followed by aldehyde oxidation by the ubiquitous enzyme aldehyde dehydrogenase, represents a major and rapid pathway of TA_1 production. The measurement of endogenous brain levels of T_1AM and TA_1 indicated that TA_1 represents 1.7% of amine levels. After pharmacological administration of T_1AM, a concomitant increase in T_1AM and TA_1 brain levels is observed, such that their ratio is kept at the same (physiological) value (1.7). This result confirms that T_1AM can be converted into TA_1 in vivo and that, at condition of thyroid homeostasis, the two metabolites maintain a constant reciprocal relationship of concentration.

The pretreatment of mice with clorgyline, a MAO inhibitor, that prevents the oxidative deamination of T_1AM, reducing the formation of TA_1, dampens T_1AM effects on memory. This suggests that TA_1 might, directly or indirectly, be part of the T_1AM pharmacological effects. Indeed, injection in mice of equimolar doses of TA_1 reproduced the pro-learning effects induced by T_1AM. Notably, recent studies showed that TA_1 as well as T_1AM pro-learning effects were modulated by histaminergic antagonists [164,165]. These findings corroborate the hypothesis that T_1AM, through biotransformation into TA_1, might be part of the same signaling network linking the thyroid with histamine, and

that TA_1 might be considered the active metabolite of T_1AM responsible for memory-enhancing effects.

Numerous evidences suggest that dysregulation of the neuronal histaminergic system is present in neurodegenerative disorders including Parkinson [166,167] and Alzheimer diseases[168]. In particular, histamine levels were found increased in various brain regions of Parkinson disease patients, whereas they were reduced in Alzheimer disease patients[169]. Therefore, the maintenance of a correct link between thyroid and histaminergic neurons, through the mediation of T_1AM, might constitute a warrant of preservation of behavioral circuits, including those involved in memory and learning. In addition, the evaluation of TA_1/T_1AM could potentially represent a novel marker for neurodegenerative disease diagnosis, to be used as an index of its severity as well as a target for drugs sustaining cognitive functions.

Recently, a small panel of synthetic halogen-free diphenylmethane analogs of T1AM have been described (see Fig.2 and 3) [170].

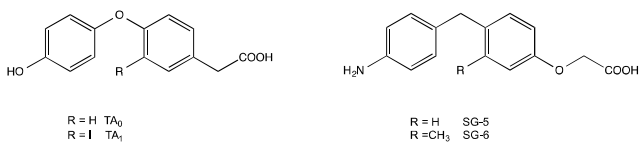

Figure 3. Endogenous thyroacetic acids (TA_0 and TA_1) and potential oxidative deamination catabolites of synthetic thyronamine-like analogues SG-1 (SG-5) and SG-2 (SG-6).

When tested in vivo some of these compounds were found to produce a good mimic of T_1AM neuronal effects. In particular, the 3-methyl T_1AM analog named SG-2, and its potential oxidative deamination derivative SG-6, which ultimately can be considered as the 3-methyl analog of TA1, when injected i.p. to mice at dosages of 4 and 11 microg/Kg, appeared to enhance memory with a potency comparable to that of T_1AM and TA_1, respectively[171]. Notably, in agreement with previous findings on T_1AM, SG-2 effects were lost after pretreatment with the MAO inhibitor clorgyline or with the H1 antagonist pyrilamine. Similarly, the hyperalgesic effect induced by SG-6 was also completely abolished by pretreatment with pyrilamine, as previously observed with TA_1. Even though these results are still at a preliminary level, they strongly suggest that oxidative metabolites contribute, at least in part, to the neurological effects observed after systemic administration of either endogenous or synthetic thyronamines to mice.

CONCLUSION

The review of the available data support the hypothesis that classical and non-classical thyroid hormones are not only fundamental during brain development but are also involved in adult brain functioning.

Thyroid hormones act as neuroprotective agents in physiological (adult neurogenesis) and pathological settings (acute brain ischemia). They were demonstrated to modulate behavioral responses in the cognitive domain of learning of memory and to induce electrophysiological and molecular effects in the hippocampus, an area that plays a central role in memory. Also, TH metabolites may represent a means to explore the protective effects produced by TH in AD and to evaluate their potential role as a therapeutic agents in this disease and, potentially, also in other neurodegenerative disorders.

In conclusion, from the evaluation of the body of evidence we presented, it appears clear that the macroscopic effect that thyroid hormones induce in the adult brain results from a complex network of metabolites. The research on the neurological effects of TH metabolite promises to open an exciting field of discoveries that may also be applied to diagnosis and treatment of severe neurodegenerative disorders.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

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