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Pharmacological effects of 3-iodothyronamine: implications for the treatment of neurological disorders

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Abstract

Trace amines (TAs) are primary amines structurally related to classic monoamines derived from aminoacid metabolism. Their fast rate of degradation and/or inability to accumulate in substantial concentrations in synaptic vesicles determines their presence in trace in brain tissues. The role of TAs in mammalian physiology remains less well defined. The identification of targets for TAs, namely trace amine associated receptors (TAARs) raised the interest around the physiopathological role of TAs in neurodegenerative diseases.

Thyroid hormone metabolism produces a series of primary amines, namely thyronamines, at different degree of iodination, including 3-iodothyronamine (T1AM). From that is known, T1AM presents some, but not all, the requisites to be defined as a TA. In fact, T1AM recognizes TAARs but its ubiquitous degradation does not exhaust its signaling activity. Interestingly, T1AM is endowed of pro-learning and anti-amnesic features revealing the existence of novel endogenous players in the relation between the thyroid and brain functions.

Key words

Trace amines; 3-iodothyronamine; thyroid; memory and learning; monoamine oxidases, neurodegeneration

Background

Thyroid hormone metabolism generates a family of derivatives which can be classified according to their chemical structure as thyronines (amino acidic) thyronamines (primary amines), thyroacetic acids, each of them at different degree of iodination. The discovery of the physio-pathological significance of tissue levels of such compounds became recently an attractive area of research interest per their possible implications as markers of thyroid disease or pathogenic events in their clinical manifestations.

Even if the synthetic pathways involved in the generation of thyroid hormone derivatives remain to be clarified, a plethora of iodinated compounds became potentially available for local or systemic effects in tissue targets of thyroid hormone. This possibility offers the rationale for defining thyroid hormone metabolite functions in relation with those of thyroid hormone. Since thyroid hormone metabolites do not exert genomic functions the growing hypothesis is that they could represent the non-genomic harm of thyroid hormone [1].

Pharmacological evidence collected around thyronamines and thyroacetic acids have indicated they behave as hormones as well as neuromodulators, thus interfering with animal behavior and metabolism. Collectively such evidence point on the importance to measure their tissue levels and to identify their molecular targets to open new perspectives in the diagnosis, the care of thyroid diseases and their neurological manifestations.

3-iodothyronamine, one among the thyronamines, is considered a trace amine

Evidence against and in favor

Trace amine circulates "in trace"

3-iodothyronamine (T1AM), is a monoiodinated thyronamine found circulating in mammals and accumulating in several tissues including the brain. Considering its low levels recovered in tissues (nanomolar range), T1AM has been included within the category of the trace amines. Paradigmatically, trace amines are endogenous primary amines related to the classical monoaminergic mediators and, in some case, by-products of aminergic synthesis. Evidence indicate that T1AM has some, but not all, the characteristics to be considered as such.

Trace amines are produced by aromatic decarboxylase activity and transported inside cells by specific mechanisms

The exact origin of T1AM remains elusive yet[2] but, irrespective of the initial substrate, decarboxylase and deiodinase activities are essential for producing T1AM and all the thyronamines. Differently from other trace amines, the decarboxylase activity involved in T1AM synthesis is not the aromatic amino acid decarboxylase.

T1AM can enter inside cells but the mechanism of transport is different from that chosen by other monoamines or thyroid hormones[3] .

The metabolism of trace amine interrupts their signaling activities

Once inside cells, T1AM undergoes towards enzyme degradation by the activity of ubiquitous enzymes, including monoamine oxidase (MAO) and deiodinases, producing the 3-iodothyroacteic acid (TA1) and thyronamine (T0AM), or conjugated to organic acids. The measurement of endogenous brain levels of T1AM and of TA1, indicated the they relay in a specific ratio of which TA1 represent 1.7% of amine levels. After pharmacological administration of T1AM, a concomitant increase of T1AM and of TA1 brain levels is achieved but their ratio re-set to the same (physiological) value (1.7)[4]. This result confirms that T1AM can be converted into TA1 *in vivo* and that, at condition

of thyroid homeostasis, the two metabolites have to maintain a constant reciprocal relationship of concentration. This ratio might change at condition of thyroid diseases and then assume diagnostic value. Moreover, differently from classical trace amines, TA1 and T0AM are still pharmacologically active and experimental evidence indicate that TA1 formation is an essential event in T1AM pharmacological effects[4].

Trace amines are agonists at the trace amine associated receptors

The discovery of a family of G-protein coupled receptors, present in several isoforms, selectively activated by trace amines (TAARs) (Borowsky et al. 2001; Bunzow et al. 2001), has prompted a resurgence of interest and forced a re-evaluation of the potential physiological relevance of these compounds.

As the canonical trace amines, T1AM does activate TAARs. In fact, T1AM was first described as an high affinity ligand for the TAAR1[5] and, more recently for the type 8 (TAAR8). At TAAR8, T1AM would behave as an inverse agonist [6].

However, T1AM skeleton includes a β-phenylethylamine-like structure, a feature which potentially allows T1AM to recognize multiple cell targets including other G-coupled receptors and ion channels. In fact, T1AM binds in the micromolar range to the pancreatic alfa-2 adrenoreceptor likely behaving as an inverse agonist[7,8]. Almost in parallel, Khajavi et al[9] described the capacity of T1AM to modulate TRPM8 of conjunctival cells, thus introducing the possibility that T1AM might modulate store operated ion channels. Activation of such targets encourages the investigation of T1AM effects on functions governed by sensory neurons activation. In addition, activation of ion channels could explain the rapid timing of occurrence of the effects evoked by T1AM pharmacologically administered and the non-linear dose-effect relationship often observed. However, whether these targets are involved in the

pharmacological effects of T1AM remains to be demonstrated [10]. In addition, the range of affinity values showed by the amine towards such targets does not always correlate with its potency in vivo. In particular, T1AM reduced body temperature when injected in mice at 25-100 mg/kg[5]. This effect was ascribed to the activation of TAAR1, a receptor for which T1AM shows a potency within the nanomolar range of concentrations, a finding revealing a discrepancy between the potency of the amine in vitro vs. in vivo settings. However, T1AM is able to modifies mice behavior also when administered at doses close to its physiological levels (μg/kg). At this latter conditions, most of the behavioral and metabolic effects induced by T1AM were prevented or reduced in animals pre-treated with clorgyline, an MAO inhibitor. Such condition prevents the oxidative deamination of T1AM reducing the formation TA1, which might directly or indirectly, be part of T1AM pharmacological effects.

Further, pharmacological injection of μg/kg T1AM modifies mice behavior and metabolism including feeding (producing hypo and hyperfagia, depending on the doses injected), stimulation of learning and memory, reduction of the threshold to painful stimuli, increase of plasma glycemia which raises a transient insulin resistance mediated by glucagon release[13]. Interestingly enough, all these effects were reduced or prevented by clorgyline (2.5 mg/kg) pre-treatment and dose-effects curves were not linear [11,12,13].

Getting further inside the relation between T1AM and TA1, we found that TA1, injected to mice at doses equimolar to those used for T1AM, induced most of the effects observed injecting T1AM. In fact, TA1 exerted a pro-learning but also an amnestic behavior without giving consolidation of memory, it increased plasma glycemia and it reduced the threshold to hot stimuli[12]. In addition, at the doses simulating memory, TA1 reverted scopolamine and diazepam-induced amnesia (unpublished data).

Having ascertained that TA1 was able to reproduce the effects of T1AM, we then tried to investigate the mechanism responsible for TA1 effects. In line with this, we found that TA1 pro-learning and hyperalgesic effects were modulated by histaminergic antagonists and that hyperalgesia was not observed in histidine decarboxylase knock-out mice (HDC-/-) [11,12] . These findings indicated the participation of histamine in TA1 hyperalgesia and in its pro-learning effects. Then, if TA1 is the active metabolite of T1AM responsible for inducing the release of histamine, then, T1AM effects should also be modulated by histaminergic antagonists or reduced in HDC knock-out mice. Evidence indicated it was so, corroborating the hypothesis that T1AM, throughout the biotransformation into TA1, is part of the same signaling network linking the thyroid with histamine.

To now it is unknown whether T1AM could be stored in vesicles displacing monoamines.

T1AM and/or TA1 are neuromodulators of the histaminergic system

Paradigmatically, a neuromodulator is a compound which does not produce any effects di per se but it enhances the effect of a specific neurotransmitter. In addition, a neuromodulator is a compound released from a neuron which causes no change in the excitability of post-synaptic cells in the absence of neurotransmitters. Further, a neuromodulator acts to modify the action (increase or decrease) of a coexisting neurotransmitter.

Trace amines function just as neuromodulators of the monoaminergic systems fulfilling an important role in amplification/reinforcement mechanisms of the monoaminergic tone. Intuitively, such functions have important implications in brain function including such that as basal monoaminergic tone fluctuates trace amine synthesis is altered to

maintain the status quo. Accordingly, thyronamine levels could be altered in case of thyroid dysfunctions. To now, this hypothesis remains to be demonstrated.

As previously cited, T1AM, but also TA1, can be considered as neuromodulators of the histaminergic system and, because of this, regulators of the functions governed by this autacoid. This evidence reveals the existence of a novel link between the thyroid and the histaminergic tone. The possibility that T1AM also regulate aminergic functions remains to be investigated.

Histamine is classically referred as one among the most potent inflammatory, pruritogenic mediators. Further, histamine impacts with on the sleep/arousal cycle, on pain, on memory and feeding[15,16]. Consistently, TA1 elicits itch, reduction of the threshold to noxious and to painful heat stimuli, it stimulates learning with a mechanism involving histamine release [11]. As far as we known, the system T1AM /TA1 can be considered as the first endogenous neuromodulator of the histaminergic system.

T1AM and TA1 effects on memory: any role in neurodegeneration?

As already mentioned, T1AM stimulates learning and memory and TA1 stimulates learning but not memory consolidation. Further, T1AM and TA1 can revert amnesia by scopolamine and diazepam (unpublished results). These latter findings offer the rationale for sustaining a role for these metabolites in memory impairment conditions typical of neurodegenerative disorders but also an hypothetic mechanism explaining memory disorders associated with thyroid diseases [17].

T1AM and TA1 effects on memory where obtained when the drugs were given before the training session of the passive avoidance task and these effects are depdnent on histamine release and on MAO activity.

It is rather well established that the cholinergic system is essential for the maintenance of memory processes. In fact, pharmacological inhibition or pathological degeneration of cholinergic neurons or, alternatively, activation of inhibitory signals, including GABAergic neurons, reduces the efficacy of memory circuits mimicking aging and memory impairments typical of neurodegenerative disorders. Accordingly, muscarinic receptor antagonists, including scopolamine, and activators of GABA-A receptors, including diazepam, are often used to produce experimental models of amnesia.

T1AM, given to mice, reverted amnesia induced by low, not analgesic or sedative doses, of scopolamine or diazepam. Again, the anti-amnesic effect of T1AM was prevented in mice pre-treated with clorgyline, thus reinforcing the evidence that TA1 is the active principle mediating both the pro-learning and the anti-amnesic effects of T1AM. Interestingly enough, T1AM is more potent as anti-amnesic than as pro-learning, thus indicating that the removal of the cholinergic tone, by using scopolamine, amplifies T1AM effects. The mechanism might relay in the production of TA1 which, in turn, activates the histaminergic system. Accordingly, histaminergic drugs have proved anti-amnesic efficacy at different tasks including diazepam-induced amnesia[18].

Actually, TA1 produces amnesia at 0.4 μg/kg and stimulation of learning at 1.32 and 4 μg/kg, doses at which T1AM resulted only pro-learning. Locally, at conditions of limited distribution, T1AM has the potential to be completely transformed into TA1, with a small percentage of T1AM converted into T0AM[4]. The difference between T1AM and TA1 behavior on learning and memory might relay just on T0AM production. IN any case, again, the system T1AM-TA1-histamine represents an endogenous regulator of neuronal circuits implicated in learning and memory. To now the upstream mechanism responsible for TA1-induced release of histamine is unknown. In this respect, recent evidence point on the role of histamine type 3 receptor (H_3R)

antagonists as novel tools for treating cognitive impairments[19]. The H3R is a presynaptic auto- and/or hetero-receptor regulating the synthesis and/or release of histamine[20] as well as of a variety of other neurotransmitters including acethylcholine, glutamate and GABA[21]. The possibility that TA1 worked as an antagonist at H3R cannot be ruled out even if the chemical structure of TA1 makes this hypothesis unlikely. Rather, TA1 structure recalls the possibility to activate GABAergic or glutamatergic receptors, without excluding any interactions at channels activated by H^+. Up to now, we can disregard that TA1 interacts at GABA-A receptor and at its allosteric sites (unpublished data). In line with the role of histaminergic neurons which are the neurons of the attention, of the awaking if activated before the challenge with any negative, depressive, signals, TA1 given before the training session, reverts diazepam-induced (or scopolamine) amnesia. These finding indicate that activation of the histaminergic neurons can circumvent inhibitory tones including the GABAegic and the blockade of the cholinergic systems.

This finding points on the importance of respecting the timing of T1AM/TA1 administration to evoke the release of histamine and to obtain increase in attention and awaking behavior. Consequently one can speculate that thyroid function (including hormone metabolism) could be somehow implicated in maintaining learning circuits in healthy conditions. This statement needs to be supported by further experimental and clinical data.

Thyroid function and dementia: thyroid hormone metabolites as therapeutic or diagnostic tools?

Thyroid hormone has an incontrovertible pre-natal role on the harmonious development of the brain. However, thyroid hormone has important actions in the adult brain too. In fact, hypo and hyper-thyroidism associate with neuropsychiatric complaints and

symptoms including increased susceptibility to depression and reductions in health-related quality of life. Neuropsychiatric symptoms refer to a spectrum of emotional, melancholic depression and dementia and cognitive problems that are directly related to changes in the brain secondary to multiple factors, including the direct effects of thyroid disease, as well as changes in hormone levels in brain tissue. Neuropsychiatric symptoms tend to improve with treatment and normalization to a euthyroid state, though the pattern is inconsistent and complete recovery is uncertain. However, the importance of homeostatic hormone levels in neuropsychiatry is further sustained by the impact of subclinical hypothyroidism on mood and cognitive functions [21]. Patients with subclinical hypothyroidism, often experience neurological complications including cognition and sleep/arousal cycle impairments, altered threshold to noxious and heat stimuli, itch, and effects related to altered cholinergic transmission. Despite of these, the relationship between TSH and/or T4 plasma levels and neurological deficit scores remains to be demonstrated making inconsistent the clinical assessment of a causal relationship between thyroid hormone levels and cognitive decline including aging [23,24]. Instead, evidence indicate that, in old women, low T(4) levels, but still within the euthyroid range, were associated with a greater risk of cognitive decline over a 3-year period[25] and with future dementia risk[26, 27]. Further evidence indicate that hypothyroidism double the risk of Alzhemier disease[28]. In this disease, alteration in expression levels of enzymes involved in thyroid hormone synthesis and metabolism including deiodinases and monoamine have been documented [29),30.] At these conditions, irrespective of the source of T1AM, its production is expected to be reduced, potentially contributing to cognitive impairments.

Furthermore, the function of the neuronal histaminergic system has been reported to be dysregulated in neurodegenerative disorders including Parkionson's [31,32] and

Alzheimer disease[33]. Since current treatment options for those diseases are highly limited and drugs used have several side-effects and/or are only partly effective in ameliorating the cognitive symptoms, brain histamine could represent a potential target to combat the cognitive symptoms. An interesting novel area is the pharmacology of H3 antagonists[34] .

As prospected for H3 antagonists, T1AM can represent an add-on therapy in counteracting cognitive disorders when administered at the early phases of the disease, according to the role of the histaminergic system. Administration of T1AM, as a pro-drug, might represent a strategy to increase TA1 levels and then the firing of the histaminergic neurons. This condition would ameliorate some of the symptoms associated with neurodegeneration including amnesia, disturbances in the sleep/awake cycle and in alimentary behavior.

In summary, the evaluation of TA1/T1AM, resuming thyroid hormone metabolism, could potentially represent a novel marker in neurodegenerative diseases pathology, an index of severity and a novel target for drugs sustaining cognition functions.

To this goal, more extensive data on T1AM/TA1 levels in neurodegenerative diseases should be obtained in order to validate the diagnostic significance of such ratio. Further, the identification of active T1AM doses might also represent a novel therapeutic option for selected patients..

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Fig.1 T1AM works as a neuromodulator of the histaminergic system

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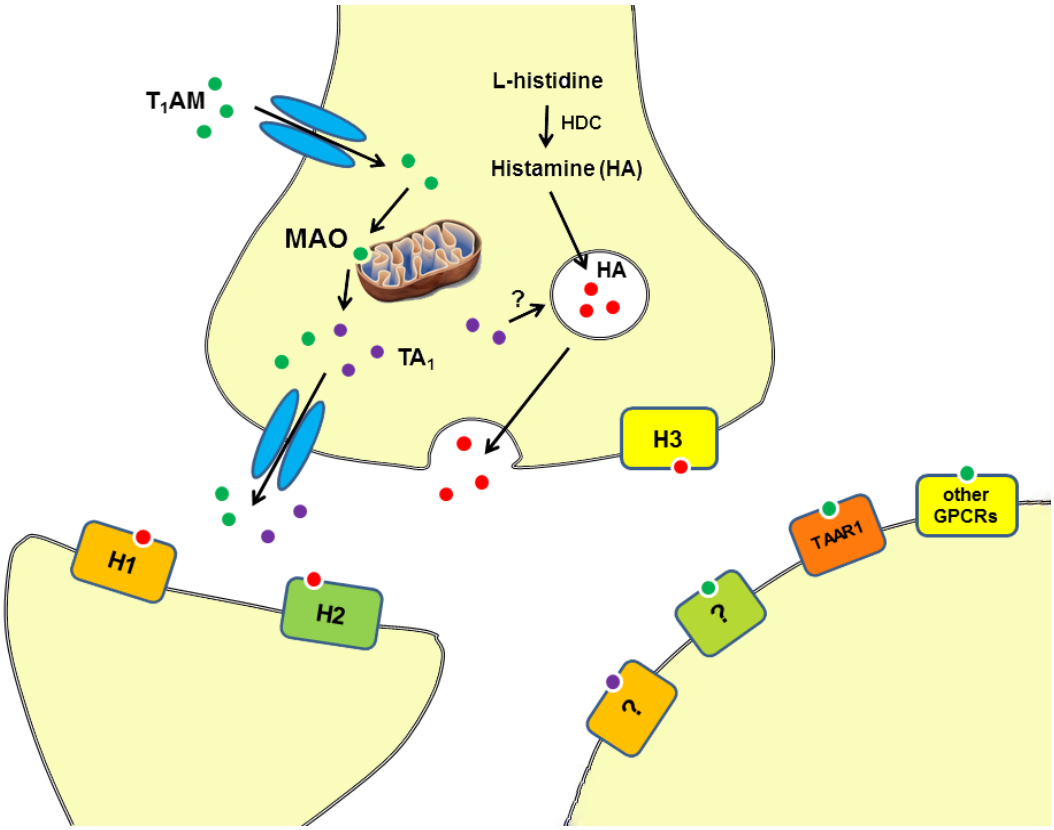

Legend.
T1AM can enter inside cells and oxidatively deaminated by MAO activity to TA1. TA1 promotes HA release or it can exit the cells and interact with unknown targets. HA released stimulates its own receptors and produces effects.

T1AM, 3-iodothyronamine; TA1, 3-iodothyroacetic acid; HA, histamine; H1,H2 and H3, histamine type 1 and 2 and 3 receptors; MAO, mitochondrial monoamine oxidase; HDC, histidine decarboxylase; TAAR1, trace amine associated receptor type 1; GPCRs, G-protein coupled receptors.