

# Thyroid hormone metabolites: what does the thyroid hide?

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## THYROID HORMONE

Thyroid homeostasis critically governs the harmonious development of embryonic tissues and directs functions and metabolism of target tissues after birth. Among thyroid hormone (TH) tissue targets are the brain, the bone, the heart, the adipose tissue, the liver. Consistently, patients suffering from thyroid diseases manifest clinical symptoms of TH target organ dysfunctions.

TH works by genomic mechanisms. However, non-genomic effects have been described for TH in the adult mammals. Experimental evidence indicate that thyroid function does not exhaust with TH degradation but, rather, some TH metabolites may have an own signaling activity. Increasing consisting evidence suggest that the characterization of TH metabolite function/role represents a novel challenge of the basic research around the thyroid.

In order to disseminate further the knowledge about TH metabolites we here summarize some points which would merit to be exploited further and the reasons why TH metabolites have the chance to become novel drugs or diagnostic tools:

- TH alternative degradation generates a large family of compounds at different degree of iodination circulating in rodents and in humans belonging to three different chemical classes including amino acids, primary amines (thyronamines) and carboxylic acids (thyroacetic acids; Figure 1). From this it derives that different TH metabolites can be produced depending on cell/tissue enzyme machinery including deiodinase isoforms and amine oxidases. It is possible that each cell type may produce, on-demand, a specific TH metabolite for its own needs. The physio-pathological significance of such production is largely unknown.
- When administered pharmacologically to rodents, thyronamines and thyroacetic acids produced similar but also opposite effects to those elicited by TH [1]. Such effects might change at pathological conditions characterized by altered deiodinase and amine oxidase tissue levels, as in diabetes and hyperthyroidism, or when treatments inhibiting amine oxidases or deiodinases are using. To now, the impact of pharmacological therapies on TH metabolites tissue levels and on their functions is completely unknown. One interesting hypothesis is, in turn, that accumulation of thyroid hormone metabolites may be responsible for side effects of drug therapies;

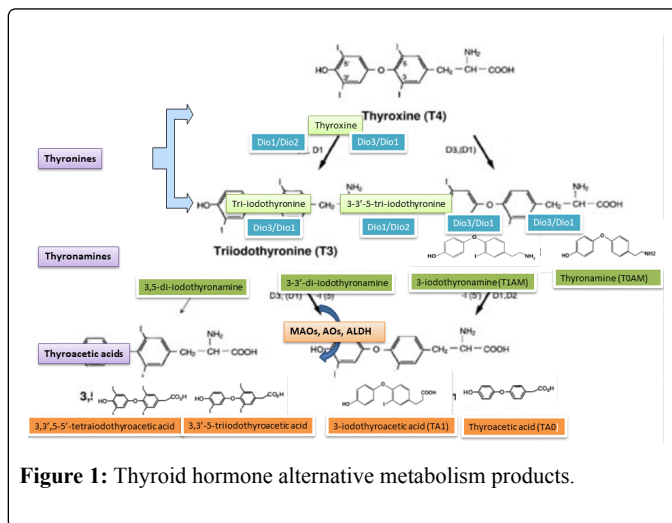


Figure 1: Thyroid hormone alternative metabolism products.

- The identification of thyroid hormone metabolites opens questions regarding the possible physio-pathological meaning of their respective plasma/tissue levels. We have previously demonstrated that in the brain of mice, 3-iodothyronamine (TIAM) endogenous levels are in equilibrium with those of 3-iodothyroacetic acid (TA1) and that this equilibrium is conserved following pharmacological administration of TIAM [2]. These evidence suggest that TA1/TIAM tissue levels may be homeostatically regulated thus potentially represent a bio-marker for the diagnosis of thyroid diseases;
- In the last years, the interest around TH metabolites concentrated on the characterization of TIAM pharmacological effects. TIAM is, in fact, one among the last primary amines generated from TH metabolism and because of this; its further degradation produces a restricted number of possible active metabolites. According to the relationship among the metabolites, in fact, the administration of thyronamines at higher degree of iodination than TIAM makes hard the identification of the active principle responsible for an observed effect. It is well known that the identification of an active principle is the first step for the development of a drug. Experimental evidence indicate that TIAM and its oxidative metabolite, TA1 have outstanding pharmacological profiles including acute stimulation of memory and learning [2,3], reversion of amnesia [4] and pro-waking effects [5]. Evidence indicates that TA1 formation from TIAM may be responsible for some, but not all, the effects observed following TIAM administration. Because of this, the two metabolites should have, as expected by their chemical structure, different pharmacodynamic features. Consistently, while several TIAM targets, including G-protein coupled receptors and ion channels [6] have been reported but none of these targets are instead recognized by TA1. Furthermore, TIAM has affinity for these targets in the micromolar range of concentrations while TIAM in vivo potency is in the

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nanomolar range. The reasons of this discrepancy are not known yet. One possible explanation is that in vivo activity of T1AM or (of TA1) is the result of the release of some neurotransmitters independently on T1AM recognition of putative receptors or ion channels. There is evidence supporting this hypothesis. In particular, we indicated that T1AM and TA1 work as neuromodulators of the histaminergic system [2,7], thus suggesting that T1AM or TA1 may have profile similar to those of type 3 receptor antagonists. The pharmacological administration of an endogenous compound makes somehow unpredictable its concentration at the target. This degree of uncertainty can be minimized if the endogenous compound is administered at the lowest effective dose; in the past several observations were obtained treating rodents with high doses (mg/kg) of T1AM; it is time to study T1AM or TA1 effects at doses close to their endogenous levels; if studied properly, it is possible that much remains to be discovered of T1AM and TA1 central and peripheral effects;

- After entering inside cells, T1AM is oxidatively deaminated by mitochondrial monoamine oxidases (MAO) with the formation of hydrogen peroxide and the corresponding aldehyde as secondary products. If hydrogen peroxide is quickly scavenged by catalase, the aldehyde is rapidly converted to TA1 by the activity of aldehyde dehydrogenase. However, in case of exhausted cell defenses, both hydrogen peroxide and aldehyde, can trigger oxidative and carbonyl stress respectively.
- The possible consequences on cell redox state of T1AM degradation remains to be investigated at physic as well as at pathological conditions, including diabetes Figure 2. In this pathology in fact there is an over expression of MAO and of other amine oxidases implicated in T1AM degradation. In addition, experimental evidence indicates that T1AM raises plasma glycemia in fasted mice [3]. The individuation of a causal relationship between hyperglycemia and TH metabolites might offer opportunities to discover novel drug targets for diabetes treatments and/or identify T1AM plasma levels as biomarkers of hyperglycemia severity.

- The pharmacological armamentarium of the therapy of thyroid diseases includes drugs targeting TH synthesis or its degradation. This latter strategy may impact on TH metabolite production [8]. It would be interesting to assay TH metabolites at condition of hypo- and hyperthyroidism or of pharmacological inhibition of TH degradation; such knowledge may help to indicate a pathogenic role of TH metabolites in thyroid diseases.

In conclusions, it is likely time to consider that another face of the thyroid secretome exists. The investigation on TH metabolite effects became of extreme interest to clarify if

- They represent the non-genomic portion of the thyroid gland;
- Their respective tissue levels may help diagnosis of thyroid diseases;
- They may have therapeutic effectiveness in the treatment of thyroid diseases and their clinical manifestations. A growing engagement of the basic research around this topic in the coming years would be desirable.

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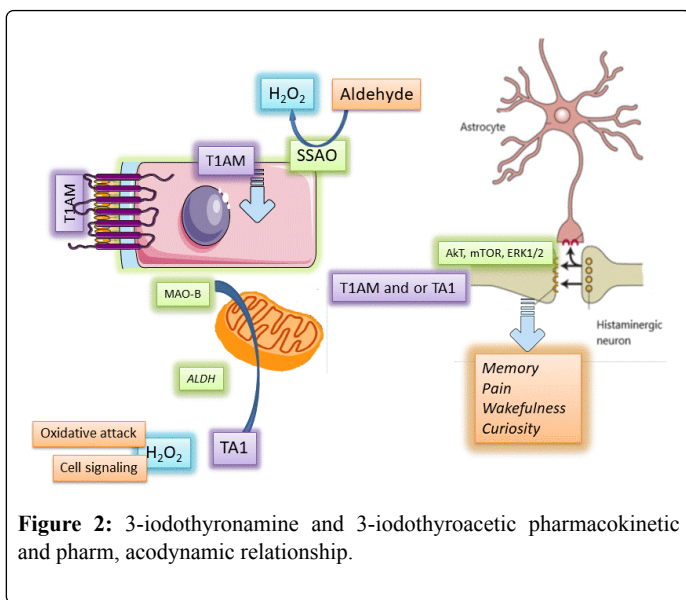


Figure 2: 3-iodothyronamine and 3-iodothyroacetic pharmacokinetic and pharm, acodynamic relationship.