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3-Iodothyronamine (T₁AM): A new thyroid hormone?

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Kathryn Schuff obtained her M.D. degree from the University of New Mexico, then completed Internal Medicine and Endocrinology training at Oregon Health & Science University. She is currently Associate Professor of Medicine and Associate Endocrinology Fellowship Program Director in the Division of Endocrinology and Director of Regulatory Support Services in the Oregon Clinical and Translational Research Institute at Oregon Health & Sciences University. Her research activities include studies of the effects of altered thyroid hormone levels on neurocognition and metabolic function in humans, identification and elucidation of the role of novel thyroid



Kathryn Schuff – Tom Scanlan – Barbara Hettinger

hormone metabolites and the role of molecular diagnostics in thyroid cancer diagnosis, prognosis and management. She is the Clinical Co-Chair of the American Thyroid Association Program Committee.

Tom Scanlan obtained his Ph.D. in chemistry from Stanford University in 1987 and then pursued postdoctoral studies at the University of California-Berkeley as a Damon Runyon Cancer Research Fellow. He

began his independent research career in 1991 as an Assistant Professor in the Department of Pharmaceutical Chemistry at the University of California-San Francisco (UCSF). In 1995, he became interested in molecular endocrinology and began applying his background in organic chemistry to the study of thyroid hormone action. Dr. Scanlan's lab synthesized and characterized a thyroid hormone analog that was selective for the beta-subtype of the thyroid hormone receptor. This compound originally called GC-1, was found to be devoid of the detrimental cardiac effects of thyroid hormone, yet retained the beneficial effect of reducing serum cholesterol. GC-1 is now called Sobetirome, and is in clinical development as a cholesterol-lowering agent. In addition, Dr. Scanlan recently discovered a novel class of biogenic amines related to thyroid hormone called thyronamines that have biological activities distinct from those of thyroxine and thyronine-based metabolites such as T₃. In 2006 Dr. Scanlan moved from UCSF to the Oregon Health & Science University in Portland, Oregon, where he is Professor of Physiology & Pharmacology, and Director of the Program in Chemical Biology. Dr. Scanlan's honors include the National Science Foundation Career Award, the Alfred P. Sloan Research Fellow Award, and the Arthur C. Cope Scholar Award from the American Chemical Society.

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Introduction

Thyronamines, endogenous compounds presumed to be a product of decarboxylation and deiodination of thyronines the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃), were initially synthesized in the 1930s-1970s by several groups studying the metabolism of thyroid hormones.¹⁻³ Early investigation also provided some evidence that thyronamines themselves had pharmacologic effects in both smooth and cardiac muscle. It was not until 2004 that Scanlan et al.⁴ were able to provide evidence that the thyronamines were endog-

enous compounds and that 3-iodothyronamine (T₁AM) and other thyronamines had interesting hypometabolic actions in rodent models. In this review, we describe some of the historical experiments on thyronamines followed by the current understanding of the pharmacology of T₁AM in particular. Although characterization of thyronamine action is not yet complete, important effects on cardiac function and metabolism have been documented.

Background

The classic thyroid hormones have pleiotropic actions in animals ranging from tadpole metamorphosis to regulation of metabolism, cardiac function, fuel utilization and CNS development in humans.⁵ The mechanism of action of thyroid hormones has been extensively studied, particularly with respect to classic effects mediated through nuclear hormone receptors and ultimately leading to transcriptional regulation. Thyroid hormone has been noted to have rapid and delayed nongenomic functions as well,^{6,7} which are less well characterized. Derived from tyrosine, thyronines are amino acids and,

like other amino acids, have been proposed to undergo decarboxylation followed by or preceded by various degrees of deiodination giving rise to a class of compounds known as thyronamines.¹⁻³ Several putative pathways by which thyronines give rise to thyronamines are outlined in *Figure 1*. Early investigation of thyroid hormone metabolites was limited by the inability to detect the presence of endogenous thyronamines. Several groups, however, were able to synthesize thyronamines which allowed for the initial characterization of their pharmacologic function.⁸⁻¹¹

Early Characterization

Interest in thyronamines dates back to the 1960s – although characterization was initially limited. In 1966, Buu-Hoi et al.⁹ published an early method of thyronamine synthesis and used the noniodinated thyronamine (T₀AM) to evaluate the action on various smooth muscle systems: rabbit jejunum, guinea pig duodenum and rat uterus. T₀AM produced reversible relaxation, which functionally inhibited histaminergic and serotonergic effects. It also antagonized the effects of oxytocin on rat uterus. In a follow up study, Buu-Hoi et al.¹⁰ demonstrated a T₀AM dose-dependent increase in the contractile force of the heart without significant effects on arterial blood pressure leading this group to propose a “purely positive inotropic effect”. A later study by

Boissier et al.,⁸ in an attempt to further characterize this effect, demonstrated that thyronamine (T₀AM) produced a dose-related increase in myocardial contractile force. Additionally, they determined that cardiac output and left ventricular work also increased, although they did not see a direct change in heart rate. These effects were hypothesized to be modulated via release of endogenous catecholamines acting on β -adrenergic receptors. In support of this theory, in a canine model, T₀AM acted primarily as a sympathomimetic agent acting via catecholamine release with a minor thyronamine-specific inotropic effect which persisted despite α - and β -adrenergic blockade as well as parasympathetic blockade.¹¹ Thus, it appeared that thyronamines

(at least T₀AM) had intrinsic rapid effects on cardiac function which occurred within a shorter time frame than those attributed to the transcriptional effects of thyroid hormone, the putative precursor to these compounds. In 1974, Dratman¹² reviewed the mechanism of action of thyroxine and hypothesized that metabolites of thyroxine produce transient, rapid effects simi-

lar to the biogenic amines with which they share significant structural similarity. Despite the early theories of thyronamine biosynthesis and this demonstration of pharmacological activity, convincing evidence of the endogenous presence of these compounds was elusive until the early 2000s.

Detection of endogenous thyronamines and identification of receptor binding

In 2004, Scanlan and coworkers were the first to provide evidence that thyronamines were in fact endogenous compounds in rodent, and later human, tissues.^{13,14} The thyroid hormones, T₃ and T₄, were noted to be similar in structure to aromatic amino acids which are decarboxylated by amino acid decarboxylase to yield the biogenic amine neurotransmitters such as serotonin and dopamine.^{4,13} This led to the idea that endogenous thyronamines may arise as a product of decarboxylation of thyroid hormone and that a G protein coupled receptor (GPCR), similar to those specific for serotonin and dopamine, could be a potential site of action of thyronamines.⁴ By screening a series of orphan GPCRs, several thyronamines were found to specifically bind members of the trace amino acid receptor (TAAR) family.^{4,14} Of greatest interest were two of the least iodinated thyronamines, 3'-iodothyronamine (T₁AM) and noniodinated thyronamine (T₀AM). T₁AM was the most potent agonist of rat and mouse TAAR1 receptors expressed in HEK293 cells with an EC₅₀ of 14 nM (rat) and 112 nM (mouse), and produced a dose dependent increase in cyclic AMP (cAMP).⁴ T₀AM was less potent at the rat receptor and ineffective at the mouse TAAR1 in cAMP accumulation assays. The potency of T₁AM at TAAR1 was roughly equal to that of other biogenic amine neurotransmitters at their respective receptors. As a control, neither T₁AM nor T₀AM had a significant affinity for thyroid hormone nuclear receptors (TR α and TR β) confirming a different potential mechanism of action. Development of a liquid chromatography/tandem mass spectroscopy assay and biogenic amine liquid-liquid extraction method allowed for the detection of T₁AM and T₀AM in rodent sera and tissues.⁴ With the ability to synthesize thyronamines and detect

the presence of endogenous thyronamines, it became possible to evaluate the pharmacologic response to thyronamines in various model systems. Subsequent analysis has focused primarily on the effects of T₁AM, as they were most pronounced in the in vitro assays mentioned above.

In addition to putative action at TAAR1, there is evidence that thyronamines may also act through other signaling pathways. For instance, Regard et al.¹⁵ demonstrated that T₁AM acts at the α_{2A} adrenergic receptor in pancreatic beta cells to produce hyperglycemia and hypoinsulinemia. T₁AM was found to bind specifically to the α_{2A} adrenergic receptor with a K_i of 0.36 μ M. Furthermore, in an α_{2A} adrenergic receptor knock out mouse model, T₁AM-induced hyperglycemia was abolished, indicating that the physiological effects of T₁AM may be mediated, at least in part, mediated via adrenergic signaling pathways.

Thyronamines have also been suggested to modulate the function of other neurotransmitters. Snead et al. have demonstrated, in both synaptosomal preparations and heterologous expression systems, that thyronamines act as specific dopamine and norepinephrine transporter reuptake inhibitors, as well as inhibitors of the uptake of monoamines into synaptic vesicles by vesicular monoamine transporter 2.¹⁶ Each of these transporters appears to have a slightly different profile of sensitivity to the various thyronamines. It remains unclear whether the pharmacologic effects of thyronamine are related to direct effects of thyronamines on TAAR1 versus the α_{2A} adrenergic receptor, by modulation of release of catecholamine neurotransmitters or by some alternate pathway, not yet described.

Furthermore, although T₁AM does not bind nuclear thyroid hormone receptors,⁴ it does appear to be transported intracellularly. Ianculescu et al. described a transport mechanism that is specific for thyronamines but distinct from that for thyroid hormone, classical aromatic amine neurotransmitters and other organic ions.¹⁷ They incubated a variety of cultured cell lines

derived from a number of tissues with ¹²⁵I-T₁AM and demonstrated that uptake into cells was inhibited by various thyronamines. Libraries of potential transporters were evaluated and a preliminary list of candidate T₁AM transporters was determined. However direct testing has not conclusively identified a thyronamine transporter.

Putative pathways of thyronamine synthesis and modification

Although the biosynthetic pathway of endogenous thyronamines has yet to be definitively determined, it is attractive to hypothesize that thyronamines are derived from thyronines through a series of deiodination and decarboxylation steps. Deiodinases have been demonstrated to tightly control levels of thyroxine and have the potential to also control levels of thyronamines in a tissue-specific fashion during different developmental stages and disease states, as well as in normal physiological function. A number of excellent reviews outline the critical role of deiodinases in thyroid hormone regulation¹⁸⁻²¹ and it is possible that similar mechanisms could regulate thyronamine production and degradation.

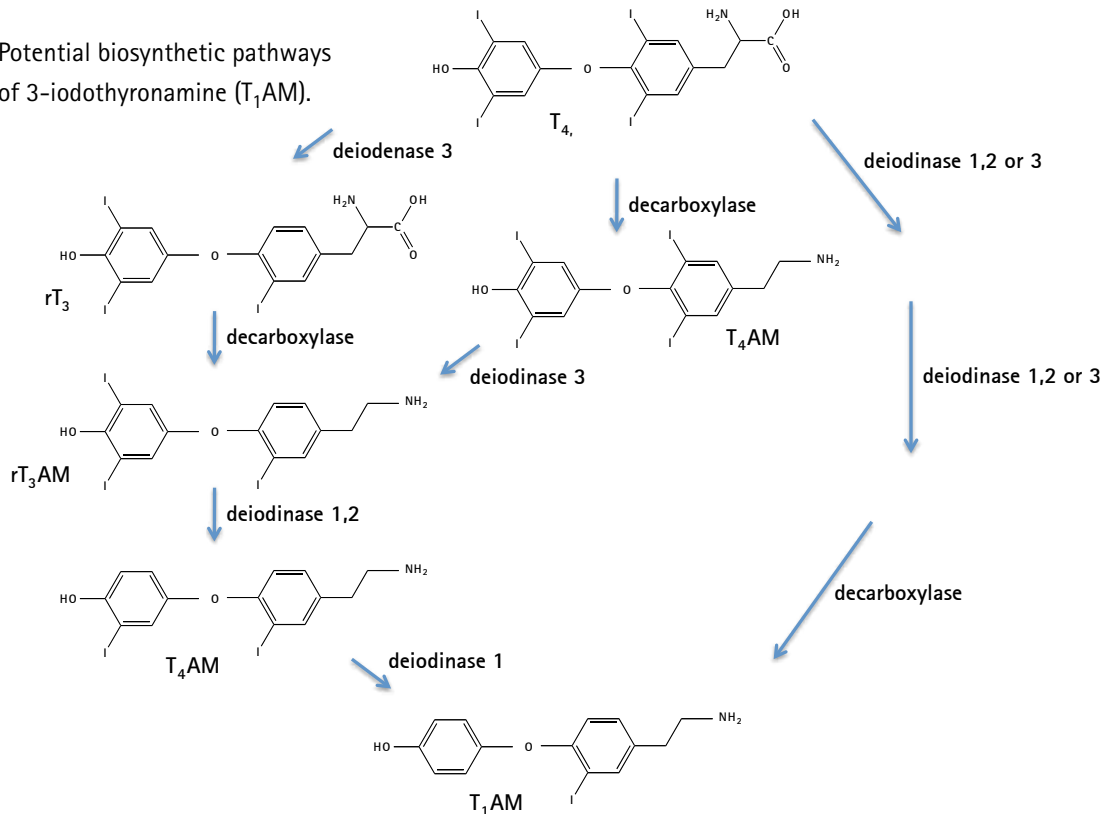
In an elegant study designed to investigate whether the proposed biosynthesis of thyronamines from thyronines via decarboxylation and deiodination was feasible, Piehl et al.²² incubated various thyronamines with type 1, 2 and 3 deiodinases and analyzed the deiodination products by liquid chromatography and tandem mass spectrometry (LC-MS/MS). A similar study by the same group was performed evaluating the deiodination of thyronines as well.²³ These investigators found specificity of the deiodinases for different thyronamines and demonstrated sequential deiodination from T₄AM to T₀AM, suggesting that there is a role for deiodinases in the synthesis of T₁AM and other thyronamines. Specifically, T₄AM may be deiodinated by type 3 deiodinase to yield reverse T₃AM (rT₃AM) but is not deiodinated to T₃AM, whereas rT₃AM can be deiodinated either to 3',5'-T₂AM by type 3 deiodinase or to 3,3'-T₂AM by either type 1 or type 2 deiodinase. It is not clear at which step the decarboxylation from a thyronine compound to a thyronamine

derivative occurs in this overall scheme but several putative pathways are diagrammed in *Figure 1*.

Thyronines, in addition to deiodination, undergo other chemical modifications which may serve to modulate their function. Reviews by Wu et al.²⁴ and Moreno²⁵ discuss several possible pathways of thyroxine metabolism and modification in addition to deiodination. These include sulfation, glucuronidation, deamination and decarboxylation. Similar pathways may also modify the thyronamines, given their structural similarity to thyronines. For example, thyronamines have been demonstrated to be substrates for sulfotransferase activity²⁶ as well as deaminases.²⁷ Cytosolic sulfotransferases play a role in the regulation of other monoamine neurotransmitters and Pietsch et al.²⁶ demonstrated the specificity of human liver sulfotransferase 1A3 (SULT1A3) for T₀AM, T₁AM and T₃AM. They also showed that SULT1A1 was active primarily on T₃AM, whereas other sulfotransferases had minimal specificity for thyronamines.

Deamination, which converts thyronines to the functional metabolites 3,3',5,5' tetraiodothyroacetic acid (Tetrac) and 3,3',5 triiodothyroacetic acid (Triac),²⁴ is another pathway whereby thyronamines could be degraded. In cell and tissue extracts, both T₁AM and T₃AM have been shown to undergo deamination, resulting in the production of iodothyroacetic acids.²⁷ This deamination was inhibited by monoamine oxidase as well as the semicarbazide-sensitive amine oxidase. The deamination product of T₁AM, 3-iodothyroacetic acid (TA₁) is found endogenously in human serum and its level is increased in T₁AM-treated rats²⁷ suggesting that

Figure 1. Potential biosynthetic pathways of 3-iodothyronamine (T_1AM).



Based on studies which demonstrated specificity of the deiodinase enzymes for thyronamines and lack of specificity of the decarboxylases, there are several potential biosynthetic pathways which have been proposed for the endogenous synthesis of T_1AM . Thyroxine (T_4) is synthesized in the thyroid and can be converted to reverse triiodothyronine (rT_3) by the type 3 deiodinase. In turn, rT_3 could be decarboxylated to yield reverse triiodothyronamine (rT_3AM) and subsequently deiodinated by type 1 or 2 deiodinases to form 3,3'-diiodothyronamine (T_2AM) and then 3-iodothyronamine (T_1AM) via type 1 deiodinase. An alternate possibility would be an initial decarboxylation step leading to the production of T_4 amine (T_4AM) followed by deiodination by the type 3 deiodinase to form rT_3AM with the remainder of the pathway as described above. Decarboxylation could also be the last step in the production, preceding a series of deiodinations by a combination of the deiodinases (shown on the right).

deamination is an endogenous pathway for degradation of T_1AM .

Significant progress has been made in characterizing thyronamine compounds. However, although a number of potential pathways for both biosynthesis and degradation of T_1AM have been demonstrated, its endogenous

synthetic pathway has yet to be definitely identified. T_1AM has been shown to be present endogenously, with measurable levels in rodent and human tissues, and there appear to be several potential functional receptors for T_1AM . However, it remains uncertain whether T_1AM is, in fact, a functional endogenous hormone.

Pharmacologic Effects of Thyronamines

Cardiac Effects

Thyronines have significant effects on the cardiac system, including increased heart rate and myocardial contractility, which are a result of both classic nuclear hormone receptor-mediated effects and nongenomic

effects.^{6,7} These often rapid effects of thyronines have several demonstrated mechanisms, including direct action on membrane receptors. In addition, the thyronine metabolite Tetrac has previously been shown to inhibit some of the nongenomic functions of thyronines, probably by inhibiting thyroxine binding to a membrane receptor.⁷

With a precedent for a metabolite acting to regulate the function of its parent compound, it has been hypothesized that thyronamines might counter the cardiac effects of thyroid hormones, particularly as they may be synthesized and degraded locally in cardiac tissue (as suggested by Zucchi et al.²⁸). Consistent with this hypothesis, intraperitoneal injection of T₁AM resulted in a rapid dose-dependent decrease in heart rate, and in working *ex vivo* heart preparations, both cardiac output and systolic aortic pressure were decreased.⁴ T₀AM also produced a decrease (though less robust) in cardiac output notably in contrast to previously reported positive inotropic effects.⁸⁻¹¹

Over the past couple of years, a better understanding of the mechanism of thyronamine action in cardiac tissue has developed. Thyronamines were initially thought to exert their effects via the TAAR receptor family. Several TAAR family members were found to be expressed in cardiac tissue and several trace amines (including octopamine, β -phenylethylamine, tryptamine, T₀AM and T₁AM) were demonstrated to produce a dose-dependent reduction in cardiac output in isolated rat heart preparations.²⁹ The effect was most pronounced with T₁AM (IC₅₀ > 27 μ M) and T₀AM (IC₅₀ > 94 μ M). However, the rank order of binding suggested that the response was mediated not by TAAR₁ or TAAR₄ but by other members of the TAAR family that are more specific to cardiac tissue.²⁹ In addition to this specific pharmacologic effect noted in isolated rat hearts, mRNA expression of several TAAR subtypes was found in normal rat hearts and T₁AM specific binding sites were demonstrated in adult rat cardiac membranes.³⁰ In whole animals, cardiac output was rapidly and dose-dependently decreased with T₁AM, but not T₃. Systolic blood pressure, heart rate and coronary flow were also decreased with T₁AM,³⁰ confirming both negative inotropic and chronotropic activities of T₁AM, which were rapid and reversible. These effects are opposite to those of both the classic genomic as well as nongenomic actions of thyroid hormones which suggests a model whereby T₁AM modulates thyroid function in the heart by counteracting the effects of thyronines.

In an effort to further characterize the signaling pathway mediating cardiac T₁AM effects, Chiellini et al.

have investigated the effect of various kinase and phosphatase inhibitors on working heart preparations.^{30,31} T₁AM mediated decreases in cardiac output were diminished by the addition of the protein tyrosine kinase inhibitor genistein whereas the tyrosine phosphatase inhibitor vanadate had the opposite effect, suggesting that T₁AM exerts its effect via tyrosine phosphorylation/dephosphorylation. Inhibitors of protein kinase A, protein kinase C, phosphatidylinositol 3 kinase, calcium-calmodulin kinase, MAP kinase and inhibitory G proteins were not effective in modulating T₁AM-mediated effects in this system.³⁰

In a recent study by Ghelardoni et al.,³² T₁AM function in cardiac tissue was evaluated further by studying its effect on ion channels. In isolated rat hearts, T₁AM, as noted previously, was shown to have a negative inotropic effect, which occurred prior to any decrease in oxygen consumption or glucose uptake in the tissue.^{30,32} In cardiomyocytes, these negative inotropic effects of T₁AM, manifest as reduced cellular shortening, were hypothesized to be related to a reduction in intracellular calcium stores. In contrast, the negative chronotropic effect of T₁AM, appears to be mediated by prolongation of the action potential, which can be explained by T₁AM inhibition of specific potassium currents in the cardiomyocytes.³²

The evidence thus suggests that T₁AM is endogenously present in cardiac tissues, that there are specific binding sites for T₁AM in cardiac tissue, that TAARs as well as other potential targets for T₁AM are expressed in these tissues, and that T₁AM produces dramatic physiological effects.³⁰ However, the mechanism of T₁AM effects remains unclear with evidence that they are mediated by tyrosine phosphorylation as well as effects on various ion channels. Further, it is an intriguing hypothesis that endogenous T₁AM may act physiologically in a homeostatic relationship with thyroid hormones, acting to counter the cardiac effects of thyroid hormone.

Metabolic Effects

In addition to cardiac effects, administration of T₁AM produces marked changes in metabolism. A single

intraperitoneal injection of T₁AM in both mice^{4,33} and hamsters³³ resulted in a rapid dose-related drop in body temperature as well as diminished activity level. Core body temperature dropped by nearly 20% at 1–2 hours after injection with return to normothermia and normal activity levels by 6–8 hours post-injection.⁴ The maximal decrease in temperature without adverse effects was 50 mg/kg for T₁AM and T₁AM produced a more dramatic effect than T₀AM (greater magnitude of decrease as well as longer duration of action).⁴ These effects, initially seen in mice, were replicated in Djungarian hamsters *Phodopus sungorus* which have been used as a model animal to study the aspects of the temporary hibernation state, torpor.³³ These animals typically switch to a hypometabolic state during torpor which results in decreased basal body temperature, decreased heart rate, decreased volume of oxygen consumed (VO₂) representing a decreased metabolic rate and a change in fuel metabolism from one of mixed/carbohydrate metabolism to one of primarily lipid metabolism. Injection of Djungarian hamsters with T₁AM resulted in a rapid and transient change in the respiratory quotient (RQ) from 1.0 (primarily carbohydrate metabolism) to 0.7 (lipid predominant) indicating a change in fuel utilization mimicking the changes seen in hibernating animals.³³ Similar effects on RQ were also found in a non-hibernating species, C57BL/6 mice.³³ Further evidence that T₁AM increased the utilization of lipids as the primary fuel source in hamsters was the correlation of RQ shift with a spike in urine ketone measurement following T₁AM injection. In addition, body weight in the hamsters was decreased after a single administration of T₁AM with a gradual return to normal over several days. DEXA analysis revealed that there was a decrease in fat mass with no change in lean mass after a single injection of T₁AM, consistent with body composition changes seen in hibernation.³³ The striking similarity of T₁AM-induced effects on body temperature, fuel utilization and body composition to features of hibernation raise the possibility that T₁AM is an endogenous trigger for that physiological state.

In addition to a change in fuel substrate utilization, Regard et al.¹⁵ demonstrated that T₁AM also has pronounced effects on glucose metabolism. The authors

developed a method to screen for G protein-coupled receptors (GPCR) coupled to inhibitory G proteins (G_iα and G_oα) that might be important for regulation of insulin secretion. This screening assay suggested that the newly described trace amino acid receptor, TAAR1, could be important in insulin secretion. The authors investigated whether T₁AM, recently characterized as a ligand of TAAR1, would alter insulin secretion. Intraperitoneal administration of 50 mg/kg T₁AM resulted in increased blood glucose and decreased insulin levels. The time course was similar to other acute effects of T₁AM (hypothermia, decreased cardiac output, RQ shift) in that the maximum effect was seen at approximately two hours following injection with a gradual return to normal levels by 8 hours. A simultaneous increase in glucagon level was also found, suggesting increased hepatic production of glucose as the mechanism for the hyperglycemia.¹⁵ These insulin and glucose effects were absent in animals overexpressing pertussis toxin (which blocks inhibitory G protein function) suggesting that T₁AM was acting via a receptor coupled to G_iα. *In vitro*, however, T₁AM administration to cells expressing TAAR1 increases cAMP.⁴ It is possible that this contradiction represents a difference between *in vitro* and *in vivo coupling*, involvement of an intermediary target, or tissue specific differences in the action of T₁AM. In addition, earlier it was found that T₁AM was acting in the pancreatic beta cells not via TAAR1 but rather through the α_{2A} adrenergic receptor,¹⁵ further indicates that the mechanism of these effects remains unclear.

In a further evaluation of T₁AM regulation of glucose metabolism and insulin levels, Klieverik et al.³⁴ demonstrated that intracerebroventricular (ICV) infusion of T₁AM and other thyronamines mimicked the effects of intraperitoneal T₁AM injection, with increases in serum glucose and glucagon levels and concomitant decreases in insulin levels occurring in a similar time frame. T₀AM was less effective at eliciting these responses. This same group had previously demonstrated that thyroid hormone could modulate liver glucose production, potentially mediated by sympathetic hypothalamic pathways initiated in the paraventricular nucleus of the hypothalamus.³⁵ They now hypothesize that the

thyronamines also mediate their metabolic effects via central mechanisms, likely via the hypothalamus.³⁴

Based on these experiments, an emerging theory is that many of the functions of T₁AM may be mediated centrally. An additional example of central actions of T₁AM were presented in a study by Dhillon et al.,³⁶ wherein very low doses of T₁AM were suggested to act as orexigenic factors potentially mediated by the arcuate nucleus of the hypothalamus. Intraperitoneal injection of T₁AM resulted in an increase in food intake only at a very low dose, 4 nmol/kg (1.3 mcg/kg), and was not

associated with a change in metabolic rate (VO₂) or activity level. Both ICV and intra-arcuate nuclear administration of T₁AM were also associated with increases in food intake, suggesting that T₁AM may be acting centrally to mediate its orexigenic effect, although there was not a clear dose response for the effect. C-fos was followed as a marker of cellular activity and there was an increase in arcuate nucleus staining in T₁AM treated animals. This study suggests that T₁AM may exert at least some effects in specific regions of the brain.

Potential Clinical Applications

Because of the demonstrated changes in calcium mobilization and ion channel activity, T₁AM was evaluated in murine models of both cardiac ischemia and stroke. An abstract presented by Frascarelli et al.³⁷ reported a direct cardioprotective effect of T₁AM which was not related to the hypothermic effects of T₁AM. Similarly, T₁AM has been shown to be neuroprotective in a murine model of stroke.³⁸ In contrast, the protective effect of T₁AM was not seen in murine cerebral cortical cell primary culture and when controlled for the hypothermia induced by T₁AM, the neuroprotective effect in vivo was abolished. It is interesting that the protective effects of T₁AM are direct in cardiac tissue but second-

ary to hypothermia in the central nervous system.^{37,38} The clinical promise of these agents is improved by the interesting finding that the neuroprotection afforded by T₁AM was present even if these agents were administered up to one hour following the ischemic event.³⁸ Thyronamines could thus be developed as agents to provide neural or cardiac protection via post-ischemia cooling. Finally, the profound metabolic effect of T₁AM resulted in changes in substrate utilization, weight and glucose regulation which raises interesting questions about its endogenous role and exciting possibilities for therapeutic applications in the field of obesity and metabolic syndrome.

Conclusion

Thyronamines are emerging as important putative metabolites of thyroid hormone which could either play a role in the modulation of thyroid hormone action or may act as endogenous regulators of other pathways. Evidence is mounting for T₁AM (and to a lesser degree T₀AM) effects at cardiac, metabolic and central nervous system targets. However, most studies to date have used pharmacologic doses of T₁AM and the role of endogenous T₁AM in these systems is not clear. The hypometabolic effects of T₁AM are providing insights into the initiation of torpor/hibernation, but could also be exploited pharmacologically as a means minimize path-

ological damage in ischemic tissues. Thyronamines may also be involved in thyroid hormone regulation of cardiac function either by local modulation of thyroid hormone action or the action of other neurotransmitters. Although further investigation is needed, the ability of T₁AM to alter fuel utilization could potentially be important for understanding obesity and adiposity. There remain, however crucial questions that must be answered, including the role of endogenous T₁AM and its relationship to thyronine action, its mechanism of action, and the pathways for biosynthesis and degradation of this family of compounds.

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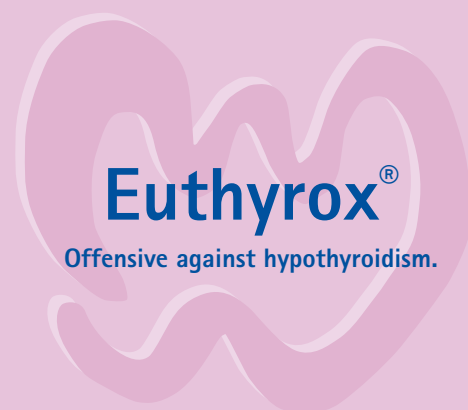


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