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Thyronamines – decarboxylated derivatives of thyroid hormones – new family of endogenous signaling molecules?

Tyronaminy – dekarboksylowane pochodne hormonów tarczycy – nowa rodzina cząsteczek sygnałowych?

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S u m m a r y

Thyronamines (TAMs) are derivatives of thyroid hormones, produced *via* decarboxylation of the alanine chain. They act as endogenous signaling molecules and were firstly discovered in early 50thies of the XXth century. They were rediscovered for modern science in 2004 by Thomas S. Scalan. Thyronamines exert various effects in organisms, including hypothermia, negative chronotropy, negative ionotropy, hyperglicemia, reduced Respiratory Quotient. On the molecular level they are known to inhibit thyroid hormone and monoamine transporters. TAMs have been detected in different mammals but their physiological concentrations have not been clearly determined up to date. TAMs are believed to act *via* specific receptors. The most well recognized so far are two GPCRs (G-Protein Coupled Receptors), TAAR1 and Adra2A, involved in the regulation synthesis of cyclic AMP. Two pathways of TAMs catabolism, sulfation and oxidative deamination, have been proposed. Although exact physiological role of thyronamines is still unclear, some therapeutical applications were suggested. This review summarizes the current knowledge about thyronamines, which is still fragmentary. Thyronamines deserve further investigation and it can be assumed that the nearest future will bring new exciting data about these fascinating signaling compounds.

Key words: thyronamines, iodothyronamines, thyroid hormones

S t r e s z c z e n i e

Tyronaminy (TAM) są powstającymi w wyniku dekarboksylacji pochodnymi hormonów tarczycy. Działają jako cząsteczki sygnałowe. Zostały po raz pierwszy opisane w latach pięćdziesiątych XX wieku, dla współczesnej nauki ponownie odkrył je Thomas S. Scalan w 2004 r. Tyronaminy mają zróżnicowany wpływ na organizm, m.in. powodują hipotermię, negatywne efekty chronotropowe i inotropowe, hiperglikemię, obniżenie współczynnika oddechowego. Tyronaminy są również inhibitorami transporterów hormonów tarczycy i monoamin. TAM są wykrywalne w organizmach, jednak ich fizjologiczne stężenie nie zostało jednoznacznie określone. Przypuszcza się, że działają one za pośrednictwem specyficznych receptorów. Sugeruje się, że są to receptory TAAR1 i Adra2A. Oba te receptory należą do rodziny receptorów związanych z białkami G (GPCR), ale jeden z nich powoduje stymulację a drugi inhibicje syntezy cAMP. Zaproponowano dwa szlaki na drodze których tyronaminy są degradowane – sulfonowanie i oksydatywna deaminację. Pomimo, że fizjologiczna rola tyronamin jest wciąż niejasna, uważa się, że mogą znaleźć zastosowanie terapeutyczne. Niniejsza praca przeglądowa podsumowuje obecną, wciąż fragmentaryczną, wiedzę na temat tyronamin.

Słowa kluczowe: tyronaminy, jodotyronaminy, hormony tarczycy

INTRODUCTION

Thyronamines are derivatives or metabolites of thyroid hormones – thyroxine (T4) and triiodothyronine (T3). These endogenous signaling compounds were firstly discovered in early 50thies of XXth century. It was revealed then that those decarboxylated forms of thyroid hormones sensitize inhibitory effect of adrenaline on isolated rabbit intestine (1), prevent goiter formation and stimulate oxygen consumption in rats (2). Iodothyronamines were rediscovered in 2004 by Scalan group (3). They showed that iodothyronamine (T1AM) and thyronamine (T0AM) act by binding to TAAR1 receptor and have very strong effects on thermoregulation and cardiac function. Since then, plenty of new information about those very interesting molecules has been issued annually, including data on synthesis, *in vivo*

detection, transport, degradation, receptors, pharmacological and physiological actions and many others. Thyronamine-related research can be divided in two periods: the first from the early 50thies to 80s of XXth century and the second period lasting since 2004 until now. In the first period, thyronamines were investigated as one of the groups of many derivatives of thyroid hormones. In 2004, Scalan and coworkers rediscovered thyronamines. From that time, a new era of thyronamines investigation begun. In this review we summarize knowledge about thyronamines that emerged from both thyronamines research periods.

CHEMICAL CONSTITUTION

Chemically, thyronamines are decarboxylated forms of thyroxine (3,5,3',5'-tetraiodothyronine) and its deiodinated derivatives, lacking the carboxyl group of the alanine chain. In thyronamines, alanine chain is replaced by ethylamine chain (fig. 1). TAMs may have from 0 to 4 atoms of iodine per molecule (1, 3). Interestingly, only T1AM and T0AM appear to be biologically active.

NATURALLY OCCURRING THYRONAMINES, THEIR CONCENTRATIONS AND TRANSPORTERS IN BLOOD

Thyronamines can be detected *in vivo* by liquid chromatography tandem mass spectrometry (LC-MS/MS). Until now only two of them have been detected in living organisms – thyronamine (T0AM) and 3-iodothyronamine (T1AM). They were detected in blood, heart, liver, adipose tissue, thyroid and brain of rodents (1). Those observations, however, might result from not well established methods of thyronamines detection by mass spectrometry, therefore it cannot be excluded that other thyronamines are present in living organisms. In the first period of thyronamines research ^{131}I-labeled T4AM (decarboxylated thyroxine) was detected by butanolic extraction and subsequent chromatographic separation. Radioactively labeled T4AM was detected in plasma and thyroid glands of rats treated with ^{131}I and in plasma of two patients with thyroid tumors who were also treated by high doses of ^{131}I (1).

The physiological concentrations of thyronamines are not well known and differ depending on the type of experiment, tissue and method of detection. T4AM was postulated to occur in healthy organisms in serum concentrations reaching 1-2% of thyroxin concentration. T1AM concentrations vary in both tissue- and organism-specific manner. Its quantities in brains of Long-Evans rats is about subpicomoles per gram (3), in hearts of male Wistar rats is estimated to 68 pmol per gram but in fact varies in individuals ranging from 1 to 120 pmol/g (4). In Djungarian hamsters, 3-iodothyronamine was detected in concentration of about 6 nM (5). In mouse tissues, as analyzed by LC-MS/MS method, the levels of T1AM were determined in the range of 1-120 pmol/g (1). In human tissues concentrations of thyronamines were firstly measured in 2008, and in thyroid, skeletal muscle, adipose tissue, prostate and serum, achieved 60 nM concentrations (T1AM) (1). There are still many of controversies about methods of detection and quantification of T1AM. Those difficulties result from the fact that T1AM strongly binds to apolipoprotein B100, leading to low serum levels of free T1AM (about 60 nM) in human (1).

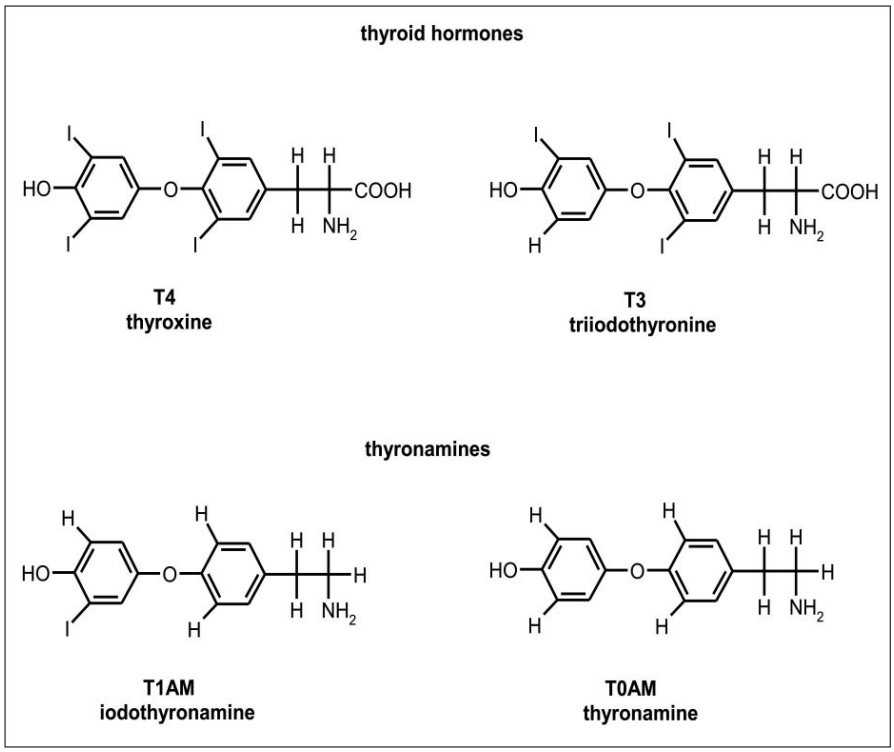

Fig. 1. Structure of thyroid hormones (T4 – thyroxine and T3 – triiodothyronine) and two most investigated thyronamines (T1AM – iodothyronamine, T0AM – thyronamine).

Until now there is no procedure which allows to determine absolute TAMs concentrations.

SYNTHESIS

Pathways leading to TAM biosynthesis are still unknown; however, there are two proposed and possible ways of TAM biosynthesis. Firstly, TAM can be produced *via* decarboxylation of thyroid hormones and their deiodinated derivatives. It was proposed that aromatic L-amino acid decarboxylase could be an enzyme responsible for that reaction (3). It is not clear whether deiodinated derivatives of thyroid hormones, apart from non-processed thyroid hormones may serve as substrates in these reactions. It is possible that T1AM and T0AM result from decarboxylation of deiodinated thyroid hormones. This type of reaction would require TAMs being substrates of iodothyronine deiodinases. Indeed, it was shown that T3AM and T2AM are deiodinated by type 1 and type 3 iodothyronine deiodinases (Dio1 and Dio3), T4AM and T1AM are processed by Dio3, while T3AM, rT3AM are substrates of Dio1 and Dio2 (6).

INTRACELLULAR TRANSPORT OF THYRONAMINES

It is well recognized that thyroid hormones are transported across the cellular membrane by specific transporters. Therefore many researchers focused on the mechanisms of TAMs membrane transport. Ianculescu and coworkers (7) analyzed TAMs transport mechanisms in several types of cell lines lines (L6-rat skeletal muscle; BC3H1-mouse brain tumor; insect Sf9 cells, Caki-1 – human kidney cancer, U2OS- human osteosarcoma; HepG2-human hepatocellular carcinoma; HISM – smooth intestine; HeLa – cervical carcinoma; HEK-293 – human embrional kidney; 293T – human kidney) and discovered that TAMs indeed have the specific cellular transporters. Those observations suggested that TAMs could possibly act in majority of tissue types, exerting their specific effects not only *via* membrane bound receptors but also intracellulary. Using new high-throughput RNAi screening method 34 possible T1AM transporters were identified. Direct *in vitro* studies on the identified transporter genes remained inconclusive, however. Knockouts of several transporter coding genes resulted in decrease in TAMs transport while the overexpression of the respective receptor protein did not cause increase in transport. The authors concluded that although they proved that T1AMs are actively transported across plasma membranes, the identification of specific transporters which are responsible for T1AM uptake into cells needs further investigation. They hypothesized that the knowledge about T1AM transport mechanisms could help us not only in understanding the T1AM action but also its potential implications for thyroid hormone regulation and possible involvement in thyroid – related pathologies (7).

RECEPTORS

As for June 2011, no specific receptor for TAMs has been identified, although some strong candidates have been investigated and experimentally qualified as potential TAMs receptors.

During the first period of TAMs research, several proteins interacting with ^{131}I labeled thyronamines were detected. It was revealed that T4AM displaced T4 and T3 from cytosolic and nuclear protein fractions of human leukocytes, while T3AM, T2AM and T0AM interfered with binding of a ligand to β-adrenergic receptor in plasma membrane of turkey erythrocytes and inhibited activation of cAMP synthesis (1). The abovementioned and other experiments from the early TAMs research period suggest interaction between TAMs and β-adreneric receptors.

Basing on the structural similarity between TAMs and TAAR1 receptor (trace amines associated receptor 1) it was suggested that TAAR1 could serve as the TAMs receptor as well (3). TAAR1 is a membrane bound G protein coupled receptor, activating cAMP synthesis. Scalan and coworkers observed in 2004 that TAMs stimulated accumulation of cAMP in HEK-293 cell line expressing TAAR1 (3). The fact that TAAR1 is expressed in tissues in which TAMs are active (heart, brain, pancreas) additionally supports the hypothesis that TAAR1 is a physiological TAMs receptor. Zucchi suggested the involvement of TAAR4 or TAAR8a in thyronamine signaling. (8).

On the contrary, other experiments suggest that TAMs react with a receptor coupled to G protein ($G\alpha_i$) which inhibits cAMP synthesis (9). The other receptor suggested to be the TAMs receptor is α_{2A} adrenergic receptor (Adra2A), which is also GPCR (G protein coupled receptor) but coupled to G protein that inhibits cyclic AMP synthase. *In vitro* studies demonstrated that 3-T1AM has higher affinity to α_{2A} adrenergic receptor when compared with adrenaline. Administration of Adra2A antagonist inhibits T1AM hyperglycemic effects in mice (9).

Some researchers suggest that both abovementioned receptors play a role in mediating the TAMs signaling. Probably the effects of TAMs are dependent on TAAR1/Adra2A ratio. For instance, T1AM inhibits glucose-dependent insulin release in murine and human pancreas (9), while in MIN6 insulinoma cell line it stimulates insulin release. Both analyzed cell types differ in the ratio of TAAR1 and Adra2A which regulate insulin release in opposite manner. TAAR1 activate insulin secretion *via* activation of cyclic AMP synthase and Adra2A inhibits insulin release by inhibiting synthesis of this signaling molecule. Probably both these receptors interact with TAM and the final effect on the cell metabolism depends on the ratio between receptors or presence or absence of one of them.

EFFECTS OF TAMS

TAMs exert numerous spectacular effects. However, it is not clear whether those effects are pharmacological or physiological and this question will not be solved until methods for measurement of TAMs concentration are finally elaborated. In the first Scalan's group experi-

ments the effects of T1AM and T0AM were very spectacular. They investigated TAMs influence on specific aspects of metabolism – thermoregulation and cardiac function (3).

Hypothermia

The most impressive effect on TAMs administration, observed in mice, was hypothermia. Injection of 59 or 178 μmol/kg of 3-T1AM and T0AM, respectively, caused an 8°C drop in body temperature in 30 minutes. The effect was reversible – mice recovered from hypothermia after 6 to 8 hours. The animals were not anesthetized (they had reflexes retained) and what is most important did not display compensatory reactions such us shivering, huddling and piloerection (3). Almost the same effects were observed in Djungarian hamsters (5).

Cardiac effects

It was not only hypothermia, however, that came as an interesting result of Scalan's experiments, as injection of TAMs also caused bradycardia (3). The TAMs effect was reversible. They caused decrease of heart rate from 600 to about 350 beats per minute. The effect was reversed in 6 to 8 hours after injection. Chronotropic effect was direct, as it was investigated also on perfused hearts. In isolated rat hearts, 38 μM T1AM resulted in reduction of heart rate within minutes. The T1AM caused not only chronotropic but also inotropic effects, as injection of 29 μM T1AM caused decrease of cardiac output. Scalan and coworkers concluded that 3-T1AM has chronotropic and inotropic effects on heart with different potencies (3). The most important is that until now only few endogenous negative inotropic agents were identified, including adenosine, IL-6 and TNFα (4). More in depth studies revealed that 20 μM 3-T1AM decreases cardiac contractility but does not lower oxygen consumption and glucose uptake of perfused hearts (10). In contrast, higher, 25 μM doses of TAM result in decrease of oxygen consumption.

TAMs-mediated cardiac effects seem to result from reduced amplitude and duration of calcium transient, probably due to abolished mechanism of Ca^{2+} current facilitation by membrane depolarization, reduced ryaonodine binding to sarcoplasmatic reticulum calcium release channel, significant increase in Ca^{2+} leak by the closed channel or/and the action of potential prolongation by reducing the transient outward current and background current (10, 11). Although some studies suggest involvement of other signaling pathways, Chiellini *et al.* proposed T1AM as an inductor of dephosphorylation of critical tyrosine residues implying T1AMs influence on tyrosine kinase-mediated actions. On the other hand, cAMP, PKA, PKC, CaMKII, PI3K and MAPK are probably not involved in TAMs action (4).

Hyperglycemia

Regard and coworkers revealed that injection of 140 μM/kg T1AM results in increase of glucose blood level in mice (9). This effect was detectable in the first minutes after injection and the maximum glucose level (2.5 fold of normal level) was observed 2 hours after treatment. Hyperglycemia, similarly as hypothermia and cardiac effects, was reversed after 8 hours. The drop in blood insulin levels and increase in glucagon levels were observed in mice with TAMs induced hyperglycemia. Because insulin treatment reversed the above effect it was suggested that peripheral tissues were insulin sensitive. *In vitro* studies showed that T1AM causes inhibition of insulin release from pancreatic β-cells (9). Moreover, Klieverik and coworkers demonstrated increase in plasma levels of glucose and glucagon in rats injected with T1AM (12).

Respiratory Quotient

Braulke in 2008 revealed that in mice and Djungarian hamsters, intraperitoneal injection of T1AM decreased Respirator Quotient from 0.9 to 0.7 (5). TAMs injection also changed metabolism. Carbohydrates, the main metabolic substrates before injection, were subsituted by lipids after T1AM administration. The most significant effect was observed in 3-4 hours after injection, and 24 hours were needed to return to normal metabolism. Changes in fuel utilization were confirmed – it was shown that after TAM injection ketone bodies were detectable in urine and a severe weight decrease, connected with fat mass loss was observed (5).

Influence on liver oxidative capacity

Venditti and coworkers revealed that TAMs reduced oxygen consumption in mitochondria and increased H_2O_2 release (13). Thyronamines reduced the activity of Complex III, an element of an oxidative chain. T1AM and T0AM inhibited mitochondrial function. The physiological implications of these findings need further investigation (13). As thyroid hormones are stimulators of oxygen consumption and mitochondrial function, this is another example of opposite actions of effect of TAMs and thyroid hormones.

Inhibition of thyroid hormones transport

T1AM, the most potent and the most studied thyronamine is an inhibitor of thyroid hormone transporters. The proper transport of thyroid hormones is critical for their correct action in target cells. T1AM-mediated regulation of this mechanism could be therefore one of the most important roles of thyronamines. Ianculescu and coworkers investigated the influence of T1AM on OATP and MCT transporters. They revealed that T1AM inhibits transport of thyroid hormones by OATP1A2, OATP1C1 and MCT8. Influencing thyroid hormones transport, TAMS could affect all the thyroid-hormone mediated signaling pathways (14). This partially explains why effects of thyronamines action are often opposite to effects mediated by thyroid hormones (hypothermia, hyperglycemia, *etc*.).

Influence on monoamine transporters family

Weatherman (15) suggests that thyronamines could react with monoamine transporters. Monoamine transporters mediate reuptake of neurotransmitters in neuronal synapses. There are known transporters for dopamine (DAT), serotonin (SERT) and norepinephrine (NET), as well as a transporter responsible for packing monoamines into secretory vesicles (VMAT2). It was shown that T1AM inhibits uptake of dopamine and norepinephrine in synapses. In other experiments on synaptic vesicle preparations and investigation of membranes of transfected cell lines it was shown that T1AM also inhibits VMAT2. Those experiments showed the new pathway of TAMs action, which apparently can act as neuromodulators. The question that arises from the abovementioned studies is which mechanism of TAMs action is involved in mediation of hypothermia or bradycardia. The other well known inhibitors of monoamine transporters – cocaine and amphetamine – have opposite effects on temperature regulation and heart action. It is also possibile that the observed effects are indirect and are partially mediated by TAAR1. As many previously reported effects, inhibition of monoamine transporters needs further investigation (15,16)

Other effects

Some experiments involved administration of different doses of TAMs than 50 mg/kg. Intracerebroventicular infusion of 0.5 mg/kg caused stronger effects on glucose metabolism in Wistar rats (12). Furthermore, TAMs (especially 3-T1AM) activate the hypothalamus-pituitary-adrenal axis, causing increase in corticosterone serum levels. Intraperitoneal (IP) administration of TAMs reduced levels of TSH, thyroxine and triiodothyronine, but when TAMs were administered intracerebroventicularly (ICV), no such effects were observed. After direct injection of TAMs to arcuate nucleus, rodents showed increased food intake (3 folds) suggesting that orexigenic effect of TAMs is regulated on hypothalamic level (17). Increased food intake was also observed in animals after IP or ICV injection of low doses of TAMs (4 mg/kg in mice; 1.2 mg/kg in rats). No changes in oxygen consumption and locomotor activity were observed in those animals (17).

METABOLISM OF THYRONAMINES

The first studies on TAMs metabolism focused on the role of 4'OH group in TAMs action. TAMs derivatives that lack or have the 4'OH group modified exert toxic effects (18). Since 4'OH can undergo sulfation and glucuronidation, it was investigated whether sulfation can be one of the pathways of TAMs catabolism. Pietsch and coworkers (19) found that T1AM and T0AM are substrates of sulfotransferase SULT1A3, while T3AM is sulfated by SULT1A1. Moreover, it appeared that sulfotransferases are activated by TAMs.

The other metabolic pathway proposed to take part in TAMs utilization is an oxidative deamination. For the first time it was suggested for TAMs in 1958 by Hillmann (1). In 2009 Wood and coworkers (20) proved that oxidative deamination is one of pathways of TAMs degradation. They showed that TA1 (thyroacetic acid corresponding to amine oxidase action on T1AM) is present in serum in very low concentrations (less then 0.1 nM) but increases to 3-12 nM after injection of 20 mg/kg T1AM (20). In 2011 Agretti and coworkers (21) showed that in FRTL5 cell line exogenous T1AM was catabolized to T0AM, and next to TA1 and TA0, supporting hypothesis that oxidative deamination is responsible for TAMs utilization.

As mentioned before, thyronamines are also substrates for iodothyronine deiodinases (6). However, it is still unclear if deiodination is solely a pathway leading to TAMs synthesis or if it might also lead to TAMs degradation. Probably, deiodination is involved in both these metabolic processes.

THYRONAMINES AS THERAPEUTIC AGENTS

Hypothermia is known to have neuroprotective effect in the stroke and this phenomenon is mediated by many mechanisms, such as reduction of metabolic rate, ROS formation, reperfusion injury or glutamate release (22). Because pharmacologically induced hypothermia seems to be promising alternative to physical cooling methods and because it was shown that TAMs caused hypothermia, possible use of TAMs in stroke therapies have been analyzed. The neuroprotective effects of TAMs in rodents stroke model was investigated by Doyle *et al*. (22). They showed that T1AM and T0AM prevented ischemic injury when administrated acutely after stroke. It was shown for the first time that cryogen (T1AM) may be prophylactically administrated in situations of anticipated ischemic injury (22). Because the thermal inertia in humans is much higher, the promising results obtained on mice should be tested on larger animals to determine the depth of hypothermia that can be achieved. The authors concluded that TAMs could be used to induce therapeutic hypothermia although their potential applications as ischemia protective agents need further investigation (22). However, despite of promising results, the physiological role of TAMs seems not to be recognized enough to enable their use as therapeutic agents and requires further investigation of their role both as cryogens and hormones or signaling molecules.

CONCLUSIONS

TAMs have been identified as endogenous signaling molecules, causing *in vivo* very strong effects on metabolism: hypothermia, hyperglycemia, reduction of RQ, negative chrono and inotropy etc. Because more in depth studies on TAMs have in fact started in 2004 after Scalan *et al.* (3) rediscovered TAMs, our knowledge about those very interesting derivatives of thyroid hormones is insufficient. The field of TAMs biology research is open and TAMs need further investigation in all aspects, including their metabolism, synthesis, intracellular transport, physiological and pharmacological

effects, concentrations in living organisms and many others. Establishing of physiological concentrations of TAMs remains to be of special importance. Some recent reports have suggested that concentrations of TAMs are a magnitude higher than those previously reported (1). The observed effects of TAMs are often opposite to those caused by thyroid hormones (HTs). Briefly, TAMs reduce metabolism while THs stimulate it. This suggests that thyronamines could play a role of compensatory agent in the organisms – being metabolites or derivatives of thyroid hormones they could prevent organisms from long and strong effects of high doses of thyroid hormones by inhibiting or moderating thyroid hormones effects. There is also possibility that thyronamines are a new type of thyroid hormones.

In conclusion, thyronamines constitute a group of very interesting newly discovered signaling molecules, but our knowlege about them is still fragmentary. Thyronamines therefore deserve further investigation and it can be assumed that the nearest future will bring new exciting data about thyronamines.

BIBLIOGRAPHY

1. Piehl S, Hoefig CS, Scanlan TS, Köhrle J. Thyronamines-past, present, and future. Endocr Rev 2011; 32(1): 64-80
2. Tomita K, Lardy HA: Synthesis and biological activity of some triiodinated analogues of thyroxine. J Biol Chem 1956; 219(2): 595-604
3. Scanlan TS, Suchland KL, Hart ME et al.: 3-Iodothyronamine is an endogenous and rapid-acting derivative ofthyroid hormone. Nat Med 2004; 10(6): 638-42.
4. Chiellini G, Frascarelli S, Ghelardoni S et al.: Cardiac effects of 3-iodothyronamine: a new aminergic system modulating cardiac function. FASEB J 2007; 21(7): 1597-608.
5. Braulke LJ, Klingenspor M, DeBarber A et al.: 3-Iodothyronamine: a novel hormone controlling the balance betweenglucose and lipid utilisation. J Comp Physiol B 2008; 178(2): 167-77.
6. Piehl S, Heberer T, Balizs G et al.: Thyronamines are isozyme-specific substrates of deiodinases. Endocrinology 2008; 149(6): 3037-45.
7. Ianculescu AG, Giacomini KM, Scanlan TS: Identification and characterization of 3-iodothyronamine intracellular transport. Endocrinology 2009; 150(4): 1991-9.
8. Zucchi R, Ghelardoni S, Chiellini G: Cardiac effects of thyronamines. Heart Fail Rev 2010;15(2): 171-6.
9. Regard JB, Kataoka H, Cano DA et al.: Probing cell type-specific functions of Gi in vivo identifies GPCR regulators of insulin secretion. J Clin Invest 2007; 117(12): 4034-43.
10. Ghelardoni S, Suffredini S, Frascarelli S et al.: Modulation of cardiac ionic homeostasis by 3-iodothyronamine. J Cell Mol Med 2009; 13(9B): 3082-90.
11. Axelband F, Dias J, Ferrão FM, Einicker-Lamas M: Nongenomic signaling pathways triggered by thyroid hormones and their metabolite 3-iodothyronamine on the cardiovascular system. J Cell Physiol 2011; 226(1): 21-8.
12. Klieverik LP, Foppen E, Ackermans MT et al.: Central effects of thyronamines on glucose metabolism in rats. J Endocrinol 2009; 201(3): 377-86.
13. Venditti P, Napolitano G, Di Stefano L et al.: Effects of the thyroid hormone derivatives 3-iodothyronamine and thyronamine on rat liver oxidative capacity. Mol Cell Endocrinol 2011 [Epub ahead of print].
14. Ianculescu AG, Friesema EC, Visser TJ et al.: Transport of thyroid hormones is selectively inhibited by 3-iodothyronamine. Mol Biosyst 2010; 6(8): 1403-10.
15. Weatherman RV: A triple play for thyroid hormone. ACS Chem Biol 2007; 15, 2(6): 377-9.
16. Snead AN, Santos MS, Seal RP et al.: Thyronamines inhibit plasma membrane and vesicular monoamine transport. ACS Chem Biol. 2007; 15, 2(6): 390-8.
17. Dhillo WS, Bewick GA, White NE et al.: The thyroid hormone derivative 3-iodothyronamine increases food intake in rodents. Diabetes Obes Metab 2009; 11(3): 251-60.
18. Hart ME, Suchland KL, Miyakawa M et al.: Trace amine-associated receptor agonists: synthesis and evaluation of thyronamines and related analogues. J Med Chem 2006; 9, 49(3): 1101-12.
19. Pietsch CA, Scanlan TS, Anderson RJ: Thyronamines are substrates for human liver sulfotransferases. Endocrinology 2007; 148(4): 1921-7.
20. Wood WJ, Geraci T, Nilsen A et al.: Iodothyronamines are oxidatively deaminated to iodothyroacetic acids in vivo. Chembiochem 2009; 26, 10(2): 361-5.
21. Agretti P, De Marco G, Russo L et al.: 3-Iodothyronamine metabolism and functional effects in FRTL5 thyroid cells. J Mol Endocrinol. 2011 [Epub ahead of print]
22. Doyle KP, Suchland KL, Ciesielski TM et al.: Novel thyroxine derivatives, thyronamine and 3-iodothyronamine, induce transient hypothermia and marked neuroprotection against stroke injury. Stroke 2007; 38(9): 2569-76.

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