Thyroid: Iodine Beyond the Thyronines

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Abstract: Although thyroid gland function is mainly under the control of pituitary TSH, other factors may also play a role in this process. Iodine is not used only by the thyroid to synthesize thyroid hormones but also directly influences a number of parameters such as thyroid proliferation and function. Thyroid autoregulation has been related to intraglandular content of an unknown putative iodocompound. The thyroid is capable of producing different iodolipids such as 6-iodo-deltalactone (ILδ) and 2-iodohexadecanal (2-IHDA). Data from different laboratories have shown that these iodolipids can inhibit several thyroid parameters suggesting that these compounds may be the intermediates in the thyroid autoregulation process.

Keywords: Iodine, iodocompounds, iodohexadecanal, iodolactone, iodolipids, thyroid.

INTRODUCTION

Iodine plays an important role in thyroid physiology and biochemistry. It is essential for hormone biosynthesis since it is the limiting factor in normal conditions but also directly influences a number of thyroid parameters such as thyroid proliferation and function [1]. The capability of the intracellular content of iodide to modulate the gland function may be defined as **thyroid autoregulation**. Inhibitory actions of iodide include iodide organification (Wolff-Chaikoff effect), hormone secretion, cyclic 3′,5′-adenosine monophosphate (cAMP) generation, thyroglobulin proteolysis, glucose and aminoacid transport, protein and RNA biosynthesis, thyroid blood flow, thyroid growth, etc., [2, 3].

THYROID GLAND AND PROLIFERATION

Iodine depletion generates hypersensitivity to TSH action. Chapman in 1941 [4] observed that when hypophysectomized rats were fed with a low iodine diet (LID) during two months, thyroid weight and epithelial height were greater than those observed in animals fed with a normal diet.

Bray described in 1968 [5] that hypophysectomized rats fed with a LID, developed a larger goiter produced by exogenous TSH than those animals that received a normal diet. Moreover when the intrathyroidal iodide content was significantly decreased thyroid enlargement occurred before a significant increase in TSH serum levels [6-8], which explains the coexistence of goiter with normal serum TSH levels in areas of Argentina [9]. Hellstren *et al*. [10] observed an inverse relationship between goiter size and the iodine content in the thyroid.

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During goiter formation, the earliest event is the vascular activation mediated by the expression of the Vascular Endothelial Growth Factor (VEGF). This process has two phases; the first is a TSH independent effect. Gérard *et al*. [11] have demonstrated that intracellular iodide content has a role in this early event. Moreover there is an inverse relationship between the rate of iodide supply and the local rate of angiogenesis [12]. The iodide deficiency induced-generation of angiogenic signals is related to the release of VEGF-A via a reactive oxygen species/hypoxia-inducible factor-1-dependent pathway [13].

On the other hand, iodide excess has the opposite effect. It has been shown that iodide inhibits a number of thyroid parameters such as thyroid proliferation and function, both *in vivo* and *in vitro*. Abbassi and McKenzie [14] reported that iodide inhibited the goitrogenic action of TSH in hypophysectomized rats. Pisarev and Itoiz [15] observed that KI decreased the action of TSH and cAMP on thyroid growth and protein synthesis. On the contrary Kanno *et al*. [16] reported that an excess of iodide induced a significant increase in thyroid weight, pituitary weight, serum TSH, and T_4 in growing rats.

Yamada *et al*. [17] demonstrated that iodide at high concentration decreased the expression of the angiogenic factors VEGF-A, VEGF-B, and placental growth factor (PGF), accompanied by an increase in the expression of possible antiangiogenic factors such as the urokinase-type plasminogen activator (PLAU).

In *in vitro* studies it has been demonstrated also that iodine inhibits thyroid cell proliferation [18]. It has been proposed that iodine would act arresting the cell cycle; while organified iodine may mediate the cell cycle arrest in the G2M phase, inorganic iodide may be responsible for the inhibitory effects at G0G1 phases [19] although high concentrations of iodide were used in this study.

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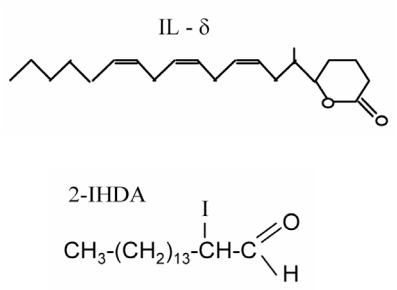

Fig. (1). Chemical structure of 6-iodo-5-hydroxy-eicosatrienoic acid or 6-Iodo-deltalactone (IL-δ) and 2-iodohexadecanal (2-IHDA.

THYROID FUNCTION

One of the early effects of iodide is to inhibit its organification: the Wolff–Chaikoff effect. The objective of this autoregulation is to maintain a constant thyroid hormone secretion, independently of variations in iodine intake. Morton *et al*. [20], reported that iodine inhibited the formation *in vitro* of thyroxine and diiodotyrosine and Wolff and Chaikoff [21] observed that *in vivo* the administration of high doses of iodide caused an acute block in its organification. This inhibition is temporary and the reaction reassumes a normal rate despite the maintenance of high levels of circulating iodide; this phenomenon is called "escape" or "adaptation".

The blockade of organification is produced by inhibition of H_2O_2-generating systems (NADPH oxidase, now known as DUOX1 and DUOX2) with the subsequent decrease in the levels of H_2O_2 [22-24] although stimulation at lower concentrations and for a shorter incubation time with iodide has been observed [25].

Regarding thyroid hormone secretion, De Groot and Greer [26] reported that iodide decreased the release of ^{131}I from thyroid and many studies have confirmed this effect [27]. It has been also demonstrated in *in vivo* and *in vitro* studies that the halogen inhibits iodide transport. NIS mRNA levels are also regulated by iodide [28-30] at a transcriptional step, although a regulation at a posttranscriptional level may be not discarded [31-33]. It is postulated that the decrease in NIS is responsible of the "escape" from the acute Wolff-Chaikoff effect [29].

TSH regulates thyroid growth and function through cAMP (differentiation, hormone secretion, growth and proliferation) and phospholipase cascades (H_2O_2 generation) and iodine regulates these two pathways [1, 3].

Other effects regulated by iodide include: total protein and thyroglobulin synthesis [34, 35], proteolysis of Tg [36], the uptake of glucose [37], amino acids [38] and uridine [39], the synthesis of TPO and NIS, but not TSH receptor [28], thyroid blood flow [12] among others [27].

As some of the inhibitory effects of iodide excess on several parameters, such as iodide uptake, cell proliferation, and cAMP accumulation are reproduced by transforming growth factor beta-1 (TGF- β1) [40] it was postulated a possible role of this growth factor in thyroid autoregulation [41]. *In vitro* studies demonstrated that the effect of iodide on DNA synthesis is reversed by anti- TGF-β1 antiserum [40], and that iodide stimulates TGF-β1mRNA and protein synthesis [42, 43]. In normal human thyroid cells, iodide increases the synthesis of TGF-β1, whereas this response was decreased in cells obtained from thyroid nodules [44]. However in thyroid pig follicles, it was not observed effect of iodide in TGF- β1 expression [45].

MECHANISMS OF IODIDE ACTION

Since most of the inhibitory effects of iodide on thyroid function (except the effect on thyroid blood flow and vascularization) and growth are reversed by thionamides, drugs that block the action of thyroid peroxidase such as metilmercaptoimidazol (MMI) or propylthiouracil (PTU), it was proposed that an organic iodocompound, called XI, might be the mediator in the auto regulatory mechanism [46].

The nature of the putative iodocompounds involved in this autoregulatory mechanism has been the subject of extensive work. Different compounds have been proposed to be such mediators, such as an iodoprotein [47] or T_3 [48], but their possible role remains controversial, although it has been postulated that TRβ (one of the receptors for T_3) plays a role in thyroid cancer [49]. The biosynthesis of iodolipids has been observed in the thyroid gland from several species and their participation in thyroid auto regulation has been suggested. Boeynaems and Hubbard [50] have reported the conversion of exogenous free arachidonic acid into 5-hydroxy-6 iodo-8, 11, 14-eicosatrienoic delta lactone (IL-δ) in rat thyroid and Dugrillon *et al*. [51] demonstrated that this compound is synthesized by the human gland. Pereira *et al*. [52] found α-iodohexadecanal (2-IHDA) as the major iodolipid in horse thyroid. Both IL-δ and 2-IHDA mimic some of the inhibitory effects of excess iodide on several thyroid parameters.

IODOLACTONE

In 1980 Boeynaems *et al*. [50] demonstrated that in the presence of iodide and hydrogen peroxide, lactoperoxidase catalyzed the conversion of arachidonic acid into several iodinated products. The major product was identified as 6-iodo-5-hydroxy-eicosatrienoic acid, delta-lactone (iodolactone, IL-δ). MMI inhibited the formation and release of the iodolactone when rat thyroid lobes were incubated with iodide and arachidonic suggesting a participation of a thyroid peroxidase.

Dugrillon *et al*. [51] demonstrated that this compound is synthesized by the human gland but only after treating the patients with high doses of iodine before thyroidectomy. It may be mentioned that the he formation of IL-δ in other species could not be detected unless exogenous arachidonic acid was added.

In *in vitro* studies it was demonstrated that IL-δ inhibits proliferation induced by TSH or forskolin in FRTL-5 cells [53]. Since in this model TSH regulates cell proliferation through the cAMP pathway, the authors suggested that the inhibitory action of IL-δ could be related to a decrease in the levels of cAMP or a downstream step. However, in pig thyrocytes IL-δ inhibits the proliferative action of EGF and the formation of phosphatidyl inositol (IP3) stimulated by EGF,

but has no effect on cAMP accumulation or IP3 induced by TSH [54, 55]. In this model it was also demonstrated that IL-δ stimulates apoptosis [56]. In cultured human thyroid cells IL-δ inhibits phorbol ester stimulated proliferation [51]. In *in vivo* studies IL-δ prevents goiter in rats [57, 58]. These results show that the antigoitrogenic action of IL-δ is not due to an inhibition of pituitary TSH synthesis or secretion in rats, since serum TSH, which was increased by MMI injection, remained the same in rats treated with MMI and IL-δ. Moreover intrathyroidal cAMP levels, which are involved in the goitrogenic action of TSH [1], were reduced by the injection of IL-δ, demonstrating a direct effect of the iodolipid on the thyroid. The action of the iodolipid cannot be ascribed to the iodide that would originate from their possible dehalogenation since injection of KI failed to cause a change in thyroid growth as a consequence of the MMI treatment. Then, depending on the model, IL-δ has an inhibitory effect at the cAMP, calcium or protein kinase C pathway.

Regarding iodine metabolism, IL-δ inhibited iodide uptake [59], H_2O_2 production [22], total protein and Tg synthesis but only iodide had an effect on NIS and Tg mRNAs levels. Both compounds inhibited Na^+/K^+ ATPase and deoxyglucose uptake [30, 60]. PAX8, FOXE1 and TITF1 are thyroid specific transcription factors involved in the regulation of thyroid specific genes; it was analyzed the action of iodide and IL-δ on their mRNA. While iodide inhibited the expression of the first two, that of TITF1 was stimulated by iodide while IL-δ had no effect on these parameters [30]. As it can be observed IL-δ can not reproduce all the effects of iodide. Dugrillon *et al*. [54] observed that IL-δ inhibited the stimulatory effect of EGF on porcine thyroid cell proliferation but did not reproduce the inhibitory effects of KI on cAMP accumulation. Moreover since excess iodine increases TGF-β1 mRNA expression in sheep thyroid cells [43] and its protein synthesis in porcine thyroid cells cultured in monolayer [41], as it was mentioned, it was expected that iodolactone could also induce TGF-β1 biosynthesis. However in porcine follicles [45] and in *in vivo* studies in rats IL-δ did not regulate TGF-β1 synthesis, while KI increased its expression [61].

It is interesting to mention that the synthesis of iodolactone is not only restricted to the thyroid, but has also been reported in the mammary gland, which organifies iodide. It was shown that I_2 inhibited the proliferation, inducing apoptosis, of different breast cancer cell lines and this effect may be due to the synthesis on intracellular iodolipids [62, 63]. Moreover, IL-δ had a 4-fold more potent antiproliferative effect on breast cancer cells than that of I_2 [63]. Nuñez-Anita *et al*., [64] showed the antiproliferative and pro-apoptotic effect of IL-δ in a breast cancer cell line (MCF-7) and demonstrated that PPAR-γ pathway is involved in these processes. IL-δ is a specific ligand of PPARs with almost 6-fold higher affinity than AA, and activates specifically the PPAR gamma isoform.

Recently it was shown an antiproliferative effect of I_2 and IL-δ in several human cancer cell lines [65]. This effect was due to a mitochondrial mediated apoptosis mechanism. We have observed also that IL-δ inhibits cell proliferation and induces apoptosis cell death in the colon cancer cell line, HT-29 (Results not published)

IODOHEXADECANAL (2-IHDA)

2-iodohexadecanal (2-IHDA) was isolated as the major iodolipid formed in horse thyroid slices incubated *in vitro* with radioiodide [52] while Panneels *et al*. [66] have shown the synthesis of this iodocompound in cultured dog thyroid cells. It has been demonstrated *in vivo* the synthesis of this compound in rat thyroid after the intraperitoneal injection of KI [52]. Its biosynthesis is likely to involve the addition of iodine to the vinyl ether group of plasmalogens present in the basolateral membrane.

In porcine thyroid membranes 2-IHDA inhibits DUOX1 and DUOX2 [67], and in culture dog thyroid cells 2-IHDA decreases H_2O_2 production [68] and cAMP accumulation by directly inhibiting the activity of adenylate cyclase [69]. 2-IHDA would be the mediator of two important regulatory mechanisms in the thyroid gland: the Wolff-Chaikoff effect and inhibition of adenylate cyclase [3].

We have recently demonstrated that this compound has antigoitrogenic activity, decreasing the intracellular levels of cAMP, reducing the number of cells and the glandular epithelial height [70]. 2-IHDA was able not only to prevent the growth of MMI induced goiter but also caused the involution of performed goiter. The iodolipid caused a significant reduction in goiter weight after 3 days compared with the spontaneous involution and iodide failed to alter this value. On the other hand a direct inhibition of thyroid growth caused by 2-IHDA was observed in *in vitro* cell culture studies with FRTL-5 cells inhibiting not only cAMP pathway but also protein kinase C induced proliferation. In the same system we have shown that 2-IHDA negatively regulates the effect of TSH on thyroid-specific gene expression [24].

In conclusion it is well accepted the role of iodide in the regulation of thyroid cell function and proliferation. Altough iodolipids seem to be the intermediates in the autoregulatory process the possibility that more than one compound participate of this process can not be ruled out since the identity of XI has not been yet established.

We apologize to authors whose work could not be cited in this review due to size limitations.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ABBREVIATIONS

camp	=	Cyclic 3′,5′-adenosine monophosphate
DUOX1, DUOX2	=	Thyroid NADPH oxidases
2-IHDA	=	2-Iodohexadecanal
ILδ	=	6-Iodo-deltalactone
IP3	=	Phosphatidyl inositol
LID	=	Low iodine diet
MMI	=	Metilmercaptoimidazol

NIS = Sodium/Iodide symporter

PGF = Placental growth factor

PLAU = Urokinase-type plasminogen activator

PTU = Propylthiouracil

VEGF = Vascular Endothelial Growth Factor

ACKNOWLEDGEMENT

This work was supported by grants from the Argentine National Research Council (CONICET), the National Agency for the Promotion of Science and Technology (ANPCYT). G.J.J and M.A.P. are Established Researchs from CONICET, L.T. and L.S are doctoral fellows from CNEA, R.O. and L.R are doctoral fellows from the ANPCYT.

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Received: December 22, 2010 Revised: April 25, 2011 Accepted: May 01, 2011