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Role of iodine in pathogenesis of thyroid disease – Is induction of apoptosis consequence of iodine cytotoxicity?

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Улога јода у патогенези болести штитасте жлезде: Да ли је апоптоза у штитастој жлезди узрокована цитотоксичношћу јода?

SUMMARY

Iodine is one of the best-characterized environmental factors associated with autoimmune thyroid disease (AT). Epidemiological studies have shown that AT incidence has increased following the introduction of salt iodination in the 1920s; in addition, AT patients can improve upon iodine restriction. In animal models such as BioBreeding/Worcester and Buffalo rats , obese chicken strain , and non obese diabetic H-2h4 mice excess iodine is associated with autoimmunity. Analysis in Hashimoto thyroiditis (HT) have shown enlarge number of apoptotic follicular cells, and destruction is effect of death receptor-mediated apoptosis. Excess iodine induce rapid apoptosis of goitrogen Wistar pretreated rats, possibly connected with inhibition of polyamine synthesis, inhibitors of DNA fragmentation. Percentage of apoptotic cells was statistically higher in patients with HT than in those with euthyroid goiter, with significant increase of caspase 32. Genes for Bcl-2 and Bax proteins are under the transcriptional control of p53. In TAD-2 cell cultures apoptosis is p53 independed, suggesting that DNA damage is not a primary evoked by KI. High concentration of NaI increase proportion of apoptotic cells in FTRL5 thyroid cell line. Iodide cytototoxicity was inhibited by a TPO inhibitor and was relieved with an anti-oxidant agent. Chronic iodine excess induces apoptosis and necrosis of thyroid follicular and endothelial cells on, leading to thyroglobulin accumulation in connective tissue. Iodide excess requires peroxidase enzymatic activity to induce apoptosis. Ionic iodide is not directly toxic, whereas its molecular form I_2, mediates the apoptotic effect of KI.

Keywords: iodine; apoptosis; autoimmune thyroiditis

САЖЕТАК

Јод је један од најпознатијих егзогених етиолошких фактора повезан са аутоимуним тироидитисом (АТ). Епидемиолошке студије су показале да је инциденција АТ порасла након увођења јодирања соли 1920. године. Такође, стање особа који болују од АТ се може поправити смањењем уноса јода. На животињским моделима као што су BioBreeding/Worcester и Buffalo пацови, пилићи гојазног соја, као и NOD.H-2h4 мишеви, показана је повезаност вишка јода са аутоимуношћу. У Хашимотовом тироидитису (ХТ) је повећан број апоптотичних фоликуларних ћелија у жлезди. Вишак јода узрокује брзу апоптозу у струми Wistar пацова, што је можда подстакнуто кочењем синтезе полиамина, инхибитора ДНК фрагментације. Проценат ћелија у апоптози је статистички значајно већи у ХТ него у еутироидној струми. Једнократно давање јода довело је до повећање каспазе 32 у штитастој жлезди. Гени Bcl2 и Bax су под транскрипцијском контролом p53. У TAD 2 ћелијским културама тиреоцита апоптоза је p53 независна, из чега произилази да ДНК оштећење није примарно узроковано калијум јодидом (КЈ). Високе концентрације натријум јодида (NaJ) повећавају процента ћелија у апоптози у FTRL5 ћелијској линији тиреоцита. Цитотоксичност јода је спречена инхибитором ТРО, а слаби применом антиоксидансног агенса. Хронични вишак јода узрокује апоптозу и некрозу фоликуларних и ендотелних ћелија, те се онда у везивном ткиву нагомилава тиреоглобулин. Вишак јода подстиче активност пероксидазе у индукцији апоптоза. Јон јод није директно токсичан, док је молекулски облик J_2 медијатор апоптотског ефекта КЈ.

Кључне речи: јод; апоптоза; аутоимуни тиреоидитис

INTRODUCTION

Iodine is a necessary component of normal thyroid hormonogenesis. It is incorporated into tyrosine moieties of Tg as mono-iodotyrosine and di-iodotyrosine residues that subsequently undergo an oxidative coupling event leading to the formation of triiodothyronine (T3) and thyroxine (T4) [1]. The recommended daily allowance of iodine by the World Health Organization is 150 μg for adults [2] (median urinary iodine concentration (UIC): 100–199 μg/l[3]). However, there is a relatively narrow interval of optimal iodine intake[4] and both iodine deficiency and iodine excess can result in an increased prevalence of thyroid disorders[5]. Environmental iodine deficiency was long a cause of iodine deficiency disorders round the world. It has been substantially reduced thanks to the implementation of programs of mandatory food iodine fortification in numerous countries. However, while this endeavor has led to the virtual eradication in these regions of severe iodine deficiency, it has in parallel resulted in an increase in the prevalence of AIT. Meanwhile, it has recently been noted in various parts of the world that a decrease in iodine intake results in a lowering of the incidence of AIT [6].

Nowadays, the average dietary iodide intake can often exceed recommended level [2]. Although, it is usually considered to be safe to ingest a relatively large amount of iodine from the diet, as most people are highly tolerant to iodine, the elderly population, pregnant women, fetuses, neonates and those with pre-existing goiter or iodine deficiency are more susceptible to excess iodine-induced disorders, including autoimmune thyroid disease (ATD). Thus, iodine is indeed an environmental risk factor for the development of ATD, especially in susceptible individuals [7].

Epidemiologic studies in humans have reported an increased prevalence of thyroiditis with the administration of supplementary dietary iodine[1] . In addition, different animal models indicate that excess iodine is associated with thyroid autoimmunity. BioBreeding/Worcester (BB/W rats) [8], an obese chicken strain [9], Buffalo rats [10] and non obese diabetic (NOD). H-2h4 mice [11, 12] are all prone to develop autoimmune thyroiditis after high iodide intake. Also, high doses of iodide have been known to cause direct thyroid cell injury on human thyroid follicles in vitro [2]. In vitro iodide is cytotoxic, inhibits cell growth, and induces morphological changes in thyroid cells of some species [13].

Apoptosis (or programmed cell death) is an active process of cell self destruction requiring the activation of a genetic program, leading to changes in morphology, DNA fragmentation, and protein cross-linking [13]. Physiological cell death is an essential mechanism which contributes for the growth and permanent maintenance of the human body[14]. The apoptotic pathways are activated by physiological stimuli such as environmental signals, cytokines, and growth factors[13] e.g. p53, caspases 2, 3, 8, and 9, BCL-XS and Bax[14]; they can also be induced by pathological stimuli, radiation, and anticancer drugs [13]. However , other mediators like B cell lymphoma/leukemia-2 protein (Bcl-2), Bcl-XL, and are antiapoptotic [14].

The two main pathways by which apoptosis can be initiated are (1) the mitochondrial or intrinsic apoptosis pathway; and (2) the death receptor-mediated or extrinsic apoptosis pathway.

(1) A number of internal stimuli cause an increase in mitochondrial membrane permeability. These different stressors are recognized by several intracellular proteins that send the signal to the mitochondria, ending in Mitochondrial Outer Membrane Permeabilization (MOMP). MOMP is most commonly mediated via a variety of proteinmembrane and protein-protein interactions of the B-cell lymphoma 2 protein (BCL-2) family. Following apoptotic stimuli, members of BCL-2 family (BAX and BAK) activate and insert into the outer mitochondrial membrane to cause the release of cytochrome c and other mitochondrial proteins. Subsequently, in the cytosol, cytochrome c interacts

with apoptosis protease-activating factor 1 (Apaf- 1), and forms a complex recognized as the apoptosome . The apoptosome, a multi-protein platform comprising a seven-spoke ring-shaped complex , leads to activation of initiator caspase (usually caspase-9), which in turn activates executioner caspase-3 and initiates a caspase cascade, which eventually leads to demolition of the cell [15]. Mitochondria-mediated apoptosis may be caspase-independent and it is mediated through apoptosis-inducing factor (AIF)3 and endonuclease G[16].

(2) Apoptosis can be instigated through oligomerization of death receptors like Fas, TNFR, DR3, TRAIL-R4, and TRAIL-R5 after associating with their corresponding ligands. This oligomerization further leads to employment of adaptor proteins and stimulation of caspase cascades. Preliminary stimulation of caspase-8 triggers apoptosis in two ways: it can directly cleave and initiate caspase-3 or, it can cleave BH3 interacting domain death agonist (Bid), a proapoptotic Bcl2 family member. This cleaved (or truncated) bid (tBid) is relocated to mitochondria, stimulating cytochrome-c release, consecutively provoking caspases-9 and caspase-3 that eventually leads to DNA fragmentation and cell death[14].

In the past decade, it became apparent that immune mediated cell death in a number of autoimmune endocrine diseases was due to the induction of apoptosis in target organ cells. This was conclusively demonstrated for thyroid follicular cells in Hashimoto's (destructive autoimmune) thyroiditis (HT), but the mechanisms underlying this cell death were not clear [17].

APOPTOSIS AND AUTOIMMUNE THYROID DISEASE

Autoimmune thyroiditis, also known as Hashimoto’s thyroiditis(HT), is an organ-specific autoimmune disorder, characterized by infiltration of the thyroid gland by inflammatory cells, often followed by hypothyroidism due to destruction of the thyroid follicles and eventual fibrous replacement of the parenchymal tissue. Autoantibodies to thyroid-specific antigens also develop[18]. In autoimmune thyroiditis, lymphocytic infiltration and thyroid follicular cells apoptosis are important for the self-destructive process[19]. Thyroid gland immunohistochemycal analysis in HT have shown enlarge number of apoptotic follicular cells, inmost in periphery of lymphocyte infiltrates[20] , furthermore in HT caspase-3 and caspase-8 are upregulated and activated [21]. Thyreocit destruction in HT might be conceequence of inadequate expression of Fas or TRAIL and reduced Bcl-2 induced by cytokines realized from infiltrated lymphocytes[20]. Analysis of cytokine expression in autoimmune thyroid diseases has shown, with a few exceptions, a prevalence of TH1 cytokines in Hashimoto’s thyroiditis. TH1 cells secrete IFN-γ and other cytokines that are associated with inflammation and cell-mediated immune response. IFN-γ treatment increases caspase-3 and caspase-8 expression and primes Hashimoto’s thyroiditis thyrocytes for CD95-mediated destruction[21]. In addition, some in vitro investigations have shown that low concentration of TSH induce apoptosis and that TSH can prevent Fas mediated apoptosis in HT. Nevertheless, some evidence suggest thyroid cell destruction in autoimmune hypothyroidism is dependent on T cell-mediated cytotoxicity with the likely additional effect of death receptor-mediated apoptosis [20].

In addition, we perform study in order to determine the role of apoptosis in the pathogenesis of lymphocytic thyroiditis (LT) and the existence of difference between HT and LT. We evaluated the apoptosis by in situ Cell Death Detection-TUNEL and the expression of Bcl2 and Bax by immunohistochemistry in thyroid tissues from patient with HT and with LT. Patients with euthyroid goiter-EG served like control group. We found that apoptosis of thyrocytes in HT and LT was statistically significantly higher than EG. Therefore, we concluded that apoptosis represents one of significant mechanisms in the pathogenesis of both HT and LT [22].

IODINE EXCESS AND THYROID DISEASE

Although the mechanisms are not fully elucidated, excess iodine is a well-recognized environmental factor for autoimmune thyroid disease (ATD) in autoimmune-prone individuals, particularly autoimmune thyroiditis (AIT) [7].

In animal studies it was shown that high-dose iodine induced thyrocyte injury in both the wild-type and obese strain (OS) that has a genetic background prone to spontaneous autoimmune thyroiditis. However, significant and sustained lymphocytic infiltration composed of CD4+T-cells, CD8+ T-cells, B-cells and macrophages was only observed in OS chickens following iodine-induced cell injury. Pre-treatment with the antioxidant drug, completely prevented both thyrocyte injury and the following lymphocytic infiltration induced by iodine . This study suggests excess iodine can induce oxidative stress-related thyrocyte injury in individuals, although whether this cell injury leads to lymphocytic infiltration will depend on the additional effects of genetic factors [7]. Interestingly, in the recent study, we notice mild lymphocytic thyroiditis in thyroid section from wild-type rats receiving KI. This lymphocytic thyroiditis was characterized by diffuse mononuclear cell infiltration with lymphocytes and just a few plasma cells in the follicles and in the spaces between the follicles with the destruction of gland acini and connective tissue proliferation [23].

Also, in one of our studies, we analysed the histological changes of the thyroid gland after administration of different doses of KI in Wistar rat animal model. We have revealed the thyroid gland architecture was seriously damaged after KI administration. We compared the intensity of histological changes between rats from the Wistar strain that were treated with a low (LKI) and with a high iodine dose (HKI) while untreated nonimmunized animals served as controls. The difference between them was statistically significant. Comparing controls and the group treated with LKI, statistically a highly significant difference was found , which was also the case with the group treated with HKI. However, test revealed no statistically significant differences in animals treated with different doses of KI. Same article proves iodine induce cell necrosis and inflammation in the nonimmunized animals without the genetic susceptibility. Therefore this is, in fact, a new experimental model of the LT[24].

Several underlying mechanisms may explain how iodine induce AIT. Intake of large iodine quantities results in its increased incorporation in the Tg molecule. This highly iodinated Tg is characterized by alterations in its stereochemical conformation. The modifications that occur in Tg structure can change its properties, leading to loss of antigenic epitopes and creation of novel, iodine containing ones. New antigenic determinants may be created by tyrosine iodination at critical points within the Tg molecule. When presented to T and/or B lymphocytes, these new determinants exhibit an increased affinity for the T cell receptor or the MHC-presenting molecule on antigen-presenting cells (APCs). This may consequently enhance the Tg presentation by APCs and lead to specific T lymphocyte activation, thereby iniinitiating the autoimmune process. Excessive iodination of Tg can thus heighten its immunogenic potential compared with Tg containing fewer iodine atoms. Another suggested mechanism is direct iodine toxicity to thyrocytes, possibly through induction of oxidative stress. Excessive amounts of iodine may comprise a direct threat for thyrocytes. TPO rapidly oxidizes excessive amounts of iodine in the hyperplastic thyrocytes and generates oxidative intermediates of iodine. These oxidative elements are highly reactive and able to bind to proteins, nucleic acids and membrane lipids, forming iodocompounds which damage thyroid cell and mitochondrial membrane integrity. Oxidative stress caused by the generation of free radicals can also lead to thyroid cell necrosis, while autoantigens may be released[25].

IODINE EXCESS AND THYROID CELLS APOPTOSIS

The iodide-induced cytotoxic effect on rat thyrocytes included necrotic and apoptotic features, indicating the involvement of a controlled process of cell death [13].

In vitro study by Vitales's laboratory in immortalized thyroid cell line (TAD-2) treated with KI demonstrate that human thyroid follicular cells react to an excess of iodide activating a cell suicide program. Similar sensitivity to KI excess was shown by thyroid primary cultures, whereas cells of nonthyroid origin were resistant, indicating that iodide cytotoxicity is tissue specific [13]. In line with this results, Smerdely et al. demonstrated that high concentration of NaI increase proportion of cells undergoing apoptosis in FTRL5 thyroid cell line[26]. Golstein and Dumont confirmed iodide induce apoptosis in FTRL-5 cell line, but they also notice necrosis[27]. In the same article, iodide cytotototoxicity was inhibited by a thyroid peroxidase inhibitor and was relieved with an anti-oxidant agent [26], indicating involvement of ROS in iodine induced thyroid cell apoptosis. In contrast, dog thyrocytes in primary culture wasn't sensitive to iodide[27].

However, Kostić et al. had failed to demonstrated KI induced apoptosis in primary human thyroid cells[28] and Pitsiavas et al. haven't demonstrated apopotosis on electron microscopy nether in Wistar rats nor in BB/W rats thyroid gland treated with iodide water[29]. Nevertheless, one recent study sustained Vitale's findings demonstrating KI induce thyroid cell apoptosis in human thyroid follicular cells in vitro (Nthy-ori 3-1 cells) [30]. Furthermore, Gao J. at al demonstrated excess iodine intake induces thyroid cell apoptosis in Wistar rat animal model[31] and one in vivo study on healthy

Wistar rats showed that long term excessive iodine exposure promoted apoptosis of thyrocyts through the ROS pathway. This effect was reversible with iodine restriction. Interestingly, this tretmant had no influence on either serum levels of TSH and FT 4 or the expression of Bcl-2 and Bax [32]. Genes for Bcl-2 and Bax proteins are known to be under the transcriptional control of p53. According Vitale's results apoptosis in TAD-2 cell cultures is also p53 independent suggesting that DNA damage is not a primary event evoked by KI. In the same article Vitale et al. show that this type of apoptosis is a process independent of protein synthesis. One of the Bcl-2 family member Bad, does not require neosynthesis to regulate apoptosis, because his activity is regulated at posttranscriptional level. Therefore, Vitale propose that factors altered by KI excess might trigger apoptosis at a posttranscriptional level [13]. Basalaeva and al. have demonstrated significant increase of caspase 32 cocentration in thyroid gland from inbred female rats of local laboratory strain, after single iodide dose of 8 μg/100 g . This data suggest iodide is inducing caspase dependent apoptosis in thyroid [33].

Iodide excess requires peroxidase enzymatic activity to induce apoptosis. Ionic iodide is not directly toxic for the follicular cell, whereas its molecular form I_2, produced by TPO oxidation, mediates the apoptotic effect of KI excess [13, 34]. It is demonstrated that molecular iodine excess induce apoptosis in thyrocytes through formation of free oxygen radicals that induce mitochondrial damage and citochrom C realize [35].

Iodine is taken up by the thyrocite, organified, and inserted in the Tg molecule through the enzymatic action of thyroidperoxidase. In doing so, there is the generation of ROS such as superoxide anion and hydrogen peroxide(H_2O_2) which works as a donor of oxidative equivalents for thyroperoxidase [36]. Low H_2O_2 concentrations induced apoptosis in various cell types, including pig thyrocytes [37], which once more indicate iodine induces oxidative stress might be involved in thyroid apoptosis.

I_2 is a highly reactive molecule, able to react with proteins, lipids, and nucleic acids to form iodocompounds. Different types of iodolipids are produced when iodide binds to membrane lipids, and this could determine the loss of cell and mitochondrial membrane integrity with generation of ROS and peroxidation of lipids [13]. One of them, delta-iodolactone (i.e., 5-iodo-delta lactone) of arachidonic acid (IL-d), was demonstrated by electron microscopy to induce apoptosis in porcine thyroid follicles ex vivo in a three-dimensional tissue culture. Interestingly, the induction of apoptosis was lowered by preincubating human thyroid follicles with low concentrations of selenium, which induced glutathionperoxidase activity. This is one more evidence the induction of apoptosis is mediated by free oxygen radicals in mitochondria [34]. Furthermore, IL-d has the goiter inhibitory activity due to the inhibition of cell proliferation and the transient stimulation of apoptosis. Interestingly, apoptosis in this case does not involve oxidative stress [38].

Another important iodolipid is 2-iodohexadecanal (2-IHDA), compound proposed to be responsible for the Wolff-Chaikoff-effect [39]. An increase in Bax/Bcl-2 ratio, in the percentage of apoptotic cells and caspase-3 activity was observed on FRTL-5 thyroid cell line treated with 2-IHDA. Activation of the caspase-3 pathway is a hallmark of apoptosis [40].

It was shown that excess iodine could induce apoptosis in the thyroid gland of goitrogen Wistar pretreated rats. This effect is very rapid and possibly connected with inhibition of polyamine synthesis, which are potent inhibitors of oligonucleosomal DNA fragmentation [41]. In line with this results, Boechat and al. found higher levels of FasL expression, in NOD mice with methimazole inducied goiter after the administration of potassium iodide(KI) in animals sacrificed 4 days after the administration [42].

Some authors consider that follicular cell injury, apoptosis and necrosis precede lymphocytic infiltration in the thyroid and they are considered the initial events in, and prerequisites for, the development of iodine-induced autoimmune thyroiditis [7].

We have previously shown that percentage of cells undergoing apoptosis was statistically higher in patients with HT than in those with euthyroid goiter [43]. In addition, we have shown enhance expression of Bax pro-apoptotic proteins in the Wistar rat experimental model of thyroiditis induced by administration of different doses of potassium iodide (KI), which can be regarded as a model of Hashimoto’s Thyroiditis. This findings indicate roll of apoptosis in the pathogenesis of lymphocytic thyroiditis in Wistar rats [44].

Swist et al. demonstrated that high levels of iodine increased mRNA and protein levels of Cidec (also known as fat-specific protein 27, Fsp27) in thyroiditis-prone BioBreeding (BBdp) rats[45]. Cidec was reported to induce apoptosis via the mitochondrial pathway through the cleavage of caspases-3, -7, and -9, and release of cytochrome c from mitochondria [41], although there are also evidence that CIDEC-induced apoptosis is dependent on activation of caspase-8, but independent on Fas-Associated protein with Death Domain (FADD) [47]. Nevertheless, iodine doesn’t have this effect in thyroiditis-resistant BioBreeding rats (BBc) [45]. These results suggests that iodine induce apoptosis in thyroiditis pron animals.

Cultured thyrocytes, from NOD.H2h4 mice prone to develop autoimmune thyroiditis after high iodide intake, exposed to low NaI concentrations in vitro, are more susceptible to apoptosis compared to thyrocytes from CBA/J mice, which are resistant to iodide-accelerated spontaneous autoimmune thyroiditis. Explanation possibly lies in a fact that NaI intake upregulates the expression of 22 genes involved in ROS metabolism and/or antioxidant function in CBA/J thyrocytes, whereas only two of these genes were upregulated in NOD.H2h4 thyrocytes. The results demonstrate that an impaired control of oxidative stress mechanisms is associated with the observed high susceptibility of NOD.H2h4 thyrocytes to NaI-mediated apoptosis [48]. Iodine induced apoptosis in autoimmune thyroiditis might be through mechanisms that involve activation of BID proapoptotic protein. BH3 interacting-domain death agonist (BID) is a proapoptotic Bcl-2 family member that functions as a bridge molecule between two classic apoptotic pathways, cell death receptors and mitochondrial elements, to augment apoptotic signaling. It was demonstrated that the increasing BID expression specifically in thyroid in CBA/J (H-2 k) mice does not cause autoimmune thyroiditis. However, same strains of mice with thyroid-specific BID over expression that were given iodine water are at high risk of development of autoimmune thyroiditis [49].

A number of apoptosis signaling pathways, including Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), are thought to be implicated in destructive thyroiditis[6]. Excessive iodine could induce TRAIL and DR5 abnormal expression in thyroid. Furthermore, one study suggest TRAIL band with DR5 to promote follicular cells apoptosis thus mediate thyroid destruction in Experimental autoimmune thyroiditis (EAT) in NOD mice [19].

Amiodarone, a potent antiarhythmic drug containing two iodine atoms per molecule, may induce either hypo- or hyperthyroidism [13]. Rats receiving amiodarone expressed hypothyroidism with specific ultra structural features of necrosis and apoptosis of the thyroid gland. Amiodarone induce thyroiditis that might be form of endoplasmatic reticulum storage disease. This could be explained by excess iodide, from AMD or its metabolites, resulting in heavily iodinated proteins such as thyroglobulin and other polypeptides which cannot be processed, folded or transported to appropriate sites. Disruption in protein production may prevent synthesis of apoptosis inhibitors such as Bcl-2 or loss of essential proteins involved in cellular homeostasis, leading to cellular death [29].

Some works indicate that amiodaron and its metabolite DEA (desethylamiodarone) induce apoptosis in thyroid and nonthyroid cells through an Iodine-Independent mechanism. Apoptosis induced by amiodaron and its main metabolite DEA is not mediated by modulation of p53, Bcl-2, Bcl-XL, or Bax protein expression and does not involve the generation of free radicals, whereas it induces the release of mitochondrial cytochrome c into the cytosol [50]. Since there are evidence iodine induce apoptosis in thyrocytes [13,28] it remains to be resolved if apoptosis in amiodarone-induced hypothyroidism is iodine-induced or is result of direct drug cytotoxicity.

Also iodine can induce apoptosis in some non thyroid tissues. Excess iodine increased the apoptosis rate in rat aorta endothelial cells that were cultured with iodide ion for 48 h. Iodine also reduced the activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and concentrations of glutathione (GSH) suggesting that excess iodine exposure increased oxidative stress [51]. Furthermore, it has been shown experimentally that IL-d is able to trigger apoptosis in various cancer cell lines, including thyroid cancer and breast cancer [39]. Epidemiological studies have shown that sufficient iodine supply can prevent the development of thyroid cancer. Iodine can induce mitochondrial-mediated apoptosis in three different types of thyroid cancer cells.Thus, iodine-induced apoptosis may be a key mechanism that contributes to its preventing the development of thyroid cancer [52]. In addition, iodine induce apoptosis in cultured human breast cancer cell lines, namely MCF-7, MDA-MB-453, ZR-75–1, and T-47D. In MCF-7 cells iodine treatment activates a caspase-independent and mitochondria-mediated apoptotic pathway. Interesting fact is that iodine tretmant leads to decrease in cellular ROS in MCF-7 after 24 h [16].

CONCLUSION

Interesting questions whether iodide itself displays cytotoxic effects on thyroid cells in human thyroid gland so as on experimental models or its cytotoxicity represents an apoptotic phenomenon, still remains to be completely elucidated.

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