Two hundred years after discovery of iodine - less known functions of the element in human organism

Dwieście lat od odkrycia jodu - mniej znane funkcje tego pierwsiakta w ludzkim organizmie

The main role of iodine in human organism is related to biosynthesis of thyroid hormones. The less known metabolic pathway of the element is formation of iodolipids (mainly iodoaldehydes and iodolactones). One of the compounds, 6-iodo-5-hydroxy-eicosatrienoic acid (6-IL), is believed to inhibit goiter growth, to modulate the cell response on some growth factors, and to trigger apoptosis in some types of cells. Another one, 2-iodohexadecanal (2-IHDA), probably also inhibits goiter growth and mediates the Wolff-Chaikoff-effect. Epidemiological and experimental data suggest a relation of iodine to some tumor diseases. Preventing of iodine deficiency diminishes prevalence of goiter as well as some non-goiter diseases.

Glówną rolą jodu w organizmie człowieka jest udział w biosynteze hormonów tarczycowych. Mniej znaną drogą metaboliczną jest tworzenie związków jodolipidowych (głównie jodoaldehydów i jodolaktonów). Jeden z tych związków, 6-jodo-5-hydroksy-eikozanotrienowego (6-IL), prawdopodobnie uczestniczy w hamowaniu wzrostu woli, w regulowaniu odpowiedzi komórek na niektóre czynniki wzrostu oraz w wywoływaniu apoptozy w niektórych typach komórek. Inny, 2-jodoheksadekan (2-IHDA, aldehyd α-jodo-palmitonowy), najprawdopodobniej także hamuje wzrost woli oraz pośredniczy w efekcie Wolff-Chaikoffa. Badania epidemiologiczne oraz doświadczalne wskazują na po-wiązanie jodu z niektórymi chorobami nowotworowymi. Zapobieganie niedoborowi jodu zmniejsza ilość zachorowań na woli oraz niektóre choroby pozatarczycowe.

Introduction
Iodine was discovered by a French chemist Bernard Courtois (1777-1838) in 1811 [1]. The element has atomic number 53. From its several characterized isotopes, only one, with the mass number 127, is stable.

Elemental iodine is a reactive substance. Its most stable oxidation states are -1 and +7, less stable: +1, +3 and +5. Its electronegativity according to the Pauling scale is 2.66 (oxygen: 3.44, selenium: 2.55). On the other hand, it is easily released especially from organic compounds, including radiologic contrast media iomeprol and iopromide, and organic compounds, including radiologic contrast media iomeprol and iopromide, and organic compounds, including radiologic contrast media iomeprol and iopromide, and organic compounds, including radiologic contrast media iomeprol and iopromide, and organic compounds, including radiologic contrast media iomeprol and iopromide.

Synthesis of thyroid hormones
The main role of iodine in human organism is related to production of thyroxine - a hormone first isolated from extracts of animal thyroid glands by an American chemist Edward Calvin Kendall (1886-1972) in 1914 [2]. The synthesis of thyroxine follows in some steps. First, iodine (in the form of iodide anion: I-) enters thyreocytes via natrium-iodide symporter (NIS) localized in their basal membranes [3]. In the thyreocytes, concentration of iodide exceeds its concentration in serum 20- to 100-fold under normal circumstances [4]. Further, iodide is transported mainly via pendrin [5] localized in the thyreocyte’s apical membrane into the lumen of thyroid follicle. There, it undergoes oxidation to more reactive species, as atomic iodine (I) and iodinium cations (I⁺). This reaction is catalyzed by an enzyme thyroid peroxidase (TPO) [6, 7, 8], whereby intermediates, including hydrogen peroxide (H₂O₂), are formed. Antithyroid drugs, as methimazole, interfere with this process [9]. Subsequently, it is incorporated into thyrosyl rests of thyroglobulin (reaction referred to as “organification”), which after cleavage releases hormones (mainly thyroxin - tetraiodothyronine, T₄). Conversion to the more potent triiodothyronine (T₃) takes place mainly in peripheral tissues and is catalyzed by 5'-thyroxine deiodinase - an enzyme containing an amino-acid selenocysteine [10]. The action of the thyroid hormones in target tissues is executed by interaction with nuclear receptors [11]. Due to high rate of binding to proteins in serum (>99.9% for T₄ and >99% for T₃), their biological half-times are long: about 5-8 days for T₄ and about 19 hours for T₃ [12]. Their catabolism follows by further deiodination, and hepatic glucuronidation or sulfation [12, 13].

Additional key words:
iodine
iodide
iodolipid
6-iodo-5-hydroxy-eicosatrienoic acid (6-IL)
2-iodohexadecanal (2-IHDA)
goiter
Wolff-Chaikoff-effect

Dodatkowe słowa kluczowe:
jod
jodolipidy
α-laktón kwasu
6-jodo-5-hydroksy-eikozanotrienowego (6-IL)
wôle
efekt Wolff-Chaikoffa

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Synthesis and function of iodolipids

It has been shown that iodine can add to double bonds of several unsaturated fatty acids of cellular membranes, including cervonic acid (DHA, all-cis-docosa-4,7,10,13,16,19-hexaenoic acid, an ω3-polyunsaturated fatty acid), limnodronic acid (EPA, all-cis-5,8,11,14,17-eicosapentaenoic acid ω3), and arachidonic acid (AA, all-cis-5,8,11,14-eicosatetraenoic acid, ω6) [14]. Such additions is believed to make the membranes less susceptible to reactive oxygen species, particularly in a cooperation with selenium-containing antioxidants (due to the electonegativity of iodine between that of oxygen and selenium).

The group of the best known iodolipids includes 6-iodo-5-hydroxy-eicosatrienoic acid 5-lactone (6-IL). Its synthesis can be inhibited by methimazole [15] and consists of three steps: oxidation of iodide, saturation of the double bond in the position 5 of arachidonic acid (with iodine in the position 6 and hydroxy-group in 5) and lactonization (forming a cyclic ester between this hydroxyl- and the 1-carboxyl-group - there arises a six-membered ring with an oxygen heteroatom). Oxidation of iodide to iodine (or iodinium) can be catalyzed by TPO or, in tissues other than thyroid, by other oxidases, including lactoperoxidase [16, 17] present naturally in breast tissue. The latter enzyme is frequently used in experimental models. 6-IL was detected in human thyroid [18] after treatment with iodide.

6-IL has an inhibitory effect on thyroid cell growth in experiments with thyroid follicles. Contrary to a similar effect caused by iodide, it cannot be abolished by methimazole [18]. In experiments with methimazole-induced goiter growth, 6-IL was able to inhibit thyreocytes proliferation in 50-fold lower concentrations than iodide [19]. It has been shown that 6-IL not only inhibits growth of thyreocytes in the follicles, but also induces transient limited apoptosis of these cells [20, 21]. Goiter inhibitory effect of 6-IL was confirmed also by in vivo experiments in rats [22].

It has been shown experimentally that 6-IL is able to trigger apoptosis in various cancer cell lines, including thyroid [23] and breast cancer [17, 23, 24]. Experiments with rat models of induced cancers showed markedly reduced both incidence and size of tumors in animals treated with 6-IL [25]. It has been emphasized in many studies that such influence of 6-IL was limited to tumor cells, whereas normal ones (e.g. fibroblasts) were spared [25, 27]. Lower content of AA (the precursor of 6-IL) in tumor cells does not seem to explain this phenomenon.

The precise mechanism of action of 6-IL remains unclear. It has been postulated that the substance can exert a blocking influence on calcium-dependent protein kinase C (PKC) and directly inhibit phosphatases [25]. Other observations suggest a possible binding to peroxisomes and alteration of both expression and action of peroxisome proliferator-activated receptors (PPARs) [30]. Cyclic adenosine monophosphate (cAMP) signaling cascade was shown not to be influenced by the action of 6-IL [19, 29].

The next iodolipid identified in the thyroid was a iodoaldehyde, 2-iiodohexadecanal (2-IHDA) [31]. It is synthesized from plasmalogens [32] - a type of phospholipids characterized by the presence of a vinyl ether linkage at the sn-1 position (instead of ester-linkage typical for other lipids). 2-IHDA arises via an attack of reactive iodine (oxidized iodide) on this vinyl ether group. This compound exerts its action by reduction of cAMP formation [29, 33, 34]. It was proven to inhibit activity of oxidases [35] and to decrease production of H2O2 [36]. In rats, 2-IHDA has been shown to prevent methimazole-induced goiter growth [34]. Because of long time of its metabolism (to 2-iiodohexadecanol, 2-IHDO) and influencing the cAMP-dependent signaling system, this compound was proposed to be responsible for the Wolff-Chaikoff-effect [35]. Contrary to 6-IL, there are no data about possible antitumoral properties of 2-IHDA.

Other iodolipids seem to have a lower significance. They include: 14-iodo-15-hydroxy-5,8,11-eicosatrienoic acid (I-HO-A) [37] (inhibits H2O2-production and iodine organification), 14-iodo-20-hydroxy-eicosatrienoic acid (2-IHDA) [22] (anti-goitrogenic effect) and 6-iodo-7,10,13,16,19-docosapentaenoic acid 5-lactone [28] (little or no effect in the thyroid).

Summing up, iodolipids are believed to take part in some important regulatory processes in the thyroid, including inhibition of goiter growth and mediating of the Wolff-Chaikoff-effect, as well as to have some cancer-protective effects extending beyond the organ.

Iodine deficiency - non-goiter consequences

The problem of benign goiter in endemic iodine-deficient areas is widely known [12]. However, the overall incidence of malignant thyroid disorders does not seem to be markedly influenced by iodine deficiency in humans [38]. On the other hand, iodine deficiency seems to favor a shift in distribution of the cancer types from papillary to follicular and extremely aggressive anaplastic form of thyroid cancer.

Goiter was more frequently noticed in patients with malignant and benign breast diseases [17, 39], hence iodine was proposed to have prophylactic properties. In experiments with breast cancer cell cultures, iodine was proposed to have also a possible curative effect by influencing expression of gens responsible for reaction to estrogens [40].

Iodine supply is believed to influence the incidence of stomach cancer. After implementation of household salt iodisation in southern Poland in 1996, increased ioduria and decreased goiter prevalence was observed. It was accompanied by diminished incidence of stomach cancer [41]. Similar results have been obtained by other authors [42] in a Chinese population. In patients with stomach cancer, a statistically lower iodine excretion with urine has been detected in comparison to control group [43], suggesting iodine depletion as one of the factors, what could predispose for the disease.

Epidemiological correlation between iodine supply and other cancer types is not as pronounced as in breast and stomach cancer, although laboratory experiments proved a considerable susceptibility of many tumor cell lines (including neuroblastoma) to 6-IL [24]. On the other hand, the experience of nuclear medicine practitioners shows only few organs to accumulate radioactive iodine. Indeed, except of the thyroid, the group includes stomach, breast and salivary glands. Molecular studies confirmed the distribution of NIS between organs to be similar to that of hot spots observed during scintigraphy [44]. As stated above, accumulation of iodide and presence of an enzyme able to oxidize it are the conditions necessary for generating of 6-IL - the substance believed to mediate the antitumoral effect of iodine.

It is important to emphasize the possible side-effects of iodine [45]. Although data about toxicity in large doses are not available, the ability to trigger autoimmune inflammatory processes (including the Hashimoto and Graves diseases) are controversial, iodine supplementation is obviously contraindicated in patients with any non-excluded hyperthyreotic state, as Graves disease and autonomic nodes.

World iodine deficit

Iodine deficit in several regions of the world has been recognized as the main cause of goiter (pathology referred to as "endemic goiter") [46]. The correlation between low iodine supply and the morbidity rate of the other diseases, as breast and stomach cancers, was noticed through 1990's, because these diseases have been known to have numerous other and better correlating risk factors. Iodine deficiency is particularly dangerous in pregnancy; it can result in miscarriage, stillbirth, preterm delivery and congenital abnormalities in the baby including cretinism and deaf mutism.
crease of autoimmune diseases.

In Europe, it is achieved by enrichment of edible salt with about 15-45 ppm sodium/potassium iodide (NaI, KI). Alternatively, sodium/potassium iodate (NaIO³, KIO³) can be used. In the past, especially beyond Europe, a lodesation of edible oil has been applied, a iodisation of edible oil has been recommended iodine supplementation.

As mentioned above, supplementation with iodine improved the situation related to the goiter-related disorders, as well as contributed to a slight decrease of some non-thyroid cancers. It has also been shown that chronic iodine deficiency can cause goiter and subclinical (compensated) under iodine deficiency after a long-lasting deficiency can lead to a temporal increase of the rate of hyperthyroidism [48]. It can be assumed that iodine prophylaxis - the protective factor against thyroid cancer in iodine deficient areas. Eur. J. Nutr. 2007, 46, 251.

References