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Importance of Iodine Intake Beyond the Thyroid

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Abstract

During the last century, the focus on iodine nutrition was mainly to eradicate the worldwide iodine deficiency accompanied by goiter and cretinism. The importance however, on the role of iodine for the health of breast tissue had been out of this focus. Up to now, several *in vitro* as well as *in vivo* studies clearly demonstrate that iodine is not only important for the thyroid hormone homeostasis but probably higher iodine intake is necessary for the prevention of benign as well as malignant breast diseases and even might be an efficient adjuvant treatment for breast cancer.

Epidemiological studies revealed that women with high iodine intake, especially through seaweed consumption have 5-times less breast cancer compared to women with low iodine intake. Iodine deficiency in the rats induces both, thyroid and breast susceptibility for atypia, dysplasia and hyperplasia. Female rats in iodine deficiency not only develop thyroid nodules but also nodules and even carcinomas of the breast. Furthermore, iodine or watery extracts of seaweed reduces the incidence of chemically induced breast cancer in rodents. Iodine treatment of women with mastopathy lead to a remission of disease symptoms. The iodine metabolism in thyroid and breast tissue is comparable, especially the pathways that control growth and apoptosis.

Typically, breast tissue of lactating women expresses the same sodium-iodine symporter (NIS), like the thyroid, but not breast tissue from non-lactating women. In human breast cancer cell lines, it could be shown that molecular iodine, but not iodide inhibit growth and induces apoptosis. Iodine exposure of thyroid cells as well as breast cancer cells create a specific d-iodolactone, an iodinated product of the arachidonic acid of the cell membrane. This d-iodolactone seems to be involved in the antiproliferative and apoptotic pathway of both, thyroid as well as epithelial breast cancer cells. Prospective controlled studies in humans are lacking, but the results of the *in vitro* as well as experimental animal studies should emphasize the need for adjuvant treatment of women with breast cancer with either seaweed extracts or iodine.

Keywords: *Iodine; Delta-Iodolactone; Goiter; Breast Cancer; Mastopathy; IGF-1*

Abbreviations

d-lactone: 6-Iodo-5-Hydroxy-8,11,14-Eicosatrienoic Acid; EGF: Epidermal Growth Factor; FGF: Fibroblast Growth Factor; IGF-1: Insulin-Like Growth Factor 1; PPAR: Peroxisome-Proliferator-Activated Receptor; TSH: Thyroid Stimulating Hormone; VEGF: Vascular Endothelial Growth Factor

Introduction

There is a long ongoing debate, whether there is an epidemiological as well as pathophysiological connection between thyroid and breast diseases [1,2]. A recent meta-analysis [3] found a weak, but significant correlation between the prevalence of papillary thyroid

cancer and breast cancer. Iodine deficiency not only is associated with goiter and thyroid neoplasia but also breast neoplasia [4,5]. Women with high iodine intake in form of seaweed have around 5-times lower incidence of breast cancer [6,7]. It even had been proposed, that the lower dietary iodine intake especially in young women in the United States might be the reason for the increased incidence of breast cancer [8]. Focusing on the important common iodine pathway of both tissues, advantages had been achieved in the last 2 - 3 decades with important insights and probably important preventative and therapeutic impact.

The role of iodine and IGF-1 in thyroid growth regulation

Several iodolipids in thyroid extracts have been detected after radioiodine incorporation studies since the early 1950th. Their physiological role was unknown, but as there was one compound with a saturation curve, this was suggested to be involved in thyroid autoregulation [9]. Boeynams [10] first described a specific iodinated compound, that was generated by incubation of radioactive iodide with rat thyroid slices and was inhibited by methimazole. This specific 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid (d -lactone) is an iodinated compound of the arachidonic acid of the thyroid cell membrane. It can be synthesized in-vitro by incubation of arachidonic acid, iodide, lactoperoxidase and H_2O_2, purified by silica gel chromatography and identified by gas chromatography-mass spectrometry (GC-MS) [10]. It was also isolated from human thyroid goiter derived from a patient treated with high doses of iodine before surgery [11]. This specific d-iodolactone dose-dependently inhibited growth and induced apoptosis in isolated porcine thyroid follicles *ex vivo* in micro molecular concentrations, likewise to iodine, but in 50-100-fold lower concentrations. It has no effect on cAMP formation in porcine thyroid follicles and seems to be exclusively involved in cAMP-independent growth control [12]. It inhibits inositol-1,4,5-triphosphate [IP3] formation induced by EGF but not on TSH induced IP3 formation. Therefore, it had been postulated that iodide exposure to thyroid follicular cells induces the formation of d-iodolactone within the thyroid follicular cell membrane, which then interferes with the phosphokinase pathway [13] and inhibits growth factor-induced thyroid cell proliferation not only in porcine primary cell culture but also thyroid epithelial cell lines [14].

Iodide and also d-iodolactone, in 50-fold lower concentration than iodide not only inhibit proliferation but also induce apoptosis in porcine thyroid follicles *ex vivo* in a three-dimensional tissue culture [15]. These effects of iodide are inhibited by methimazole, but not that of d-iodolactone, indicating that peroxidase activity is necessary to generate d-iodolactone.

During goitrogenesis, endothelial and vascular growth precedes the proliferation of thyroid epithelial cells [16]. Thyroid follicles *ex vivo* are releasing a paracrine endothelial growth factor (FGF1) which stimulates fibroblasts and endothelial cell growth. Epidermal growth factor enhanced but iodine abolished the release of this growth factor [17]. Iodine deficient normal and malignant thyroid cells are expressing more mRNA of the vascular endothelial growth factor (VEGF) [18]. In iodine deficient porcine thyroid follicles mRNA of IGF-1 is increased, but decreased by iodine and TSH [19]. The conclusion from these experiments is, that TSH is not the main regulator of thyroid growth, but IGF-1 and this is under control of iodine. Recent studies using human thyroid cells *in vitro* [20] confirmed these results and animal trials with thyroid specific IGF-1 receptor knock out mice came to the same conclusion [21]. From epidemiological studies, it became obvious, that not TSH but IGF-1 is elevated in patients with goiter or thyroid nodules [22]. There also is raising evidence, that high insulin levels, caused by obesity and genetic insulin resistant is associated with thyroid growth and neoplasia [23].

Similarity of growth regulation between thyroid and breast epithelial cells

In a systemic review and meta-analysis, it turned out, that there is a significantly increased risk of differentiated thyroid cancer following breast cancer and vice versa [24]. The reason for this clear association and co-occurrence of both malignancies might be multifactorial, that has been discussed recently [25]. Other trace elements like magnesium also may play a major role in both the thyroid and breast tissue. Magnesium deficiency might not only increase the risk to develop breast cancer [26] but also be involved in the progression of the disease [27]. Magnesium deficiency also is involved in thyroid pathologies like autoimmune thyroid disease [28] and hypothyroidism [29].

However, the similarities between thyroid and breast tissue concerning the iodine metabolism are well documented. The proliferation of breast cancer cells is under the comparable control through the iodinated compound of the arachidonic acid, d-iodolactone [30]. The uptake of molecular iodine in the established breast cancer cell line MCF-7 is saturable and the identical d -iodolactone, identified in thyroid epithelial cells could be isolated [31]. Molecular iodine as well as d-iodolactone but not iodide inhibited proliferation and induced apoptosis in MCF-7 cells [32]. When rats with chemical (methyl-nitrosourea) induced breast cancer were treated with molecular iodine in drinking water, a significant reduction of cancer incidence as well as tumor size is seen. Only the tumor cells exhibit high concentrations of d-iodolactone and the proliferation index was significantly lower, less blood vessel density was seen and also less PPARa, but significantly more PPARg [33]. These results indicate that the antineoplastic effect of d-iodolactone might be mediated through binding to PPRAg. The PPARs are nuclear transcription factors, involved in cancer cell proliferation [34].

The effect of molecular iodine on the growth and invasive capacity of xenograft of breast cancer cells with low metastatic capacity (MCF 7) were compared with the xenograft of breast cancer cells with high metastatic capacity (MDA-MB231) in athymic nude mice [35]. Molecular iodine decreases the proliferation as well as the invasive potential of the malignant xenografts and even activates the antitumor immune response by increasing the lymphocyte invasion. This confirms, that molecular iodine not only *in vitro*, but also *in vivo* inhibits breast cancer growth and invasion.

This not only antiproliferative but also apoptotic effect of molecular iodine and d-iodolactone also is shown in malignant epithelial cell lines like thyroid [36], lung, pancreas, neuroblastoma [37] with comparable effects to breast cancer cells. Interestingly, the growth of benign mammary epithelial cells (MCF-10) *in vitro* was not affected by iodine [37].

Molecular iodine obviously is able to oxidize arachidonic acid to d-iodolactone, both *in vitro* as well as *in vivo*, which then exerts the inhibition of proliferation, invasion and induces apoptosis of neoplastic breast tissue. For malignant thyroid cells the induction of apoptosis only *in vitro* [36], not yet *in vivo* had been shown.

What is the difference between organic iodine, iodide and aqueous molecular iodine

Seaweed is an important dietary product in the Asian community. It contains several organic forms of iodine as well as inorganic forms (I^-, I_2 and IO_3) and the iodine intake is about 5-fold higher compared to the Western countries. The high seaweed consumption is associated with the 5-times lower breast cancer prevalence in humans [38]. Seaweed significantly decreases the progression of chemical induced breast cancer in rats [39]. Seaweed not only contains several iodine compounds, but also several components with anticancer capacity [40]. Therefore, seaweed consumption probably has additional anticancer effects, exceeding that of iodine [41].

The iodine deficiency worldwide had been partial successfully eradicated by the introduction of iodized salt and the recommended daily intake is 100 - 200 µg iodide in form of iodized household salt. Pregnant and breast-feeding women need around 150 - 250 µg of iodide per day. These dosages are necessary to guarantee the normal development of the fetus and prevent goiter development in adolescents [42]. These dosages are not harmful even for individuals with thyroid pathologies; they do not cause thyroid dysfunction. However, considering iodine as an anticancer and antioxidant agent, not iodide but molecular iodine or iodine compounds in seaweed are necessary. In contrast to iodide, the distribution of molecular iodine after oral intake in the body is different [4,5]. All organs with the ability to express the sodium-iodide-symporter (NIS) trap iodide, mainly the thyroid. But also, salivary gland, gastric mucosa, lactating mammary gland and to less amounts, the choroid plexus, lacrimal gland, ovary, prostate and pancreas [43]. Molecular iodine (I_2) is hydrophobic, but together with iodide or acid, I_2 is water-soluble and is in equilibrium with OI^- and IO^{3-} with high oxidative potency [44]. These oxidants might then react with lipids, proteins and amino acids, including d-iodolactone *in vivo*.

The effect of high amounts of iodine intake on the thyroid function is a matter of concern. However, as summarized in [43], daily consumption of more than 2 mg/day of potassium iodide causes transient hypothyroidism and in 2 - 10% thyrotoxicosis. In contrast, daily

seaweed consumption containing 1 - 3 mg of iodine for weeks and months induces only in 1 - 10% of the population a transient subclinical hypothyroidism. However, the consumption of molecular iodine, 1 - 6 mg per day for months and years does not affect the thyroid function [45].

Conclusion

Thyroid proliferation is under the control of iodine intake, which has a direct auto regulative potency, independent of thyroid hormone synthesis, storage and secretion [11-15]. It controls the autocrine and paracrine activity of the thyroid follicles [17,19] and is mediated through a specific iodinated compound, the d-iodolactone of the arachidonic acid. This compound obviously plays a comparable role in malignant breast and thyroid epithelial cells as both have a similar iodide metabolism.

Modern biochemistry and preclinical trials [28-31,35] achieved new and important insights into the possible mechanism of the anticancer activity of natural iodine in seaweed and also molecular aqueous iodine. These are promising results and clinical trials are mandatory to show whether these important results also can be seen in humans. A daily seaweed consumption equivalent to 1 - 3 mg organic iodine is save and might not only be preventative but also a beneficial adjuvant treatment of women with breast cancer without severely affecting the thyroid function. Also, the effect of an adjuvant treatment of breast cancer with high doses of molecular iodine (1 - 6 mg/day) should be evaluated in controlled trials.

For differentiated thyroid malignancy, radioactive iodine might be the best option of treatment, but in radioiodine negative thyroid cancer adjuvant treatment with seaweed or molecular iodine might be considered.

Conflict of Interest

There is no financial interest or any conflict of interest exists.

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