

Is Iodine A Gatekeeper of the Integrity of the Mammary Gland?

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This paper reviews evidence showing iodine as an antioxidant and antiproliferative agent contributing to the integrity of normal mammary gland. Seaweed is an important dietary component in Asian communities and a rich source of iodine in several chemical forms. The high consumption of this element (25 times more than in Occident) has been associated with the low incidence of benign and cancer breast disease in Japanese women. In animal and human studies, molecular iodine (I₂) supplementation exerts a suppressive effect on the development and size of both benign and cancer neoplasias. This effect is accompanied by a significant reduction in cellular lipoperoxidation. Iodine, in addition to its incorporation into thyroid hormones, is bound into antiproliferative iodolipids in the thyroid called iodolactones, which may also play a role in the proliferative control of mammary gland. We propose that an I₂ supplement should be considered as an adjuvant in breast cancer therapy.

KEY WORDS: mammary gland; iodine; deiodinase; breast cancer; antioxidant; lipoperoxidation.

INTRODUCTION

Most of the investigations of iodine status in humans and animals have been focused on the role of iodine in thyroid function. Relatively little attention has been given to its extra thyroidal roles. Iodides are necessary for all living vegetable and animal cells, but only vertebrates possess a thyroid gland and its iodinated hormones. In humans the total amount of iodine in the body is about 30–50 mg; less than 30% is present in the thyroid gland and its hormones. About 60–80% of the total iodine is non-hormonal and is concentrated in extrathyroidal tissues, but its biological role is still unknown (1). Recently some groups have postulated that iodide may have an ancestral antioxidant function in all iodide-concentrating cells, from primitive algae to more recent vertebrates (1–3). In these cells iodide acts as an electron donor

in the presence of H₂O₂ and peroxidase; the remaining iodine atoms readily iodinate tyrosine, histidine and certain specific lipids. In fact, iodine can attach to double bonds of some polyunsaturated fatty acids in cellular membranes, making them less reactive to free oxygen radicals (4). Moreover, it has been demonstrated that iodine distribution in the organism depends on the chemical form of iodine ingested (5), and that molecular iodide (I₂) is not reduced to iodine (I⁻) in the blood before it is absorbed systemically from the gastrointestinal tract (6). Indeed, in iodine deficiency conditions, I⁻ appears more efficient than I₂ in restoring the thyroid gland to normal from goitrous state, whereas I₂ is distinctly more effective in diminishing mammary dysplasia and atypia

Abbreviations used: H₂O₂, hydrogen peroxide; I₂, molecular iodine; I⁻, iodide; I⁺, iodinium; I⁰, iodine free radical; I^{*}, oxidized iodine species; IO⁻, hypoiodite; IO₃⁻, iodate; KI, potassium iodide; LPO, lactoperoxidase; MNU, *N*-methyl-*N*-nitrosourea; NIS, sodium iodide symporter; O₂, single oxygen; O₂⁻, superoxide anions; •OH, hydroxyl radicals; PEN, pendrin; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; T₃, triiodothyronine; T₄, thyroxine; TPO, thyroperoxidase.

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secondary to iodine deficiency (7,8). In this paper, we review the different reports related to non-thyroidal iodine functions described in normal and neoplastic mammary glands.

IODINE AND NORMAL MAMMARY GLAND

A large body of data has demonstrated that the mammary gland during pregnancy and lactation is highly effective in capturing iodide, even more efficiently than the thyroid gland (9,10). The physiological significance of this mammary I^- avidity has been explained as a vital evolutionary mechanism to provide the neonate with iodine to make his/her own thyroid hormones necessary to normal neural development (10). Lactating mammary gland takes up iodide principally by the sodium/iodide symporter (NIS) and by a specific peroxidase called lactoperoxidase (LPO), by which I^- is oxidized and bound to the lactoprotein casein, which together with free iodine is secreted into milk (11,12). Although it was reported that the mammary gland from sexually mature virgin animals does not express NIS, recent studies have demonstrated that during this period mammary gland expresses another I^- transporter called pendrin (PEN) and exhibits I^- capture (13,14). Studies related to uptake and metabolism of I^- or other iodine components, such as I_2 , during virgin or other physiological states relative to non-thyroidal functions are scarce; however, it has been demonstrated that iodine contributes to the maintenance of the normal integrity of the mammary gland. Eskin *et al.* (7) showed that an iodine deficiency alters the structure and function of mammary gland in virgin rats, and that I_2 is effective in diminishing ductal hyperplasia and perilobular fibrosis secondary to this iodine deficiency (7). Similarly, I_2 treatment of patients with benign breast disease is accompanied by a significant bilateral reduction in breast size, in addition to causing a remission of disease symptoms, which is not observed when I^- or protein-bound iodide is administered (8). The importance of I_2 in the treatments for mammary gland dysfunctions has been corroborated in human and animal models. Seaweeds, such as *wakame*, *nori* or *mekabu* (used in sushi, soup, salads, and in powdered form as a condiment), are widely consumed in Asian countries and contain high quantities of iodine in several chemical forms, (i.e. I^- , I_2 , IO_3^-), and protein-associated (15,16). This element has been associated with the low incidence of benign and malignant breast disease

in Japanese women (iodine average consumption in the Japanese population is 5,280 $\mu\text{g}/\text{day}$ versus 166–209 $\mu\text{g}/\text{day}$ in the UK and USA, respectively) (2). It is possible that different chemical forms of iodine exhibit a differential function in the diverse organs. This notion is supported by recent data obtained in our laboratory. Mammary gland expresses two different deiodinase enzymes, which locally convert the prohormone T4 into the active thyroid hormone, T3. This conversion results in variable intracellular concentrations of free iodine: Higher levels during pubertal, pregnancy, and lactation mediated by deiodinase type 1, and lower but continuous amounts in virgin or postpartum conditions catalyzed by deiodinase type 2 (17). Although the chemical form of the iodine that results from deiodination has not been determined, it possibly corresponds to a different and perhaps more reactive form than I^- . As shown in Fig. 1, the Na^{125}I uptake exhibits a different compartmental profile than that of ^{125}I generated by local deiodination of ^{125}I -T4 in lactating mammary glands. Na^{125}I is avidly taken up, and 12 h later 80% of radiolabeled agent (as free iodine or associated with the protein fraction) is present in the milk. In contrast, labeled ^{125}I from T4 remained in the mammary gland (only 10% was present in the milk 12 h later) as ^{125}I -T3 or ^{125}I -labeled components in lipids, proteins, and nuclear fractions. These data agree with recent findings (18), in which we demonstrated that in mammary gland homogenates from virgin rats, the addition of I_2 , but not potassium iodide (KI), significantly decreases lipoperoxidation measured by the thiobarbituric acid reaction and expressed as malondialdehyde (MDA). The lack of effect of I^- in decreasing lipoperoxidation may be explained by the absence of LPO in mammary glands from virgin rats, being only present during pregnancy and lactation (19). LPO is a homologue protein of thyroperoxidase (TPO); both enzymes are able to oxidize I^- to link iodine to proteins or lipids. A specific iodination species generated from LPO activity has not yet been identified but several candidates exist, such as I^+ (iodinium), I^0 (iodine free radical), IO^- (hypoiodite), and I_2 (3). Thus, we hypothesize that iodine generated by LPO activity is bound to an abundant and specific protein (e.g. thyroglobulin in the thyroid and casein in lactating mammary gland), whereas I_2 or other oxidized iodine component, obtained by deiodination or in the diet, binds primarily to lipids and/or other membrane or nuclear components. Thus, iodine generated continuously by deiodination acts primarily as an antioxidant,

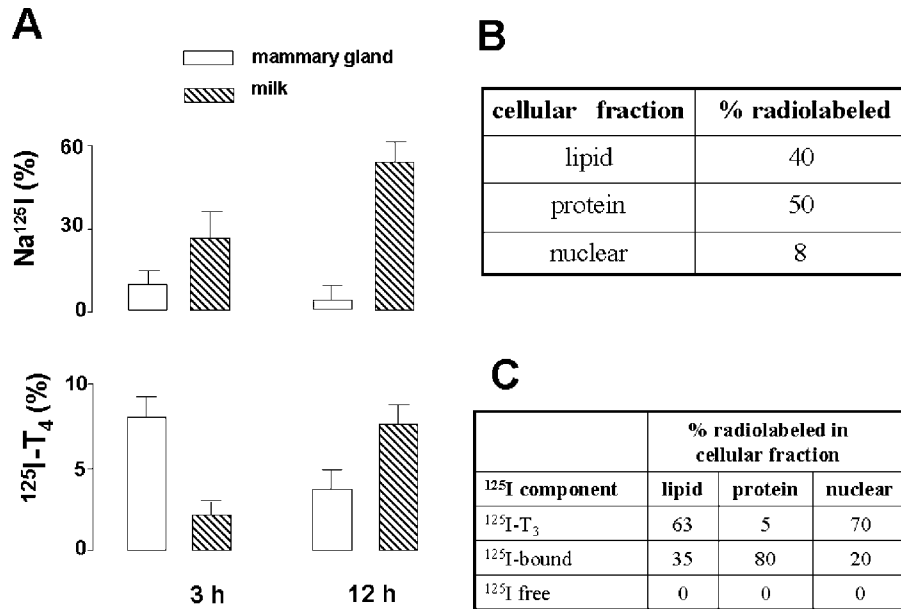


Fig. 1. Differential uptake and cellular compartmentalization of radiolabeled iodine. Primiparous lactating animals (10 days postpartum/8 pups) received one i.p. injection of 100 μ Ci of Na¹²⁵I or ¹²⁵I-T₄. After 3 or 12 h animals were anesthetized (Ketamine/Xylazine 30/6 mg/Kg BW). Milk was obtained by administration of oxytocin (30 mU; i.p.) 1 min before sacrifice (*panel A*). On mammary glands from 3 h post-¹²⁵I-T₄ injected animals, cellular fraction and ¹²⁵I components are analyzed. Lipid fraction was obtained by methanol/chloroform extraction (1:2); protein fraction by 10% trichloroacetic acid, and nuclear fraction by centrifugation 800 g, 10 min 4°C (*panel B*). The identity of the components was made by paper descending chromatography (solvent system, teramyl alcohol, 2N NH₄OH, hexane 5:6:1) (*panel C*). In Na¹²⁵I injected animals 80% of the labeled components corresponded to ¹²⁵I free (not bound to cellular components or T₃, data not shown).

whereas the iodine capture as iodide and the iodine-bound-casein generated by LPO during lactation contributes to the iodine pool in milk.

REPRODUCTIVE FACTORS AND BREAST CANCER RISK

Epidemiological studies indicate sexual reproductive history as the most important risk factor for breast cancer. A very interesting hypothesis by Wynne-Edwards (20) suggests that from an evolutionary perspective the modern increased risk in breast cancer is the result of recent cultural and reproductive changes in women's lives. These include: (a) an increased exposure to endogenous estrogen which is a weak carcinogen (via early menarche, low parity, abbreviated breast feeding, and pharmaceutical hormone manipulation) (21) and (b) an increased risk of breast cancer by altering the proportion our lives spent in developmental stages of

breast tissue with an underlying high rate of mitotic cell division (cell breast tissue that has never undergone differentiation to produce milk divides 20 times more often than cells that have acquired the terminal phenotype) (22). There are no studies relating the role of iodine and estrogen effects, but it has been observed that during pregnancy and lactation, hormonal stimulation of mammary gland leads to glandular differentiation that dramatically enhance both iodide absorption and local generation of free iodine by deiodination (17,23). It is interesting to note that this generation occurs in the same lobuloalveolar epithelium where the majority of breast cancer arises (17,19,24). A high iodine concentration in breast tissue may also explain the reduction in modularity and tissue density that are often observed following pregnancy and lactation (25). Thus, a link may exist between enhanced breast iodine content during pregnancy/lactation and subsequent reduction in breast cancer risk. It has been suggested that these reproductive periods may be protective

against breast cancer given the lobuloalveolar differentiation present during these stages (24). Cann *et al.* (2) have proposed that increased iodine content may also play a pivotal role in this differentiation process. For example, most studies in Asia have found lactation to be protective in preventing subsequent breast cancer development in both pre- and post-menopausal women (26,27). In contrast, studies conducted in North America and Europe have generally shown breastfeeding to be protective only in pre-menopausal women (28), or not at all (29). Thus, recent cultural and reproductive changes and/or the lower levels of iodine intake may be responsible for these differences.

IODINE IN NEOPLASTIC MAMMARY GLAND

In mammary cancer from humans or animals the cell oxidative status is disrupted (30,31). It has also been postulated that reactive oxygen species (ROS) such as single oxygen (O_2), superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\bullet OH$) are intimately related in the etiology of cancer (31,32). A substantial amount of H_2O_2 is produced by human tumor cells (32). ROS have a wide range of cellular and molecular effects resulting in mutagenicity, cytotoxicity, and changes in gene expression. G-C base pairs in CpG dinucleotide sequences are a common site for point mutations in *p53* tumor suppressor gene closely related to breast cancer (33). Cellular genes are usually converted into oncogenes, particularly *ras* family oncogenes in codons 12 and 13 (34). It has been demonstrated that these G-C sites are the main targets of oxidative damage (35). In this respect, we and others postulate that I_2 or other oxidized iodine species (I^*), either act in competition with ROS for different cellular components, or neutralize $\bullet OH$ radicals by the formation of HOI, resulting in less cellular oxidative damage. Thus, assuming that iodine may exert this antioxidant effect, it is evident that carcinogenic mechanisms may involve the turning off of genes related to the local generation of oxidized iodine components. Although in a wide variety of primary or immortalized mammary tumors, cells express NIS and PEN (12,36) and are capable of taking up I^- , effectively, the LPO necessary to oxidize it is not present (37,38). Moreover, cancer progression in thyroid or mammary glands from animals and humans is generally accompanied by the loss of the deiodinative capacity,

impaired by the local generation of oxidized iodines (39-41).

The notion that oxidized iodine is the active chemical form with a tumor suppressive effect is strongly supported by data showing that anticarcinogenic effects of seaweeds or iodine supplements contain in both cases a portion of oxidized iodine. Previously, we mentioned that seaweeds contain iodine in several chemical forms although the exact proportion is not known (15,16). Traditional eastern breast cancer medicine has long used iodine-rich seaweeds as a cancer treatment to "soften" tumors and "reduce" nodulation. Teas *et al.* (42) showed that the addition in the diet of 5% of *Laminaria angustata* significantly delays the occurrence of tumors in animals treated with the chemical carcinogen, 7,12-dimethylbenzanthracene (DMBA). Yamamoto *et al.* (43) found that only 2% of *Porphyra tenera*, *Laminaria religiosa* or *Laminaria japonica var ochotensis* is necessary to obtain the same protective effect. Funahashi *et al.* (44) reported that 1 and 5% of *wakame* seaweed in the diet reduce significantly the size of tumors generated by DMBA and showed that the consumption of algae is accompanied by increased levels of iodine in the serum with no changes in the thyroid hormone, thyroxine (T4).

In mammary carcinomas induced by DMBA in rats, Lugol's solution (mixture of I^- and I_2) supplementation exerts a suppressive effect on the development and size of the neoplasias (45). This suppressive effect is enhanced when Lugol treatment is combined with progesterone (medroxy-progesterone acetate). The suppressed tumors were found to have a significantly higher mean iodine content than non-suppressed tumors, with uptake apparently enhanced by progesterone (46). The enhancement of iodine uptake by progesterone has been observed in other hormone-dependent tissues, including the uterus and ovary (47). Data generated in our laboratory have shown that chronic administration of I_2 exhibits a potent protective effect (70%) on mammary cancer induced by the carcinogen *N*-methyl-*N*-nitrosourea (MNU). This effect is exerted only by I_2 but not by KI or T4. The suppression by I_2 treatment is accompanied by the development of latent mammary cancers that do not progress to overt cancers, suggesting that the mechanism of action of I_2 is due to a decrease in carcinogenesis at the promotion level. Moreover, this protective effect of I_2 is accompanied by a significant reduction in lipoperoxidation, which is significantly higher in "normal" mammary glands from animals treated with MNU or in patent tumors (18).

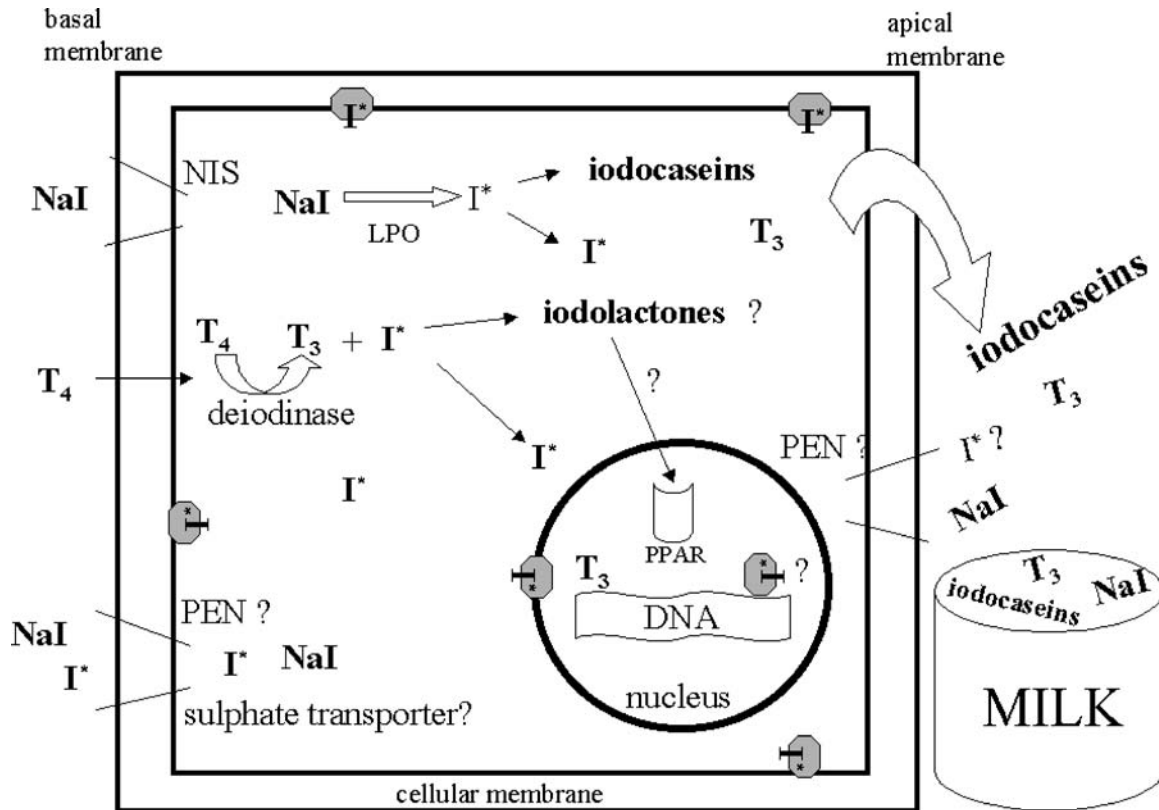


Fig. 2. Model of different ways of action of iodine in the mammary gland. In this model iodine is captured as: Iodide (NaI), thyroid hormone component (T_4) or as oxidized iodine species (I^*). Iodide is transformed in I^* by the lactoperoxidase enzyme (LPO) and binds primarily to the protein casein (iodocasein) to be driven to the milk, or is maintained in the cell as I^- . The I^- obtained by direct capture, by LPO action or by deiodination is mainly bound to membrane components (gray hexagon) and acts as antioxidant or joins to iodolactones regulating the proliferative cycle through its union with peroxisome proliferator-activated receptor (PPAR). Finally iodine may participate as a T_3 component, in the turning off or on of genes through its union to nuclear thyroid receptors. Interrogation signal denotes non demonstrated event or component.

Another important effect of iodine on the thyroid is its ability to diminish the hypervascularity and hyperplasia characteristic of the diffuse goiter in Graves' disease. The molecular mechanism of this phenomenon widely used to facilitate surgical therapy of this disorder is uncertain, but it has been postulated that iodine might be oxidized to a more reactive form, bind to organic components and, as a consequence, interfere with metabolic or molecular processes necessary for the maintenance of hyperplasia (48,49). Vitale *et al.* (50) showed that an excess of KI induces apoptosis in cultured thyroid cells, but if TPO activity is blocked with propylthiouracil, the apoptotic effect of KI is cancelled. Besides, Zhang *et al.* (37), using lung cancer cells transfected with NIS or NIS/TPO, observed that only in NIS/TPO transfected cells does a KI excess induce apoptosis, indicating that I^- from KI needs to be

oxidized to have a cytotoxic effect. The postulated mechanism of iodine's ability to induce apoptosis is the formation of specific iodinated lipids called iodolactones (51). The iodolactones of arachidonic acid are capable of inhibiting *in vitro* thyroid cell proliferation and inducing apoptosis (52–53). Our group recently reported that in the human breast cancer cell line MCF-7, I_2 and KI administration significantly decrease (50 and 25%, respectively) the cellular proliferative rate, and that in agreement with this effect, $^{125}I_2$ is internalized more rapidly and effectively than $Na^{125}I$, even in the absence of NIS (54). The possibility that this I_2 antiproliferative effect in mammary cells is secondary to the generation of iodolactones is now being analyzed by our laboratory.

Iodolactone toxicity to thyroid or mammary gland cells at the molecular level has not yet been

fully documented, although the involvement of different apoptotic pathways has been hypothesized (52). In this respect, we and others have found no differences in p53 expression due to *in vivo* or *in vitro* iodine treatments (18,50); however, it is possible that I₂ or other oxidized iodine components (such as iodolactones) participate in anti-proliferation or apoptotic mechanisms unrelated to p53. In this respect, we have postulated that the peroxisome proliferator-activated receptor (PPAR) may be an excellent candidate. PPARs, originally related only to the regulation of lipid metabolism, are widely expressed in almost every tissue, and form part of the nuclear receptor family that binds thyroid hormones, steroids, and vitamins (55). Recently, PPARs have been implicated in mechanisms involved in cellular differentiation, proliferation and apoptosis (56). Polyunsaturated fatty acids such as linoleic acid, eicosanoids, and arachidonic acid (one of the targets of oxidized iodine) have been identified as endogenous PPAR ligands (57).

In conclusion and as summarized in Fig. 2, it is possible that iodine in vertebrates exhibits the following different ways of action:

1. As an antioxidant by exerting a competition with free radicals for membrane lipids, proteins, and DNA to help stabilize the cells. This antioxidant action can be exerted through oxidized iodine species (I^{*}) obtained by the diet or by local deiodination.
2. As inducers of antiproliferative and apoptotic mechanisms through the formation of iodolactones.
3. As a constitutive part of thyroid hormones.

As other authors and ourselves (7,8,18,45,46) have demonstrated, a chronic I₂ diet supplement is not accompanied by any harmful secondary effects on the health of women or animals (body weight, thyroid economy, reproductive cycle). Thus, we propose that I₂ supplementation should be considered for use in clinical trials of breast cancer therapies.

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