Role of Iodine in Evolution and Carcinogenesis of Thyroid, Breast and Stomach

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Summary

The authors have hypothesized that dietary iodine (deficiency or excess) is associated with the development of some gastric and mammary cancers, as it is well-known for thyroid cancer. They report a short review of their own work and of the general literature on this correlation and on the antioxidant function of iodide in stomach, breast and thyroid. Thyroid cells phylogenetically derived from primitive iodide-concentrating gastroenteric cells which, during evolution, migrated and specialized in uptake and storage of iodine, also in order to adapt the organisms from iodine-rich sea to iodine-deficient land. Mammary cells also derived from primitive iodide-concentrating ectoderm. Stomach, breast and thyroid share an important iodide-concentrating ability and an efficient peroxidase activity, which transfers electrons from iodides to the oxygen of hydrogen peroxide and so protects the cells from damage caused by lipid peroxidation. The authors suggest that iodide might have an ancestral antioxidant function in all iodide-concentrating cells from primitive Algae to more recent Vertebrates. In Italy, gastric cancer is more frequent in farmers and in iodine-deficient populations, living in mountainous and hilly areas, than in fishermen. In the last two decades, Italian decrease of gastric cancer seems to be correlated more to the higher dietary consumption of iodine-rich fish rather than to consumption of fruit and vegetables, which indeed has decreased in Italy.

Key words: iodine, iodide, antioxidant, evolution, thyroid, breast cancer, stomach cancer, selenium.

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Iodine is the required element in the diet richest in electrons. Inorganic iodides are necessary for all living vegetable and animal cells, but only the Vertebrates have the thyroid gland and its iodinated hormones. In humans, the total amount of iodine is about 30-50 mg and less than 30% is present in the thyroid gland and its hormones. About 60-80% of total iodine is non-hormonal and it is concentrated in extrathyroidal tissues, but its biological role is still unknown. Recently we have hypothesized that iodide might have an ancestral antioxidant function in all iodide-concentrating cells from primitive Algae to more recent Vertebrates (1-4). Into these cells, iodide acts as an electron donor in the presence of H2O2 and peroxidase (5), the remaining iodine readily iodinates the tyrosine and (more slowly) the histidine or some specific lipid (6), and so, neutralizes its own high oxidant power.

Iodine, Thyroxin and Evolution

Over three billion years ago, Algae, which contain the highest amount of iodine, were the first living cells to produce oxygen, which was toxic at that time, in the terrestrial atmosphere. So, algal cells required a protective antioxidant action in which iodides might have had this specific role. In fact, iodides are greatly present and available in sea-waters, where algal phytoplankton acts as a biological accumulator of iodides. Recently our hypothesis of the ancestral antioxidant action of iodides has experimentally been confirmed in some algae by an important study carried out by Kupper et al. (7). From about 700 million years ago, thyroxin (T4) is present in fibrous exoskeletal scleroproteins of the lowest invertebrates (Porifera and Anthozoa) (8), without showing any hormonal action. When some primitive marine vertebrates started to emerge from the iodine-rich sea and transferred to iodine-deficient fresh water and finally land, their diet became iodine deficient and also harbored vegetable iodide-competitors such as nitrates, nitrites, thiocyanates and some glycosides. Hence, these animals needed an efficient thyroid gland also as reservoir of iodine compounds. Therefore we believe that, during progressive slow adaptation to terrestrial life, the primitive Chordates learned to use the primitive, but not antagonized, T4 in order to transport antioxidant iodide into the cells. So, the remaining triiodothyronine (T3), the real active hormone, became active in the metamorphosis and thermogenesis for a better adaptation of the organisms to terrestrial environment (atmosphere, fresh water, gravity, temperature and diet). The new hormonal action was made possible by the formation of T3-receptors in the cells of vertebrates. Firstly, about 600-500 million years ago, in primitive Chordata the alpha T3-receptors appeared with a prevalent metamorphosing action and then, about 250-150 million years ago, in the Birds and Mammalia the beta T3-receptors appeared with metabolic and thermogenetic actions. So, during human embryogenesis alpha T3-receptor genes are expressed before the beta receptors. Gastric iodide-pump, phylogenetically more primitive than the thyroid one, has a lower affinity for iodide and does not respond to the more recent TSH (Thyrotropin). In fact, in a pregnant mouse, fetal gastric mucosa shows iodine-concentrating ability earlier than fetal thyroid (9). On the other hand, from a biochemical point of view, as inhibitors of lipid peroxidation, by 5'-monodeiodinase activity (a seleno-enzyme), T4 and reverse-T3 (but not T3) became and were found to be more effective in this antioxidant activity than vitamin E, glutathione and ascorbic acid (10). In fact maternal T4, and not T3, plays a crucial role in protecting fetal brain from damage caused by hypothyroidism (11). Virgili et al. (12) reported that treatment with thyroxin protects from peroxidative intestinal damage, induced by zinc-deficiency in rats. Dietary iodides are able to defend brain and liver cells from lipid peroxidation in rats (13). The antioxidant action of iodides has also been described in isolated rabbit eyes (14). Rieger et al. (15), Winkler et al. (16) and Buchberger et al. (17) reported a beneficial and antioxidant action of iodides in many chronic diseases and in eye cataractogenesis.

Iodine and Selenium

Researchers reported the cooperation between selenium and iodine. In fact selenium is present in peroxidase enzymes and in type 1 and type 3 deiodinases, which are able to oxidize iodides and the latter enzymes produce iodides from iodothyronines. Thyroid-peroxidase is an important selenium-glutathione-enzyme which utilizes...
Fig. 1. Distribution of $^{131}$I in the body of a pregnant mouse 1 min after intravenous injection. High concentration in the mucosa of the fundus of the stomach; no radioactivity as yet in the foetuses.

Fig. 2. Distribution of $^{131}$I in the body of a pregnant mouse 1 hour after intravenous injection. High concentration in the gastric mucosa of the foetus.

Fig. 3. Distribution of $^{131}$I in the abdomen of a pregnant mouse 24 hours after intravenous injection. Four foetuses with high concentration of $^{35}$I in the thyroid gland, the thymus and the gastric mucosa; the concentration is also high in the intestinal content and in the milk gland of the mother.

Figures 1, 2, 3 show the distribution of $^{131}$-iodine and $^{35}$I in radioautographies of the body of a pregnant mouse, at 1 minute, 1 hour and 24 hours after intravenous injection of radioiodine. The high iodide-concentrating ability of gastric mucosa and milk gland of the mother and stomach, placenta and thymus of fetuses is evident. (from Ullberg and Ewaldsson, 1964; courtesy of Acta Radiologica)
iodides in order to transfer electrons to the oxygen of hydrogen peroxide. Thyroid gland is the richest tissue in selenium and iodine, whose deficiencies constitute an important risk factor for thyroid morbidity and carcinogenesis (18). Furthermore there is an interesting chemical gradient of electronegativity, according to Pauling-scale units, among Oxygen (3.44), Iodine (2.66), Selenium (2.55) and Hydrogen (2.00). This gradient might clear up the possible role of iodides in electron transfer.

Extrathyroidal Iodine concentrating organs

In Mammalia several extrathyroidal organs (Figures 1, 2, 3) share the same gene expression of sodium / iodide symporter of thyroidal iodide-pump and particularly stomach mucosa and lactating mammary gland (19). Salivary glands, thymus, epidermis, choroid plexus and articular, arterial and skeletal systems (20) have iodide-concentrating ability too. But what role does iodide play in animal cells? We may chronologically differentiate on the basis of the phylogenesis and embryogenesis three ways of action of iodine:

1) an ancient and direct action, on endodermal fore-gut and stomach and on ectodermal epidermis, where inorganic iodides probably act as antioxidants.

2) a recent and direct action, on fetal prehormonal thyroid and on salivary and mammary glands, thymus, ovary and on nervous, arterial and skeletal systems, where inorganic iodides are active.

3) a recent and indirect action of the thyroid and its iodinated hormones, on all vertebrate cells, which makes use of specific organic iodine-compounds: thyroxin (T4) and triiodothyronine (T3), which act in very small quantities and utilize T3-receptors. Indeed thyroid hormones contain less than 1 mg of iodine and less than 1/30 - 1/50 of total iodine amount.

We believe that all these actions of iodine may still take place into the cells of modern vertebrates (3-4). In fact, Evans et al. (21) reported that 5 mg of potassium iodide (daily injected) acts as 0.25 micrograms of L-thyroxin in recovering the impaired functions of many organs of thyroidectomized rats. Thyroid cells phylogenetically derived from primitive iodide-concentrating gastroenteric cells which, during evolution, migrated and specialized in uptake of iodides and storage and elaboration of iodine compounds, in order to adapt to iodine-deficient terrestrial life. Mammary cells also embryologically derived from primitive iodide-concentrating ectoderm. The thyroid gland is, in evolutionary terms, a modern organ and its function started and was improved from primitive Chordata to more recent Mammalia in which the thyroideotomy and hypothyroidism might be considered like a sort of phylogenetical and metabolic regression to a former stage of “reptilian life”. In fact, reptilian features seem to be restored in hypothyroid humans such as a dry, hairless, scaly, cold skin and a general slowdown of metabolism, digestion, heart rate, nervous reflexes with lethargic cerebration, hyperuricemia and hyperthermia.

Iodine and carcinogenesis of the thyroid, breast and stomach

Human stomach (Fig. 4), breast and thyroid share an important iodide-concentrating ability and an efficient peroxidase activity. In a previous paper we reviewed the studies about overall general extrathyroidal diseases in relation to dietary iodine deficiency (22). Here we reported a short review of some works on the carcinogenesis of these organs in relation to dietary iodine deficiency or, in some cases, excess.

A) Thyroid

Ward and Ohshima (23) and recently also the World Cancer Research Fund and the American Institute for Cancer Research (24) reported that dietary iodine deficiency and excess are tumor promoters and carcinogens in the thyroid gland.

B) Mammary gland

Exclusively during pregnancy (Fig. 3) and lactation, which are considered protective conditions against breast cancer, the mammary gland has a high, but temporary, ability in concentrating iodides and also in forming iodoproteins (25) in alveolar and ductular cells by specific peroxidase (26). Strum (27) reported that when female rats are kept iodide-deficient, atrophy and necrosis takes place in the mammary gland and areas of dysplasia and atypia are seen, and in pregnant mice, mammary tumor cells lose their ability to
iodinate proteins (28). Eskin and coworkers reported that iodine deficiency causes breast dysplasia and cancer in rats and probably in humans (29), and showed a mammary tumor reduction in rats after iodine treatment (30-31). Funahashi et al. reported that Japanese edible Wakame seaweed and a direct uptake of inorganic iodine by tumor has experimentally a suppressive effect on DMBA-induced breast tumors growth in the rat (33). Statistical correlations have been carried out by Ellerker (34), Stadel (35) and Serra-Majem et al. (36). Recently also Smyth et al. (37) and Giani et al. (38) reported an epidemiological correlation between thyroid diseases and breast cancer. Beatson reported an adjuvant use of thyroid extract in some breast cancers in the “Lancet”, as far back as 1896 (39).

C) Stomach
In early statistical works, Stocks (40) and Spencer (41), reported that iodine-deficient goiter constitute a risk for gastric cancer, and Diesing reported, in an early work (1911), of the adjuvant therapy of thyroid-extract in some gastric tumors (42). Recently, as other researchers on thyroid cancer stated, we hypothesized that iodine-deficiency (or excess) might constitute a risk factor for gastric cancer and atrophic gastritis (1-4, 43). This action of iodide on gastric mucosa might be due to antioxidant activity, and to antagonism against several iodide-inhibitors, such as nitrates, thiocyanates and salt (44), which are well-known risk-factors for gastric carcinogenesis. In previous works (1, 22) we reported that, in Italy, gastric cancer, thyroid cancer and goiter are statistically correlated and more frequent in iodine deficient areas, such as in Alpine and Apennines valleys, and in regions of northern and central Italy compared to southern Italy where the majority of the population lives in sea-side areas. In fact, Italy has never carried out significant iodine prophylaxis and, despite the fact that its inland is an endemic goiter area, only less than 3% of kitchen salt is iodized. Gastric cancer is more frequent in farmers than in fishermen, whose diet is richer in iodine (45). Recently the Italian National Organization “Istituto Nazionale della Nutrizione”, comparing the years 1980 to 1995, found that Italians, whose gastric cancer mortality has decreased, have in fact increased their yearly fish consumption (from 8.7 to 14.4 Kg per person) and decreased their consumptions of fruit (from 86.6 to 84.9 Kg per person) and vegetables (from 111.4 to 108.2 Kg per person) (46). A recent study suggests that, in northern Italy, the consumption of even small amounts of fish, which is rich in iodine, is a favorable indicator of the risk of several cancers, especially of the digestive tract and stomach (47). On the other hand, an excess of dietary iodine (more than 2 mg) im-
pairs the iodide-pump and the functions of some permanently-concentrating tissues (thyroid, stomach and salivary glands) causing, in the case of greater and prolonged quantities, degenerative, necrotic and also neoplastic lesions, which are well-known in thyroid gland (48). The fact that the iodine-excess is able to damage the stomach too, should be examined carefully if we consider that the coastal populations of Japan (49) and China (50), which have the highest rate of gastric cancer mortality in the world, frequently eat an excessive and harmful quantity of marine algae (seaweeds), which are very rich in iodine (up to 200 mg/daily/per person). Several researchers reported also a general anti-tumor activity of iodine-rich edible marine algae (in moderate amount) and a favorable activity in human chemoprevention of oral cancer, not due to the action of retinol or beta-carotene (51). Noda et al. showed that per-iodate oxidation is necessary to the anti-tumor activity of algae (52). The high iodide-concentration of thymus (Fig. 3) explains the important role of iodine in immune system. We also reported that iodine deficiency impairs immunity (53) and so might reduce the defense against tumor cells.

In conclusion, we believe that the knowledge of antioxidant action and presumed antitumor activity of iodide might be important for preventive purposes. We should point out that extrathyroidal action of iodide might be an important new area for investigation.

References


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