

## LETTER TO THE EDITOR

**Iodide, thyroid and stomach carcinogenesis: evolutionary story of a primitive antioxidant?**

The thyroid gland is, embryogenetically and phylogenetically, derived from the primitive gut, and we may consider the thyroid cells as primitive gastroenteric cells which, during evolution, migrated and specialized in the uptake of iodide and in the storage and elaboration of iodine compounds.

The stomach and the thyroid share iodide-concentrating ability and many morphological and functional similarities such as cell polarity and apical microvilli, similar organ-specific antigens and associated autoimmune diseases (1), the secretion of glycoproteins (thyroglobulin and mucin) and peptide hormones, the ability to digest and reabsorb and, lastly, a similar ability to form iodotyrosines by peroxidase activity, where iodide acts as an electron donor in the presence of  $H_2O_2$  (2). However, the gastric iodide pump, phylogenetically more primitive than the thyroidal one, has lower affinity for iodide and does not respond to more evolutionary recent thyrotrophin (TSH). Thus, in the pregnant mouse, the fetal gastric mucosa shows iodide-concentrating ability at an earlier time than the fetal thyroid (3). During human total body  $^{131}I$  scintiscans, the radioiodine remains on the stomach for more than 72 hours.

A similar finding has been reported in bovine abomasum, since cows have an efficient iodine recycling system via the gastrointestinal tract which conserves iodine and can protect them against low dietary iodine (4). In the primitive reptilian stomach of the lizard radioiodine remains for more than 8 days (5).

But what is the role of iodide in the pathophysiology of the stomach? In rats dietary iodides are able to defend brain cells from lipid peroxidation (6). In normal thyroid hormonogenesis, iodide in giving its electron to oxygen reduces  $H_2O_2$  by peroxidase activity. The remaining iodine readily iodates the tyrosine and so neutralizes its own high oxidant power.

The antioxidant action of iodide has also been described in isolated rabbit eyes (7).

In early works, Stocks (8) and Spencer (9) reported that iodine-deficient goitre constitutes a risk factor for gastric cancer. Recently, we reported (10) that iodine deficiency (or excess) might represent a risk factor for gastric cancer and atrophic gastritis, by regulating gastric trophism and by antagonizing (in thyroid cells and in gastric mucosa) the action of several iodine inhibitors such as nitrates, thiocyanates and salt (11), which are well-known risk factors for gastric carcinogenesis.

Furthermore, the mammary gland has a high ability to concentrate iodide and to form iodoproteins via mammary peroxidase exclusively during pregnancy and

lactation, which are considered protective conditions against breast cancer (12). Recently, we have hypothesized that since the appearance of primitive Algae and the primitive gastral cavity of Porifera, iodide might have an antioxidant role in iodide-concentrating organs, and particularly in the stomach of the Vertebrates (13, 14) and it has now been confirmed experimentally in Algae by a study carried out by Küpper *et al.* (15).

In fact, three billion years ago Algae, which contain a high 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 a specific role. The thyroid gland is, phylogenetically, a modern organ and its function appeared and was improved upon from the primitive Chordates to the more recent Mammalia. The tri-iodothyronine ( $T_3$ ) receptors are also recent in evolutionary terms in comparison with primitive thyroxine ( $T_4$ ). In fact,  $T_4$  is present in fibrous exoskeletal tissues of the lowest animals (Invertebrates) without showing any hormonal action (15). When the primitive marine animals started to emerge from the sea, which is rich in iodine, and transferred to the iodine-deficient mainland, their terrestrial diet became deficient in iodine and rich in iodine competitors (nitrates, nitrites, thiocyanates, some glycosides, etc.). Therefore, we believe that during their adaptation to a terrestrial life, these animals learned to use the primitive  $T_4$  in place of the competitivized iodide, in order to transport this antioxidant trace element into the cells, utilizing the remaining  $T_3$ , the active hormone of modern Vertebrates, for the new hormonal action of metamorphosis and thermogenesis through the formation of  $T_3$  receptors (16).

As inhibitors of lipid peroxidation, via 5'-monodeiodinase activity,  $T_4$  and reverse  $T_3$  were found to be more effective in this antioxidant activity than vitamin E, glutathione and ascorbic acid (17).

In conclusion, we believe that the evolutionary story of iodide and the thyroid might suggest and explain a primitive antioxidant activity of this trace element. We should point out that extrathyroidal action of iodide might be an important new area for investigation.

**References**

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Sebastiano Venturi and Marta Venturi, Servizio di Igiene e Sanità Pubblica, USL n.1. Regione Marche, 61016 Pennabilli (PS), Italy. Correspondence should be addressed to S Venturi, Servizio d'Igiene, USL n.1, Regione Marche, via Tre Genghe 2, 61016-Pennabilli (PS), Italy

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