Iodine, PUFAs and Iodolipids in Health and Diseases: An Evolutionary Perspective

The structural, metabolic and synergic actions of iodine and polyunsaturated fatty acids (PUFAs) in life evolution and in the ‘membrane lipid language’ of cells are reviewed. Iodine is one of the most electron-rich atoms in the diet of marine and terrestrial organisms and, as iodide (I⁻), acts as an ancestral electron-donor through peroxidase enzymes. It is the most primitive inorganic antioxidant in all iodide-concentrating cells, from primitive marine algae to more recent vertebrates. About 500 million years ago, the thyroid cells originated from the primitive gut of vertebrates, then migrated and specialized in the uptake and storage of iodocompounds in the thyroid, a new follicular organ. In parallel, ectodermic cells, differentiated into neuronal cells, became the primitive nervous system and brain. Both these cells synthesized iodolipids, as novel ‘words’ of the chemical ‘lipid language’ developed among cell membranes during the evolution of life, for better adaptation to terrestrial environments. The study of iodolipids is a new area of investigation, which might be useful for research on apoptosis, carcinogenesis and degenerative diseases, as well as for trying to understand some problems discussed regarding human evolution.

Forward

Evolution of the hominin lineage was marked by progressive brain expansion and complexity, in concomitance with coordinated changes in other morphological and behavioral traits that characterized speciation events. In addition to gene variation, changes in climate, habitat, and diet are well-recognized environmental stimuli for evolutionary changes. Iodine is an environmental stimulus to which living organisms react, something particularly evident in amphibian metamorphosis and also in hominin evolution (Venturi & Bégin, 2010). A common biochemical control mechanism could potentially be responsible for coordinating a suite of physiological, morphological and behavioral changes as important as brain evolution. In a process such as this, iodine and polyunsaturated fatty acids (PUFAs) are important components, both by themselves and also via iodolipid molecules, as new ‘words’ of the chemical ‘lipid language’ developed among cell membranes during life evolution, for a better adaptation to terrestrial environments (Figures 1 & 2). Iodine is the richest in electrons of the elements presently considered essential in animal and human diets. Inorganic iodide appears to be necessary for all living animal cells, but only vertebrates have the thyroid gland and its iodinated hormones. Iodine (I) is scarce in the earth’s surface because over hundreds of millions of years it
Figure 1. Phospholipid bilayers of cellular membranes are 2 fatty acids, one saturated and one unsaturated (shown by the double bond) that are linked to a glycerol.

Figure 2. Arachidonic Acid Pathway (Leukotriene, Prostaglandin, Thromboxane Synthesis).
has been washed away by rain and glaciations and transported from the terrestrial crust to the sea, which is enriched in iodine in the form of iodide (I-) and iodates (Truesdale et al., 1995; Venturi & Venturi, 2007; Küpper et al., 2011; Stroev & Churilov, 2012). Seawater contains about 60 micrograms (mcg) of iodine per litre, whereas terrestrial freshwater (estuaries, rivers, lakes) contain 10-to 200-fold lower quantities. In the sea, algal phytoplankton, the basis of the marine food chain, acts as a biological accumulator of iodides, selenium and polyunsaturated fatty acids (PUFAs) (Venturi & Venturi, 2007). Our research group suggested that iodine and selenium played an important role in protecting the fragile membrane of PUFAs, proteins and DNA in primitive algae from oxidation (Cocchi & Venturi, 2000; Küpper et al., 2008; Venturi, 2011; Milczarek et al., 2013), and for the same reason, these elements are also important in human brain evolution (Crawford, 2009; Cunnane, 2005, 2010; Venturi & Bégin, 2010; Stenzel & Huttner, 2013). Iodide (I-) is a mild reducing agent, which is a chemical term for an antioxidant. Its antioxidant properties can be expressed quantitatively as a redox potential:

\[ I^- + \frac{1}{2} I_2 + e^- (electrons) = - 0.54 \text{ Volt} \]

Because iodide (I-) is easily oxidized, some enzymes convert it into electrophilic iodinating agents, as required for the biosynthesis of numerous I-containing natural products. In an evolutionary sense, iodides are the most ancient and powerful antioxidant (Packer, 2008). As such, they are the oldest defence mechanism against radical oxygen species (ROS). Iodides and peroxidases were present in primitive oxygenic and photosynthetic *Cyanobacteria* about 3 billion years ago (Venturi, 1985, Venturi et al., 2000a, 2009). The production of volatile iodine (molecular iodine: I2) and iodocompounds by marine algae was the result of the development of photosynthesis, oxygen production and respiration, some 3 billion years ago, probably as an adaptation to utilising light in order to reduce the amount of poisonous ROS (Küpper et al., 2008; Pedersén et al., 1996; Packer, 2008). The importance of antioxidants as protective substances against chronic and degenerative diseases, such as cancer and cardiovascular diseases, has been studied for many years. However, the utility of well-known vegetable antioxidant vitamins as protection against, or as a cure for, these diseases has not yet been demonstrated (Bjelakovic, 2010; Sato et al., 2005). A recent study tracking the eating habits of 478,000 Europeans also suggested that consuming high amounts of fruit and vegetables has little, if any, preventative effect against cancer (Boffetta et al., 2010). For this reason, we have hypothesized an ‘evolutionary hierarchy’ for the wide range of antioxidants, where the most ancient might be more essential than the ‘modern’ ones in protecting developmental stages of animal and human organisms (Venturi & Venturi, 2007). Deficiency of iodine, the most primitive antioxidant, causes more damage in developing embryos than deficiencies of some other ‘modern’ antioxidants. I-deficiency causes abortions and stillborns in pregnant women, and cretinism and neuropsychological disorders in human infants (Dunn & Delange, 2001; Stenzel & Huttner, 2013).
**Introduction**

In humans, surprisingly, the total amount of iodine in the human body is still controversial (Hays, 2001), but it is believed to be 25–50 mg. About 50–70% of total iodine is non-hormonal and is concentrated in extrathyroidal tissue (Brown-Grant, 1961; Venturi, 1985; Spitzweg et al., 1998), where its biological role is still unknown. Venturi (1985, 1999) hypothesized that iodide might have an ancestral antioxidant function in all I-concentrating cells, from primitive marine algae to more recent terrestrial vertebrates. In these cells, iodide acts as an electron donor in the presence of H2O2 and peroxidases. The remaining iodine atom readily iodinates tyrosine, histidine and unsaturated lipids, and thus neutralizes its own oxidant power (Table A & Table B).

The membrane metabolites of PUFAs have an essential role in intercellular biochemical communications. Crawford (2010) in his chapter ‘Long-chain polyunsaturated fatty acids in human brain evolution’ reported, with regard to the ‘language of lipids,’ that the importance of the increased complexity of these lipids was brought about by aerobic metabolism: whereby the simple language of prokaryotes, with only a few words, was developed into a vocabulary of over 1,000 words, in eukaryote cells. In the PUFAs, the presence of a double bond between two carbons (or carbon-carbon double bond) provides them with the possibility of changing their molecular structure through enzymes such as phospholipases, cyclooxygenases and lipoxygenases, etc. The resulting substances, called eicosanoids: prostaglandins (PG), leukotrienes (LT), lipoxins and tromboxane (TX); and docosanoids: resolvins, protectins, and maresins, are powerful lipid mediators that produce specific actions in the organism; they organize inflammation, hemodynamic, immune response and the repair of tissue (Figure 2). Many PUFAs cannot be synthesized by animal organisms and are considered ‘essential,’ and therefore should be incorporated into diets. These are: linoleic acid (C18:2 n-6), omega-6 and alpha-linolenic (C18:3 n-3) omega-3, arachidonic acid (AA) - omega - 6 (C20: 4n-6), and docosahexaenoic acid (DHA) - omega -3 (C22:6n-3). These PUFAs are incorporated into the phospholipidic membrane of all the cells of an organism. Omega-3 PUFAs are present in a large quantity in “fish oil”. However, fish do not produce them, but only accumulate them by eating algae from which antioxidant iodide and selenium are able to protect their fragile membrane lipids from peroxidation (Venturi et al., 2000a, b). Milczarek et al. (2013) reported that iodide, used in doses generally recommended in iodide prophylaxis, may prevent oxidative damage to membrane lipids. Küpper et al. (2008) showed that iodide scavenges ROS in algae, and that it was the first inorganic antioxidant to be described in a living system. PUFAs and iodides combine together to form iodolipids. Throughout the evolution of life, these iodolipids appeared to be novel biochemical signals among cells, since contact and modification of membranes in multicellular organisms formed the bases of adaptation to terrestrial environments. Roussset et al. (1980) showed that iodination only occurs in the lipid components of cellular membrane where peroxidise enzymes are firmly bound. The US Food and Nutrition Board
Table A. Proposed antioxidant biochemical mechanism of iodides (Venturi, 2003).

\[ 2I^- \rightarrow I_2 + 2e^- \text{(electrons)} = -0.54 \text{ Volt}; \]

\[ 2I^- + \text{Peroxidase} + H_2O_2 + 2 \text{Tyrosine} \rightarrow 2 \text{Iodo-Tyrosine} + H_2O + 2e^- \text{(antioxidants)}; \]

\[ 2e^- + H_2O_2 + 2H^+ \text{(of intracellular water-solution)} \rightarrow 2H_2O \]

Table B. Proposed antioxidant biochemical mechanism of iodides, probably the most ancient mechanisms of defence from poisonous reactive oxygen species (Venturi, 1985).

\[ 2I^- + \text{Peroxidase} + H_2O_2 + \text{Tyrosine, Histidine, Lipids, Carbons} \rightarrow \text{Iodo-Compounds} + H_2O + 2e^- \text{(antioxidants)} \]

Iodocompounds: Iodo-Tyrosine, Iodo-Histidine, Iodo-Lipids, Iodo-Carbons

and the Institute of Medicine (2001) recommended a daily allowance of iodine ranging from 150 mcg/day, for adult humans, to 290 mcg/day, for lactating mothers. However, the thyroid gland needs no more than 70 mcg/day in order to synthesize the required daily amounts of thyroid hormones (T4 and T3). These higher daily recommended levels of iodine seem to be necessary for the optimal functioning of a number of body systems, including many non-thyroidal I-concentrating organs (Venturi et al., 2000a, 2011; Stroev & Churilov, 2012). In terrestrial food, the supply of iodine is insufficient for the needs of living animals, though not for plants which, about 500 million years ago (MYA), developed a different metabolism without iodine. In fact, to reach the minimum iodine intake for children of 100 mcg/day, the consumption of 5 grams of dried marine kelp or 135 grams of marine fish or seafood would be necessary. By comparison, it would require about 3 kg of freshwater fish or meat. Indeed, in countries such as Japan, and in some of the coastal populations of Asia, Iceland, Ireland, Wales and Denmark, dried algae are currently widely eaten (Rodale, 1998).

The increase of oxygen in the Earth’s atmosphere and its biological consequences

The evolution of oxygen-producing cells was probably the most significant event in the history of life, after the beginning of life itself. Oxygen is a potent oxidant and its accumulation in the atmosphere forever changed the surface chemistry of the Earth (Canfield, 2005). By the start of the Cambrian period, 570 MYA, oxygen levels had increased enough to permit the rapid evolution of large, oxygen-utilising, multicellular
organisms. At the same time, endogenous protection systems were needed to counteract the deleterious effects of oxygen oxidations. In the primitive sea, mineral antioxidants, such as some reduced compounds of Rubidium, Vanadium, Zinc, Iron, Molybdenum, Copper, Selenium and Iodine, seem to have played an important role in electron transfer and in redox chemical reactions. In animals, the primary antioxidant enzymes are superoxide dismutase, glutathione peroxidase, catalase and peroxiredoxins (Benzie, 2003). Angiosperms (the dominant type of plants today) and most of their antioxidant pigments evolved more recently during the late Jurassic period (about 200-100 MYA).

Iodide/iodine and iodide/thyroxine: evolutionary history of a primitive antioxidant

Seawater algae contain the highest amount of iodine (1-3% of its dry weight) (Colin et al., 2003; Carpenter et al., 1999). This amount is huge when compared to its content in the human body, which should be little less than one kilogram of iodine per person. This large quantity suggests ‘per se’ the importance of this trace element in the metabolism of marine algae, which continually fight against ROS produced by photosynthesis. It is hypothesized that 80% of the Earth’s oxygen is produced by algae and Cyanobacteria inhabiting the sea close to the surface. There is an increased emission of iodinated halocarbons and I2, both from kelp beds at low tide during the daytime and from kelp plants incubated under high solar irradiation, causing photo-oxidative stress. Brown algae (seaweed) accumulate iodine at more than 30,000 times its concentration in seawater (Küpper et al., 2008; Pedersén et al., 1996; Stroev & Churilov, 2012). Primitive marine prokaryotes seem to have an efficient, active ‘iodide pump’, ancestor of the pump of multicellular eukaryotic algae and of mammalian iodide-transporters. The inhibition of sodium/iodine symporter (NIS) by an excessive quantity of iodine seems to be an ancient defence mechanism when, in the primitive sea, excess iodide impaired cellular trophism and the functions of I-concentrating organisms. This well-known ‘Wolff-Chaikoff effect’ now occurs in the thyroid of animals and humans with a dosage in excess of 2 mg iodide (Wolff, 1964; Joanta et al., 2006).

Evolutionary transformation of iodine from non-hormonal to hormonal functions

Since 800 MYA, thyroxine has been present in fibrous exoskeletal scleroproteins of the lowest marine invertebrates (sponges and corals) without any known hormonal action (Roche, 1952). Iodine concentration decreases stepwise from seawater (60 microgram/L) to estuaries (about 5 mcg/L) to river sources (less than 0.2 mcg/L in some Triassic mountain regions of northern Italy), and in parallel, saltwater fish (herring) contains 500-800 mcg of iodine per kg compared to freshwater trout, which has about 20 mcg per kg (Venturi et al., 2000a). Thus, in terrestrial I-deficient freshwater, some
trout and other salmonids (anadromous migratory fish) may suffer thyroid hypertrophy or related metabolic disorders, as do some sharks in captivity (Venturi et al., 2000b; Venturi & Venturi, 2007). When anadromous migratory fish (like seawater lamprey and salmonids), after metamorphosis, die in freshwater after reproducing (Youson & Sower, 2001), they release iodides, selenium and PUFAs into the environment, where these substances are beneficial for the life and health of native animals and humans, bringing essential elements back upstream from the sea to the I-deficient inland (Venturi & Venturi, 2007; Eales, 1997). The new hormonal action of T4 and T3 was made possible by the formation of nuclear thyroid-hormone receptors (THRs) in the cells of vertebrates. About 500 million years ago (MYA), primitive THRs with a metamorphosing action first appeared in marine chordates, and then, about 200 MYA, more recent THRs with metabolic and thermogenic actions evolved in birds and mammals. The role of iodine in marine and freshwater fish is not yet completely understood, but it has been reported that I-deficient freshwater fish suffer from higher incidences of neoplastic, infective and atherosclerotic diseases than marine fish (Walsh et al., 2006; Farrel, 2002). In amphibians, environmental iodine and T4 are the essential metamorphic factors that stimulate the spectacular apoptosis (programmed cell death) of the cells of larval tadpole gills, tails and fins, transforming the aquatic vegetarian tadpole into a ‘more developed’ terrestrial carnivorous frog (Figure 3).

Amphibian frog *Xenopus laevis* serves as an ideal model system for the study of the mechanisms of apoptosis (Ikuzawa et al., 2005). Neoteny has been observed in all amphibian salamander families, in which it seems to be a survival mechanism in aquatic hill and

![Image of amphibian metamorphosis](image)

Figure 3. Iodide and T4 trigger the amphibian metamorphosis that transforms the **vegetarian** tadpole into an adult **carnivorous frog**, with better neurological, visuospatial, olfactory and cognitive abilities for hunting, as seen in other predatory animals. In amphibian metamorphosis, environmental iodine and T4 stimulate the spectacular apoptosis (programmed cell death) of the cells of the larval gills, tails and fins, transforming the aquatic tadpole into the ‘more advanced’ terrestrial frog.
mountain environments only, with little food, and particularly, with little iodine. In this way, salamanders can reproduce and survive in the form of smaller larval stages, which are aquatic and vegetarian and require a lower quality and quantity of food compared to the big adults, which are terrestrial carnivores. If salamander larvae ingest sufficient amounts of iodine, directly or indirectly through cannibalism, they quickly begin metamorphosis and transform into bigger terrestrial adults, with higher dietary requirements (Venturi, 2004). In some high mountain lakes, dwarf forms of salmonids exist caused by food deficiencies, and in particular iodine, which causes dwarfism with cretinism due to hypothyroidism, as it does in humans.

Venturi et al. (2000a) hypothesized, the reverse of amphibian metamorphosis, that thyroidectomy and hypothyroidism in mammals may be considered a sort of phylogenetic and metabolic regression to a former stage of reptilian life. Indeed, many disorders that seem to afflict hypothyroid humans have reptilian-like features, such as dry, hairless, scaly, cold skin and a general slowdown of metabolism, digestion, heart rate and nervous reflexes, with lethargic cerebration, hyperuricemia and hypothermia.

Iodine in terrestrial organisms

Around 350 MYA, when some living plants and animals began to transfer from the sea to rivers and land, environmental I-deficiency was a challenge for the evolution of terrestrial life.

The terrestrial food resources of freshwater fish, animals and plants became deficient in iodine, selenium and omega-3 (Venturi, 2000a). Two different strategies against I-deficiency were developed by animals and plants. Land plants optimized the production of some PU-FAs, such as omega-6 fatty acids: linoleic acid and arachidonic acid (AA) (the precursors for some prostaglandins and other physiologically active molecules) and developed novel endogenous organic antioxidants, such as ascorbic acid, polyphenols, carotenoids, flavonoids, tocopherols, etc., some of which became the essential ‘vitamins’ in the diet of terrestrial animals (vitamins A, E, and in humans, vitamin C) (Venturi, 2007). Many plants have adapted to I-deficient land by excluding iodine from their metabolism (Coic & Coppenet, 1990; Lamand, 1991; Bernroitner et al., 2009). Specifically, plant cyanates and some glycosides, by acting as antiparasitic molecules, are able to impair and to block the transport of iodide and NIS in animals. Indeed, some plant pesticides are cyanogenic glycosides which, via cyanide, release block ‘cytochrome c oxidase’ and NIS. Such a mechanism is poisonous for a large number of parasites and herbivores, but not for the plants in which it is useful for their ‘seed dormancy’ phase. However, in contrast with terrestrial plants, iodine is still essential for animals. About 500 MYA, some chordates began to use the novel ‘thyroidal’ follicles as a reservoir for iodine and T4, which is able to transport antioxidant iodide and triiodothyronine (T3) into peripheral cells.
Iodocompounds and iodolipids in animal cells

In vertebrates, I-concentrating cells of gastric mucosa, salivary and mammary glands can produce iodothyronines, iodoproteins and iodolipids, in the same way as the thyroid gland (Banerjee, 1985; Venturi, 2007; Swietaszczak & Pilecki, 2012). In chemical terms, this is called ‘iodine value’ or ‘iodine number’ and these are often used to determine the amount of unsaturation in PUFAs. This unsaturation is in the form of double bonds which react with I-compounds (Thomas, 2002). Some iodolipids have been shown to regulate cellular metabolism (Pereira et al., 1990; Thomasz et al., 2010, 2013) and several authors have reported their effects on growth inhibition and apoptosis in different tumoral cells (Dugrillon, 1996; Aceves et al., 2005, 2006). The fact that radioiodine (131-I) is also detectable in the radioautographies of rats, 5 days after injection, in organs such as the stomach, fetal thymus, salivary glands and the retina, and after 14 days in oral mucosa, skin, hair and arterial walls, would suggest a local formation of little known iodocompounds, probably iodolipids and iodoproteins (Pellerin, 1961; Ullberg & Ewaldsson, 1964). See Figure 2. AA is one of the primary lipid molecules to be iodinated (DHA is another) and it is stored within the cell membrane, esterified to glycerol in phospholipids (Figure 3). The binding of certain chemical signals to receptors on the cell membranes can initiate phospholipid hydrolysis and releases AA-metabolites, which modulate the activities of ion channels, protein kinases, ion pumps, and other uptake systems outside the original cell, at a distance (Natarajan et al., 1997, 1998; Tong et al., 2002). Boeynaems et al. (1981) demonstrated the transformation of AA into several different iodolactones by lactoperoxidase in the mammary glands. The iodinating species generated by peroxidase enzymes are highly polarizable and hydrophobic molecules are 50-100 times more soluble in organic solvents than in water. Lactoperoxidase, like thyroid peroxidase, is a membrane bound protein and iodine that diffused from the active site can be found in adjacent lipid layers. Aceves et al. (2005) reported that iodine contributes to the integrity of normal mammary glands and showed that the percentage of radio-iodide in cellular homogenate of breast tissue is distributed 40 % in lipid fraction, 8 % in nuclear fraction and 50 % in protein fraction, mostly in mitochondria (Carr & Riggs, 1953). Indeed, the mitochondria of eukaryotes contain specific receptors for T3 and its lipid bilayer inner membrane, rich in PUFAs, is the site of electron transport of the respiratory chain and the major source of ROS, which play a crucial role in many degenerative diseases (Psarra et al., 2006). Venturi et al. (1993) also found that homogenates of normal gastric mucosa contain more iodine than mucosa affected by chronic atrophic gastritis. On the other hand, high quantities of iodine intake are toxic and cause degenerative, necrotic and neoplastic lesions in thyroid, stomach and salivary glands (Venturi & Venturi, 2009; Janta et al., 2006; Küpper et al., 2011; Stroev & Churilov, 2012), but not in the lactating breast where the toxic hyperaccumulation of iodine is not possible. On the contrary, Japanese women, who have the highest dietary iodine intake (largely from seaweed) of 1-3 mg/day, have the lowest breast cancer mortality in the world. Japanese people also
have the highest world life expectancy and the lowest infant mortality rate (Zava & Zava, 2011). Many researchers studied the antiproliferative, apoptotic and therapeutic effects of iodine and/or 6-iodolactone (6-IL) in I-concentrating organs including: breasts (Eskin, 1977; Ghent et al., 1993; Smyth, 2003; Aceves et al., 2005, 2006; Funahashi et al., 1996, 2001; Sekiya, 2005; Venturi & Venturi, 2009; Yu et al., 2013); stomach (Venturi et al., 1993, 2003, 2011; Behrouzian & Aghdami, 2004; Gulaboglu et al., 2005; Kandemir et al., 2005; Abnet et al., 2006; Tabaeizadeh, 2013); salivary glands (Venturi & Venturi, 2009); retina (Rieger et al., 2010; McLean & Podell, 1995); prostate (Aranda et al., 2013); and arterial walls (Venturi, 2011; Boggio et al., 2011; Tseng et al., 2012; La Vignera et al., 2012). Indeed, the normal and cancerous cells of these organs can take up iodine which exerts an apoptotic effect, both in vitro and in vivo, via iodolipid chemical messengers. The delta-iodolactones of AA inhibit the Epidermal Growth Factor receptor and delta-iodolactone of EPA exerts the antiproliferative effect in the nanomolar range, and neither AA by itself nor other iodolactones (besides delta-iodolactones) can perform this action (Figures 4 & 5). Iodolactone formation occurs in any organ (breast, gastric

![Figure 4. Structure formulae of DHA-iodolactone (5-ido-4-hydroxy-7,10,13,16,19-docosapentaenoic acid, gamma-lactone) and AA-iodolactone (6-ido-5-hydroxy-8,11,14-eicosatrienoic acid, delta-iodolactone).](image1)

![Figure 5. Structure formulae of some best known iodolipid molecules.](image2)
mucosa, salivary glands, retina) that contains peroxidases and iodine (Panneels et al., 1994a, 1994b). 2-Iodohexadecanal (IHDA), which can be formed by the addition of iodine to the vinyl ether group of plasmalogens, has been identified as a major thyroid iodolipid, which is able to inhibit human adenylyl cyclase. Dugrillon and Gartner (1995) reported that delta-iodolactones decrease EGF-induced proliferation and inositol-1,4,5-trisphosphate generation. The inhibition of serum protein-bound with 125-I formation in calf thyroid caused by 14-iodo-15-hydroxy-eicosatrienoic acid is due to decreased H2O2 availability (Pisarev, 1992; Krawiec et al., 1988). Yamada et al. (2006) demonstrated that iodide, at a high concentration, decreased the expression of angiogenic factors VEGF-A and VEGF-B, as well as the placental growth factor, accompanied by an increase in the expression of possible antiangiogenic factors, such as the urokinase-type plasminogen activator.

**Iodine and iodocompounds in human evolution**

Iodine deficiency and hypothyroidism (whereby the thyroid gland does not produce enough thyroid hormone) causes cretinism in childhood with poor growth and brain development (dwarfism and mental retardation). In human adults, they can cause myxedema, lack of energy and reduced resistance to disease. Dobson (1998) suggested that Neanderthal Man suffered from I-deficiency disorders caused by his inland environment and a genetic difference in his thyroid, compared with that of modern Homo sapiens. Cretins suffer from physical, neurological, mental, immune, reproductive and skeletal diseases. Obendorf et al. (2008) and Oxnard et al. (2010) hypothesized that Homo floresiensis, a pygmy-sized, microcephalic hominin, who lived from 95,000 to 13,000 years ago on the Indonesian island of Flores, were myxoedematous endemic cretins. Iodine and PUFAs of marine food resources have favoured the development and evolution of the brain of Homo sapiens (Cunnane, 2005, 2010). Our own research group studied cases of cretinism which afflicted about 0.3 % of the I-deficient population of Montefeltro (in the central Apennines of Italy) (Venturi, 1985; Donati et al., 1992). In cretins, we demonstrated a high prevalence of microcephaly with neurological disorders, immune deficiencies, hip dysplasia, arthrosis, oral, dental and atherosclerotic diseases (Venturi, 1985; Venturi et al., 2009, 2011). Price, in his famous world investigation *Nutrition and Physical Degeneration* (1939), reported that fish and seafood, two rich sources of these essential elements, are very important for the prevention of physical, skeletal and oral diseases in coastal populations. Cordain et al. (2005) indicated that the significant changes in diet that began with the introduction of agriculture and animal husbandry, approximately 10,000 years ago, occurred too recently on an evolutionary time scale for the human genome to adjust. In conjunction with this discordance between ancient, genetically determined biology of hunter-gatherer and fish-gatherer human societies and the nutritional patterns of contemporary Western populations, many of the so-called dis-
eases of civilization have emerged. It is our own opinion that I-deficiency was probably one of several dietary variations introduced during the Neolithic and Industrial Periods which have altered crucial nutritional characteristics of the ancestral human diet. Hence, the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilizations.

**Iodolips and the brain**

About 60% of the dry weight of the brain is lipid. Among lipids, dietary sources of PUFAs are required to maintain the structural complexity, function and size of the human brain. Human babies greatly require two dietary PUFAs, namely AA and DHA, to fuel the normal growth of the foetal and infant brain and retina (Figure 6 & 7). Neuroprotectin D1 is a docosanoid derived from PUFAs and it is formed in retinal pigmented epithelial cells, which are rich in iodolipids. When nervous cells are confronted with oxidative stress, as in brain cells in culture, neuroprotectin D1 displays potent anti-inflammatory and protective bioactivity (Bazan, 2012). Aceves et al. (2005) reported that in cellular homogenates of the breast, radioiodide is about 40% in lipid fraction. The liposome membranes of brain neurons show maximal accumulation of iodicompounds and thyroid hormones in the middle of the phospholipid bilayer. Between the lipid and the aqueous phase, the concentration of T4 is about 20,000 times more than that of T3. Choroid plexus of the brain shows an active radioiodine uptake by NIS (Dickson et al., 1987). Through the choroid plexus, the thyroid hormones T4 and T3 reach the cerebrospinal fluid and then the neuronal cells of the brain and the retina (Figure 8). Moreover, the fourth atom of iodine in T4 is more important as an antioxidant, compared to 3 atoms in T3. In fact, Calvo (1990) has shown that only T4, and not T3, was able to prevent severe brain damage caused by hypothyroidism in the foetus and the newborn. In this way, the antioxidant actions of iodides, released from T4 via deiodinase enzymes, protect PUFAs of the membrane phospholipids of brain cells, making the neuronal transmission more efficient. Orzalesi and Calabria (1967) showed that the retinal pigment epithelium and the choroid of the eye have considerable uptakes of 131-I (Figures 6 & 7). The outer segment of retina harboring visual pigments is primarily composed of lipids containing PUFAs, mostly DHA, which play an important role in the development, survival and function of retinal photoreceptors, and are very susceptible to peroxidation, which is considered one of the causative factors of many retinal diseases, such as age-related macular degeneration and diabetic retinopathy (Roy et al., 2011). As there is a relatively high iodine enrichment in the retina, Rieger et al. (1995, 2010) proposed a therapy with iodide iontophoresis in some retinal diseases and reported that iodides are able to defend the eye against oxidative effects. Triiodothyronine 5'-deiodinases of type I and type II, both containing selenium, are enzymes belonging to the class of oxidoreductases, which catalyze the following reaction (Körhle, 2000, 2005):

\[
\text{L-thyroxine (T4)} + \text{AH}_2 \rightarrow 3,5,3'\text{-triiodo-L-thyronine (T3)} + \text{iodide} + \text{A + H}
\]
**Figure 6.** Distribution of 131-iodine (white) in radioautography of the head of a mouse 2 hours after an intravenous injection. High and rapid concentration is present in iodolipids and iodoproteins of the retina, choroid plexus and salivary gland. (From Ullberg and Ewaldsson, 1964; Courtesy of Acta Radiologica).

**Figure 7.** Distribution of 131-iodine (half-life: 8 days) in black in radioautographies of the body of a rat after a subcutaneous injection of radioiodine. High I-concentration is evident in the iodocompounds of the choroid plexus, retina, hypothalamus, gastric mucosa and epidermis, where it is detectable up to 5 days after the injection. (Reproduced with permission from Pellerin, 1961; Courtesy of Path Biol.).
Figure 8. Sequence of 123-iodide human scintiscans after an intravenous injection. From left to right: after 30 minutes, 20 hours, and 48 hours. High and rapid concentration of radio-iodide is evident in periencephalic liquor and cerebrospinal fluid, choroid plexus, salivary glands, oral mucosa and stomach. In the thyroid gland I-concentration is more progressive, like in a reservoir, from 1% of the total injected dose after 30 minutes, to 5.8% of the total dose after 48 hours (Venturi, 2010).

Figure 9. Distribution of 131-I (white) in the abdomen of a pregnant mouse 24 hours after an intravenous injection. Two fetuses are evident with a high concentration of radio-iodine in their thymus, thyroid gland, placenta and gastric mucosa, and in the endodermal and ectodermal tissue, also in the milk gland of their mother (right). (Reproduced with the permission of Acta Radiologica).

This enzyme activity has been demonstrated only in the direction of 5'-deiodination, which makes T3 (the real hormone acting on nuclear T3-receptors) more active than T4. Likewise, Katamine et al. (1985) reported that dietary iodides protected the brain cells of rats from ROS. Ware and Wishner (1968), Cash et al. (1966) and Tseng and Latham (1984) showed that, as inhibitors of lipid peroxidation by 5'-monodeiodinase activity, T4 and reverse-T3 (but not T3) are more effective than vitamin E, glutathione and ascorbic acid. Peroxidases and deiodinases are able to take electrons from iodides, and the latter enzymes to take iodides from iodothyronines. Iodide and T4 trigger amphibian
metamorphosis which transforms vegetarian tadpoles into adult carnivorous frogs, with the better neurological, visuospatial, olfactory and cognitive abilities necessary for hunting, characteristic of carnivorous predatory animals. In 1883, Kocher observed that the accumulation of fatty material and cholesterol in arterial walls frequently appeared following thyroidectomies, suggesting that hypothyroidism is causally associated with the atherosclerotic process (Cann, 2006; Venturi, 2011). Turner (1933) reported that atherosclerosis can be prevented by dietary iodine or desiccated thyroid in laboratory rabbits. Indeed, Pellerin (1961) and Ullberg and Ewaldsson (1964) showed a high and prolonged uptake of radio-iodine in arterial walls and in immunocompetent fetal thymus (Figure 9). Cunnane (2005, 2010) suggested that, “iodine is the primary brain selective nutrient in human brain evolution”. According to Crawford (2006; 2012), DHA has been conserved in neural signalling systems in the cephalopods, fish, amphibians, reptiles, birds, mammals, primates and humans. This extreme conservation, despite wide genomic changes over 500 million years, testifies the uniqueness of this molecule in the brain. The brain selectively incorporates DHA, and its rate of incorporation into the developing brain has been shown to be greater than ten times more efficient than its synthesis from omega 3 fatty acids of land plant origin. Recently, Stenzel and Huttner (2013) reported the important role of maternal thyroid hormones in the developing neocortex and during human evolution, showing that iodine intake has been related to the expansion of the brain and associated with the increased cognitive capacities during human evolution, because thyroid hormones regulate transcriptional activity of target genes via their nuclear thyroid hormone receptors (THRs), even mild and transient changes in maternal thyroid hormone levels can directly affect and alter the gene expression profile, and thus disturb fetal brain development.

Conclusions

Systematic investigations into iodinated biomolecules started only 40 years ago. Seaweed and marine organisms have more than 3000 of these molecules. Dembitsky and Tolstikov (2003) reported that more than 110 iodocompounds are chemically analysed in these organisms and some seem to possess anticancer and antibacterial properties. The action of iodolipids is an important new area of investigation, which might be useful for the study of apoptosis, carcinogenesis and degenerative diseases, and also for trying to answer some of the biochemical questions discussed regarding human evolution.

Conflicts of interest — The authors hereby declare that there are no conflicts of interest.

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