INTRODUCTION

Evolution of the hominin lineage is marked by progressive brain expansion and complexity concomitant with coordinated changes in other morphological and behavioral traits that characterize speciation events. In addition to gene variation, changes in climate, habitat, and diet are well-recognized environmental stimuli for evolutionary change. Iodine is an environmental stimulus to which living organisms react, a point particularly evident in amphibian metamorphosis and potentially also in hominin evolution. In toto, selection pressures effecting evolutionary change involve biological mechanisms permitting adaptation and evolution under changing environmental conditions. A common biological control mechanism could potentially coordinate a suite of physiological, morphological, and behavioral changes as important as brain evolution. We contend here that such a mechanism was hormonal and that thyroid hormone and iodine were pivotal components of such a mechanism.

The principal fossil sites of hominins correlated in space and time with volcanic and fissural local or nearby iodine sources (Borensztejn, 2005). In vertebrates, iodine is incorporated into thyroid hormone in the thyroid gland. Crockford (2003, 2008) provided solid evidence that changing thyroid function, specifically rhythms of thyroid hormone secretion, is crucial for speciation events taking place over decades. The same thyroid hormone mechanism can be applied to the process of humanizing australopithecines. Here, we postulate a link between thyroid function, iodine, and evolutionary changes as they apply to the evolution of hominins and, more specifically, the large brain of Homo sapiens. We emphasize changes in habitat and the connection between enhanced dietary availability of iodine, selenium, and polyunsaturated fatty acids as brain-selective nutrients necessary for thyroid function and hominin brain expansion.

THYROID HORMONE METABOLISM AND FUNCTION

Thyroid hormone is formed from iodine atoms attaching to two tyrosines and has the same structure in all organisms. In all vertebrates, thyroid hormone is manufactured and stored in the thyroid gland. Thyroid hormone takes two forms that have slightly different actions and effects depending on the number or placement of the attached iodine atoms. Unless otherwise stated, thyroid hormone will refer to its two main forms: thyroxine (with four atoms of iodine, also called T4), and triiodothyronine (with three atoms of iodine, also...
called T3). Of particular relevance to evolutionary processes, if thyroid hormone is consumed in food, it can be absorbed intact through the digestive tract.

During their adaptation to terrestrial life, the primitive marine chordates started to use T4 in order to transport T3 and iodide into the cells. In vertebrates, T3 is the most active thyroid hormone form in metamorphosis and in thermogenesis, permitting better adaptation to terrestrial environments (freshwaters, atmosphere, gravity, temperature, and diet). Iodine and thyroid hormone with its nuclear thyroid hormone receptors are the essential factors in amphibian metamorphosis, transforming the aquatic and vegetarian tadpole into a more complex terrestrial and carnivorous frog. This new hormonal action of T3 was made possible by the evolution of nuclear thyroid hormone receptors.

Thyroid hormone, and therefore iodine, has unique biological attributes that are highly relevant from an evolutionary perspective. Thyroid hormone influences many biological functions in a time- and dose-dependent manner (Hadley, 2000; Hulbert, 2000; Crockford, 2003, 2008). It controls brain and body growth, metamorphosis of body forms, all aspects of reproduction, and all the steps involved in basic metabolism. It regulates many key biochemical reactions, especially protein synthesis, enzymatic activity, and hormonal activity. In addition, thyroid hormone synchronizes the body’s response to stress.

Iodine and thyroid hormone have direct effects on brain expansion. For example, Roth (1946) demonstrated brain hypertrophy of the frog tadpole by iodine injection. With a frog tadpole, if one grafts an additional thyroid gland to a frog tadpole, its brain hypertrophies so much so that the cranium can sometimes burst (Rey, 1948, cited in Borensztejn, 2005). On the other hand, the brain atrophies in tadpoles in which the thyroid gland is removed. Thyroid hormone, specifically T3, is crucial to communication within the brain because it is required for the proper functioning of brain synapses and for the control of brain-specific genes (Jones et al., 2005). Cooperation between thyroid hormone, selenium, and the ω-3 polyunsaturated fatty acid, docosahexaenoic acid, is also necessary for brain development and function (Cunnane, 2005; see also Chapters 3 and 4 by Cunnane and Brenna, respectively, this volume). More precisely, docosahexaenoic acid is a major brain cell membrane component and is needed for the production of transthyretin, which is the protein carrier transporting thyroid hormone to the brain (Episkopou et al., 1993; Horrobin, 1997, 2001 Horrobin and Bennett, 1999; Kitajka et al., 2002). Selenium is required for the conversion of T4 in the brain into T3 by the deiodinase D2 enzyme whose activity depends on the presence of selenium. This relationship between thyroid hormone, docosahexaenoic acid, and selenium means that sufficient amounts of docosahexaenoic acid, selenium and thyroid hormone, specifically T3, must be present for optimal brain function.

Via nuclear thyroid hormone receptors, thyroid hormone also coordinates the expression of the genes that control development and reproductive functions in animals. Thyroid hormone controls cell division and differentiation, thereby orchestrating the timing and duration of development. Thyroid hormone required by a human embryo for body and brain growth comes initially from its mother directly through the placenta. Because a human embryo needs thyroid hormone in order to grow, its provision by the mother controls the growth of one generation to the next in a way that is independent of the genetic makeup of the embryo (Crockford, 2003, 2008). As a consequence, thyroid hormone connects individuals to the environment and to the generations that came before and after in a way that is partially independent of specific gene action. In effect, thyroid function appears to be central to translating environmental factors into physiological and developmental responses that lead to effective genetic variations that, in turn, mediate speciation events.
Thyroid hormone appears responsible for coordinating other hormonal responses necessary for an individual to adapt and to evolve to changing environmental conditions. Through hormonal interaction and interdependence, thyroid hormone is the only factor known to link the morphological, reproductive, and behavioral traits that change in coordinated fashion over evolutionary time. Many effects of thyroid hormone involve the action of genes, which means that changing hormone levels can have the same effect as a mutation to the genes themselves (Crockford, 2003, 2008).

Cyclicity and pulsatile secretion are well-established characteristics of thyroid hormone production, with rhythms and patterns that are species-specific during early development (Eales, 1997; Manzon and Youson, 1997; Crockford, 2008). Fluctuations of thyroid hormone concentration in blood and tissues that result from rhythmic secretion appear to be critical to brain growth and development. These thyroid rhythms and the modular effect of thyroid hormone on other hormones produced by the pineal gland, hypothalamus, pituitary, adrenal, and gonads, give the thyroid a crucial pacemaker role exerted by no other organ. Given the time- and dose-dependent relationship that exists between thyroid hormone and other hormones, as a pacemaker hormone, thyroid hormone coordinates the adaptive response of the body to short- and long-term environmental changes, a process that may explain evolutionary change.

Thyroid hormone secretion is controlled by complex interactions between the cells of the suprachiasmatic nucleus of the anterior hypothalamus and the neurohormone melatonin, produced by the pineal gland. The suprachiasmatic nucleus is responsible for controlling endogenous circadian rhythms. Its neurohormonal activities regulate many different body functions over a 24-h period. Light, temperature, and emotional signals are transmitted to the pineal gland, which responds with release of melatonin. This pathway can be increased or overridden by electrical and/or hormonal output from the suprachiasmatic nucleus (Hadley, 2000; Wright, 2002). Thus, hormonal stimulation from the suprachiasmatic nucleus or the pineal gland stimulates pulsatile secretion of thyrotropin-releasing hormone from the hypothalamus, which stimulates release of thyroid stimulating hormone from the pituitary gland. This stimulates pulsatile release of thyroid hormone from the thyroid gland. In addition, two direct neural mechanisms have been demonstrated: (1) the direct connection between the suprachiasmatic nucleus and the retina, such that the suprachiasmatic nucleus and its neurohormones can be governed by melatonin rhythms released by the pineal gland or stimulated directly by retinal nerves (Scheer et al., 2001; Reppert and Weaver, 2002); and (2) the direct connection between the suprachiasmatic nucleus and the thyroid gland, which can stimulate or dampen thyroid function independently of changing thyroid stimulating hormone concentrations (Kalsbeek et al., 2000; Young et al., 2005). Since electrical signals from the retina and suprachiasmatic nucleus are produced intermittently, thyroid hormone is also secreted in a rhythmic manner as a result of direct nerve stimulation.

Rhythms of thyroid hormone secretion have a genetic basis, but the precise mechanism is not well understood. Many genes governing the rhythmic pattern of thyroid hormone secretion are located in brain cells and include the clock and rhythm genes, those controlling the deiodinase enzymes (necessary for the conversion of T4 into its derivatives), and the gene-modulating factors (corepressors or coactivators, retinoid X receptor, thyroid hormone receptor) required for normal gene expression and regulation. The genetic constitution and physical relationship of these cells to one another are jointly responsible for the precise profile of individually unique and species-specific thyroid hormone rhythms. A shift in thyroid hormone rhythms can modify gene expression, that is, the amount of a specific protein produced by a specific gene, as well as proteins of many other genes at the same time, including those involved in fetal development, postnatal growth, and behavior.
FETAL DEVELOPMENT

Thyroid hormone is crucial to fetal development. Thyroid hormone supplied by the mother is required for embryonic growth at all stages, particularly for brain tissue (Yen, 2001, 2003; Jones et al., 2005). For example, the migration and maturation of emerging brain cells (including epidermal and choroidal pigment cells, neurons and glia of the peripheral nervous system, neuroendocrine and inner ear sensory cells) are controlled by thyroid hormone in a time- and dose-dependent manner (Barres et al., 1994; Cowling et al., 1994; Crockford, 2008). T3 influences the transcription of a wide variety of genes, including nerve and epidermal growth factors and a large number of crucial brain function proteins (Oppenheimer and Schwartz, 1997; Körhle, 2000; Anderson et al., 2003; Jones et al., 2005). In the rat, both T4 and T3 are essential for oligodendrocyte differentiation, axonal myelination, dendritic and axonal growth, neurotransmitter regulation, and synaptogenesis in the central nervous system (Anderson et al., 2000; Chán and Kilby, 2000; Dubois-Dalcq and Murray, 2000; Park et al., 2001; Smallridge and Laidenson, 2001; Anderson et al., 2003; Lavado-Autric et al., 2003; Garcia-Segura and McCarthy, 2004; Jones et al., 2005).

Virtually all target genes, cells, and tissues that require thyroid hormone during the embryonic and postnatal growth periods respond to it in a dose- and time-dependent manner (Lavado-Autric et al., 2003; Zoeller, 2003; Garcia-Segura and McCarthy, 2004). This suggests that precision in timing and absolute thyroid hormone circulating levels must be critical to species-specific growth and body functions, and therefore, that the rhythms of thyroid hormone secretion are probably species-specific (Crockford, 2008). Because thyroid hormone is crucial to fetal development, when it passes from the mother through the placenta in a species-specific rhythm, it results in the fetus growing at a precise species-specific rate. The precise endocrine physiology of the mother controls the early development of offspring, and continues to influence growth until they are born (Burrow, 1997; Piosik et al., 1997; Wilson and McNabb, 1997; Chan and Kilby, 2000).

ANTIOXIDANT ACTIVITY OF IODINE

Aside from its role in thyroid hormone production, iodine, as iodide (I-), is essential for all aerobic organisms because it has an antioxidant activity which protects against damage caused by reactive oxygen species. Küpper et al. (2008) showed that iodide scavenges reactive oxygen species in algae and that iodide was the first inorganic antioxidant to be described in a living system, a hypothesis first proposed by Venturi (1985) and by Venturi and Venturi (1999). A biochemical mechanism of iodides as antioxidants is proposed in Table 6.1. The primary event in the use of iodides by cells was the development of their capacity to collect iodide ion and bind it to the amino acids – tyrosine and histidine – forming iodoproteins and to polyunsaturated fatty acids forming iodolipids. In vertebrate cells, iodide acts as an electron donor in the presence of hydrogen peroxide and the peroxidase enzyme. The remaining iodine atom readily iodinates tyrosine, histidine, and certain specific lipids forming iodocompounds such as iodotyrosines, iodohistidines, iodo-

<table>
<thead>
<tr>
<th>TABLE 6.1 Proposed antioxidant biochemical mechanism of iodides</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 I- → I2 + 2 e- (electrons) = -0.54 Volt;</td>
</tr>
<tr>
<td>2 I- + Peroxidase + H2O2 + 2 Tyrosine → 2 Iodo-Tyrosine + H2O + 2 e– (antioxidants);</td>
</tr>
<tr>
<td>2 e– + H2O2 + 2 H+ (of intracellular water solution) → 2 H2O</td>
</tr>
</tbody>
</table>
thyronines (including thyroid hormone), iodoproteins, iodolipids, and iodocarbons (Gelb et al., 1962; Banerjee et al., 1985; Aceves et al., 2005). The effects of iodine may be better understood when its hormonal and nonhormonal actions are considered separately.

Iodide, as a primary antioxidant, may play a key role in the protection of vulnerable brain polyunsaturated fatty acids from lipid peroxidation. The existence of an evolutionary antioxidant biochemical cooperation between polyunsaturated fatty acids, selenium, and iodides was first suggested by Venturi and colleagues (Venturi and Venturi, 1999; Cocchi and Venturi, 2000). Arachidonic acid and docosahexaenoic acid are two polyunsaturated fatty acids essential for cell membrane structure and function of the brain, and can be iodinated by two mechanisms. One mechanism consists of the addition of iodine to double bonds of docosahexaenoic acid and arachidonic acid, making them less reactive to free oxygen radicals. In the second mechanism, in the presence of iodides and hydrogen peroxide, peroxidase catalyzes the iodolactonization of docosahexaenoic and arachidonic acids. Arachidonic acid can then be converted to 6-iodo-5-hydroxy-eicosatrienoic acid, delta-iodolactone, as well as various omega-lactones. Transformation of docosahexaenoic acid into 5-iodo-4-hydroxy-docosapentaenoic acid, gamma-lactone, has also been reported (Fig. 6.1). The requirements for docosahexaenoic acid and arachidonic acid iodolactone formation are (1) the enzyme – iodo-peroxidase, (2) an elevated concentration of iodide, and (3) hydrogen peroxide. These conditions can be met in various tissues, including the thyroid gland and extrathyroidal tissues including choriod plexus in the brain.

Multiple iodolipid classes comprising iodolactones and iodoaldehydes (α-iodohexadecanal) have been identified that have structural and metabolic functions in plant, animal, and human cells (Cocchi and Venturi, 2000; Dembtsky and Tolstikov, 2003). For example, arachidonic acid iodolactones specifically inhibit signal transduction pathways induced by local growth factors such as epidermal growth factor and basic fibroblast growth factor (Chazembalk et al., 1988; Tramontano et al., 1989). Delta-iodolactones, at physiological concentrations, have antiproliferative effects (Banerjee et al., 1985; Pisarev et al., 1988; Dugrillon, 1996; Cann et al., 2000; Cocchi and Venturi, 2000; Venturi et al., 2000a,b; Aceves et al., 2005) and could be intermediates in iodine-induced autoregulation of cell proliferation, especially of the thyroid gland (Pisarev et al., 1988, 1992). This inhibition could suppress goiter formation and induce its shrinking (Pisarev et al., 1988, 1992). Interestingly, 2-iodohexadecanal biosynthesis involves the addition of iodine to thyroid and brain plasmalogen (Pereira et al., 1990). It was also suggested that iodolipids could play a role in the transport of iodide and in T4 formation and secretion (Pereira et al., 1990).
T4, reverse-T3 and other iodothyronines (T2, T1), may function as iodine transporters, and are important antioxidants and inhibitors of lipid peroxidation. In fact, they are more effective than vitamin E, glutathione, and ascorbic acid (Cash et al., 1966; Ware and Wishner, 1968; Tseng and Latham, 1984; Winkler et al., 2000; Oziol et al., 2001; Berking et al., 2005). Selenium is an antioxidant mineral and an essential component of families of enzymes including glutathione peroxidases, deiodinases, and glutathione-S-transferases. Glutathione peroxidases repair damaged cell membranes while glutathione S-transferases repair damaged DNA and prevents mutations (Low and Berry, 1996; Stadman, 1996). Several selenoproteins participate in the protection of thyroid cells from damage by hydrogen peroxide produced during thyroid hormone biosynthesis. Extrathyroidal or peripheral T4 metabolism is mediated by three deiodinases (type I deiodinase [D1], type II deiodinase [D2] and type III deiodinase [D3]). The distribution of deiodinase enzymes varies between tissues and each has a distinct developmental profile (Hulbert, 2000; Beckett and Arthur, 2005; Bianco and Kim, 2006). D1 and D2 catalyze the conversion of T4 into T3. D2 is very active in the brain. D3 catalyzes the inactivation of T4 into reverse-T3 and of T3 into 3,3'-T2. In this way, D3 delivers peripheral cells with one or two atoms of iodide per molecule of T4, thereby allowing iodides to exert their antioxidant activity. D3 protein is also expressed by granulocytes and monocarboxylate transporter 8, a very active and specific T4 transporter, is also present at the site of inflammation (Friesema et al., 2003; Stone, 1988). Iodide efficiently scavenges reactive oxygen species in human blood cells (Küpper et al., 2008) and contributes to regulating the inflammatory response (Stone, 1988).

Beneficial effects of the antioxidant activity of iodides have been reported for many chronic diseases including cancer, arteriosclerosis, cataract, cardiovascular, and articular diseases (Eskin, 1970, 1977; Elstner et al., 1985; Venturi et al., 1987; Buchberger et al., 1991; Rieger et al., 1995; Funahashi et al., 1996, 2001; Winkler et al., 2000; Venturi et al., 2000b; Venturi, 2001; Smyth, 2003a,b; Kessler, 2004; Muranov et al., 2004; Szybinski et al., 2004; Aceves et al., 2005; Abnet et al., 2006; Cann, 2006; Golkowski et al., 2007). Katamine et al. (1985) demonstrated that dietary iodides protect rat brain cells from lipid peroxidation. Liu (2000a,b) showed that reactive oxygen species and lipid peroxidation increase in iodine-deficient rats and children.

**DIETARY SOURCES OF IODINE**

Oceans and seawater are the principal reservoirs of iodine. Underground iodine is distributed into the atmosphere by volcanic activity and fissural fault emissions. Such activities were characteristic of the Pliocene and affected not only most of Europe (Western and Eastern Mediterranean, Greece, Italy, the Massif Central, Kaiserstuhl, Rhenish Schistous Massif, Czechoslovakia, etc.) but also America (Western United States, Patagonia) and Africa (East Africa Rift Valley, South Africa Great Dyke) (Borensztejn, 2005). Once in the atmosphere, iodine incorporates into rain and is thereafter carried into streams, rivers, ponds, lakes, and then to the ocean. Thus, iodine distribution is closely associated with the water cycle. Because iodine is volatile, it is constantly emitted back into the atmosphere.

The sea is rich in iodine (containing about 60 µg/L in coastal seawaters) since this is where most of the iodine accumulates after being washed away by rain or removed from the soil by glaciation. In the open ocean, the total iodine concentration is around 0.06 ppm (Elderfield and Truesdale, 1980). The major iodine species in coastal seawaters are iodate (IO3-) and iodide, along with smaller concentrations of molecular iodine, hypoiodous acid, and iodinated organic compounds (Truesdale et al., 1995).
Iodine required for the production of thyroid hormone is derived from dietary sources. Algal *phytoplankton*, the basis of marine food chain, are biological accumulators of iodides, selenium, and polyunsaturated fatty acids (Venturi and Venturi, 1999; Cocchi and Venturi, 2000, 2007; Küpper et al., 2008). Brown algae (seaweed) accumulate iodine to more than 30,000 times the concentration of this element in seawater, up to levels as high as 1–3% of dry weight (Colin et al., 2003; Teas et al., 2004). Iodine concentration decreases stepwise from seawater to estuary (about 5 µg/L) and river sources (less than 0.2 µg/L in some Triassic mountain regions of northern Italy).

The distribution of iodine varies geographically: maritime regions are most likely to be iodine-rich while inland and mountainous regions are most likely to be iodine-deficient. Marine fish contain 40–100 times more iodine than foods of terrestrial origin (Bernard, 1930; Dahl and Meltzer, 2009). Saltwater fish such as herring contain iodine at about 500–800 µg/kg compared to freshwater (i.e., trout) about 20 µg/kg (Venturi and Venturi, 1999; Venturi et al., 2000a,b, 2003). On land, iodine is taken up by plants. Herbivorous animals get their iodine from plants or by drinking iodine-containing water. Carnivores acquire iodine mostly from thyroid hormone that is present in the blood and tissues (thyroid gland, liver, kidneys, brain, bone marrow) of the prey animals (including their eggs) they eat and also from iodine in drinking water. Food resources on the littoral provide the richest dietary source of iodine (fish, shellfish, etc.; see also Chapter 3 by Cunnane, this volume) and preformed thyroid hormone (mammals, birds, reptiles, amphibians, and both primitive and advanced forms of fish).

**IODINE DEFICIENCY DISORDERS**

Thyroid hormone deficiency can be caused by iodine deficiency or by a genetic defect in thyroid hormone production or in thyroid function. Prolonged dietary iodine deficiency results in chronic reduction of thyroid hormone and clinical symptoms of hypothyroidism. Iodine deficiency leads to inadequate production of thyroid hormone that is indispensable for brain growth and development (Delange, 2000, 2001), but the precise mechanism by which iodine deficiency impairs brain development is not yet known. Hence, hypothyroidism produces a wide spectrum of pathological effects ranging, in increasing order of severity, from lethargy, dwarfism, deaf-mutism, to mental retardation and *cretinism*.

Deficiency of iodine, as an antioxidant, causes damage in developing embryos and in their brain tissues and results in a global loss of 10–15 IQ points at a population level. Iodine deficiency is the world’s single most significant cause of preventable brain damage and mental retardation (Dunn and Delange, 2001). Maternal *hypothyroxinaemia* during early pregnancy is a key factor in the development of the brain damage in the cretin. Calvo et al. (1990) demonstrated that maternal T4 (but not T3) plays a crucial role in protecting the fetal brain from damage caused by hypothyroidism. Hence, in this case, we would emphasize the effective difference between T4 and T3 in brain cell metabolism, and in particular, the effectiveness of the fourth iodine atom of T4. In pregnant women, iodine deficiency causes abortions and stillbirths. This damage seems not to be caused by thyroid hormone deficiency, but rather by iodine deficiency per se (Wolff, 1964; Goethe et al., 1999).

Dobson (1998) proposed that Neanderthals suffered iodine-deficiency disorders (see section Phase 3: From *H. erectus* to early *H. sapiens*). Recently, Obendorf et al. (2008) 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*, who are born without a functioning thyroid. Their congenital hypothyroidism leads to severe dwarfism, mental retardation, and reduced brain size.
Nowadays, iodine-deficient humans, like endemic cretins, suffer physical, neurological, mental, immune, and reproductive diseases. In collaboration with U.S. and Pisa University researchers, 15 cases of endemic cretinism were studied in the territory of Montefeltro, in the central Apennines of Italy (Venturi, 1985; Donati et al., 1989, 1992). In the Montefeltro region, endemic cretinism was still present in the 1980s, with goiter prevalence of 55% and mean urinary iodine level of 39µg/g of creatinine. Human cretins represented about 0.4% of the overall population. Clinical and biochemical features of patients with myxedematous and neurologic cretinism were studied. All the cases of myxedematous cretinism had some neurologic disorders (hyperreflexia, increased muscle tone, disorder of gait, Babinski sign, hypoacusia, and mental impairment). Some cases of microcephaly were also observed (Venturi, 1985). These findings suggested that brain damage reflected a diffuse insult to the developing fetal nervous system. An important degree of immune deficiency was also observed in iodine-deficient schoolchildren in the Montefeltro region, but they had normal values of T4, T3, and thyroid-stimulating hormone (Venturi, 1985; Marani and Venturi, 1985; Marani et al., 1986).

According to current global WHO statistics, more than 3 billion people live in iodine-deficient countries. Based on the National Health and Nutrition Examination Surveys data in the United States, moderate to severe iodine deficiency is currently present in 11.7% of the U.S. population, with a clear increasing trend over the past 20 years.
caused by reduced iodized table salt usage (Hollowell et al., 1998; Dasgupta et al., 2008). The U.S. Food and Nutrition Board (2001) recommended daily allowance of iodine ranges from 150µg/d for adult humans to 290µg/d for lactating mothers. However, the thyroid gland needs no more than 70µg/d to synthesize the requisite daily amounts of T4 and T3. These higher recommended daily allowance levels of iodine seem necessary for optimal function of a number of body systems, including choroid plexus and cerebrospinal fluid, eye, gastric mucosa, thymus, and salivary glands (Miller, 2006; Venturi and Venturi, 2007).

In humans, the total body content is about 20–50mg of which about 50–70% iodine is nonhormonal and is concentrated in extrathyroidal tissues. For all its importance in thyroid function, more iodine is actually located outside the thyroid gland than within it (Venturi et al., 1993; Venturi and Venturi, 1999, 2007). Active iodide transport is facilitated by three transporters: sodium-iodide symporter, pendrin, and the recently described apical iodide transporter. All three transporters are expressed in the thyroid gland and in extra-thyroidal tissues (Rodriguez et al., 2002; Burbridge et al., 2005). Iodine is present, in different concentrations, in every organ and tissue of the human body, not just the thyroid gland (Fig. 6.2). Organs transiently concentrating iodide includes white blood cells, salivary and lacrimal glands, choroid plexus, eye, renal cortex, pancreas, liver, gastric, small and large intestinal mucosa, nasopharynx, skin, adrenal cortex, mammary gland, placenta, uterus, and ovary (Brown-Grant, 1961). Recently, Thrall et al. (2009) reported that fetal stomach showed the highest accumulation of radioiodides compared to thyroid tissues.

HUMAN BRAIN EVOLUTION

Human brain evolution can be viewed as a sequence of speciation events divided into four major broad phases (Cunnane, 2005). Four broad phases of human brain evolution are proposed in Table 6.2, with the major species involved and the corresponding changes in diet, habitat and brain size. The link between them is briefly described below with emphasis on the potentially important role of thyroid function.

Phase 1: Australopithecines

Hominins evolved from the Australopithecines, which were bipedal ancestors appearing in the fossil record at ca. 4.4 million years ago in East Africa, Tchad and South Africa (Ehrlich, 2000). According to available specimens, the Australopithecine brain size evolved on average from 450g to 700g in H. habilis. This increase in brain size corresponds to 40% increase in the relative brain size (“encephalization quotient,” [EQ]) because brain growth exceeded body growth. EQ expresses the proportion of brain weight relative to body weight, which gives a more accurate measure of brain expansion than brain size alone (Cunnane, 2005). Australopithecine habitat is thought to have changed from closed forests or forests mixed with bush (Reed, 1997; deMenocal, 2004) to woodland habitats. As evidenced by the wear patterns of their teeth, their predominant diet was probably mixed with fruits and nuts.

New foods associated with a changing habitat (i.e., insects and grubs, bird eggs and fledgling birds, small mammals, reptiles, and amphibians) as determined by carbon isotope analysis (Crockford, 2008), necessarily involved the consumption of significant amounts of thyroid hormone and higher iodine intakes. Continued consumption of large quantities of foods containing thyroid hormone could have had a major impact on their populations, especially on females of reproductive age. High enough dietary doses of thyroid hormone
could even have resulted in birth defects (Weetman, 1997; Arem, 1999; Porterfield, 2000; Crockford, 2002, 2003; Cudd et al., 2002; Rovet, 2004). Thus, as a consequence of dietary changes associated with colonization of new habitats, it is possible that disruptively high levels of thyroid hormone intake by certain australopithecine clades may have altered thyroid hormone rhythms in the offspring. The thyroid hormone pattern produced by the australopithecine mother could have induced slight differences in brain development during embryonic growth of the fetus. As a consequence, slight individual variations in thyroid hormone rhythms were bound to occur due to mutations in the genes of the biological clock and rhythm cells, or to gradual changes in the relationship between these cells. Plausibly, higher exposure to thyroid hormone and to iodine, and changes in thyroid hormone rhythms could have induced changes in embryonic brain cellular architecture sufficient to stimulate brain expansion concomitant with a prolongation of fetal development, thereby extending the duration of neurogenesis (Smith, 1992; Finlay and Darlington, 1995; McKinney, 1998).

Australopithecines with a physiological tolerance to excessive dietary thyroid hormone and with offspring with skeletal changes toward primitive bipedalism seem to have formed a new colonizing population. Indeed, colonizing a new habitat may offer both many advantages and new stresses that have to be dealt with by each colonizing individual.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Approximate duration</th>
<th>Hominin species involved</th>
<th>Habitat</th>
<th>Diet</th>
<th>Brain size</th>
<th>Weight (grams)</th>
<th>Relative EQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1:</td>
<td>1.5 million years (from 4.4 to 2.5 millions years ago)</td>
<td>Australopithecines</td>
<td>From closed woodland forests or forests mixed with bush to woodland with small animals; shores</td>
<td>Fruits, nuts, small animals, and probably crustaceans</td>
<td></td>
<td>450</td>
<td>42</td>
</tr>
<tr>
<td>Phase 2:</td>
<td>1 million years (from 2.5 to 1.7 millions years ago)</td>
<td><em>H. habilis</em></td>
<td>More open habitats with abundant bovid species; shores</td>
<td>Vegetation, small animals, scavenged carcasses of large species; shellfish and fish</td>
<td></td>
<td>700</td>
<td>58</td>
</tr>
<tr>
<td>Phase 3:</td>
<td>400,000 years (from 1.5 to 0.4 millions years ago)</td>
<td><em>H. erectus</em> to early <em>H. sapiens</em></td>
<td>Savanna-type; artic steppe; tundra; mountains; shores</td>
<td>Raw meat from medium- and large-sized terrestrial mammals; shellfish and fish</td>
<td></td>
<td>1100</td>
<td>76</td>
</tr>
<tr>
<td>Phase 4:</td>
<td>30,000 years (from 100,000 years ago to present)</td>
<td>Early to present <em>H. sapiens</em></td>
<td>Shores</td>
<td>Raw and/or cooked marine foods; meat from terrestrial animals</td>
<td></td>
<td>1360</td>
<td>100</td>
</tr>
</tbody>
</table>

* From Cunnane (2005).

b Averaged values from Cunnane (2005) in which values for living *H. sapiens* are set at 100 and comparisons become percentages of the human value.

c For early *H. sapiens* (100,000–10,000 years ago): 102.
The new habitat would have preferentially attracted physiologically stress-tolerant individuals over less stress-tolerant ones. As a consequence, the colonizing group consisted of stress-tolerant individuals with similar particular thyroid hormone rhythms, which become established within their descendants. Over many generations and with continuous exposure to higher dietary iodine and thyroid hormone from small animals and amphibians, the descendants would have undergone changes in morphology and behavioral traits leading the way for the emergence of *H. habilis*.

**Phase 2: *H. habilis***

The second phase of human brain evolution is represented by *H. habilis*, currently still recognized as the first hominin and the first tool user. Diverging from a late australopithecine, possibly *Australopithecus afarensis* or one of a closely related species, *H. habilis* appeared about 2.3 million years ago and lived for roughly 600,000 years in somewhat drier and more exposed habitats where bovid species were plentiful (Reed, 1997). Not unlike australopithecines, their diet probably consisted principally of vegetation, some small animals, and scavenged carcasses of large species, the latter providing a substantial amount of bone marrow and brain (Fleagle, 1999; Crockford, 2003, 2008). Such a diet would have been proportionately richer in *brain-selective nutrients* including the polyunsaturated fatty acids – arachidonic acid and docosahexaenoic acid, both of which were necessary for brain development and function (see Chapters 3 and 4 by Cunnane and Brenna, respectively, this volume; Horrobin, 2001). These conditions would have favored higher thyroid hormone intake and therefore the emergence of more stress-tolerant individuals with a somewhat larger brain who colonized new open habitats.

*H. habilis* and its close relatives were the first human ancestors to show traces of asymmetry in the brain’s left hemisphere that is associated with development of areas for speech and language (Ehrlich, 2000). Compared to the australopithecines, change in *H. habilis’* relative brain size was minimal because body and brain growth occurred in parallel (Cunnane, 2005). With their slightly larger brain, the effects of their diet on brain development in *H. habilis* may have been less dramatic than those on early australopithecine, but still advantageous in such a way as to support more manual dexterity for tool manufacture and use, as well as better visuospatial skills, foresight capacities, and decision-making abilities. Indeed, docosahexaenoic acid is a major component of the neocortex (O’Brian and Sampson, 1965; Svennerholm, 1968) and is required for the production of transthyretin (Kitajka et al., 2002), which transports thyroid hormone to the brain. It is also possible that its combination with thyroid hormone resulted in better functioning of brain cellular membranes (Hulbert, 2000; Horrocks and Farooqui, 2004) and in greater cognitive development that would have conferred survival advantages.

**Phase 3: From *H. erectus* to early *H. sapiens***

*H. erectus* was a hunting hominin with a larger body and brain than *H. habilis* and represents the start of the third major speciation event in the hominin lineage. During this phase, the main change in brain size corresponded to a roughly 60% increase in EQ because brain growth exceeded body growth. *H. erectus* hunted a wide range of medium- and large-sized terrestrial mammals (Ehrlich, 2000; Crockford, 2003, 2008). As primary predators of such prey, *H. erectus* would have had ready access to iodine and thyroid hormone-rich organs such as thyroid gland, liver, kidney, and brain. As a consequence, increased consumption of dietary iodine and thyroid hormone would have triggered further shifts in thyroid hormone rhythms and stimulated the continuing enlargement of the brain and changes in
body proportions. Individuals with thyroid hormone rhythms that were adapted to increased consumption of dietary thyroid hormone, larger body size, more complex brain, increased manual dexterity, and better reproduction became the first hominin to move beyond Africa. *H. erectus* fossils have been found in southern (Indonesia) and western Asia (Georgia). Some paleoanthropologists have referred to the initial African form of this hominin as *Homo ergaster* and to the Asian form as *H. erectus*, but recent fossil records confirm that they probably formed a single species (Asfaw et al., 2002). In any event, this hominin was the first to live successfully in both Asian and African habitats and appears to be the direct ancestor of *H. sapiens*.

Within the same phase, the next major step in the evolution of the hominin lineage was the evolution of *H. erectus* into contemporaneous but distinct forms of *H. sapiens*, represented by *H. heidelbergensis, H. neanderthalensis* and, eventually, early *H. sapiens*. Many paleoanthropologists consider *H. heidelbergensis* to be the common ancestor of *H. neanderthalensis* in Eurasia, and of early *H. sapiens* in Africa. The emergence of the large-bodied and large-brained *H. heidelbergensis* coincided with a major global climate change that brought colder temperatures and drier Pleistocene environments leading to important changes in many habitats and animal populations around the world. For hominins, such changes probably meant less scavenging and more hunting inland as well as more fishing on the shorelines. Because of the intensified hunting and fishing activities, these hominins could have increased their relative proportions of both exogenous thyroid hormone, iodine, and docosahexaenoic acid compared to their predecessors. Again, individuals with the particular thyroid hormone rhythms adapted to higher levels of thyroid hormone without disruption of reproductive function would have been favored. Conversely, individuals with cold-sensitive thyroid hormone rhythms would have been eliminated from the populations (Crockford, 2003, 2008). *H. neanderthalensis* colonized Arctic steppes and tundra and, since thyroid hormone controls the body temperature, must have been cold-tolerant variants with particular thyroid hormone rhythms originating from the *H. heidelbergensis* populations. Neanderthals had brain sizes larger but also differently shaped than humans. Their diet appears to have been composed mainly of raw red meat because far fewer edible plants would have been available (Mellars, 1996; Balter et al., 2001). Plausibly, they also practiced foraging and fishing along shorelines. Thus, Neanderthals were exposed to high levels of dietary thyroid hormone and iodine.

A different perspective suggests that some Neanderthals actually suffered iodine-deficiency disorders probably caused by inland environment or by a genetic difference of their thyroid compared to the thyroid of modern *H. sapiens* (Dobson, 1998). These two scenarios, based on high intake of thyroid hormone for one, or on iodine deficiency for the other, appear incompatible. One plausible explanation for their apparent divergence may be that, as the climate got colder, Neanderthal populations probably migrated inland and/or higher up in the mountains distant from coastal habitats rich in thyroid hormone and an iodine-rich diet, such as shorelines near hunting grounds. Some of them, especially those living in iodine-deficient inland and mountainous regions, could have suffered from endemic cretinism due to iodine deficiency. On the other hand, hyperthyroidism could be another possibility since severe chronic hyperthyroidism has been shown to produce cretinoid offspring in rats (Waterman, 1958).

Four arguments suggest that *H. neanderthalensis* and *H. sapiens* were distinct species. First, Neanderthals had faster postnatal growth rates of tooth enamel than do modern humans (Ramirez Rozzi, 2002; Crockford, 2008). Second, Neanderthals had a faster craniofacial growth rate during early childhood growth periods than that of humans and chimpanzees (Williams et al., 2002). Third, analysis of mitochondrial DNA sequences suggests that Neanderthals were genetically distinct and reproductively isolated from
humans for a considerable length of time (Lindahl, 1997; Krings et al., 1997; Fabre et al., 2009). Finally, Neanderthals may have had a turnover rate for thyroid hormone similar to that of carnivorous modern dogs and cats (about 12–13h) compared to about 7 days for modern humans (Kaptein et al., 1994). If true, a faster turnover rate for thyroid hormone implies that Neanderthals possessed a distinctly different thyroid hormone rhythm, a criterion for distinguishing discrete species (Crockford, 2008).

Phase 4: From early to present day *H. sapiens*

The fourth and last phase toward humans concerns the great leap in creativity that took place from early *H. sapiens* to present *H. sapiens*, starting around 100,000 years ago. Brain size, while it provides a foundation from which creativity might develop, differs from creativity. Creativity probably depends more on increasing complexity in neuronal connections. During this phase, the brain and skull changed shape together along with the addition of neurological pathways were added that had not been present before (Parker and McKinney, 1999; McKinney, 2002), circuits which led to art, religion, music, warfare, and cultural diversity.

Modern *H. sapiens* (Cro-Magnon type) succeeded *H. heidelbergensis* as a successful, widely distributed species. Modern *H. sapiens* expanded their ecological niche to include less hospitable habitats, and migrated from East Africa to the Middle East, to South Africa, to Europe, to Central Asia then toward the New World (Ehrlich, 2000; Borensztejn, 2005). This geographic expansion of human distribution may have been made possible by enhanced trade, hunting skills and organization, regular use of fire for cooking, and by following coasts and river valleys. Migrating groups may have begun to take iodine or its source materials with them to the interior. They probably had the technology to store fish and other marine foods for future use, perhaps by drying, or salting. At that time, marine shells are found several hundred kilometers from their sources (Ehrlich, 2000). Initially, transport of shellfish could have occurred due to cultural preference for certain foods from the sea. Later, regular trade may have developed. If so, then a continual supply became ubiquitously available after 30,000 years ago (Ehrlich, 2000; Borensztejn, 2005). Other possible sources of iodine on land include the return of saltwater salmon to streams that had been blocked by glaciers, Dillehay et al. (2008) found from the analysis of archeological sites that the earliest Americans used marine algae (richest in iodine) and other marine resources for food and medicine. Evidence that the first Americans came by sea from Asia and spread throughout the New World by at least 14,000 years ago, supports the hypothesis that they took the coastal route rather than traveling inland. Significant quantities of iodides, thyroid hormone, and polyunsaturated fatty acids are found in marine fish, in eggs of freshwater and teleost fishes, and in egg yolk from land animals.

**THYROID HORMONE, IODINE, AND HUMAN BRAIN EVOLUTION**

Human dependence on dietary sources of iodine and thyroid hormone suggests that the evolutionary changes responsible for physiological differences between early and present-day *H. sapiens* may have occurred in an iodine-rich and therefore probably coastal or estuarine environment (see also Chapter 3 by Cunnane, this volume). Anatomically modern human remains dating from 120 to 100,000 years ago have been found in South Africa, Israel, and Northwestern Africa (Dobson, 1998). All these early modern human sites are close to coastal iodine-rich food resources.
Shore-based habitats would have created a cognitive niche for early humans (Crawford and Marsh, 1989; Cunnane, 2005). For the most part, life on freshwater shore-based habitats could have been one of relatively low stress around food resources, with hunting as a play (Cunnane, 2005). They would have had more time to devote to planning, communication, and coordination with others in their group, and, by doing so, an enriched opportunity to form a cognitive niche. As populations grew and group sizes increased, they would have gained superior capacity for information storage and greater manipulation of the environment within and outside of groups. This increased capacity in knowledge and manipulation would have been accompanied by changes in brain organization that allowed them to become culturally more advanced and much more innovative. Both cultural and genetic changes would have been advantageous, especially the genes controlling brain development that are thyroid hormone dependent, because the selection pressures would have favored the thyroid hormone rhythm that worked best with the new living conditions.

Ongoing proximity to riverine, lacustrine, and maritime diets is crucial for optimal brain development and function (Crawford and Marsh, 1989; Cunnane et al., 1993; Ellis, 1993; Stewart, 1994, 1996; Walter et al., 2000; Broadhurst et al., 2002; Cunnane, 2005). As early as 4 million years ago, marine organisms such as crustaceans appear to have been an important food for some australopithecines (Walter et al., 2000). Based on fish fossil sites, Stewart (1994, 1996) demonstrated that catfish and perch fishing were practiced by H. habilis 2 million years ago. Marine food resources (shellfish, crustaceans, fish, mollusks, frogs, reptiles, aquatic birds, eggs, marine plants and seaweed, etc.) provide a rich source of brain-selective nutrients, including preformed docosahexaenoic acid, iodine, selenium, and other trace elements (copper, zinc) and minerals, especially iron, which are in short supply on land.

Cordain et al. (2005) recently reported that the profound 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 (see also Chapter 5 by Muskiet and Kuipers, this volume). In conjunction with this discordance between hunter-gatherer and fisher-gatherer societies on the one hand and the nutritional patterns of contemporary Western populations on the other, many of the so-called degenerative diseases of civilization have emerged. Cordain et al. (2005) suggests that micronutrient density (including iodine) was probably one change, among other dietary variations including fiber and polyunsaturated fatty acids contents, introduced during the neolithic and industrial periods which have altered simultaneously crucial nutritional characteristics of ancestral human diets. The evolutionary collision of our ancient genome with the poorer nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization.

CONCLUSION

Iodine and thyroid hormone are crucial for brain development and functioning throughout human evolution. Hormonal and nonhormonal actions of iodine may provide the basis for a biological mechanism explaining evolutionary change in response to changing environmental conditions. Although much is known about how it might work, the precise biochemical mechanisms, including quantitative measurements of thyroid hormone rhythms, remain yet to be established.

Adequate iodine uptake and thyroid function are essential for normal human development and brain functioning throughout life (Loosen, 1992; Bégin et al., 2008). Indeed,
CHAPTER 6  THYROID HORMONE AND IODINE  119

about one-fifth of the total human population consumes diets that are inadequate in supporting brain development. Human communities in inland or mountainous regions of Europe, India, Southeast Asia, North and South Americas, and Africa, are at grave risk of iodine deficiency. Compared to other common food groups (fish, eggs, pulses, cereals, meat, nuts, vegetables, fruits, and milk), shellfish is best able to meet the adult daily requirement for the brain-selective minerals. Thus, regular inclusion of any quantity of shellfish in the diet would help to improve the supply of these minerals, thereby contributing to optimal human brain function. In view of the high risk of iodine deficiency and of the insufficient intake of foods that are good sources of iodine (shellfish, fish, eggs, meat, milk), governments legislate supplementation of iodine, as iodized table salt, in the human food supply. However, salt intake has been decreasing in the last decades due to the perceived risk of excess dietary salt for hypertension. Ironically, food groups consisting of cereals, vegetables, and fruits, presently promoted as the basis of a healthy diet, are very likely to be deficient in iodine.

Although vegetables and fruits have been widely promoted as being protective against many chronic and degenerative diseases, such as cancer and cardiovascular, the efficacy of vegetable antioxidants (i.e., carotenoids, vitamins A, C, and E) in these diseases has not been recently supported by statistical data. Furthermore, their utility in prevention of these diseases has not been recently confirmed by epidemiological data (Morris and Carson, 2003; Bjelakovic et al., 2004, 2007; Hung et al., 2004; Lin et al., 2005; Sato et al., 2005; Tsubono et al., 2005). Moreover, vegetables and fruits contain goiterogens that deplete the body of iodine. This problem can be avoided by reducing intake of iodine-depleting foods while increasing consumption of iodine-containing foods such as shellfish, fish, and/or eggs.

Presently, humans are living beyond the optimal nutrient limits for intake of brain-selective nutrients, particularly iodine and iron. Changes in dietary habits are necessary by making marine foods and/or iodinated supplements more widely available, or we put ourselves at risk of reducing human cognitive capacity over a short period of time.

REFERENCES


Cunnane—Human Brain Evolution


Manzon, R.G. and Younson, J.H. 1997. The effects of exogenous thyroxine (T4) or triiodothyronine (T3), in the presence and absence of potassium perchlorate, on the incidence of metamorphosis and on serum T4 and T3 concentrations in larval sea lampreys (*Petromyzon marinus L.*). *General Comparative Endocrinology* **106**:211–220.


Perera, A., Braekman, J.-C., Dumont, J.E. et al. 1990. Identification of a major iodolipid from the horse thyroid


AUTHOR QUERY FORM

Dear Author

During the preparation of your manuscript for publication, the questions listed below have arisen. Please attend to these matters and return this form with your proof.

Many thanks for your assistance.

<table>
<thead>
<tr>
<th>Query References</th>
<th>Query</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Running head</td>
<td>AUTHOR: Since some of the heads are too long to fit, please check and advise whether the shortened running heads are correct.</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>AUTHOR: Roth 1946 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>AUTHOR: Rey 1948 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>AUTHOR: Horrobin 1997 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>AUTHOR: Horrobin and Bennett 1999 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>AUTHOR: Yen 2003 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>AUTHOR: Venturi et al., 2000b, 2001 has been changed to Venturi et al., 2000b; Venturi 2001 so that these citations match the list.</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>AUTHOR: Cocchi and Venturi 2007 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>AUTHOR: Bernard 1938 has been changed to Bernard 1930 so as to match the list. Is this correct?</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Author: Burbridge 2005 has been changed to Burbridge et al. 2005 so as to match the list. Is this correct?</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>AUTHOR: Williams et al., 2002 has not been found in the list. Please provide full reference details or delete from the citation.</td>
<td></td>
</tr>
</tbody>
</table>
11. AUTHOR: Please confirm if the year range is correct or if it should be 120,000 to 100,000 years.

12. AUTHOR: Stewart 1994, 1996 has not been found in the list. Please provide full reference details or delete from the citation.

13. AUTHOR: Walter et al. 2000 has not been found in the list. Please provide full reference details or delete from the citation.

14. AUTHOR: Please provide the publisher for Anderson et al. 2000.

15. AUTHOR: Please provide the page range for Begin et al. 2008.

16. Author: Cann et al., 1999 has not been cited in the text. Please provide a text citation or delete from the list.

17. AUTHOR: Colin et al. 2005 has not been cited in the text. Please provide a text citation or delete from the list.

18. AUTHOR: Please confirm if the details of Dasgupta et al. 2008 are correct, and please provide the page range.

19. AUTHOR: Grzesiuk 2009 has not been cited in the text. Please provide a text citation or delete from the list.

20. AUTHOR: Lucy and Lichti 1969 has not been cited in the text. Please provide a text citation or delete from the list.

21. AUTHOR: Minugh-Purvis 2002 has not been cited in the text. Please provide a text citation or delete from the list.

22. AUTHOR: Please provide accessed date for Venturi and Venturi 2007.