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# The incorporation of iodine in thyroid hormone may stem from its role as a prehistoric signal of ecologic opportunity: An evolutionary perspective and implications for modern diseases

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**Summary** To optimize fitness under conditions of varying Darwinian opportunity, organisms demonstrate tremendous plasticity in their life-history strategies based on their perception of available resources. Higher-energy environments generally promote more aggressive life-history strategies, such as faster growth, larger adult size, greater genetic variation, shorter lifespan, larger brood sizes, and offspring ratio skewed towards the larger-sized gender. While numerous mechanisms regulate life-history plasticity including genetic imprinting, methylation, and growth factors, evidence suggests that thyroid hormone plays a central role. Given the pivotal adaptive role of thyroid hormone, the teleology of its dependence on dietary iodine for production remains unexplained. We hypothesize that iodine may have emerged as a substrate for production of thyroid hormone in prehistoric ecosystems because the former represented a reliable proxy for ecologic potential that enabled the latter to modulate growth, reproduction, metabolic rate, and lifespan. Such a scenario may have existed in early marine ecosystems where ocean-surface vegetation, which concentrates iodine for its antimicrobial and antioxidant properties, formed the basis of the food chain. Teleologic parallels can be drawn to the food-chain accumulation of antimicrobials that also exhibit antioxidant properties and promote adult size, brood size, and offspring quality by modulating central hormonal axes. As each higher species in the food chain tunes its life-history strategy based on iodine intake, the coupling of this functional role of iodine with its value as a resource signal to the next member of the food-chain may promote runaway evolution. Whereas predators in prehistoric ecosystems successfully tuned their life-history strategy using iodine as a major input, the strategy may prove maladaptive in modern humans for whom the pattern of iodine intake is decoupled from resource availability. Iodine acquired through sodium iodide supplementation may independently contribute to some biologic dysfunctions currently attributed to sodium.

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## Hypothesis

Thyroid hormone function is significantly influenced by dietary intake of iodine [1]. On the one hand, iodine deficiency has been ascribed to declines in iodine reservoirs in the soil and in the terrestrial food-chain from glaciation and the leaching effects of groundwater [1]. On the other hand, it has been attributed to increasing biologic demand in conjunction with increasing thyroid hormone requirements [1] due to modern dietary shifts towards carbohydrates, trace elements, pollutants, and genetic factors [2]. Although excess iodine intake has been reported in certain Asian cultures [3], relative iodine deficiency is thought to exist in many parts of the world. Many nations have initiated salt iodization to augment intake [4,5].

Chronobiologic considerations and compensatory mechanisms may play a role in determining thyroid response to iodine intake. After a period of iodine deficiency, a surge in iodine supply can induce thyrotoxicosis in patients with functionally autonomous thyroid nodules [6,7]. Rich sources of iodine, such as amiodarone and iodinated contrast can cause thyrotoxicosis [8,9] but acute administration of these agents has also been shown to induce transient hypothyroidism [8,10,11]. Goiter and thyrotoxicosis are diagnosed at higher rates in regions where iodine supply increased rapidly due to supplementation as compared to areas with high baseline iodine intake, [12,13] but high consumption of dietary iodine has also been implicated in subclinical hypothyroidism in Asian countries with high intake of seaweed [7,14,15]. Induction of hypothyroidism by excessive iodine administration may occur via reduction of organic binding of iodine by the thyroid gland [16]. The intricacy of the relationship between iodine input and thyroid hormone output remains unresolved [17].

Why thyroid hormone production became linked to iodine intake remains a mystery. We hypothesize that iodine may have emerged as a substrate for production of thyroid hormone in prehistoric ecosystems because the former represented a reliable proxy for ecologic potential that enabled the latter to modulate growth, reproduction, metabolic rate, and lifespan. Whereas predators in prehistoric ecosystems successfully tuned their life-history strategy using iodine as a major input, the strategy may prove maladaptive in modern humans for whom the pattern of iodine intake is a less reliable indicator of resource availability. Understanding this teleologic link may lead to a better understanding of modern diseases related to iodine and thyroid biology.

## Evidence

### Thyroid hormone links life-history strategies to resource availability

Organisms exhibit tremendous plasticity in their ability to modulate their behavior depending on the perceived availability of resources in the environment. Resource availability may be ascertained by bottom-up data, such as caloric intake or by top-down data, such as ambient temperature. Environments with an abundance of available energy promote life-history strategies that engender greater innovation and a more aggressive allocation of biologic resources to exploit times of opportunity. Conversely, lower-energy environments favor more conservative strategies.

A proxy for increasing food sources, rising temperatures may promote evolutionary risk-taking and innovation. Fungi reproduce asexually as hyphae in lower temperatures, a more conservative evolutionary strategy, and sexually as yeast in higher temperatures, a more aggressive evolutionary approach [18]. High temperatures impair the function of heat shock protein (HSP) 90, a buffer against phenotypic variation [19,20]. Among the aggressive strategies observed during rising temperatures, a top-down proxy for increasing food sources, or high caloric intake, a bottom-up proxy, are larger brood sizes, larger adult sizes, faster rate of growth, altered length of juvenile period, and offspring gender shifts to the larger sex [21–24]. In contrast, cooler temperatures or widely varying temperatures, presumably cues of resource uncertainty, generally skew offspring gender ratios towards the smaller sex, which is usually the female [21–24]. Caloric restriction slows metabolism and extends lifespan [25]. Shorter lifespan associated with caloric abundance may function as an evolutionary accelerator that enhances inclusive fitness [26]. Obesity, presumably a signal of resource abundance, has been linked to both shortened lifespan and variations of DRD2 and DRD4 genes, thought to regulate “novelty seeking” traits similar to other methods of evolutionary risk-taking [27–29].

Many factors regulate customization of life histories, including genetic, epigenetic, and hormonal pathways. Compelling evidence exists suggesting that epigenetic processes, such as gene silencing, methylation, and genetic imprinting endow phenotype plasticity to organisms in search of higher fitness [30–33]. Developmental plasticity can engender a range of phenotypes to develop from a single genotype in response to environmental cues [30]. Numerous hormones including growth factors

enable organisms to express phenotypes optimized for the particular environment. Thyroid hormones play particularly important roles in modulating life-history strategy based on resource availability. Thyroid function is sensitive to the integration of numerous inputs that relate to environmental resource availability. Lower ambient temperature, an indirect surrogate for lower-energy availability, negatively regulates thyroid hormone production, [23] and hypothyroid states are associated with lower core body temperature [34]. Thyroid function becomes enhanced at higher temperatures, not only in warm blooded species, but also in fish, snakes, amphibians, turtles, and lizards [35,36].

Thyroid hormones can modulate development and lifespan in response to direct cues of energy availability. Reduced serum glucose and insulin levels, a direct cue of energy availability, are associated with low thyroid function [25,37,38]. Metabolic rates decline and thyroid T3 and T4 levels are lower in calorie-restricted animals [39,40]. Downregulation of T3 during caloric deprivation is observed in both endothermic and ectothermic vertebrates [41]. Low thyroid hormone levels are independently associated with smaller adult stature, reduced growth hormone, shorter juvenile period, reduced metabolic rate, decreased fertility, and longer lifespan [42–45]. In many lower species, thyroid hormones determine timing of developmental metamorphosis [46–48]. Among salmonids, T4 levels appear to regulate the smoltification changes that precede the migration from fresh water to salt water, an energy-intensive process [49]. Exogenous administration of L-thyroxine shortens intervals between broods and accelerates oocyte development in the next batch [50], consistent with hyperthyroid states. The functional link between thyroid and ovarian function, as well as diseases that involve overlap of these systems, such as struma ovarii, is reviewed elsewhere [51].

### **Iodine may be a proxy for resource availability**

Given the pivotal adaptive role that thyroid hormone plays in determining appropriate life-history strategy, the teleology of its dependence on dietary iodine for production remains puzzling. The high sensitivity of thyroid function to a broad set of inputs related to resource may suggest that iodine once represented a proxy for resource availability during prehistoric evolution.

It is generally accepted that life on earth began in the ocean, and that the earliest species likely emerged near the ocean surface where light energy

could be easily converted to forms that could drive biochemical reactions. The species that populate the ocean surface therefore comprise the foundation of the marine food chain. Kelps, order Laminariales, class Phaeophyceae, are one of many types of algae that populate the ocean surface [52], and are one of the richest sources of iodine in biology [53]. Kelps are characterized by variable life cycles that may include a microscopic filamentous gametophyte and a macroscopic sporophyte, the latter of which accumulates iodine at 30,000 times its concentration in the ocean and up to 1% of its dry weight [52,54].

Kelps are considered keystone species [55,56], and the kelp forest represents one of the foundations of the marine food chain and ecosystem [56,57]. Substantial biodiversity, trophic structures, and ecologic interactions appear supported by kelp forests [56]. Both top-down and bottom-up evolutionary forces are thought to play roles in the organization of trophic structures in the kelp forest, and upward-acting resource limitations apparently constrain consuming species [58–60]. Given their importance in the emergence of marine ecosystems, and their relatively early appearance during evolution that dates to at least the Tertiary period more than 20 million years ago [61–63], kelp forests may have had a strong influence in shaping the biology of later-appearing organisms in the Darwinian cascade.

Little is known in kelps and other marine plants about the adaptive functions of iodine as well as the mechanism involved in its concentration [52]. Iodine may play a role in the production of volatile hydrocarbons, which may represent defense metabolites that scavenge activated oxygen species and biocides [64–67]. Algae may also concentrate iodine, a key ingredient in anti-bacterial betadine [68], to protect themselves from protozoans and bacteria. While marine algae may have used iodine for self-defense, herbivores and higher-order predators further downstream in the food chain may have used dietary iodine as a surrogate sensor for overall availability of ecosystem resources. As each higher species in the food chain tuned its life-history strategy based on iodine intake, the coupling of this functional role of iodine with its value as a resource signal to the next member of the food chain could promote runaway evolution. Measurement of iodine would serve as a far more effective signal detection mechanism than pure measurement of caloric intake since the latter is subject to internal modulation. With each successive component of the food chain, the signal could be potentially dampened or distorted based on the utilization patterns of that component.

The use of a basic element, such as iodine obviates that likelihood. Marine algae, such as kelp bind iodide to tyrosine, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT) [69]. Sponges and corals harbor iodine as iodotyrosines, and MIT and DIT have been found in annelids, mollusks, starfish, crustaceae, and insects [70,71]. Protochordates, intermediate forms between vertebrates and invertebrates, were the first to demonstrate an iodination center similar to the vertebrate thyroid [72]. The protochordates may have developed a requirement for the iodinated amino acids after becoming accustomed to a supply of iodotyrosines and iodothyronines in the food chain [73].

Strong evidence exists for iodine bioaccumulation in the food chain [74–76], and consumption of intermediaries, such as fish can serve as a proxy for regional iodine availability [77]. In species as disparate as sharks and mammals, the gastrointestinal tract shares many similar biologic features with thyroid tissue, such as the presence of ciliated cells and the ability to concentrate iodide [78,79]. As an environmental cue, iodine not only flows through the food chain, but ends up also passed on to offspring during gestation and lactation [74,80]. The iodine of kelp has substantial bioavailability in humans [4]. We have previously reviewed the teleologic rationale for considering digestion not only as a resource-acquisition process but also as an information gathering process [81]. As a high-level macro-indicator of total metabolic rate in the food-chain, dietary iodine consumption may represent a superior proxy of resource availability for an individual organism making life-history decisions as compared to caloric intake.

Absorption of iodine may represent a signal of ecologic potential to organisms in other ways besides serving as a proxy for cumulative metabolic rate in the food-chain. Since the antioxidant and antimicrobial properties of iodine may endow survival advantage to its consumers, the availability of iodine in the food-chain may provide useful information to organisms regarding the ability of the environment to support life. Furthermore, by linking an antioxidant, such as iodine to metabolism, an activity which generates free radicals, organisms may be able to tailor their metabolic rate to their ability to manage redox imbalances.

The concepts described for iodine, itself an antimicrobial, may be generalized to other antimicrobials. Many antimicrobials promote adult size, brood size, and offspring quality. Supplementing animal feed with antibiotics to enhance growth has been practiced for half a century and such usage accounts for a majority of the total antimicrobial consumption in the world [82]. The growth promoting

properties of antibiotics are widely attributed to alterations in gut flora, reduced competition with bacteria for food, or thinning of the gut lining [82–84]. However, such assertions remain largely unconfirmed [83], and recent evidence suggests that addition, not reduction, of gut flora can enhance energy harvest from the gut in certain situations [85]. As may be the case with iodine, the alterations of life-history strategies such as adult size, brood size, and egg quality associated with antibiotic consumption may reflect its utility to organisms as a sensor for ecologic opportunity. It is interesting to note that antibiotics are almost universally derived from entities synthesized by microorganisms for their own defense. Antimicrobials, like iodine, have been shown to affect the hypothalamic-pituitary axis as well as thyroid function [83,86]. Antimicrobials, like iodine, may also have antioxidant properties [87]. These features of antimicrobials could make them useful proxies of Darwinian potential for members of a food-chain.

## Implications

While dietary iodine intake may have once been a useful proxy for nutritional availability, this linkage has apparently undergone decoupling in modern humans. The human diet has undergone substantial changes in composition in the modern age. In particular, the emergence of a high-carbohydrate diet, combined with possible depletion of iodine in the food-source, may have induced an imbalance of iodine relative to caloric intake [1]. The resulting iodine-energy imbalance may play an under-recognized role in the pathogenesis of many modern ailments. Iodine deficiency is a leading cause of hypothyroidism and many associated conditions as diverse as cretinism and hypercholesterolemia [1,5,88]. Relative iodine imbalance and endemic subclinical hypothyroidism could potentially play a role in the trend towards earlier puberty in humans during the last century [89]. Iodine imbalance and endemic subclinical hypothyroidism could potentially contribute to the extension of the human lifespan in conjunction with many other factors [90].

The same properties that render iodine useful in the biologic systems may explain its utility as a radiographic contrast agent. The k-edge of iodine at 33 keV makes it an ideal agent to use in modern imaging as it absorbs radiant energy. Organisms, especially those living on the ocean surface and exposed to maximum sunlight, may have long exploited this feature of iodine to sense energy as a signal and to also reduce oxidation induced by

radiant energy. Interestingly, allergic reactions to radiographic contrast agents are widely blamed on iodine. However, the molecular size of iodine is too small to efficiently generate an antibody reaction; the anaphylactoid reaction has a low frequency of reproducibility; and steroids generally do not ameliorate serious anaphylactoid reactions [91]. Based on our framework, perhaps the supra-physiologic administration of iodine during contrast studies produces an illegitimate biologic signal of increased environmental energy that invokes a hyperadrenergic, hypermetabolic host response. Symptoms of nausea, rash, vasomotor dysfunction, and airway dysfunction that are interpreted as allergic reactions can alternatively be explained as autonomic dysfunctions.

Although high caloric intake associated with the modern obesity epidemic is clearly a signal of resource abundance, the concurrent prevalence of hypothyroidism suggests that the body may perceive a signal of resource scarcity. This mixed interpretation of resource availability may play a role in numerous metabolic and endocrine dysfunctions. Given the link between insulin resistance and hypothyroidism [92], emerging modern pandemics, such as obesity and syndrome X may exemplify this phenomenon. Although hypothyroidism is thought to cause weight-gain by slowing metabolic rate, the possibility remains that weight gain induces hypothyroidism by exacerbating the energy-iodine imbalance. Insulin sensitizers, exercise, and weight-loss may represent new opportunities to treat hypothyroidism in place of iodine supplementation therapy.

Conversely, iodine or iodine modulators may have potential use as endocrine modulators for diseases, such as syndrome X, infertility, growth retardation, and pubertal dysfunctions. Perhaps local modulation of the female reproductive tract by iodine may explain the increased fertility of patients who undergo hysterosalpinography with oil-based iodinated contrast [93]. Links among syndrome X, insulin resistance, ovarian cysts, and polycystic ovarian syndrome (PCOS) are emerging [94]. Given the association between ovarian cysts (including PCOS) and hypothyroidism [95,96] broader investigation of co-morbid dysfunctions involving the ovary and thyroid are warranted. Increased production of thyroid hormone in the presence of high iodine levels leads to upregulation of catecholamines by thyroid hormone, which in turn may produce age-related sympathetic bias, a process that appears to drive many of the systemic dysfunctions associated with aging, particularly with respect to cardiovascular conditions [97]. Interestingly, iodine is also preferentially taken up by cancer cells, a

phenomenon that led to the development of Ethiodol-based chemoembolization therapies. Perhaps cancer cells use iodine as a resource signal and as a promoter of aggressive life-history strategies. Cancer treatment is a common trigger of hypothyroidism, suggesting that hosts may be interpreting chemotherapy or radiation as a signal of an unfavorable environment and may intentionally switch to a conservative life-history strategy. One wonders then about potential hidden risks associated with a modern policy of iodine supplementation. For instance, given that the majority of table salt is consumed in the form of sodium iodide, excess iodide intake could potentially account for many of the cardiovascular dysfunctions that are currently attributed to sodium.

Understanding the teleologic basis of the link between iodine intake and thyroid function may shed light on modern diseases related to iodine and thyroid biology.

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