TH Signalling in Human Evolution

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Thyroid hormone (TH) signalling is a universally conserved pathway with pleiotropic actions that is able to control the development, metabolism, and homeostasis of organisms. TH signalling has likely played a critical role in human evolution by facilitating the adaptive responses of early hominids to unprecedently challenging and continuously changing environments.

Keywords: Human Evolution ; Thyroid hormone ; Pleiotropic Effector

1. The Evolution of TH Signalling as a Pleiotropic Effector

The basic elements for the emergence and evolution of life were made available by distinct astronomical events such as mergers of binary systems and core-collapse supernova [1][2] that took place billions of years ago. One of these basic elements, iodine, provided the key material for the evolution of thyroid hormone (TH) signalling—a universal and crucial molecular pathway for the evolution of life on earth.

The lives of the first unicellular organisms 3.5 billion years ago were crucially dependent on the availability of iodine, as it appears to have acted as a powerful antioxidant [3].

Iodine is one of the most electron-rich atoms that is available in the diets of marine and terrestrial organisms, and through peroxidase enzymes, its anion (iodide) could have served as a primitive electron donor in order to bestow antioxidant and catalytic functions on primitive iodide-concentrating cells [3]. Starting with these ancestral antioxidant and catalyst roles, iodine then coupled with tyrosine to form a more versatile and highly reactive molecule, iodotyrosine, which eventually formed iodothyronines through subsequent coupling reactions.

Organisms that cannot produce iodothyronines must acquire them from their food reference [4][5][6], which makes these organisms highly dependent on alimentary iodine. The dependence on iodothyronines and environmental iodide may have pressed for the selection of organisms that were able to first sense the availability of environmental iodo-compounds, and second undergo morphological/anatomical changes that would increase their ability to exploit environmental resources, as happens with echinoid larvae metamorphosis (for a detailed analysis of this hypothesis and supporting bibliography see Mourouzis et al [7]). In this way, iodothyronines were gradually converted from a sensing molecule into a strong regulator of both metabolism and development.

Due to these crucial roles in organisms' adaptation to environmental conditions is not surprising that, over time, natural selection favoured the evolution of a sophisticated TH signalling that could sense and transmit environmental stimuli to cellular/genetic machinery (energy production, gene regulation and DNA replication in mitochondria), and ultimately orchestrate simultaneously metabolic and developmental processes. The coordinated and differential actions of TH signalling are mediated by the binding of the active form of TH (3,3,5-triiodo-l-thyronine, T3) to its receptors—the thyroid hormone receptors alpha and beta (TRα1–3 and TRβ1–3)—through which it regulates downstream signalling pathways and transcription factors [8]. Thyroid hormone receptors have separate expression patterns and divergent functional roles during foetal and adult life that are dependent on their liganded states [7][9]. TRα1 is the predominant isoform of TRs in many developing organs, while TRβ1 is widely expressed during adulthood. During foetal life, when T3 levels are low, TRα1 is highly expressed and acts as an apo-receptor (unliganded state) to repress adult genes and activate foetal ones. After birth, when T3 levels increase, the TRα1 switches to the holoreceptor form (liganded state) to induce the expression of adult genes, thus promoting cell maturation and physiological growth. In adulthood, circulating levels of THs are strictly regulated by the hypothalamic–pituitary–thyroid axis, which acts through a fine multi-loop feedback system, ensuring thyroid homeostasis. In addition, the availability of THs to tissue is locally regulated by the action of deiodinases (DIOs, DIO1, DIO2, DIO3). These selenocysteine-containing enzymes—the spatiotemporal expression of which changes during organ development in mammals—are capable of removing iodide from iodothyronines, turning T4 into T3 (DIO1 and DIO2) or catalysing the inactivation of T4 and T3 (DIO3) [10]. Apart from genomic actions, TH signalling can also act by

interacting with the extracellular domain of a plasma membrane protein—integrin αvβ3, which has no structural homologies with TRs. Through this extranuclear (non-genomic) mechanism, TH signalling controls the proliferation, apoptosis, the trafficking of intracellular protein, and phosphorylation/activation of TRs [11].

2. The Availability of T3 as a Determinant of Human Evolution

Millions of years ago, the first hominids had to alternate habitats periodically and were often compelled by food scarcity, violent natural phenomena, and predators to colonise new territories. These changes coincided with changes in dietary habits, encountering unfamiliar climates, physical catastrophes, and biological threats, all of which required a set of global anatomical and physiological adaptations. According to a recent hypothesis, THs—which can be absorbed through the digestive system and concurrently regulate development, growth, and metabolism—must have played a pivotal role in the adaptation, survival, and thriving of early hominids.

Australopithecines were the first hominids that experienced a major ecosystem and diet shift. Apart from eating fruits, leaves, and possibly scavenging, these Homo forebears started consuming small animals, such as amphibians, birds, and reptiles. This prey was consumed whole, and the animals' thyroid glands thus provided a significant amount of TH to their hominid predators. This shift might have initially resulted in an altered TH profile for females, which probably affected fertility negatively or may even have caused congenital anomalies [12]. This first instance of biological stress caused by high levels of exogenous TH may have served as a selection filter that favoured individuals who could tolerate sharp increases in THs. Nevertheless, the high levels of THs may also have provided an evolutionary advantage to these "more tolerant" individuals, as it could accelerate development and growth, enable the rapid regulation of the metabolism, and improve neural and possibly cognitive processes.

Homo habilis later colonised exposed habitats and became a habitual scavenger. Although these earliest representatives of genus probably still ate some small animals and vegetation, their diet appears to have incorporated a substantial amount of marrow and brains from scavenged carcasses [13]. Such a diet would have been proportionally higher in essential fatty acids, which are indispensable for brain development and function [14]. Nevertheless, tissues and organs (including thyroid glands) are commonly consumed by the primary hunters of any prey and are not typically available to scavengers. As a consequence, Homo habilis probably assimilated less exogenous THs than Australopithecines, and this made the endogenous production of TH by their thyroid gland key to their survival. Thus, natural selection favoured those who, under these conditions of low TH intake, had the capacity to not only increase the endogenous production of THs but to also modulate the interactions of TH with cellular and nuclear receptors so as to efficiently respond to metabolic and other challenges.

An increase in externally received THs could be observed again in Homo erectus, who became a consumer of different types of animals. Once again, this shift may have contributed to the radical morphological changes in the body and brain of Homo erectus, which enabled their survival for over 1,000,000 years and made them capable of moving beyond Africa [13]. During this long journey through novel territories, Homo erectus encountered diverse stresses and challenges: hostile weather conditions (e.g., often low temperatures), long-distance walking, feasting–fasting cycles, and as a typical hunter-gatherer, frequent external traumas.

Intermittent food scarcity made it imperative to save energy by adopting an energy conservation hypothyroidism-like profile, which is typical of low activity and fasting periods [15][16]. On the other hand, a sharp drop in temperature or migration to cold habitats made effective thermoregulation a critical factor for survival. The cold stress that was experienced by Homo erectus in seasonal habitats at high latitudes and elevations would have favoured the selection of temperature-sensitive pathways that could rapidly thermoregulate themselves by modulating the basal metabolic rate (BMR). To this end, natural selection would have favoured the evolution of a TH signalling profile that could boost cellular metabolism, increase BMR, and promote thermoregulation on demand according to the environmental temperature.

Likewise, alternate periods of walking (long distances) and running along with periods of low activity (typical of the hunter/gatherer lifestyle) would have necessitated the evolution of mechanisms that could simultaneously regulate metabolism and muscle structure. In fact, the skeletal muscles are major targets of TH signalling, which governs their development, homeostasis and regeneration, contractile function, and growth in response to physical challenges [17]. As such, the capacity for the coordinated regulation of the metabolism and muscles by TH signalling could be a critical selective advantage.

The ability to maintain high levels of THs was decisive for Homo erectus' cognitive potential, too. In fact, TH is crucial for brain development and cognitive function throughout life, from early embryogenesis to adult brain development, since it

governs many aspects of neurogenesis, including proliferation, survival, cell fate decisions, migration, differentiation, growth, and the maturation of both neuronal and glial cells [18].

Individuals with TH signalling that could reactivate developmental programmes to heal wounds also had an evolutionary advantage. Through their nuclear receptors, THs can regenerate skin tissues by accelerating barrier formation and stimulating the proliferation of epidermal keratinocytes and dermal fibroblasts [19]. As such, individuals with imperfect TH signalling would have exhibited delayed wound healing (as happens in modern humans with hypothyroidism [20][21]) and may have been susceptible to wound contamination and its complications. The ability to efficiently heal wounds by modulating TH levels and TRs and DIOs expression could, in this way, be an important advantage for survival.

Modern humans (Homo sapiens) are the only surviving species of the genus Homo that evolved from their most likely recent ancestor, Homo erectus. According to the so-called “Out of Africa” theory—the dominant model of the geographic origins and early migration of anatomically modern humans—Homo sapiens first evolved in Africa and then spread around the world between 100,000 and 200,000 years ago, superseding all other hominid species. Again, the potential pressures that drove the evolution of modern humans were environmental conditions and/or changes in diet, efficacy in communicating and interacting socially, and dexterity.

Based on the above analysis, researchers suggest that TH signalling evolved through millions of years as a sensitive sensor that transmitted changes from their environment to organisms and drove analogous adaptive physiological responses. This makes it a major determinant in human evolution, physiology, and disease.

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