Chapter

Evolution of Thyroid Enhancement of Embryogenesis and Early Survival

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Abstract

Iodine imparts protective antioxidant actions that improve the fitness of invertebrate organisms, and peptides carrying iodine initially appear to have served in a defensive capacity. Tyrosine carries multiple iodines in some echinoderms, and these peptides transferred to progeny serve both protective and signaling purposes. This parental relationship appears to be the most likely evolutionary basis for emergence of the vertebrate thyroid endocrine system, and its critically important development-promoting actions in larval and (later) fetal ontogeny. Thyroxine (T_4) and Triiodothyronine (T_3) induce settlement and stimulate transitions to alternative feeding modes in some echinoderms. This transgenerational relationship has been conserved and elaborated in vertebrates, including humans, which share common ancestry with echinoderms. Thyroid insufficiency is damaging or can be lethal to larval fishes; egg yolk that is insufficiently primed with maternal thyroid hormones (TH) results in compromised development and high mortality rates at the time of first-feeding. Maternally-derived TH supplied to offspring supports the onset of independent feeding in fishes (eye, mouth, lateral line, swim bladder and intestinal maturation) and survival by comparable developmental mechanisms in placental mammals. Fishes evolved precise control of TH secretion and peripheral processing; early metamorphic and feeding mode actions were joined by controlled thermogenesis in homeotherms.

Keywords: Thyroid hormone, T_3, T_4, embryogenesis, larvae, fetus, metamorphosis, survival

1. Introduction

Thyroid hormones have historically been associated with their thermoregulatory roles [1] and with the control of metamorphosis, as classically described in frogs [2]. A critically important role in human fetal development [3] is also well known, and is the basis for extensive thyroid status testing of pregnant women, and for the widespread use of iodized salt [4]. Comparative and evolutionary perspectives on thyroid regulatory biology had a relatively recent arrival. The ability to measure thyroid hormones [5] led to analysis of patterns of regulatory involvement not only in amphibian metamorphoses and human fetal development, but far more broadly among vertebrates throughout early differentiation. The origin of these actions seen throughout the vertebrates can be traced to consistent associations of thyroid hormones with the successful transition from larval to juvenile forms, generally accompanied by transitions to different modes of feeding and nutrition, or movement to different habitats. Recent research suggests that larval stimulation and signaling by iodinated peptides originated in invertebrates, and that the substantial survival implications of this form of maternal chemical communication in offspring ensured its evolutionary retention [6]. Conversely, it follows that the untoward consequences of hypothyroidism can be severe or lethal. The harsh impacts of hypothyroidism in fetal humans originated in connections between iodinated peptide signaling and successful larval differentiation in advanced invertebrates, a trait that has been consistently conserved and elaborated among the vertebrata. Insufficient human maternal thyroid stimulation results in the tragic syndrome known as cretinism [3], characterized by extremely deficient fetal development, central nervous system disorders, severe retardation, abnormal digestive and skeletal differentiation, stunting, lethargy, and a sharply reduced lifespan.

2. Evolutionary origins of the vertebrate thyroid system

Iodide is a large and biologically active anion, with a capacity to reduce reactive oxygen species, and it performs protective antioxidant functions in a range of invertebrate and algal organisms [7]. It is also involved in numerous biosynthetic activities. Some multicellular organisms concentrate iodide and it is often found bound to proteins or peptides [8], particularly the amino acid tyrosine, which can carry multiple iodides. Tyrosine is derived from phenylalanine and can be processed further into dopamine and other catecholamines, and it is essential for the synthesis of thyroid hormones tri-iodothyronine (T_3) and thyroxin (T_4). The latter two compounds consist of paired tyrosine residues with three or four attached iodides, respectively.

Tyrosines become iodinated spontaneously in marine environments, and are found throughout marine invertebrates. T_4 synthesis is an ancient process, occurring when iodinated tyrosines are coupled together, and some invertebrate physiological functions have been tentatively ascribed to it [9]. Iodinated signaling is an antiquated process, probably beginning with receptors in invertebrates responding to exogenous iodinated tyrosines coming from either seawater or marine algae [10]. Certain mollusks have been found to possess genes for peroxidases, one of which is similar to thyroid peroxidase, which binds iodine to thyroglobulin in vertebrates. While mollusks do not have thyroglobulin, one of their peroxidases incorporates iodine into thyroid hormone-like molecules. This may reflect the first incidence of endogenous production of thyroid like-hormones [11]. Specialized cells for the processing of iodinanted tyrosines are present in protochordates, and are organized into thyroid-like tissues, e.g. the endostyle [12]. In agnathans, the larval endostyle is retained and reorganized in adult lampreys into thyroid follicles with iodine-concentrating capacity. Lamprey metamorphosis is at least partly thyroid hormone-driven, and is characterized by a transition from larval filter feeding to ingestion of captured materials, and the larval endostyle is altered after metamorphosis into a thyroid gland with functional follicles [13]. Interestingly, the endostyle in lampreys develops around the time of yolk sac absorption [14]. In the other cyclostome group, hagfish, the thyroid primordium appears in the area of the head adjacent to the yolk sac [15]. These examples suggest a possibility of maternal thyroid signaling in larval cyclostomes.

An emerging body of evidence suggests that signaling by iodinated tyrosines was linked to changes in feeding modes before the evolution of protochordates and chordates, and that numerous physiological functions of thyroid- and thyroid-like iodinated peptides can be found in echinoderms. Maternal / larval signaling in the echinoderms may be the ancestral origin of the maternal / juvenile regulatory relationship that prevails throughout the vertebrates, and which figures prominently in *Homo sapiens*.

2.1 Echinoderms: Iodothyronines in larval signaling

Although echinoderms have relatively simple anatomical characteristics, their embryos are classified as deuterostomes, which means the mouth develops after the anus, and chordates are also classified thusly [6]. For this reason, they are thought to share a common ancestry with chordates [16]. This common ancestor has not yet been identified but some ideas of its characteristics are being deduced using comparative genomics [17]. Iodinated tyrosines, including thyroxin, are found in a variety of living tissues including monocellular algae [18] and echinoderm embryos [19], where there is ample evidence of maternal signals carrying out beneficial regulatory roles in early development [20, 21]. A good case can be made for the echinoderms having evolved a regulatory mechanism in development that enabled progeny to respond to signals by shifting developmental modes and feeding patterns, a pattern of transgenerational communication which has been conserved to contribute later to the adaptation of juvenile vertebrates to diverse and changing environments [22].

Some evidence supports the hypothesis that dietary sources of iodide served initially as antioxidants and evolutionarily later as signaling mechanisms to promote DNA expression, thereby initiating and facilitating successful invertebrate metamorphoses [6]. Because these actions promote changes that distinctly enhance the rate of larval survival, their selective value is high and these traits promote their own conservation and propagation. Most echinoderms distribute free-swimming larvae that mature, metamorphose, and settle as benthic organisms; some are dependent on exogenous feeding prior to settlement, while others can metamorphose without feeding [20]. Many echinoderm larvae exhibit changes in developmental rate or status and distinct modifications of their developmental mode in response to iodothyronines including exogenous thyroid hormones. Exogenous T_3 and T_4 both accelerate development, metamorphosis and settlement in sand dollars (*Leodia sexiesperforata*), and appear to facilitate a transition from obligate larval feeding to an alternative mode in which metamorphosis occurs independently of exogenous nutrition [21], foretelling important advancements in vertebrate reproduction. The capacity for endogenous TH synthesis is theorized to have replaced dependence on dietary TH (an exogenous messenger), facilitating the endocrine regulation of larval development, and generating some degree of internal control over the induction of metamorphosis [19]. Endogenous synthesis of TH has been confirmed in larval sand dollars (*L. sexiesperforata)*, sea biscuits (*Clypeaster rosaceus*), and sea urchins (*Strongylocentrotus purpuratus*) [21].

The role of iodinated tyrosine shifts in echinoderms from the provision of iodine for protective purposes and responsiveness to exogenous signals, to the emergence of a regulatory endocrine system that can alter the timing of physiological and morphological changes to increase developmental competence. In the case of sea urchins, exposure to either exogenous or endogenous T_4 promotes the initiation of larval exoskeleton synthesis [21].

The effectiveness of larval regulatory signaling by TH is dependent not only on the availability of hormones of either exogenous (dietary or maternal iodotyrosines) or endogenous origin (TH biosynthesis). In the case of sea urchins, activation of the MAPK protein kinase pathway occurs after binding of thyroxin to receptors [21]. Genes for hormone receptors, appropriate intracellular response mechanisms, deiodinase enzymes and other components may be required. The roles of these signals in the acquisition of metamorphic capability in relation to exogenous larval feeding [11] is the fundamental relationship that has been conserved throughout evolution for the promotion of GI system and other physiological adaptations, enabling successful transition to exogenous feeding in fishes [22, 23] and higher vertebrates. The ancestral deuterostome likely laid the foundation for regulation of the timing of larval metamorphoses in teleost fishes, as closely associated with the initiation of exogenous feeding. We see this pattern conserved in both echinoderms [24, 25] and hemichordates [26]. These groups comprise ambulacraria, the sister clade of chordates [27].

2.2 Hemichordates: Iodine or bromine?

Hemichordates (acorn worms) are the sister group to echinoderms in the ambulacraria, the sister clade of chordates. Hemichordates and echinoderms diverged approximately 876 mya whereas ambulacraria diverged from chordates 896 mya [27]. While one species of acorn worm (not actual worms), *Saccoglossus horsti*, has been shown to iodinate tyrosine by incorporating I^{131} into monoiodotyrosine [28], other species seem to manage this process differently. Acorn worms of the genera *Ptychodera*, *Glossobalanus* and *Balanoglossus*, use bromine instead of iodine [29]. They brominate indoles and phenols, the bromoindoles being similar to iodoindoles in other species. These halogenated phenols give the animals a characteristic smell described by many as iodophoric [29]. These chemicals seem to serve an antiseptic role rather than any sort of metabolic or metamorphic role [29]. Instead, embryogenesis and metamorphosis in indirect developing acorn worms seems to be controlled by FGF (firbroblast growth factor) [30]. Therefore, if iodothyronine control is a basal deuterostome trait, then it seems to be lost in hemichordates. An alternate explanation is that it was evolved separately in echinoderms and chordates. Much more work needs to be done on this group to elucidate whether other species consolidate iodine and if actors other than FGF play a role in embryogenesis and metamorphosis.

2.3 Protochordates: TRIAC and an endostyle

Protochordates are one of the three members of the phylum chordata along with urochordates (tunicates) and vertebrates. They are considered to be the basal chordate group [31]. The representative member of this group is the lancelet (Amphioxus), comprised by two genera, *Branchiostoma* and *Asymmetron.* The active form of iodinated tyrosine in amphioxus is triiodothryoacetic acid (TRIAC), rather than the triiodothyronine (T_3) used among vertebrates [12]. TRIAC differs from T_3 by having only two rings instead of three. Both T_4 and T_3 are found in amphioxous, but it is TRIAC, a metabolite of T_3 that is the active form [32]. T_4 is converted peripherally to T_3 by deiodination and T_3 is converted to TRIAC by deamination [33]. Amphioxus embryos lack large amounts of yolk and extra-embryonic tissues. This sets them apart from the vertebrates and is thought to be a basal chordate trait [31]. As far as the authors know, no studies have been done on thyroid hormone content of protochordate yolk. It is entirely possible that TH could be present in the yolk and it has not been detected as of yet. It is important to note that in ambulacraria, direct developing larvae have large amounts of yolk and indirect developing (planktonic) larvae do not [32, 34].

It is established that TRIAC controls the metamorphosis of amphioxus from a pelagic larva to a benthic post-larva [35, 36]. Metamorphosis is triggered by TRIAC binding to thyroid hormone receptors (TR). The expression of these receptors is greatest just before metamorphosis [33]. In amphioxous, the endostyle is the site of T_4 production. The endostyle has already been thought to be the thyroid homolog in larval cyclostomes [13], but the endostyle appears to be serving as a thyroid homolog in both larval and adult amphioxous [12]. As previously stated, T_4 and T_3 are produced in the endostyle and metabolized in the periphery. To be more specific, this deiodination and deamination takes place in the hepatic caecum, which is thought to be the homolog of the vertebrate liver [12]. Indeed, in vertebrates T_4 is converted to T_3 in the liver [8].

2.4 Maternal thyroid signaling in larval fishes

Female fishes deposit thyroid hormones against a concentration gradient in eggs during ovarian maturation [37]. Larval fishes are completely dependent on thyroid hormones of maternal origin until endogenous biosynthesis begins, and the regulatory capacity of the thyroid system has been attained. From that point forward, the thyroid system products in juvenile fishes have roles in organ system maturation, and the functionality of that system becomes dependent on adequate dietary sources of iodine [23].

Groupers are a family of marine fishes with small larvae that require relatively small food organisms. Cultured larval groupers are subject to large-scale mortality at the time of first feeding, but a switch from cultured rotifers to wild copepods provides a much more substantial supply of iodine, in response to which a sharp increase in larval survival has been attributed [38]. Some investigators have ascribed initial successes with larval groupers using copepods as a first feed entirely to differences in nutritional content [39], although iodine content of copepods and enhancement of digestive enzyme secretion in response to the copepod diet have been noted by other investigators [40]. These end-points are entirely consistent with established endocrine regulatory responses to micronutrient deficiencies in captive-reared populations, as reviewed previously [41] and as discussed further, below.

Thyroid hormones stimulate an integrated complex of developmental events that are crucial for early survival, collectively enabling fish larvae to make the transition from yolk absorption to active feeding [23]. Sensory, locomotor and digestive system maturation are essential for active feeding, and mortality on a substantial scale routinely occurs in captivity around the time of initial feeding [40]. In some cases, that has been attributed to an insufficiency of maternally-derived thyroid hormones [42, 43], sometimes in response to dietary iodine deficiencies. Perception of food items depends in part on eye and lateral line function, and olfactory organ input; pursuit of prey involves efficient swimming and neutral buoyancy, and the processing of food, absorption and utilization of nutrients hinge on the effective production of digestive enzymes. The maturation of the aforementioned physiological systems is strongly regulated by thyroid hormones of maternal origin, and all of these mechanisms become active on or slightly before the time of first-feeding [44, 45]. Early maturational events in the central nervous system are also dependent on maternally-derived thyroid hormones, enabling the processing of and responsiveness to critically important information.

2.5 Functional sensory systems

The detection of potential prey items by larvae typically involves mechanosensory detection of vibrations by the lateral line and the use of vision and/or smell to locate potential prey. The thyroid axis promotes neuromast proliferation and maturation and induces expansion of the neuromast population in the trunk in zebrafish [46]. First-feeding typically occurs around day 5 in zebrafish, and is coincident with the onset of visual, lateral line, and locomotor function and acquisition of the capacity to digest prey organisms. The onset of lateral line function requires maturation of neuromasts, as well as peripheral nerve transmission and processing by the central nervous system (CNS). In addition to the development of lateral line components, maternally-derived thyroid hormones promote differentiation and maturational changes in the CNS [47, 48].

The eyes also differentiate and become functional in response to maternal thyroid signaling, just before the onset of feeding in zebrafish [45]. Experimental applications of Insulin-like Growth Factor-1 (IGF-1) receptor blockers and analysis of IGF-1 gene expression revealed that eye differentiation in response to maternal TH signaling is transduced by IGF-1. Treatment with exogenous TH causes expression of IGF-1 genes, thereby accelerating initial eye function by up to three or four days [45]. A parallel assortment of somatosensory deficiencies is reported in response to mammalian neonatal hypothyroidism [46].

2.6 Locomotor system maturation

Fin maturation is characterized by the development of fin rays and changes in the morphology of dorsal, caudal and other fins beginning just after hatching, as embyronic forms proceed in transitions into free-swimming larvae [49]. Fins and scales are established targets for thyroid-induced maturation [50, 51] and their functionality is critically important in the successful transition to autonomous feeding. Skeletal development in fins is homologous with vertebrate limb bone development [52], and regulatory actions appear to be homologous. Hypothyroid mammals are subject to severely compromised locomotor function, with evidence of musculoskeletal deficiencies, exaggerated behavioral and cognitive inhibition, and displays of increased immobility and anxiety-related behaviors [53].

In addition to fin and musculoskeletal development, buoyancy is essential for energy-efficient pursuit of prey. Larval fishes with undifferentiated or uninflated swim bladders are unable to swim efficiently and they can readily become a component of the heavy mortalities associated with failed transitions to first feeding. Swim bladder ontogeny and inflation are under the control of maternal thyroid hormones [42, 43], and TH-induced swimbladder maturation and initial function are transduced by IGF-1, as is eye development [45]. A significant improvement in swimbladder inflation rate is attributed to TH exposure [42] and a strong relationship ($p < 0.005$) was reported between egg T_3 content and survival to two weeks post-hatching in striped bass (*Morone saxatilis*), with a correlation coefficient of 0.922 [42]. Mammalian lungs are evolutionary derivatives of the piscene swim bladder, and functional use of modified swim bladders for respiratory purposes is widespread among taxonomically diverse fishes [52]. Respiratory failures are listed among responses to hypothyroidism in humans, which according to the American Thyroid Association can result in lung function slowing "to the point that they can no longer keep up critical function" [54].

2.7 Production of digestive enzymes

Aquisition of the capability to find and ingest food does not ensure larval survival; numerous cases have been reported of larvae ingesting zooplankton or other organisms followed by failures to process, absorb and utilize their nutritional content. Maturation of the intestine is also controlled by maternal thyroid signals, and in cases in which those signals are lost or weakened, acutely underdeveloped and frail larvae with poor prospects for survival can be produced. In the Japanese eel *Anguilla japonica*, for example, Kurokawa et al. [55] observed that eel leptocephali started feeding at day 7 and reportedly found ingested rotifers in larvae up to 13 days of age with no physical or immunohistochemical evidence of digestion or absorption. Growth in these leptocephali essentially stops at the completion of yolk absorption on day 7, and is usually followed by mortality within a few days [55]. Larval Anguillids are notoriously difficult to rear in captivity, and practical closure of the eel life cycle has eluded hatchery technologists for more than half a century. One possible explanation is that adult eels that mature in captivity fail to deposit adequate stimulatory endocrine signals into their eggs [56], producing seriously hypothyroid larvae with debilitating developmental deficiencies, including a sharply reduced capacity to produce digestive enzymes.

Increasing the content of the thyroid hormone T_3 in marine fish eggs advanced the timing of the onset of digestive function, and significantly improved the rate of survival [57]. Further study of numerous species of larval fishes revealed that the expression of genes encoding digestive enzymes was induced by thyroid hormones [58, 59] coincident with the time of first feeding, which was interpreted as an indication that maternal signaling is a critically important determinant of the onset of intestinal digestive competence and consequently of survival. It is noteworthy that extensive and debilitating digestive system deficiencies and often acute failures are routinely reported in humans in response to hypothyroidism [60].

2.8 Maternal endocrine status is a prime determinant of egg quality

Egg quality was a characteristic of fish eggs that for many years had a circular definition – egg quality was defined as the capability of eggs to produce viable larvae for reasons that were speculatively considered and often dismissed as technically out of reach. Poor egg quality was attributed in earlier reviews to a combination of unknown genetic and nutritional variables, but regulatory materials such as endocrine signaling compounds (hormones and maternal mRNAs) were not yet being considered [61]. Thyroid signals deposited in fish eggs were recognized by some investigators as key determinants of egg quality more than 25 years ago [44] although numerous recent analyses of egg quality have completely overlooked the contribution of maternal thyroid hormones to larval success.

Some fish species are very reluctant to spawn in captivity, and captive-reared fishes released into wild environments often exhibit substantially compromised reproductive performance [62]. An inhibitory dopanimergic neural pathway is activated in response to a variety of stresses including environmental alterations, resulting in blockage of gonadotropin synthesis and release and imparied reproductive competence [63]. The degree of inhibition is variable, ranging from no inhibition whatsoever to erratic reproductive performance to complete reproductive failure. For this reason, challenging species are often treated with Ovaprim, the innovative spawning inducer developed by R. Peter and H-R Lin, which combines GnRH analogs and a dopamine receptor blocker [64]. Nevertheless, fertile eggs that produce larvae capable of hatching are not necessarily adequately provisioned with essential regulatory compounds to negotiate larval-juvenile metamorphoses. For these reasons, additional attention should be paid to the adequacy of maternal endocrine status during oogenesis.

Some species such as the striped bass (*M. saxatilis*) display highly variable production of viable eggs in captivity; two nearly identical-looking gravid females can display fertility rates of 4% and 94% (personal observation, unpublished). This may reflect variable endocrine status of broodstock females, since the deposition of essential regulatory hormones during oogenesis is determined by patterns of circulating hormones in maternal fishes. Larval survival in this species is highly dependent on the concentration of T_3 maternally deposited into eggs [42, 43]. Maternal endocrine status during ovarian maturation can be severely altered by variations in dietary iodine, stress, and other factors. For example, the iodine content of wild marine zooplankton was vastly higher than that of conventional aquaculture feeds, and a 700-fold concentration difference was reported in a comparison with *Artemia*. This difference was reflected in reduced circulating TH levels and an increased frequency of developmental deformities in *Artemia*-fed larval Atlantic halibuts (*Hippoglossus hippoglossus*) [65].

2.9 The net effect of maternally-stimulated sensory, locomotor, and digestive developments

The combined effect of maternally-derived thyroid stimulation during yolk absorption is the maturation of sensory (mechanoreceptor and visual) organs, fins and the swimbladder, and advancement of the timing of the onset of digestive capacity. These maturational events, together with maturation of CNS processing capability, convey a sharply increased degree of larval fitness and a much more likely successful transition to independent feeding.

Nearly complete mortality has been reported for some larval marine teleost cohorts, under both wild and hatchery conditions. In some cases, wild larvae reportedly have nearly no chance of survival during the yolk absorptive and early feeding phases, even in the absence of predators [66]. Early failure of large cohorts profoundly impacts recruitment strength and can shift patterns of speciation. Attention to and management of maternal thyroid provisioning of fish eggs has reportedly increased larval survival by up to five-fold [42].

The survival value imparted by endocrine regulatory contact with mother fishes has probably been a driving factor in the emergence of viviparity, which has occurred repeatedly among phylogenetically diverse fishes [23]. Prolonging the exposure of offspring to maternal hormones can result in nearly complete survival among the relatively mature K-selected progeny of live-bearing fishes. More primitive shark species are oviparous, but in the relatively modern viviparous placental sharks, maternal thyroid hormones are transferred to developing larvae over longer periods of time, where they promote advancements of growth, maturation, and development of juveniles [67].

Rudimentary signaling is done in echinoderms with iodinated tyrosine, in some cases with double-stranded thryoxin molecules. Protochordates show a leap forward with an actual organ, the endostyle, and production of T_4, T_3, peripheral deiodination and deamination and TRIAC signaling. However, neither of these are subject to the fine regulation found in vertebrate thyroid systems. Fishes evolved numerous thyroid-related mechanisms that are characteristic of sophisticated vertebrate endocrine systems, including efficient hormone synthesis with thryoglobulin (T_G), pituitary control of TH synthesis, hypothalamic control of pituitary regulatory mechanisms, sensitive multi-level feedback adjustment to regulate hormone synthesis and secretion, binding proteins, multiple hormone receptors, and an elaborate system of regulatory devices involved in the peripherial processing of TH. These can alter the ratios of highly biologically active T_3 to the much less potent T_4, as one means of fine-tuning local hormone concentrations and resultant levels of hormone activity. Most T_3 is derived from the deiodination of T_4, and monodeiodination can generate the much more highly biologically active T_3. It is also possible to deiodinate T_4 into the biologically inactive isomer reverse-T_3 (rT_3), as reported in some teleosts [68]. For these reasons T_4 has become recognized as essentially a prohormone that is capable of being processed into alternative endocrine products [69] with variable degrees of bioactivity. One net effect is that changing T_3/T_4 ratios can be precisely regulated as needed, and these ratios serve in higher vertebrates as indicative of metabolic states and thyroid system health.

Regulation of larval differentiation providing competence for first feeding is subject to some degree of plasticity. Glucocorticoids have some capacity to alter thyroid system activity by influencing the deiodination mechanisms mentioned above, thereby increasing the magnitude of generation of T_3. It has been proposed that alterations in maternally-circulating cortisol and other glucocorticoids can modify thyroid system function in ways that have adaptive value to fish embryos and larvae [70], by accelerating or delaying larval metamorphoses. Small alterations in the rate or timing of development can result in disproportionately large changes in anatomical or physiological outcomes, contributing importantly to adaptive radiation [52]. Integration of patterns of change in circulating thyroid and corticoid hormones have been reported in amphibian and flatfish metamorphoses, and the two endocrine systems are suspected to be functionally integrated [71].

An endocrine system with such precise control mechanisms emerged in fishes with a vital protective role toward offspring, and has been conserved. The finely-tuned control of thyroid bioactivity described above was adapted in a straightforward manner to the roles TH play in thermogenesis among birds and mammals [72].

Among important cellular mechanisms of action of maternal TH signals, many are mediated by hormonal stimulation of mitochondria. We have reported both the proliferation and activation of mitochondria in larvae in response to maternal TH signals, particularly in the intestine, the swimbladder, and neuromast cells of the lateral line [72]. Mitochondrial stimulation appears to be the basis for controlled thermogenesis in mammals, in specially-adapted brown fat tissues that evolved. It therefore appears likely that the elaboration of thyroid function initially for the enhancement of larval survival at the time of first feeding provided the mechanistic and regulatory basis needed for the later genesis of precisely-controlled thermogenesis.

3. Evolutionary implications of maternal thyroid contributions

Maternal/larval regulatory signaling has been described with an emphasis on the emergence of such interactions in advanced invertebrates, protochordates and lower vertebrates. This relationship has profound survival implications and has been retained and amplified in higher vertebrates, including humans. Comparative views of the origin and prototypical functions of physiological and biochemical interactions during development are briefly summarized in **Table 1**; a comparative perspective can be of substantial practical value [52].

Among reproducing fishes, a suite of adaptive developmental changes profoundly alters the likelihood of a successful transition from yolk absorption to exogenous feeding. Survival of this process is most likely if sensory, swimming, and digestive physiology are activated simultaneously prior to or at the time of first feeding. Visual and lateral line sensitivity, functional fins, a fully-inflated swim bladder, and the maturation of digestive enzyme secretory capability all contribute to the acquisition of nutrients after the exhaustion of yolk supplies. The development and early maturation of all of these physiological systems is under the control of thyroid signals of maternal origin that are deposited in yolk. Deficiencies of maternally-derived TH can have lethal consequences, especially in the transition to first-feeding. None of these peripheral or mechanistic functionalities are of value without effectient central processing, and regulation of the early maturation of the CNS is a major role of maternal endocrine regulation.

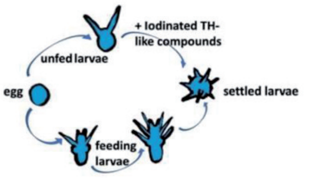
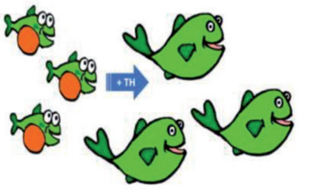
Taxonomic group		
Some echinoderms	**Fishes**	**Mammalia (humans)**
		
Outcomes		
↑ Metamorphosis, settlement independent of larval feeding	↑ survival of larval metamorphosis	↑ early growth, robust neuromuscular health
Maternally-derived chemical messengers		
TH-like iodinated peptides	Thyroid Hormones, cortisol	Thyroid Hormones, cortisol
Adaptive advantages, survival implications		
induction of metamorphosis control of settlement control, onset of feeding	CNS maturation sensory, motor integration	CNS maturation cognitive ability
New hormone targets, maturational processes		
metamorphic regulatory genes	swim bladder inflation digestive enzyme synthesis nutrient absorption lateral line function eye maturation mouth and teeth differentiation fins & locomotor mechanisms	respiratory function neural, physical integrity vigorous development sensory integration
Mechanisms evolved		
control of larval settlement	regulation of metamorphosis thyroid follicles pituitary hypothalamic control TH system feedback peripheral processing	thermoregulation

Table 1.
Evolutionary advancement of maternal regulation of larval/fetal ontogeny.

Maternal hormonal regulation of the fitness of offspring is so directly relevant to survival that it has been retained and amplified throughout vertebrate evolution. Specific consequences of neonatal hypothyroidism are numerous and can collectively be lethal, whether considered in the context of larval fishes or human infants. Central nervous system differentiation, the maturation of sensory, digestive, and locomotor organ systems all respond to maternal signaling, and they collectively facilitate transitions from embryonic and larval existence to more autonomous juvenile life.

4. Conclusions

Antioxidant functions of iodine generated a set of benefits to the parental transfer of iodinated compounds to offspring, eventually giving rise to the use of iodinated tyrosines for this purpose. These iodinated amino acids, in some cases in the form known in vertebrates as thyroid hormones, assumed signaling roles in some echinoderms, triggering metamorphic changes and alterations of modes of feeding. These signal-driven changes had substantial phenotypic value with advantages to survival, and consequently have been observed multiple times in echinoderms and chordates. Maternal provisioning of fish eggs provides a means of promoting development, altering the timing of metamorphosis and enhancing survival at the time of first-feeding, with some degree of plasticity. Regulatory maternal endocrine relationships with offspring have been retained in humans and other vertebrates, in which they are essential for normal development and survival.

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Conflict of interest

The authors declare no conflict of interest.

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