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Evolution of thyroid hormone distributor proteins

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ABSTRACT

Thyroid hormones (THs) are evolutionarily old hormones, having effects on metabolism in bacteria, invertebrates and vertebrates. THs bind specific distributor proteins (THDPs) to ensure their efficient distribution through the blood and cerebrospinal fluid in vertebrates. Albumin is a THDP in the blood of all studied species of vertebrates, so may be the original vertebrate THDP. However, albumin has weak affinity for THs. Transthyretin (TTR) has been identified in the blood across different lineages in adults vs juveniles. TTR has intermediate affinity for THs. Thyroxine-binding globulin has only been identified in mammals and has high affinity for THs. Of these THDPs, TTR is the only one known to be synthesised in the brain and is involved in moving THs from the blood into the cerebrospinal fluid. We analysed the rates of evolution of these three THDPs: TTR has been most highly conserved and albumin has had the highest rate of divergence.

1. Thyroid hormones

Thyroid hormones (THs) are derived from tyrosine residues and have a biphenolic structure with iodines substituted at specific places on the inner and outer rings. There are two main forms of thyroid hormones: 3′,5′,3,5-tetraiodo-L-thyronine (thyroxine, T4) and 5',3,5-triiodo-L-thyronine. In most vertebrates, THs are synthesised in the thyroid gland. However, many vertebrates (e.g. several groups of fish including cyclostomes, elopomorpha and spariformes) do not have a succinct, compact thyroid gland such is found in amphibians, reptiles, birds and mammals, but have diffuse islets of scattered thyroidal cells spread in the branchial region. A total of five distinct thyroidal patterns were determined from a total of 288 vertebrate species examined (Chanet and Meunier, 2014). Nevertheless, these cells synthesise thyroid hormones similarly to those in compact thyroid glands of other vertebrates such as humans.

Newly synthesised THs (predominantly T4) are secreted from thyroidal cells into the blood via TH transmembrane transporters (Hennemann et al., 2001). THs are then distributed from their site of synthesis via the blood to their target cells. In blood, >99% of THs are bound to specific THDPs, leaving only a very small fraction in the free form, which is able to enter target cells via TH transmembrane transporters. T4 is the main form of TH in the blood and in general has higher affinity than T3 for the THDPs whereas T3 has higher affinity than T4 for the thyroid hormone nuclear receptors (TRs) (Sandler et al., 2004). Inside the target cells, a family of deiodinases (D1, D2, D3) can act to either activate T4 to T3 (which has higher affinity for the TRs than T4) or inactivate T4 to rT3 (which does not activate TRs). About 80% of T3 is derived by the deiodination of T4 by specific deiodinases in the target tissues (van Doorn et al., 1985). THs in the cell can bind to cytosolic TH binding proteins (Yamauchi and Tata, 2001). Ultimately, T3 will bind to a TH receptor (TR), enter the nucleus and dimerise on the thyroid hormone response element (TRE). This will initiate association/dissociation of co-modulator proteins and the regulation (either up-regulation or down-regulation, depending on the TRE) of transcription of TH-responsive genes will proceed. Examples of positively regulated genes are those coding for malic enzyme in the liver and myelin basic protein in the brain, whereas the genes coding for thyrotropin in the anterior pituitary and β-myosin heavy chain in the heart are inhibited by T3 (Samuels et al., 1988) (and references therein).

In addition to the well-studied thyroid hormone receptor-mediated genomic actions of thyroid hormones, there are also many non-genomic actions. These include cytosolic kinase-

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initiated interactions that alter glucose metabolism (Moeller et al., 2006, 2011), membrane-initiated mechanisms via binding to specific integrins (Davis et al., 2005, 2011; Lin et al., 2012) and activation of kinases in mitochondria that alter fatty acid metabolism (Sayre and Lechleiter, 2012).

Thyroid hormones impact the metabolism of a wide variety of organisms from bacteria (Distefano et al., 1993) through to all vertebrates (Hulbert, 2000). In vertebrates, thyroid hormones greatly impact on growth and development, particularly of the brain. Therefore, it is vitally important that the THs are distributed accurately and in appropriate quantities (which vary during development) from their site of synthesis to their target cells. This important function of the distribution of THs, from their site of synthesis to their target cells, is carried out by the THDPs: albumin, transthyretin (TTR) and thyroxine-binding globulin (TBG).

2. THDPs

A clear demonstration of the role of THDPs was published by the lab of Carl Mendel (Mendel et al., 1987), where rat livers were perfused with ^{125}I-T4. In the first case, the perfusion medium did not contain THDPs and the ^{125}I-T4 partitioned into the first cells it came in contact with. However, in the second case, where the perfusion medium contained THDPs, there was an even distribution of THs throughout the liver lobule and there was still ^{125}I-T4 in the perfusate. This clearly demonstrated that the function of THDPs is to prevent avid partitioning of THs into cell membranes and to ensure a pool of sufficient size in the circulation.

The THDPs in human blood are albumin (42 g/l), transthyretin (TTR; 0.25 g/l) and thyroxine-binding globulin (TBG; 0.015 g/l). Together, these three proteins bind 99.97% of T4 and 99.70% of T3 (Mendel, 1989), thus, only a very small fraction of total TH in blood is in the free form and available to enter cells. These three THDPs have distinctly different affinities for THs: albumin has lowest affinity for T4 (7.0×10^5 M^{-1}) and T3 (1.0×10^5 M^{-1}); TTR has intermediate affinity for T4 (7.0×10^7 M^{-1}) and T3 (1.4×10^7 M^{-1}) and TBG has highest affinity for T4 (1.0×10^{10} M^{-1}) and T3 (4.6×10^8 M^{-1}) (Robbins and Edelhoch, 1986). Thus, the combination of the three THDPs with differing affinities for THs results in a buffering system to maintain the concentration of free TH constant (Schreiber and Richardson, 1997). In this respect, THs differ to many other hormones, whose concentrations cycle. However, a small but significant amount of THs are distributed via high density and low density lipoproteins (Benvenga et al., 2002). In certain disease states (e.g. Waldenström's disease (Trimarchi et al., 1982)) and many other conditions (see (Koulouri et al., 2013; Zouwail et al., 2008)), THs bind autoantibodies which cause results of thyroid function tests to be inconsistent with each other, or result in data from thyroid function tests being inconsistent with the clinical picture of the patient. Such situations are confusing to clinicians and guidelines have been established for interpretation of such discordant thyroid function tests (e.g (Koulouri et al., 2013).).

Albumin binds about 10% of TH in the blood, TTR binds about 15% and TBG binds about 75%. Consequently, it was believed by some that TBG was the most important THDP, because it bound most TH. However, this situation is analogous to Goldilocks and the Three Bears: TBG binds THs so tightly that its delivery of THs to tissues is minimal, albumin binds so weakly that it does not distribute the bound TH far, whereas TTR (with intermediate affinity) is just right, responsible for most of the bioavailability of THs to tissues (Robbins, 2000). For a more detailed discussion about THDP-TH dissociation rates, the free hormone hypothesis and the free hormone transport hypothesis, see (Richardson, 2007).

2.1. Sites of THDP synthesis in vertebrates

2.1.1. Albumin

The first known description of albumin was by Hippocrates in about 400 AD, who noted foam on urine of a patient with kidney disease (see (Peters, 1992a)). The only well characterised site of albumin synthesis is the liver (Schreiber et al., 1976), which is responsible for synthesis of all plasma proteins (see (Schreiber, 1987)). From the liver, albumin is secreted into the bloodstream where it is involved in distributing THs, steroids, fatty acids, divalent cations, bilirubin and other compounds (see (Peters, 1992b)). There are many cases of people who are analbuminemic, many of whom are asymptomatic and of those with symptoms, edema appears to be the most common (albumin.org). The molecular mass of albumin is about 68 kDa and it has a half-life of approximately 15 days in human blood. Albumin has been shown to bind THs in the blood of many groups of vertebrates including fish, amphibians, reptiles, birds and mammals (Farer et al., 1962; Larsson et al., 1985; Prapunpoj et al., 2000a; Richardson et al., 1994; Richardson et al., 1996; Tanabe et al., 1969).

2.1.2. TTR

TTR was first identified in cerebrospinal fluid (CSF) and in serum in 1942 (Kabat et al., 1942a, 1942b; Siebert and Nielson, 1942). TTR was originally called “prealbumin” (abbreviated as “PA”) as it was the only protein in serum to migrate ahead of albumin under the standard electrophoretic conditions of the time. Its name changed to “thyroxine-binding prealbumin” (TBPA) after Ingbar discovered that it bound thyroid hormones (Ingbar, 1958). In 1969, TBPA was found to bind retinol-binding protein (RBP) (Raz and Goodman, 1969) and its name was finally changed to “transthyretin” to describe its roles in TRANSport of THYroid hormones and RETINol-binding protein (Nomenclature, 1981). As new functions are being described for TTR (see (Alshehri et al., 2015)), we now know that its current name only describes two of its roles in blood and cerebrospinal fluid. However, as this review focusses on the evolution of TH distributor proteins, only the TH binding function of TTR will be considered here. TTR is a non-glycosylated homo-tetramer whose molecular mass is about 60 kDa.

TTR synthesis has been described in many tissues including the liver (Schreiber et al., 1976), choroid plexus (Dickson et al., 1985), placenta (McKinnon et al., 2005), visceral yolk sac (Sklan and Ross, 1987; Soprano et al., 1986), retinal pigment epithelia (Cavallaro et al., 1990; Ong et al., 1994), ciliary pigment epithelia (Kawaji et al., 2005), intestine (Loughna et al., 1995), pancreas (Kato et al., 1985), meninges (Blay et al., 1993) and neurons (Li et al., 2011). In terms of evolutionary studies, the synthesis of TTR by the liver (often inferred by the presence of TTR in serum) and by the choroid plexus (sometimes inferred by the presence of TTR in CSF) have been investigated in greatest detail. Many of the other tissues that synthesise TTR have only been studied in mammals and a few non-mammalian vertebrates. Therefore, this review will focus on the evolution of TTR synthesis by the liver and by the choroid plexus.

TTR synthesised by the liver is secreted into the bloodstream where it is involved in distributing THs and has a half-life of about 2 days in human blood. In this regard, TTR has a complementary role to those of albumin and TBG: each of the three THDPs have differing affinities for THs and are present in different concentrations in the blood.

The choroid plexus is a villous structure located in the lateral, third and fourth ventricles of the brain and forms the main component of the blood-CSF barrier. The barrier properties of the epithelial cells of the choroid plexus ensure that the composition of the blood and of the CSF are kept discrete. Moreover, the choroid plexus secretes about 70% of the CSF (Cserr, 1971). TTR is

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