Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 735–747

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Inherited defects of thyroxine-binding proteins

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ARTICLE INFO

Article history:
Available online 30 September 2015

Keywords:
thyroid hormone transport proteins
thyroxine-binding globulin
transthyretin
human serum albumin
TBG deficiency
familial dysalbuminemic hyperthyroxinemia
mutations

Thyroid hormones (TH) are bound to three major serum transport proteins, thyroxine-binding globulin (TBG), transthyretin (TTR) and human serum albumin (HSA). TBG has the strongest affinity for TH, whereas HSA is the most abundant protein in plasma. Individuals harboring genetic variations in TH transport proteins present with altered thyroid function tests, but are clinically euthyroid and do not require treatment. Clinical awareness and early recognition of these conditions are important to prevent unnecessary therapy with possible untoward effects. This review summarizes the gene, molecular structure and properties of these TH transport proteins and provides an overview of their inherited abnormalities, clinical presentation, genetic background and pathophysiologic mechanisms.

Introduction

Thyroxine (T_4) has a long half-life and a high serum concentration. These features are attributed to binding of the majority of T4 and the principal iodothyronines [triiodothyronine (T_3) and reverse T_3 (rT_3)] to three serum thyroid hormone (TH)-binding proteins, thyroxine-binding globulin (TBG),

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http://dx.doi.org/10.1016/j.beem.2015.09.002
1521-690X/

transthyretin (TTR) and human serum albumin (HSA) [1]. Binding of TH by other serum proteins (high density lipoproteins) is considered negligible without biological relevance. Although HSA is the most abundant TH-binding protein, its affinity for TH is significantly lower compared to that of TBG. The affinity of TBG to T_4 is 50- and 7000-fold higher than that of TTR and HSA respectively (Table 1).

These proteins function mainly as a buffer system to maintain a large extrathyroidal TH pool and stable free T_4 concentration. Only 0.03% of total serum T_4 and 0.3% of total serum T_3 are in an unbound form. In the absence of TH-binding proteins – with TBG being the major TH carrier – any abrupt decrease in TH secretion would result in a rapid depletion of the extrathyroidal T_4 pool. Additionally, TH-binding proteins may serve as a protective mechanism against urinary iodine loss. A third proposed function involves the uniform distribution of TH across cells, which enhances tissue sensitivity to circulating TH levels [2]. Lastly, TH-binding proteins may be subject to conformational changes in pathological states and regulate TH delivery to tissues. Indeed, TBG is cleaved by leukocyte elastase at sites of inflammation, which reduces its affinity for TH [3].

Abnormalities in TH-binding proteins do not result in thyroid dysfunction but rather to altered serum TH concentrations, which may be misinterpreted and lead to unneeded treatment and side effects. When the affinity for TH is impaired, assays used in clinical practice to estimate free TH levels commonly yield spurious results. In such circumstances measurement of free TH concentration by equilibrium dialysis or ultrafiltration is recommended.

Serum TH-binding protein abnormalities, both acquired and inherited, are characterized by hyper- or hypo-iodothyroninemia, while subjects are clinically euthyroid [4]. However, it is possible that other thyroid disease, such as thyrotoxicosis or hypothyroidism, may be concurrently present and further perplex both diagnosis and management [5]. The aim of this review is to provide an update on the heritable defects of serum TH-binding proteins, their structure, genetic background, laboratory tests and consequences.

Thyroxine-binding globulin (TBG)

The molecule, gene and properties

TBG is a 54 kDa single polypeptide chain synthesized by the liver. The pre-protein is an acidic glycoprotein of 415 amino acids (aa). The mature molecule (395 aa, minus the signal peptide) has four N-linked oligosaccharides. The latter are important for the correct post-translational folding and secretion of TBG and are responsible for the microheterogeneity of TBG when subjected to isoelectric

Table 1
Some properties and metabolic parameters of the principal TH-binding proteins in serum.

	TBG	TTR	HSA
Molecular weight (kDa)	54[a]	55	66.5
Structure	Monomer	Tetramer	Monomer
Carbohydrate content (%)	20	0	0
Number of binding sites for T_4 and T_3	1	2	4
Association constant, K_a (M^{-1})			
For T_4	1×10^{10}	2×10^{8}[b]	1.5×10^{6}[b]
For T_3	1×10^{9}	1×10^{6}	2×10^{5}
Concentration in serum			
Mean normal (mg/liter)	16	250	40,000
Total T_4 binding capacity (mg T_4/liter)	0.2	3	>1000
Relative distribution of T_4 and T_3 in serum (%)			
For T_4	75	20	5
For T_3	75	<5	20
Half-life (days)	5[c]	2	15
Degradation rate (mg/day)	15	650	17,000

[a] Apparent molecular weight on acrylamide gel electrophoresis 60 kDa.
[b] Value given is for the high affinity binding site only.
[c] Longer under the influence of estrogen.