Review

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Transthyretin: a multifaceted protein

Abstract: Transthyretin is a highly conserved homotetrameric protein, mainly synthetized by the liver and the choroid plexus of brain. The carrier role of TTR is well-known; however, many other functions have emerged, namely in the nervous system. Behavior, cognition, neuropeptide amidation, neurogenesis, nerve regeneration, axonal growth and 14-3-3ζ metabolism are some of the processes where TTR has an important role. TTR aggregates are responsible for many amyloidosis such as familial amyloidotic polyneuropathy and cardiomyopathy. Normal TTR can also aggregate and deposit in the heart of old people and in preeclampsia placental tissue. Differences in TTR levels have been found in several neuropathologies, but its neuroprotective role, until now, was described in ischemia and Alzheimer's disease. The aim of this review is to stress the relevance of TTR, besides its well-known role on transport of thyroxine and retinol-binding protein.

Keywords: Alzheimer; amyloid; ischemia; nerve regeneration; nervous system.

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Introduction

In 1942, a protein migrating ahead of albumin during electrophoresis of human plasma (1) and cerebrospinal fluid (CSF) (2) samples, was identified and denominated 'prealbumin'. The discovery that prealbumin could bind thyroid hormones (THs) led to a change of its name to 'thyroxine-binding prealbumin' (TBPA) (3). Later, it was found that TBPA could also bind retinol-binding protein (RBP) (4). In 1981, the International Union of Biochemists adopted the name 'transthyretin' (TTR) (5) because of its well-known role in the transport of the THs thyroxine and retinol (vitamin A) through binding to RBP.

TTR is a highly conserved protein that is found in several vertebrate species (6, 7). Recently, sequences homologous to TTR, known as transthyretin-like proteins (TLPs), have been found in bacteria, nematodes and plants. In *Escherichia coli* and *Caenorhabditis elegans* TLPs form homotetramers, like TTR, although without the ability to bind T_4 (8).

Structure

The first X-ray crystal structure of TTR was reported in 1971 (9). TTR is a 54,980 Daltons (Da) homotetrameric protein; each subunit has 13,745 Da and is composed of 127 amino acids (10). Native TTR has a globular shape with an overall size of 70 Å×55 Å×50 Å and a central hydrophobic channel. Each monomer consists of eight antiparallel β-strands (A through H), which are organized into two four-stranded β-sheets (DAGH and CBEF) and only a short α-helix located on β-strand E (11). A dimer is formed when β-strands F and H of each subunit interact by hydrogen bonds. Tetramer formation results from interaction of the residues of the loops that join β-strands G to H and A to B. It is known that low pH promotes the dissociation of TTR tetramer into monomers. The neutral crystal structure of TTR demonstrated double protonation of His88 to break the hydrogen-bond network, causing destabilization of the TTR tetramer (12).

Expression

TTR is mainly synthetized by the liver (13) and the choroid plexus of brain (14), which are the sources of TTR in plasma and CSF, respectively. In humans, 90% of plasma TTR is secreted from liver and its concentration ranges from 20 to 40 mg/dl (15). TTR levels in plasma change with age: they

are decreased in healthy newborns when compared with adults (16, 17) and start to decline after 50 years of age (18).

Synthesis of TTR by epithelial cells of the choroid plexus is the main source of CSF TTR (14). TTR concentration in CSF ranges from 5 to 20 mg/l (19), representing approximately 25% of the total CSF protein content (20). The choroid plexus has 11 times more mRNA than the liver, normalized for tissue weight, and synthetizes TTR 13 times faster than the liver (21).

TTR synthesis in brain areas, other than the choroid plexus, has been a controversial subject. The presence of TTR mRNA in murine or human brains has been detected in brain areas such as the cortex, hippocampus or cerebellum (22–25). Some authors claimed that brain TTR may be caused by neuronal synthesis of the protein in these tissues; while others proved, by laser microdissection technology and *in situ* hybridization, that TTR is not produced in brain parenchyma, suggesting that TTR contamination by choroid plexus may induce false-positive results concerning sites of TTR synthesis (26).

Besides the liver and the choroid plexus, TTR synthesis has been described in several other tissues. TTR is highly transcribed and translated in the retinal pigment epithelium (RPE), a monolayer of cells that acts as blood barrier for the retina (27). TTR is also produced in the pancreatic islet of Langerhans (α cells) (28, 29), and to a small extent in the heart, skeletal muscle, spleen (30), visceral yolk sac endoderm (31), pineal gland (32) and trophoblasts of human placenta (33). Although the expression of TTR in the stomach was previously described (30), a specific gastric cellular population of ghrelin cells was recently identified as TTR producers (34).

Metabolism

Although TTR production has been extensively studied, its catabolism is not fully understood. The biological half-life of TTR is about 2–3 days in humans (35), 23h in monkeys (36) and 29h in Buffalo rats (37). In 1988, Makover and colleagues demonstrated that the major sites of TTR degradation were the liver, muscle and skin. In their studies, 36–38% of total body TTR degradation occurred in liver, 12–15% in muscle and 8–10% in skin. In kidneys, adipose tissue, testis and gastrointestinal tract (GI), the degradation rate of body TTR was 1–8%, whereas <1% was degraded by the other tissues examined (38). No evidence was found of TTR degradation in tissues of the nervous system. Liver and kidney were the most active organs of TTR catabolism, per gram of wet weight. TTR internalization in liver and kidney is receptor-mediated. Renal uptake of TTR was shown to be megalin-[also known as low-density lipoprotein-related protein 2 (LRP2)] mediated (39). Megalin is an endocytic multi-ligand receptor of the low-density lipoprotein (LDL) receptor family, that is expressed in the epithelium of renal proximal tubes, among other epithelia. Sousa et al. demonstrated that TTR uptake in liver was mediated by a receptor member of LDL family sensitive to receptor-associated protein (RAP) (40). Inhibition of TTR uptake by RAP suggested a common pathway between TTR and lipoproteins metabolism. As megalin is not expressed in liver, further studies need to be performed in order to clarify TTR internalization in this organ.

TTR synthesis and secretion by placental trophoblasts was described (33, 41). Secretion of TTR from trophoblasts to maternal placental circulation is followed by trophoblasts uptake of TTR-T_4 complex to the fetal circulation (42) and is important for fetal development. This uptake was suggested to occur through a LRP receptor.

Functions

TTR has been mainly recognized by its role as a carrier protein of THs and retinol in plasma and CSF. However, during the last years, a role in proteolysis and in several functions in the nervous system has also been proposed.

Transport of T_4

Thyroid hormones are iodinated compounds essential for development, tissue differentiation and regulation of metabolic balance in mammals. In recent years a role in cell migration, signaling, myelination and promotion of neurite outgrowth has also been proposed (43, 44).

The thyroid gland synthetizes three THs: tetraiodothyroxine (T_4), triiodothyronine (T_3) and a biologically inactive reverse T_3 (rT_3).

T_4 is the most abundant TH secreted by the thyroid gland and circulates in plasma bound to thyroid hormone-binding proteins (THBPs) thyroxin-binding globulin (TBG), TTR and albumin. TBG has the strongest affinity to T_4, carrying 65% of the hormone (45); 15% of human plasma T_4 is transported by TTR and about 10% by albumin; finally, 0.03–0.05% circulates unbound or in a free form (46). In rodents, 50% of total T_4 is carried by TTR (47). In CSF of both rodents and humans, TTR is the main carrier of T_4, transporting 80% of the hormone (48). The

homotetrameric structure of native TTR forms a central hydrophobic channel with two binding sites for T_4 (49). As these binding sites exhibit negative cooperativity, just one molecule of T_4 is transported by TTR (50).

The delivery of T_4 in cells is not a consensual subject; while some defend that uptake of T_4 occurs bound to the carrier proteins, others claim that T_4 enters the cell by passive diffusion after dissociation from the carrier protein (51, 52). Studies on TTR null mice (53) support the free T_4 tissue uptake hypothesis. TTR null mice exhibited 50% reduction of total T_4 in blood and 30% in CSF, when compared with wild-type animals, whereas the levels of free T_4 and total circulating T_3 were unaltered. Several parameters measured in this strain of mice indicated the animals to be euthyroid (54). Taken together, the results suggest that TTR is not pivotal to TH metabolism, even in conditions of increased hormone demand as cold exposition or thyroidectomy (55).

The redundant role of TTR was also described for other THBPs, such as albumin in rats (56) and TBG in humans (57, 58). A critical role for TTR on T_4 transport across the placenta and delivery to the fetus was recently described (42, 59). Further studies need to be performed to clarify the role of TTR on T_4 delivery into tissues.

Transport of retinol

Retinol, or vitamin A, and related metabolites are obtained from the diet. Oxidation of retinol originates retinoic acid, which is very important in several functions including vision, reproduction, growth and development (60). It also modulates neurogenesis, neuronal survival and synaptic plasticity in hippocampus, olfactory bulb and hypothalamus (61). Retinoids can regulate cell differentiation, neurite outgrowth and protection against oxidative stress (62). Several studies suggest vitamin A as a possible therapeutic agent in Alzheimer disease (AD): (i) the disruption of retinoid signaling induced deposition of Aβ in the cerebral blood vessels (63); (ii) vitamin A inhibited amyloid fibril formation (64) and (iii) *in vivo* studies revealed that administration of vitamin A decreased Aβ deposition and improved spatial learning and memory (65).

The transport of retinol in circulation occurs through RBP (66). This molecule is mainly synthetized in the liver and secreted to plasma after retinol binding. TTR associates to the RBP-retinol complex before secretion into the plasma (4). The TTR-RBP complex is a very stable form of retinol transport, allowing its delivery to cells and is important to prevent RBP from being filtered and degraded in the kidney (67, 68).

TTR tetramer has four RBP-binding sites, two in each dimer at the protein's surface; because of steric hindrance, just two RBP are transported by each TTR molecule. Under physiological conditions, due to low RBP levels comparatively with TTR, just one molecule of RBP is transported by the TTR tetramer (69, 70). T_4 binding to TTR is not influenced by RBP binding (4).

Studies in TTR null mice showed a dramatic reduction of retinol and RBP plasma levels (around 95%) when compared with wild-type littermates. This finding could be explained by increased renal filtration of the retinol-RBP complex (70). Increased hepatic RBP levels were found in TTR null mice (71). However, *in vitro* and *in vivo* studies demonstrated that RBP liver secretion from plasma was unchanged (70), which indicates that diminished levels of RBP and retinol in plasma are not caused by a failure in secretion.

Symptoms of vitamin A deficiency, such as weight loss, infections and eye abnormalities were not observed in TTR mutant mice (70), suggesting that TTR role on RBP-retinol transport, does not play a critical role on retinol metabolism.

Retinol uptake was suggested to be mediated by a TTR-independent membrane receptor (72). Stra6 (a multitransmembrane domain protein) was reported as a mediator of RBP4 binding to cell membranes and as crucial for cellular uptake of retinol (73). Moreover, a new retinol transporter has recently been identified, RBPR2, and suggested to play a role in retinol absorption (74).

Proteolytic activity

Another important function of TTR besides its role in transport of T_4 and retinol is its proteolytic activity on several substrates. A small fraction of plasma TTR (1–2%) is carried by high-density lipoproteins (HDL) through binding to apolipoprotein (apo) A-I (75). The TTR-apoA-I interaction was further investigated and TTR was described as a non-canonical serine protease capable to cleave apoA-I carboxyl terminal domain (76) and to reduce cholesterol efflux (77). TTR has also the ability to cleave neuropeptide Y (NPY) (78) and Aβ peptide (79). Cleavage of Aβ can occur at several different sites, and the resulting peptides were shown to have decreased amyloidogenic potential when compared with the complete peptide. TTR was also able to degrade aggregated forms of Aβ; inhibition of TTR activity resulted in increased Aβ fibril formation (79). TTR proteolytic role on NPY and Aβ peptide need further investigation to determine its functional role in the nervous system.

TTR in the nervous system

Several studies have shown different roles for TTR in nervous system physiology. Behavior, cognition, neuropeptide amidation, neurogenesis, nerve regeneration, axonal growth and 14-3-3ζ metabolism are some of the known processes influenced by TTR as studied in TTR null mice.

TTR null animals are viable, phenotypically similar to wild-type and heterozygous littermates, and fertile (53). This strain presents reduced signs of depressive-like behavior, increased exploratory activity and anxiety (80). Increased levels of norepinephrine in the limbic forebrain could be a possible explanation for the observed phenotype. TTR null mice presented increased levels of NPY in dorsal root ganglia (DRG), sciatic nerve, spinal cord, hippocampus, cortex and CSF ascribed to up-regulation of peptidylglycine α-amidating monooxygenase (PAM) – the only enzyme that amidates neuropeptides, being crucial for the maturation process of NPY (81, 82). These findings corroborate the importance of TTR in modulating depressive behavior.

Cognitive performance analysis of young/adult TTR null mice showed memory impairment when compared with wild-type littermates (24, 83, 84). With aging, TTR wild-type animals presented worsened cognitive performance, attributable to reduced levels of CSF TTR, a fact that enhances the important role of TTR in cognition (83).

Increased locomotor activity in young/adult TTR null animals was confirmed by Fleming et al.; in older mice, a sensorimotor impairment was observed (85). No morphological differences in sciatic nerves and cerebellum were found in TTR null animals that could explain the absence of sensorimotor impairment at young ages. However, under nerve crush conditions, absence of TTR slowed nerve regeneration (85). TTR null mice have slower recovery of locomotor activity and slower nerve conduction velocity. Neuropathological parameters such as decreased levels of myelinated and unmyelinated axons were also observed in TTR null animals when compared with wild-type littermates. TTR properties as a nerve regeneration enhancer were further demonstrated when TTR delivery to crushed sciatic nerves rescued the regeneration phenotype of TTR null animals (86).

TTR has also the capacity of inducing neurite outgrowth in DGR and PC12 cells, independently of its ligands (85). Neuritogenic activity of TTR in DRG neurons depends on its internalization, a process that is clathrin-dependent and megalin-mediated. *In vivo* studies in a mouse model with reduced levels of megalin, demonstrated decreased nerve regeneration capacity. Thus, reduced megalin levels impair TTR action as an enhancer of regeneration (86).

The binding of TTR to glucose-regulated protein (Grp)78 at the plasma membrane of β-cells and its internalization was recently demonstrated (87) and hypothesized to be essential for insulin release and protection against β-cells apoptosis (88).

Finally a role for TTR in 14-3-3ζ metabolism has been suggested. Hippocampus of young TTR null mice presented lower levels of 14-3-3ζ protein, but no changes in gene expression. Lysosomal degradation of 14-3-3ζ in the absence of TTR was the mechanism proposed for the reduced 14-3-3ζ levels (89). Hippocampal slice cultures of TTR null mice did not present increased cellular death when compared wild-type animals (90), suggesting that the decreased levels of 14-3-3ζ observed in these animals are not associated with increased cellular death. Furthermore, in Creutzfeldt-Jakob disease patients, 14-3-3 proteins are used as a surrogate marker for the *in vivo* diagnosis of the disease, whereas TTR levels are the same as compared with healthy controls (91, 92). Taken together, these results suggest that the regulation of 14-3-3ζ levels by TTR is not associated with cellular death. Further studies should be performed to dissect the mechanism and the consequences of this regulation.

TTR in diseases of the nervous system

Differences in TTR levels and/or increased oxidation are found in several neuropathologies, such as Guillain-Barré syndrome (GBS), frontotemporal dementia (FDT), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). In GBS and FDT, TTR levels are elevated as compared to controls, in plasma and CSF (93, 94), whereas in ALS TTR was up regulated in rapid progression of the disease when compared with slow progression of the disease (95). Finally, plasma and CSF from PD patients present increased TTR levels when compared to controls, which led to suggest TTR as an early marker of the disease (96). Further studies should be performed in order to dissect the underlying mechanisms behind TTR role in PD.

The neuroprotective role of TTR in the central nervous system has been described in more detail in ischemia and AD and will be discussed in the next sections.

Cerebral ischemia

Ischemia is a significant cause of brain injury worldwide, leading to high mortality, physical and cognitive incapacities. TTR was identified as being differentially expressed in fluids or tissues after ischemia (97–99) and a mice model of permanent middle cerebral artery occlusion (pMCAO) showed TTR as a neuroprotective molecule. TTR null mice heterozygous for heatshock transcription factor 1 (HSF1) ($TTR^{-/-}$/$HSF1^{+/-}$) presented increased infarct area, cerebral edema and microglial-leukocyte response when compared with TTR wild-type animals ($TTR^{+/+}$/$HSF^{+/-}$), 24h after pMCAO. Interestingly, TTR was localized in disintegrated β-tubulin III-positive neurons and cell debris. Elimination of TTR secreted by liver after treatment with RNAi had no effect on the distribution of TTR in endangered neurons, indicating that TTR mobilization to neurons was of CSF origin. These results suggested the neuroprotective role of CSF TTR in cerebral ischemia (100).

An epidemiologic study revealed that the population heterozygous for T119M (a TTR mutant with increased tetrameric stability) have decreased risk of cerebrovascular disease and increased life expectancy when compared with noncarriers individuals (101).

The mechanisms behind these observations warrant further investigation.

Alzheimer's disease

AD is the most common form of dementia, affecting millions of people worldwide. The two main histopathological marks of AD are neurofibrillary tangles (aggregates of hyperphosphorylated tau protein) and senile plaques (aggregates of Aβ peptide) (102).

A role for TTR in AD has been suggested by several groups. The first description of decreased TTR levels in CSF of AD patients dates back to 1986 (103). Recently, with the use of powerful tools, a 2-fold decrease in TTR levels in CSF of AD patients was demonstrated (92, 104). As observed in CSF, TTR plasma levels are decreased in AD patients and mild-cognitive impairment (MCI) when compared with non-demented controls, suggesting TTR as an early AD biomarker (105, 106).

TTR is able to bind Aβ peptides, preventing the formation of amyloid fibrils (107). Analysis of Aβ aggregation kinetics, showed that, in the presence of TTR, the aggregation rate of this peptide is decreased (108).

Animal models of AD are a useful tool to dissect the mechanism behind the disease. Different animal models have been used but TTR role in AD is controversial.

Initially, a protective role of TTR was described in APP_{swe}/*PS1ΔE9* animals. In this strain of mice [double transgenic mice expressing the human amyloid precursor (APP) with a Swedish mutation and a human presenilin (PS) deletion] Aβ and amyloid deposits were decreased when the animals were exposed to an enriched environment (large cages, running wheels, colored tunnels, toys, and chewable material), which was attributable to TTR up-regulation (109). When these animals were in a heterozygous background for endogeneous TTR (half dose TTR), Aβ levels and deposition were increased in the hippocampus and cortex as compared with their TTR wild-type animals littermates (110). Moreover, TTR neuroprotection in AD was also observed in female APP/PS double transgenic mice bearing a PS A24E mutation; female heterozygous animals for TTR presented increased levels of Aβ42 when compared with TTR wild-type female littermates whereas no differences were found in males of the different genotypes (111). The neuroprotective role of TTR in AD was further corroborated by overexpression of human TTR in the APP23 mouse model (that expresses human APP), leading to decreased Aβ levels and deposition and improved cognition (24).

By contrast, other studies revealed a harmful role of TTR in AD. In the Tg2576 mouse model (transgenic mutant APP), absence of TTR was associated with decreased vascular Aβ burden (112). Moreover, studies in the TgCRND8 mouse strain (strain carrying combined APP mutations), demonstrated that reduction of TTR levels decreased Aβ plaque burden in the hippocampus of 4-month-old animals (113).

All together, the observed effects in the different mice strains, call attention to the interplay of genetic, hormonal and environmental factors known to exist in a complex disease such as AD.

Recently, it was demonstrated that administration of the TTR tetrameric stabilizer iododiflunisal (IDIF) to APP// PS A246E mice, heterozygous for TTR, decreased Aβ deposition and improved cognitive functions (114). Stabilization of TTR through IDIF seems to be a good mechanism to design drugs to AD treatment and sets the basis for further experiments with different TTR tetrameric stabilizers classes.

TTR as an amyloidogenic protein

When the word 'transthyretin' is mentioned, the first pathology that emerges is systemic amyloidosis. TTR

is the causative agent of a special group of diseases of protein aggregation associated with amyloid fibril deposition. The amyloidoses comprise a spectrum of diseases, either acquired or hereditary, characterized by the extracellular deposition of fibrillar material in specific organs and tissues in the form of amyloid. These fibrils are 7–10 nm wide, rigid, non-branching and are of variable lengths with a typical twisted β-pleated-sheet structure. They present unique tinctorial properties, such as apple-green birefringence under polarized light upon staining with Congo red. The excessive accumulation of these amyloid fibrils gives rise to abnormalities in the function of affected organs. Several apparently nonrelated proteins can be found as main constituents of amyloid fibrils, and this chemical heterogeneity is associated with specific clinical forms of amyloidosis.

Most forms of TTR amyloidosis are hereditary in an autosomal dominant manner; Andrade described the first form of an hereditary amyloidosis in the Northern area of Portugal, near Porto, in family members with age of onset of clinical symptoms in the third to fourth decade of life, nominated familial amyloidotic polyneuropathy (FAP) (115). Early impairment of temperature and pain sensation in the feet, and autonomic dysfunction leading to paresis, malabsorption, emaciation and death were typical clinical features (116, 117). The genetic defect in these Portuguese families has been ascribed to a single point mutation in the *TTR* gene, originating a mutant TTR (TTR Val30Met) by far, the most frequent TTR mutation associated with FAP in Portugal and elsewhere (118). Over 100 different TTR mutations have been described (119), some of these are associated with FAP clinically, not differing from the original description of the disease; others give rise to variable phenotypes, such as the presence of both neuropathy and cardiomyopathy, presentation of carpal tunnel syndrome, predominant vitreous TTR deposition and leptomeningeal involvement. A few TTR mutations are related to cardiomyopathy without neurological symptoms [familial amyloidotic cardiomyopathy (FAC)]. The most common *TTR* mutation associated with cardiac amyloidosis is Val122Ile, in the Black population after the age of 60; isolated cardiac amyloidosis is four times more common among Black people than White people in the US and 3.9% of Black people are heterozygous for Val122Ile (120).

TTR can also deposit as amyloid in the heart of elderly people; in the early days this was recognized as a post-mortem finding on 5% of autopsies, a condition termed ‘senile systemic amyloidosis’. With the evolution of imagiology tools, awareness is growing (121).

Normal TTR can also aggregate and form deposits in preeclampsia placental tissue to cause apoptosis. It is present at reduced levels in sera of preeclamptic women, as detected by a proteomic screen (122). The mechanism behind TTR aggregation under this physiological condition is highly unknown.

The precise trigger for TTR aggregation as amyloid is unknown and constitutes a major trend in TTR amyloidosis research. Structural studies correlate the amyloidogenic potential of TTR with weak interactions between subunits. These studies suggest that amyloid fibril formation by some TTR mutants might be triggered by tetramer dissociation to a compact non-native monomer with low conformational stability, which results in partially unfolded monomeric species with a high tendency for ordered aggregation into amyloid fibrils (123). In senile systemic amyloidosis where normal non-mutated TTR deposits in the heart, is has been hypothesized that amyloid formation is related to proteolytic events, or yet unidentified factors related to aging.

Outlook

In the future it is important to dissect in molecular terms the role of TTR in the nervous system, both in the central nervous system (CNS) and peripheral nervous system (PNS) – namely receptors and downstream pathways – to explain the phenotypes so far described in TTR null mice both in normal conditions and in experimental paradigms under stressful conditions. Additionally the role of TTR in other systems, such as the intestinal tract and the placenta should be developed.

Highlights

- TTR transport of thyroxine and RBP
- TTR neuroprotection
- TTR and neurite outgrowth
- TTR and 14-3-3ζ metabolism
- TTR in neurodegenerative diseases
- TTR in behavior
- Role of TTR in AD and ischemia
- TTR aggregation.

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