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Multigenic control of thyroid hormone functions in the nervous system

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Summary

Thyroid hormone (TH) has a remarkable range of actions in the development and function of the nervous system. A multigenic picture is emerging of the mechanisms that specify these diverse functions in target tissues. Distinct responses are mediated by α and β isoforms of TH receptor which act as ligand-regulated transcription factors. Receptor activity can be regulated at several levels including that of uptake of TH ligand and the activation or inactivation of ligand by deiodinase enzymes in target tissues. Processes under the control of TH range from learning and anxiety-like behaviour to sensory function. At the cellular level, TH controls events as diverse as axonal outgrowth, hippocampal synaptic activity and the patterning of opsin photopigments necessary for colour vision. Overall, TH coordinates this variety of events in both central and sensory systems to promote the function of the nervous system as a complete entity.

Keywords

Thyroid hormone; deiodinase; selenoprotein; nuclear receptor; transcription; neuronal differentiation; behavior; retina; cochlea; hearing; colour vision; photoreceptor; oligodendrocyte; mental retardation; depression; glucose utilization

Introduction

It has long been evident from human cretinism that TH is necessary for brain development (Osler, 1897, Gesell et al., 1936). The neurological retardation arising in cretinism results from TH insufficiency during critical periods of neuronal differentiation. TH insufficiency can result from impairment of the thyroid gland (congenital hypothyroidism) or from a lack of the dietary iodine necessary for biosynthesis of TH. Newborn screening and hormonal replacement have greatly reduced the occurrence of mental retardation in congenital hypothyroidism (Rovet and Daneman, 2003). Iodine deficiency remains a widespread cause of mental retardation in a number of developing countries (DeLong et al., 1985, Delange, 2001).

The symptoms of cretinism are diverse and suggest a role for TH in learning, language ability, memory, motor control and sensory function. Recent findings indicate that the spectrum of functions of TH in the mammalian nervous system is wider than may have been anticipated from general observations of cretinism and include, for example, a key role in colour vision (Ng et al., 2001a). This remarkable breadth of functions raises an obvious question: how can

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this hormone elicit so many different responses? Moreover, the responses in a given tissue change as development progresses such that a lack of TH produces different defects in the adult than in the fetus or infant. The question therefore becomes more complex: what determines the temporal as well as the cellular specificity of TH actions within the nervous system?

Genetic studies of model species and of human disease have pointed to some answers by identifying a number of genes that mediate or modify TH action in neural target tissues. Nervous system phenotypes have been identified in mice with mutations in the TH receptor α and β genes and in genes encoding deiodinase enzymes that metabolize TH (Forrest et al., 1996, Bernal, 2007, Galton et al., 2007). Human neurological defects have been associated with mutations in the TH receptor β gene (Refetoff et al., 1993, Chatterjee and Beck-Peccoz, 2001) and in the *MCT8* gene that encodes a TH transporter (Dumitrescu et al., 2004, Friesema et al., 2004). Genetic defects that interfere with TH action at any level in the target tissue may potentially cause neurological phenotypes, as shall be discussed (Figure 1, Table 1).

Although it is common knowledge that TH is generally required by the nervous system, our understanding of how this hormone elicits its functions is far from complete. This article reviews a number of functions of TH in the nervous system and the emerging view of the multigenic mechanisms that determine these actions. Evidence suggests that the selective cooperation of a limited number of genes encoding receptors, deiodinases and other components determines the nature, time and place of TH actions in the nervous system.

Early experimental studies

Pioneering investigations into the underlying actions of TH in the brain were performed by Eayrs (Eayrs and Taylor, 1951, Eayrs, 1966) and Legrand (Legrand, 1984) beginning half a century ago. These studies in model species, mainly the rat, revealed several features that are still pertinent to research today. (i) It was evident that TH has multiple different functions in the brain. Thus, hypothyroidism delayed cell migration, outgrowth of neuronal processes, synaptogenesis and myelin formation and also increased glial cell proliferation (gliosis) and neuronal cell death. In contrast, hyperthyroidism tended to promote premature differentiation, also with deleterious consequences on function. (ii) Many observations pointed to a general role for TH as a maturation factor in brain development. The general structure of the brain was formed but defects typically arose at later stages of terminal differentiation. (iii) Many actions of TH occurred within limited time windows of development. This is illustrated by an early study demonstrating a diminished electroencephalogram response in rats made hypothyroid as newborns by thyroidectomy (Bradley et al., 1960). However, if thyroidectomy was deferred until weaning, the electroencephalogram was preserved, indicating that in this system, TH acts within an early developmental period. Temporal sensitivity is a recurrent theme of TH action.

TH action at the cellular level

The nuclear TH receptor (TR) is a ligand-regulated transcription factor and has a central role in transducing the hormonal signal into a cellular response (Sap et al., 1986, Weinberger et al., 1986, Tata, 2006). The transcriptional activity of the TR is not the focus of this article but a few features relevant to the nervous system are mentioned here.

The TR can act as a ligand-regulated repressor or activator on different genes such that target genes fall into both positive (induced) and negative (repressed) categories. Much remains to be learned about the target genes that underlie the response of specific neuronal cell types *in vivo*. Screens have indicated candidate brain genes that are either up- or down-regulated by TH (Munoz et al., 1991, Lezoualc'h et al., 1992, Iglesias et al., 1996, Thompson, 1996, Anderson et al., 1997, Denver et al., 1997, Alvarez-Dolado et al., 1999, Rodriguez-Pena, 1999, Dowling et al., 2000, Poguuet et al., 2003, Quignodon et al., 2007) as has been reviewed

elsewhere (Dussault and Ruel, 1987, Thompson and Potter, 2000, Zoeller and Rovet, 2004, Bernal, 2007). In many cases it is still unknown if a gene responds directly or indirectly to TH. Indirect responses may be mediated for example, through intermediary factors or cell-cell signaling (Cuadrado et al., 1999, Lorenzo et al., 2002). It is likely that both direct and indirect target genes contribute to the overall tissue response to TH.

The TR has the ability to bind to chromatin in the absence or presence of ligand, which has implications for the T3-independent regulation of target genes both in normal and abnormal situations (Damm et al., 1989, Sap et al., 1989). Ligand-independent regulation may have a normal role in a nervous tissue niche where hormonal exposure is transiently limited at immature stages, as suggested in different species (Forrest et al., 1990). This has been suggested for example in amphibian eye development (Havis et al., 2006). However, there can be deleterious consequences in the brain in hypothyroid disease where the TR would be persistently locked into an unoccupied state causing long-term changes in gene expression (Hashimoto et al., 2001, Morte et al., 2002).

Transcriptional cofactors are involved in modifying TR activity when it is bound to the chromatin of a target gene. Several cofactors for the TR have been identified (Koenig, 1998) and some such as hairless (Potter et al., 2002), TBL1 (Guenther et al., 2000), Alien (Tenbaum et al., 2003) TRAP220 (Ito and Roeder, 2001) and NCoR (Jepsen et al., 2000) may modify TR activity in the nervous system. Also, mutations in the XPD subunit of the cofactor TFIID were found to destabilize TR binding to brain target genes and to alter myelination in mice (Compe et al., 2007). XPD mutations occur in human trichothiodystrophy, which is associated with neurological defects resembling those of hypothyroidism including mental retardation, spasticity and hypomyelination.

Non-genomic responses for TH or metabolites of TH have also been proposed based largely on *in vitro* tissue culture studies (Siegrist-Kaiser et al., 1990). It is unknown if there is a major physiological role for such responses in the nervous system *in vivo*.

TH availability in the nervous system

TR activity can be controlled at several steps preceding its interaction with a target gene. The amount of TH ligand available to neural tissues is governed initially by the activity of the thyroid gland and by the iodine present in the diet. The thyroid gland releases two major forms of TH, thyroxine (3,5,3',5'-tetraiodothyronine, T4) and 3,5,3'-triiodothyronine (T3)(Figure 1). T3 is the main active form of hormone that binds the TR although T4 is more abundant than T3 in serum. T3 is also produced locally in some tissues by deiodination of T4, which is considered to be an important mechanism in nervous tissues. T4 can also bind the TR although with much lower affinity than T3 and it is not excluded that in some situations, T4 at sufficiently high levels may directly stimulate responses, as has been discussed recently (Galton et al., 2007).

Developmentally programmed changes in TH levels in the circulation occur from early stages after conception through embryogenesis and postnatal development. Serum T4 and T3 levels are initially low in the fetus but rise in development and increase markedly around birth in humans, providing a general stimulus for many tissues (Burrow et al., 1994). TH transferred from the mother to the fetus is important, especially during early brain development before the onset of fetal thyroid function at mid-gestation in humans (Auso et al., 2004, Mitchell and Klein, 2004, Morreale de Escobar et al., 2004, Zoeller and Rovet, 2004).

The iodine supply determines the ratio of T3 and T4 synthesised by the thyroid gland (Deme et al., 1976). T4 and T3 are produced in a two-step process catalyzed by thyroid peroxidase. Tyrosine residues of thyroglobulin are iodinated yielding mono-(MIT) and diiodotyrosine

(DIT) residues, which are coupled to form either T4 or T3 residues. The relative amount of T4 and T3 depends on the DIT/MIT ratio that increases with the level of iodination. In a euthyroid state, T3 is present at only 10–25% of the level of T4 within thyroglobulin but when iodine intake is low the thyroid gland produces more T3 than T4 (Deme et al., 1976). In serum, the concentration of T3 is ~50 times lower than that of T4 which depends on the rate of secretion of T3 from the thyroid gland, its shorter half-life than that of T4 and its peripheral generation or clearance rates (Nicoloff et al., 1972). In iodine-deficiency, T4 levels in serum decline but T3 levels tend to be maintained (Delange and Ermans, 1996). This response may protect some tissues but presumably not those in the nervous system that rely upon local amplification of T3 levels by deiodination from T4. The example of the auditory system is discussed below.

The sensitivity of distinct neuronal populations to hypothyroidism at different phases of development is suggested by the varying outcomes of iodine deficiency at early or later stages of human development (Dumont et al., 1994, Morreale de Escobar et al., 2004). Deficiency at early stages *in utero* is associated with severe neurological cretinism with deaf-mutism whereas deficiency at later stages produces a myxedematous cretinism with growth and mental retardation and without severe auditory deficits. Iodine treatment protects the brain and neurological function from iodine deficiency if given early in fetal development but not if given in the third trimester or postnatally (Cao et al., 1994).

Thus, adequate systemic provision of TH is a prerequisite for the development and function of the nervous system. However, target tissues to a large extent govern their specific responses through deiodinases and receptors, as discussed below.

Deiodinases and the nervous system

In the vicinity of the target cell, the level of T3 can be amplified or depleted by deiodination (Köhrle, 1999, Bianco et al., 2002, Brown, 2005, St Germain et al., 2005). Deiodinases are selenocysteine-containing enzymes and are membrane-associated within the cell. Type 2 and type 3 deiodinases are conserved across vertebrate species and both are expressed in the nervous system (Bates et al., 1999, Marsh-Armstrong et al., 1999, Peeters et al., 2001, Yoshimura et al., 2003, Darras et al., 2006). T3 is generated from T4 by type 2 deiodinase (encoded by the *Dio2* gene) and is inactivated by type 3 deiodinase (encoded by *Dio3*) which converts both T4 and T3 into minimally active metabolites. Type 1 deiodinase encoded by *Dio1* has both activating and inactivating activities but is more important in homeostasis in liver, kidney and other tissues than it is in nervous tissues. Little or no type 1 deiodination is detected in mammalian brain (Campos-Barros et al., 1996, Kester et al., 2004) and no brain phenotype has been described in *Dio1*-deficient mice (Schneider et al., 2006). *Dio1* is expressed in *Xenopus* tadpole brain suggesting that there is variation in deiodinase function in non-mammalian species (Morvan Dubois et al., 2006).

Nervous system tissues contain relatively high ratios of T3 / T4 compared to the circulation or non-nervous tissues. A variety of concentrating mechanisms may be at play and the local generation of T3 by type 2 deiodinase is viewed as a major factor (van Doorn et al., 1985, Campos-Barros et al., 2000, Pinna et al., 2002, Kester et al., 2004). Two commonly occurring polymorphisms have been described in the human *DIO2* gene (Mentuccia et al., 2002, Peeters et al., 2005) but it is unknown if these are involved in specific changes in brain function. Polymorphisms in the *DIO2* locus have been associated with mental retardation in a Chinese population in an iodine-deficient area and it was suggested that this allelic variation may influence T3 availability in an iodine-deficient environment (Guo et al., 2004). Deafness is the most pronounced neurological phenotype known to date in *Dio2*^{-/-} mice, indicating a major role for type 2 deiodinase in the inner ear (Schneider et al., 2001, Ng et al., 2004) (Table 1). *Dio2*^{-/-} mice are also averse to descending a vertical pole and lack urgency in escaping from water, perhaps indicating a lowered state of anxiety (Galton et al., 2007). Otherwise, *Dio2*^{-/-}

mice show surprisingly little neuronal dysfunction compared to that caused by hypothyroidism, suggesting that there may be important but as yet undefined means of compensation for the absence of type 2 deiodinase mice. Current evidence therefore suggests that the primary origin of T3 ligand varies in different tissues: (i) In some brain regions, T3 obtained from the circulation may be adequate; (ii) In other brain regions and in the cochlea, additional T3 generated locally by type 2 deiodinase is required.

Less is known so far of the role of type 3 deiodinase, the TH-inactivating enzyme, in the mammalian nervous system. The *Dio3* gene is typically expressed earlier in brain development than is *Dio2* and it is generally thought to have a protective role at immature stages. Experimental demonstration of such *Dio3* functions is required but initial studies of *Dio3*^{-/-} mice suggest that there are defects in colour vision (Hernandez et al., 2006)(D.F., L. N., A. Hernandez, V. Galton D. St.Germain, unpublished data). A role for type 3 deiodinase is supported by studies in non-mammalian species. During amphibian metamorphosis, type 3 deiodinase regulates retinal cell proliferation (Marsh-Armstrong et al., 1999) and in avian species, it cooperates with type 2 deiodinase in the hypothalamic control of seasonal reproductive behaviour (Yoshimura et al., 2003, Yasuo et al., 2005). Deiodinases confer adaptability on neuronal responses in vertebrate species and further research on these enzymes in the nervous system is likely to be rewarding.

Hormonal uptake and local communication between cells

The cellular uptake of TH provides another level of control of TH action. Uptake may be mediated by various types of transporters including those of the L type amino acid, organic anion and monocarboxylate families (Abe et al., 2002, Friesema et al., 2005, Taylor and Ritchie, 2007). Mutations recently identified in the *MCT8* monocarboxylate transporter in human X-linked mental retardation and Allen-Herndon-Dudley syndrome suggest the importance of TH transport in neurological function (Dumitrescu et al., 2004, Friesema et al., 2004, Brockmann et al., 2005, Schwartz et al., 2005, Maranduba et al., 2006). Affected males exhibit psychomotor and speech defects. *Mct8*-deficient mice have reduced uptake of T3 in brain although neurological phenotypes have not been reported (Dumitrescu et al., 2006, Heuer, 2007, Trajkovic et al., 2007).

Although the deiodinase and transporter genes have been found independently to have a role in nervous tissues, an obvious implication is that their functions converge. Transporters may control not only the uptake of TH from serum or cerebrospinal fluid but also the transfer of T3 ligand between cells following the local generation of T3 by deiodination. This is suggested by the finding that in some brain tissues, glia are the main *Dio2*-expressing cells which presumably generate T3 whereas the main target cells are adjacent neurons (Guadaño-Ferraz et al., 1997). An even more marked physical separation of T3-generating and T3-responding cells exists in the cochlea. *Dio2*-expressing tissues surrounding the cochlear duct are exposed to T4 inflow in the vasculature suggesting a model whereby these supporting tissues take up T4, convert the T4 to T3, then release T3 internally to the sensory target tissues (Campos-Barros et al., 2000). Transporters would be a necessary component of these paracrine-like mechanisms. Such local hormonal communication may be the rule rather than the exception for TH action in many neuronal environments.

It is possible that other steps remain to be identified in the chain of events that lead to a cellular response to TH. The *CRYM* gene encodes mu-crystallin and has been proposed to act as an intracellular, cytosolic “holder” of T3 (Suzuki et al., 2007). Human *CRYM* mutations have been associated with non-syndromic deafness and in one case, a mutation was shown to impair the T3 binding ability of the protein (Abe et al., 2003, Oshima et al., 2006). However, unlike the human cases, *Crym*^{-/-} mice have normal auditory function, a discrepancy that is not yet understood (Suzuki et al., 2007). It is unknown if these mice have brain phenotypes.

Thyroid hormone receptors in the nervous system

Functions in the nervous system have been identified for both the *Thrb* and *Thra* receptor genes (Table 2). Vertebrate species express three conserved TR isoforms and their functions have been demonstrated by targeted deletions (knockout) and change-of-function (knock-in) mutations in mice (discussed below). *Thrb* encodes two major isoforms, TR β 1 and TR β 2, whereas *Thra* encodes a single T3 receptor, TR α 1. Other truncated or variant TR products have been found but only in isolated species (Harvey et al., 2007) and these non-canonical products lack known functions in the nervous system.

Although TR α 1, TR β 1 and TR β 2 have similar transactivation properties *in vitro*, each isoform serves distinct functions *in vivo*, which is partly determined by its expression pattern (Forrest et al., 1990, Strait et al., 1990, Mellström et al., 1991, Bradley et al., 1992). TR α 1 is expressed widely in the brain from early embryonic stages and it is also the major TR isoform in embryonic stem (ES) cells. TR α 1 mediates neuronal-like differentiation in ES cells and in the PC12 cell line (Muñoz et al., 1993, Liu et al., 2002, Liu and Brent, 2005). Together with evidence for a role in neurogenesis (Lemkine et al., 2005), these observations suggest functions for TR α 1 in neural progenitor cells, both at immature and more mature stages. The widespread expression of TR α 1 also suggests other maintenance functions in the brain.

TR β 1 is generally induced later than TR α 1 in the brain, suggestive of both overlapping and independent functions. TR β 2 has the most specialized expression pattern of any TR isoform, being restricted to cone photoreceptors, the cochlea, pituitary and paraventricular nucleus of the hypothalamus (Hodin et al., 1989, Sjöberg et al., 1992, Bradley et al., 1994, Abel et al., 2001). In the adult, TR α 1 and TR β 1 show overlapping expression patterns in many brain regions. However, the varying proportions of TR α 1 and TR β 1 in a cell type may determine whether the response is primarily governed by TR α 1 or TR β isoforms. Examples of predominant expression of a specific isoform include TR α 1 in hippocampal neurons (Guadaño-Ferraz et al., 2003) and TR β 2 in retinal cones (Ng et al., 2001a). In certain situations, however, even when TR α 1 and TR β isoforms are co-expressed in a cell, there may be differences in their target gene recognition or cofactor preference that determine independent functions, as suggested in Purkinje cells (Heuer and Mason, 2003). The progressive rise in expression of TR α 1 and TR β 1 is in accord with earlier reports of increasing T3 binding capacity in brain during development (Schwartz and Oppenheimer, 1978, Bernal and Pekonen, 1984). In the more mature brain, the total TR mass, regardless of its composition by TR α 1 or TR β isoforms, may be a determining factor in the responsiveness of some cell types.

Thrb functions

The *Thrb* gene serves a prominent role in sensory systems. *Thrb* mutations cause deafness in mice (Forrest et al., 1996, Griffith et al., 2002, Shibusawa et al., 2003) and are associated with hearing loss in humans (Brucker-Davis et al., 1996). *Thrb*-deficiency or hypothyroidism in rodents retards the maturation of many cochlear cell types including the sensory hair cells and deforms the tectorial membrane which mediates transduction of sound (Deol, 1976, Uziel, 1986). *Thrb*-deficiency retards the maturation of a potassium current in inner hair cells (Rüsch et al., 2001) and hypothyroidism retards the synaptic characteristics of both inner (Brandt et al., 2007, Sendin et al., 2007) and outer hair cells (Uziel et al., 1983). The auditory nerve and central pathways are also sensitive to TH (Dow-Edwards et al., 1986, Knipper et al., 1998).

It is unclear how TH coordinates the late differentiation of so many cell types in the auditory system. However, evidence indicates that although TR β has the major role, TR α 1 also contributes, suggesting that part of the answer lies in cooperation between the two TR genes and the relative levels of TR β and TR α 1 in individual cell types (Bradley et al., 1994, Winter et al., 2006). Indeed, TR β /TR α 1 combined mutants have exacerbated defects consistent with

cooperative functions (Rüsch et al., 2001). This role of TH as a global timing signal for the onset of hearing has been proposed to be determined by type 2 deiodinase within the cochlea rather than by TR β or by circulating T4 and T3 levels. Type 2 deiodinase is induced in the cochlea prior to the onset of hearing and *Dio2*^{-/-} mice display a cochlear phenotype like that of *Thrb*^{-/-} mice (Campos-Barros et al., 2000, Ng et al., 2004)(Figure 2). The developmental signals that induce *Dio2* expression in the cochlea are currently unknown. The auditory system thus provides a paradigm of functional cooperation between receptors and deiodinases.

A key role for *Thrb* is in the colour visual system. The TR β 2 isoform is specifically expressed in immature cone photoreceptors (Sjöberg et al., 1992, Jones et al., 2007), in which it determines the differential expression of M (medium-wave) and S (short-wave) opsin photopigments that mediate colour vision (Ng et al., 2001a, Roberts et al., 2006, Applebury et al., 2007). It has also been reported that *Thrb* influences circadian responses, at least in part because TR β 2 induces M opsin in cones. M cones are thought to contribute to light-dependent entrainment (Dkhissi-Benyahya et al., 2007).

Deletion of *Thrb* results in audiogenic seizure susceptibility, suggesting another role for TR β in the central mechanisms that constrain the propagation of the response to sustained auditory stimulation (Ng et al., 2001b). *Thrb* is also associated with changes in female mating behaviour, possibly through interactions with estrogen signaling in the hypothalamus (Dellovade et al., 2000). Behavioral phenotypes have been identified using knock-in mutations in *Thrb* that express dominant negative TR β proteins similar to those found in human resistance to thyroid hormone. The mutations in mice promote hyperactivity, impair learning in a vigilance test (Siesser et al., 2005) and in a water maze and cause motor deficiency and defects in cerebellar Purkinje cells (Hashimoto et al., 2001). Transgenic over-expression of dominant negative TR β proteins in mice also produces hyperactivity (Wong et al., 1997, McDonald et al., 1998) that may be relevant to symptoms that occur in human resistance to thyroid hormone (Leonard et al., 1995).

Human resistance to thyroid hormone typically shows autosomal dominant inheritance and involves *THRB* mutations that generate dominant negative TR β proteins. Neurological symptoms are common but vary in incidence and severity and include attention deficits, hyperactivity, hearing loss and mental retardation (Hauser et al., 1993, Refetoff et al., 1993, Brucker-Davis et al., 1996). As in mice, TR β 2 is detected in human fetal cones (Lee et al., 2006) but the possibility of colour visual defects in human thyroid disorders has not been studied systematically (Newell and Diddie, 1977, Mirabella et al., 2005).

***Thra* functions**

To date, inherited mutations in the human *THRA* gene have not been reported. In mice, *Thra* mutations produce a different spectrum of phenotypes than do *Thrb* mutations and these include defects in behaviour and synaptic function. A *Thra* knock-in mutation that over-expresses a dominant negative TR α 1 causes anxiety-like symptoms and learning defects together with abnormalities in hippocampal inhibitory neurons of the GABA (γ -amino butyric acid) class (Venero et al., 2005). *Thra* deletion also causes abnormalities in open field and fear conditioning tests (Guadaño-Ferraz et al., 2003, Wilcoxon et al., 2007). The GABAergic, parvalbumin-positive neurons in the CA1 region of the hippocampus that may underlie these defects express greater levels of TR α 1 than TR β , which could explain their being primarily regulated by TR α 1 (Guadaño-Ferraz et al., 2003).

Mutations in both *Thra* and *Thrb* genes give cerebellar phenotypes resembling in part those caused by hypothyroidism with impaired arborisation of Purkinje cells and delayed migration of granule neurons (Hashimoto et al., 2001, Venero et al., 2005). Studies in explant cultures made from knockout mice suggest that the T3-dependent formation of dendrites by Purkinje

cells is mediated by TR α 1 intrinsic to the Purkinje cell rather than in the granule neurons (Heuer and Mason, 2003). The cerebellum represents an example of cooperation whereby TR α 1 and TR β may act partly in different cell populations to accomplish the overall differentiation programme (see section on cooperation). At the cellular level, the *Thra* gene also regulates differentiation of oligodendrocytes in the optic nerve (Baas et al., 2002, Billon et al., 2002) and astroglia in the cerebellum with the latter function being suggested to involve interactions between TR α 1 and TR β 1 (Morte et al., 2004).

The *Thra* gene also regulates glucose utilization, an indicator of synaptic activity, in the brain. In mice, a dominant negative mutation in TR α 1 (TR α PV/+) but not in TR β impaired glucose utilization (Itoh et al., 2001) (Figure 3). This mutation also impaired glucose utilization following stimulation of the whisker-to-barrel pathway, a major tactile sensory function in rodents (Esaki et al., 2003). In accord with these findings, hypothyroidism delays the maturation and activity of the barrel field in rats (Berbel et al., 2001). Although the *Thrb* gene rather than *Thra* has the main known role in sensory systems, this evidence suggests that the *Thra* gene contributes to the central pathways that relay sensory information to other brain regions.

It has been reported that TR α 1-deficient mice are surprisingly resistant to the cerebellar defects that result from hypothyroidism (Morte et al., 2002). This result supports the proposal that TR α 1 in the absence of ligand is responsible for some of the deleterious consequences of hypothyroidism. This may be explained if TR α 1 is chronically locked in an unoccupied state that results in the abnormal regulation of gene networks (Bernal, 2007). Thus, some of the neurological damage in hypothyroidism may be the result of aberrant receptor activity rather than no receptor activity.

***Thra* and *Thrb* cooperative functions**

Cooperation between the *Thra* and *Thrb* genes in the nervous system is likely to be more widespread than is evident from the limited studies described to date. Cooperation may occur at several levels. First, in many scenarios, an individual cell type may express some amount of both TR α 1 and TR β , such that both TR isoforms can contribute to the joint regulation of the same target genes. Alternatively, in a more complex scenario, TR α 1 and TR β may act in distinct cell types in a tissue or organ to control an overall neurophysiological function. The cerebellum and auditory system provide examples, as has been discussed. Thus, the cochlea displays overlapping patterns of expression of the *Thra* and *Thrb* genes and both genes play a functional role in hearing (Bradley et al., 1994, Rüscher et al., 2001). All of the senses may be subject to some level of control by TH (Freeman and Sohmer, 1995) and it is likely that cooperative functions may be revealed in other sensory systems. Although the TR genes interact positively in many situations, this need not always be the case. An example of opposing functions concerns mating behaviour in mice in which the female lordosis response is reduced by TR α 1-deficiency but is increased by TR β -deficiency (Dellovade et al., 2000).

There is scope for further study of mouse strains lacking all known TRs in which no compensation is possible between TR β and TR α 1. Exacerbated or new phenotypes in the nervous system may be revealed, reflecting the total action of all TR isoforms (Calzà et al., 2000, Baas et al., 2002). Indeed, combined mutations in TR β and TR α 1 are known to exacerbate the phenotype in several non-nervous tissues (Göthe et al., 1999).

TH and the formation of neuronal connections

Eayrs and Legrand showed that a major role of TH in the brain is to promote the growth of axons and dendrites and the formation of synaptic densities. These findings have renewed relevance today in the light of studies of the underlying genes.

The cerebellum, the subject of many of these studies, represents a classical model of TH action in the brain (Figure 4). The cerebellar granule cells proliferate after birth in the external granular layer during the first two postnatal weeks. The granule cells then migrate and their axons, the parallel fibers, make synaptic contacts with the tertiary dendrites of the Purkinje cells. In hypothyroid rats, the migration of granule cells is slowed, the granule cell bodies pile up in the molecular layer and the parallel fibers are shortened. Simultaneously, the growth of the dendritic tree of Purkinje cells is impaired (Nicholson and Altman, 1972, Legrand, 1984), the number of synapses is reduced and abnormal contacts result from the delayed interaction between neurons (Vincent et al., 1982). Hypothyroidism also impairs axonal and dendritic outgrowth in other areas including the neocortex (Eayrs, 1966), hippocampus (Rami et al., 1989) and the cochlea (Uziel et al., 1983) and in neuronal cell cultures (Couchie et al., 1986, Heuer and Mason, 2003). TH can regulate axonal outgrowth indirectly by stimulating expression of neurotrophic factors such as NGF or BDNF and of neurotrophin receptors (Clos and Legrand, 1990, Lindholm et al., 1993, Muñoz et al., 1993, Neveu and Arenas, 1996).

Axonal and dendritic outgrowth and the neuronal cytoskeleton

TH regulates axonal and dendritic outgrowth largely through the growth cone, the motile tip of growing axons. The behaviour of the growth cone is driven by dynamic reorganization of actin filaments and microtubules by signaling pathways linked to guidance cue receptors (Dickson, 2002). Microtubule assembly is promoted by microtubule-associated proteins (MAPs), including Tau, which promote polymerization of the α , β tubulin dimer and by interactions with other cytoskeletal and extracellular proteins. MAPs and Tau stabilize microtubules and Tau has a role in neuronal polarity. MAP2 is dendrite specific whereas Tau is axon specific and splice variants of both are produced in development with different polymerizing activity (Mareck et al., 1980).

Hypothyroidism decreases the number of microtubules, their shape and stability in the dendritic tree of Purkinje cells in the cerebellum (Faivre et al., 1983) and in some neurons in the cochlea (Gabrion et al., 1984). TH controls the expression of tubulins and MAPs. The tubulin multigene family expresses six α and five β isotypes leading to microtubules with unique properties. During rat brain development, TH regulates total tubulin amounts (Gonzales and Geel, 1978, Takahashi, 1984), down-regulates $\alpha 1$ and $\alpha 2$ tubulins and up-regulates $\beta 4$ tubulin (Aniello et al., 1991b, Lorenzo et al., 2002).

The rate of *in vitro* microtubule assembly is reduced in brain extracts from hypothyroid rodents and is restored to normal by addition of either Tau or MAP2 (Francon et al., 1977). Reduced microtubule assembly and stability depends on the presence at immature stages of MAPs with a lower polymerization activity than adult species (Mareck et al., 1980). In the cortex and cerebellum of hypothyroid adult rats, the proportion of immature Tau proteins remains high (Aniello et al., 1991a). Figure 4 depicts a comparison of normal and hypothyroid rat cerebellum, showing defects in Purkinje cell dendrites and in the parallel fibers, shown by staining for Tau or MAP2 (Nunez et al., 1989). Expression of MAP2 and MAP1 is regulated by TH during development and in adulthood (Benjamin et al., 1988, Silva and Rudas, 1990). The changes induced by hypothyroidism in slow axonal transport protein (Stein et al., 1994) may relate to microtubule stability. TH also regulates expression of monomeric actin (Biswas et al., 1997) and neurofilaments that can alter axonal stability (Marc and Rabie, 1985).

Interestingly, the impairments caused by hypothyroidism partly resemble those described in neurodegenerative diseases. Mutations in adult Tau variants or changes in the ratio of Tau variants have been detected in the brain in frontotemporal dementia and Parkinsonism linked to chromosome 17, Alzheimer's disease and progressive supranuclear palsy (Spillantini and Goedert, 1998, Andreadis, 2005, Ezquerra et al., 2007).

Synaptic activity and glucose utilization

Maturation of the mammalian brain is accompanied by profound increases in local rates of glucose utilization (Kennedy et al., 1982). In rats made hypothyroid at birth and studied later in adulthood, rates of cerebral glucose utilization are markedly depressed with the greatest decreases occurring in the cerebral cortex and auditory pathways (Dow-Edwards et al., 1986).

Glucose is the sole nutrient used by the brain to produce the energy for synaptic activity. There is a close correlation between local neural activity and glucose metabolism in the nerve endings (Sokoloff, 1981) such that the reduced glucose utilization in the hypothyroid brain might explain some of the decrease in synaptic activity. Studies in mutant mice (Itoh et al., 2001) showed that the regulation of brain glucose utilization depends primarily upon TR α 1 rather than TR β (Figure 3). Mice with a dominant negative mutation in TR α 1 but not TR β had severely impaired utilization of radiolabeled glucose in many brain regions. It has been reported that hypothyroidism in rats impairs expression of the glucose transporter GLUT1 in the cerebral cortex, suggesting one type of target gene that may contribute to the reduction in glucose utilization caused by hypothyroidism or mutation in the *Thra* gene (Santalucia et al., 2006).

It is interesting to note that TH synchronizes the production of glucose in peripheral tissues with the requirement for glucose in the brain. Thus, enzymes involved in gluconeogenesis, glycogen synthesis and glycogenolysis are under TH control in the liver (Feng et al., 2000) and muscle (Clement et al., 2002) such that TH can contribute to increases in the circulating glucose that is required for brain synaptic activity.

Recordings of neuronal populations in hypothyroid rodents have correlated synaptic function in the hippocampus with impaired behaviour in spatial learning tasks (Gilbert and Paczkowski, 2003, Sui and Gilbert, 2003, Sui et al., 2005). These studies revealed abnormalities in hippocampal long term potentiation, a process of synaptic strengthening at the cellular level that is thought to underlie learning and memory (Gilbert and Sui, 2006). Developmental hypothyroidism in rats has been shown to impair GABAergic neurons and to diminish inhibitory synaptic function (Gilbert et al., 2007). These neurophysiological studies add a fascinating and necessary dimension to understanding how TH regulates specific cellular functions that underlie behaviour. Future studies may reveal the molecular mechanisms by which TH regulates particular forms of synaptic activity.

TH and adult brain function

TH deficiency has different consequences in adult and geriatric life than in early development. TH abnormalities in adulthood produce milder symptoms but these can have a pronounced influence on mood and anxiety. Adult abnormalities, unlike those in development, are generally reversible. The association of TH dysfunction and mood disturbance is well recognized although its prevalence is not established (Simon et al., 2002, Bunevicius et al., 2005, Jorde et al., 2006). Nonetheless, since the mood disturbances associated with hypo- and hyperthyroidism in adulthood are reversible, the evaluation of thyroid function represents a cornerstone of the assessment of patients affected by psychiatric disorders (Haggerty et al., 1993). Similarly, since hypothyroidism in the elderly can be associated with cognitive impairment, screening of thyroid function is advocated in the initial evaluation of dementia (Ladenson et al., 2000). Despite the lack of undisputed evidence of effectiveness (Siegmund et al., 2004), TH is considered a valuable adjunct therapy in the treatment of poorly responsive cases of depression (Joffe and Sokolov, 1994, Bauer et al., 2002).

In adults, it may be expected that TH influences neuronal function and maintenance rather than the more profound events that guide brain development. The nature of these adult functions is poorly defined. The question is complicated because of the difficulty in distinguishing between

a developmental or adult origin of a phenotype with most inherited mutations, whether in a mouse model or human patient. However, an innovative approach used a mouse *Thra* mutation that produces a dominant negative TR α 1 protein (Venero et al., 2005). This TR α 1 protein failed to bind T3 at normal levels but the defect could be overcome with high levels of T3, allowing the mutation to be “switched-off” at a chosen age. Heterozygous mutants exhibited anxiety-like behaviour and locomotor defects. Remarkably, treatment with T3 in adults was able to reverse the anxiety-like behaviour. The mutants exhibited defects in hippocampal GABAergic neurons, suggesting that this type of inhibitory neuron is a target for TH in the adult brain.

Studies in hypothyroid adult rats have also described impairment of long term potentiation in the hippocampal-medial prefrontal cortex pathway that is thought to be involved in learning and memory (Sui et al., 2006). Other studies of adult rats report that T4 enhances performance in a water maze and increase acetylcholinesterase levels in the prefrontal cortex and hippocampus, suggesting an interaction of TH and cholinergic pathways (Smith et al., 2002).

The sensitivity of the adult brain to TH is suggested by other studies. Hypothyroidism in adult rats reduces neurogenesis in the hippocampus (Desouza et al., 2005) and produces abnormal behaviour in a swim test, suggestive of depressive symptoms (Montero-Pedrazuela et al., 2006). Also, *Thra*-deficient mice show impaired cell proliferation in the stem cells in the sub-ventricular zone of the brain, suggesting that TR α 1 contributes to neurogenesis in adults (Lemkine et al., 2005). In addition, the expression of neuropeptides and re-myelination may be influenced by TH in adults (Calza et al., 2005), hinting at the range of functions that remain to be uncovered. A question deserving further study concerns the target genes of TH in the adult brain, of which little is known (Iniguez et al., 1992). Knowledge of downstream genes may help to illuminate the extent of overlap in the mechanisms by which TH acts in the developing and adult brain.

Concluding comments

Genetic, cellular and physiological studies have made fascinating progress in elucidating specific functions of TH in the nervous system. It is also interesting to reflect on these functions as a whole rather than as separate parts given that, in life, TH acts in the context of the whole organism.

It is noteworthy that although mice lacking all nuclear TH receptors are runted, they retain vital bodily functions and near normal longevity (Göthe et al., 1999). These observations point to TH as a signal that adjusts many organs from an immature to a mature functional state thereby enhancing the fitness of the individual for autonomous, adult life. In the brain, a similar generalization may apply. Thus, human individuals suffering from cretinism retain basal, primitive brain activities but display deficiencies in the more sophisticated features of mental function, i.e. memory, learning, representation, awareness and, more generally, intelligence. Evidence from animal models suggests that a number of these defects may be explained for example, by deficiencies of different types of synapses (Figure 5). In rodent models, hypothyroidism or receptor defects often prevent neural functions from progressing beyond an immature state. Thus, the brain attains sub-optimal levels of glucose utilization (Dow-Edwards et al., 1986) and the colour visual system acquires only shortwave (“blue”)-sensitive cones, which are thought to represent a rudimentary or default pathway of cone differentiation (Ng et al., 2001a).

The senses have received less attention than the brain but also depend upon TH. TH mediates the timely onset of sensory function during critical periods of development. Thus, the acquisition of information and environmental awareness are impaired by hypothyroidism with consequences for learning, memory and communication. Moreover, sensory inflow during

critical periods is thought to modify synaptic connections in central regions and ultimately to shape the maturation of the brain as a functional entity (Hensch, 2004). TH therefore serves an overall role in coordinating the development of both sensory and central systems to ensure that the nervous system as a whole acquires correct function.

The identification of key genes that mediate TH action has set the stage to understand how the integrated function of this relatively limited number of genes determines diverse neurophysiological and neurodevelopmental events. The receptor and deiodinase genes provide different but equally critical levels of control while TH transporters and transcriptional cofactors may further modify the response in specific neuronal populations. One may anticipate that new approaches will continue to reveal new functions for this hormone in the nervous system.

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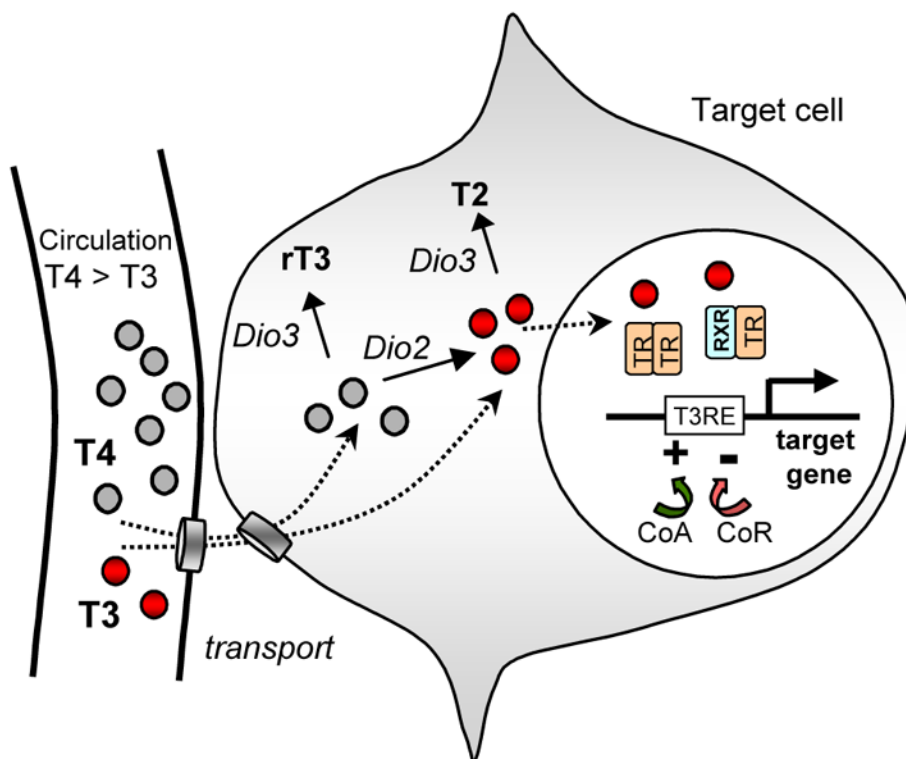


Figure 1.

An outline of the cellular response to TH. T3 ligand (small red circles) binds a nuclear receptor (TR) that acts as a transcription factor to regulate target gene expression. The TR binds a T3 response element (T3RE) in the gene and its activity is regulated by corepressors (CoR) or coactivators (CoA). TR can bind efficiently to a given T3RE as a homodimer or heterodimer with retinoid X receptor (RXR), or less efficiently as a monomer. T3 is at lower levels than T4 (small grey circles) in the circulation but T3 levels may be amplified by conversion of T4 into T3 by type 2 deiodinase (encoded by *Dio2*). Ligand may be inactivated by type 3 deiodinase (*Dio3*) which converts T4 and T3 to rT3 and T2, respectively. T2 and rT3 have minimal biological activity. It should be noted that deiodinases may act in the target cell or in nearby cells through a paracrine-like mode of control. Deiodinases are membrane-associated within the cell. Transporters can control hormone uptake into tissues and communication between cells by hormone transfer.

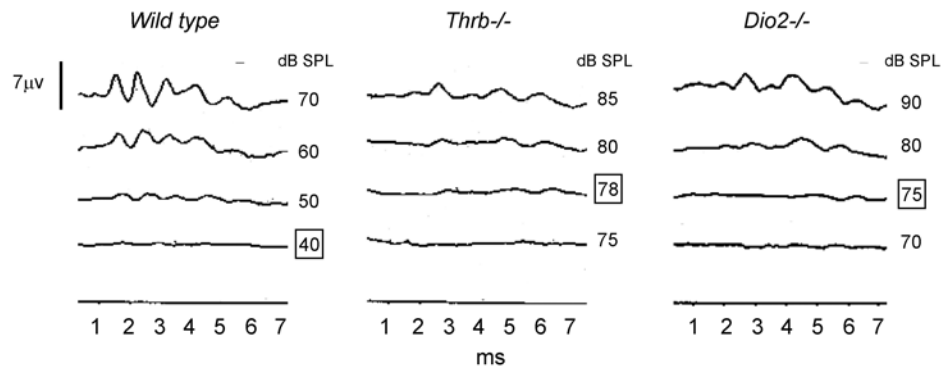


Figure 2.

Auditory deficits caused by deletion of *Thrb* or *Dio2* genes in mice. Comparable elevations in auditory thresholds occur in both strains of mice. Thresholds for a click stimulus assessed by the auditory-evoked brainstem response are ~40 dB sound pressure level (dB SPL) in a wild type mouse. Thresholds in *Thrb*^{-/-} and *Dio2*^{-/-} examples shown are 78 and 75 dB SPL, respectively (boxed).

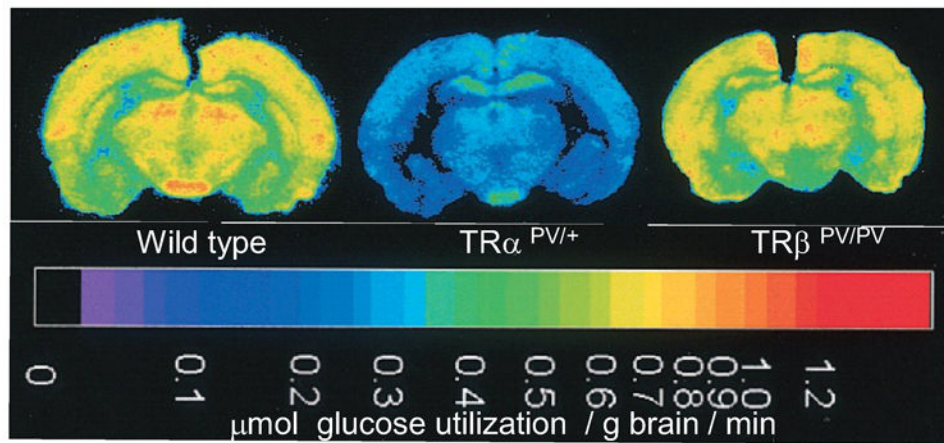


Figure 3.

Glucose utilization in the brain of mice carrying TR α or TR β mutations. Quantitative colour-coded autoradiographs of brain sections from wild type or TR α and TR β mutant mice. Local rates of glucose utilization established by the deoxyglucose method are encoded in the calibrated color scale at the bottom of the figure. Redrawn (with permission) from Itoh et al Proc. Natl Acad Sci USA, 98: 9913 (2001).

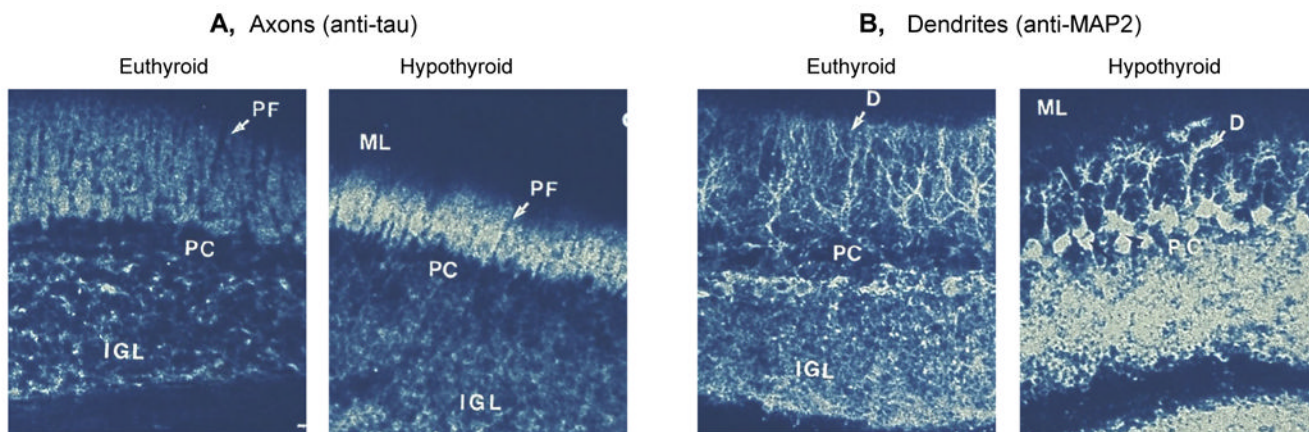


Figure 4. The cerebellum of 14 day old euthyroid and hypothyroid rats stained with antibodies against axon-specific Tau (A) and dendrite-specific MAP2 (B). IGL, internal granular layer, PF, parallel fibres (the axons of granule neurons), PC, Purkinje cell, D, dendrites (of Purkinje cells), ML, molecular layer. Note the shorter parallel fibres and Purkinje cell dendrites in the hypothyroid brain. (Redrawn from Nunez et al, 1989)

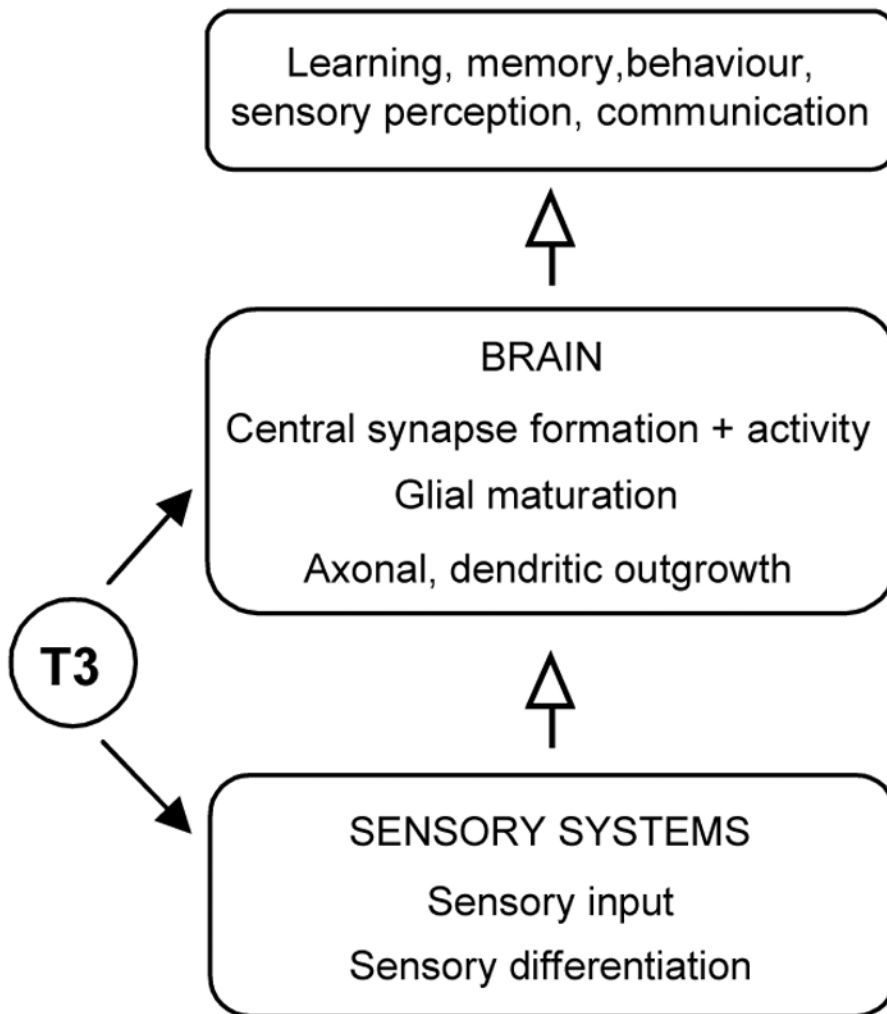


Figure 5.

A global view of TH functions in the nervous system. TH coordinates the maturation of sensory systems and the central neuronal network in the brain to promote the function of the nervous system as a complete entity.

Table 1**Nervous system phenotypes associated with mutations in genes that are involved in thyroid hormone action**

Nervous system phenotypes associated with mutations in mammalian genes that mediate thyroid hormone functions. Only general phenotypes are noted. See text for details.

Gene product	Mouse gene Location	Mouse phenotypes	Human gene Location	Human disease
thyroid hormone receptor β	<i>Thrb, Nr1a2</i> 14	Sensory deficits Behavioural defects	<i>THRB</i> 3p24.2	Syndrome of resistance to thyroid hormone
thyroid hormone receptor α	<i>Thra, Nr1a1</i> 11	Behavioural defects Synaptic abnormalities	<i>THRA</i> 17q11.2	unknown
type 2 deiodinase	<i>Dio2</i> 12	Deafness Behavioural defects (mild) Reduced T3 content in brain	<i>DIO2</i> 14q24.2-24.3	unknown
type 3 deiodinase	<i>Dio3</i> 12	Color visual defect (unpublished)	<i>DIO3</i> 14q32	unknown
monocarboxylate TH transporter	<i>Mct8, Slc16a2</i> X	Low uptake of T3 in brain	<i>MCT8</i> Xq13.2	X-linked mental retardation Allan-Herndon-Dudley syndrome
mu-crystallin, NADP-dependent TH binding protein	<i>Crym</i> 7	Low retention of T3 in brain	<i>CRYM</i> 16p13.11-12.3	Non-syndromic deafness

For references, see text.

For details of chromosome locations, see Mouse Genome Informatics, <http://www.informatics.jax.org/> and Online Mendelian Inheritance in Man, <http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM>

Table 2**Nervous system phenotypes associated with targeted mutations in thyroid hormone receptor genes in mice**

Nervous system phenotypes associated with targeted mutations in the *Thrb* and *Thra* receptor genes in mice. Compiled from studies of both null (knockout) and change-of-function (knock-in) mutations. See text for details.

<i>Thra</i> , thyroid hormone receptor α	References
Reduced glucose utilization in brain	Itoh et al, 2001
Synaptic impairment (whisker-barrel pathway)	Esaki et al, 2003
Learning deficiency	Guadano-Ferraz et al, 2003, Wilcoxon et al, 2007
Cerebellar defects	Morte et al, 2002, Venero et al, 2005
Purkinje cell defects	Heuer et al, 2003
Anxiety-like behaviour	Venero et al, 2005
GABAergic neuron defects	Morte et al, 2003, Venero et al, 2005
Oligodendrocyte differentiation defects	Billon et al, 2002, Baas et al, 2002
Astrocyte differentiation defects	Morte et al, 2004
Mating behaviour abnormality	Dellovade et al, 2000
Neurogenesis defect	Lemkine et al, 2003
<i>Thrb</i> , thyroid hormone receptor β	
Deafness	Forrest et al, 1996
Color blindness	Ng et al, 2001
Circadian entrainment defects	Dkhissi et al, 2007
Audiogenic seizure susceptibility	Ng et al, 2001
Mating behaviour abnormality	Dellovade et al, 2000
Cerebellar defects	Hashimoto et al, 2001
Hyperactivity, Impaired "vigilance"	Siesser et al, 2005

Selected references only are given. See text for additional references.