GLIOENDOCRINE SYSTEM: EFFECTS OF THYROID HORMONES IN GLIA AND THEIR FUNCTIONS IN THE CENTRAL NERVOUS SYSTEM

Mami Noda

Laboratory of Pathophysiology, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan

Abstract

Glia play a significant role in the link between the endocrine and nervous systems. Among hormones, thyroid hormones (THs) are critical for the regulation of development and differentiation of neurons and glial cells, and hence for development and function of the central nervous system (CNS). THs are transported into the CNS, metabolized in astrocytes and affect various cell types in the CNS including astrocyte itself. Since 3,3’,5-triiodo-L-thyronine (T3) is apparently released from astrocytes in the CNS, it is a typical example of glia-endocrine system.

The prevalence of thyroid disorders increases with age. Both hypothyroidism and hyperthyroidism are reported to increase the risk of cognitive impairment or Alzheimer’s disease (AD). Therefore, understanding the neuroglial effects of THs may help to solve the problem why hypothyroidism or hyperthyroidism may cause mental disorders or become a risk factor for cognitive impairment. In this review, THs are focused among wide variety of hormones related to brain function, and recent advancement in glioendocrine system is described.

Keywords

thyroid hormone • aging • microglia • astrocytes • oligodendrocyte

Abbreviations

AD......................... Alzheimer’s disease
AHDS..................... Allan-Herndon-Dudley syndrome
Akt......................... Serine/threonine kinase
albumin D-box ..... D site of albumin promoter
BBB ...................... Blood brain barrier
BHLHe22 ................. Basic helix-loop-helix family member e22
CSF ...................... Cerebrospinal fluid
CKI ......................... Cyclin-dependent kinase inhibitor
cGMP ...................... Cyclic guanosine phosphate
D2 ......................... Type 2-deiodinase
D3 ......................... Type 3-deiodinase
DBP ....................... Albumin D box-binding protein
FAO ....................... Fatty acid oxidation
GS ........................ Glutamine synthetase
NA ........................ Noradrenaline
CNS ...................... Central nervous system
GFAP ...................... Glial-fibrillary acidic protein
HADHA .................. Hydroxyacetyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase alpha
Hr ........................ Hairless
IFN-γ ...................... Interferon-gamma
iNOS ..................... Inducible NO synthase
KLF9 ...................... Kruppel-like factor 9
LAT ........................ L-type amino acid transporters
MAPK/ERK ............. Mitogen-activated protein kinase/extracellular signal-regulated kinase
MBP ....................... Myelin basic protein
MCT8 ..................... Monocarboxylate transporters 8
MOG ...................... Myelin/oligodendrocyte glycoprotein
Ncoa1 ................... Nuclear coactivator 1
Ncor1 .................... Nuclear corepressor 1
NO ........................ Nitric oxide
OATPs ..................... Organic anion-transporting polypeptides
OPCs ..................... Oligodendrocyte precursor cells
p27........................ p27/Kip1
p18 ....................... p18/INK
PI3K ...................... Phosphoinositide 3-kinase
ROS ...................... Reactive oxygen species
SLC16A2 .............. Solute carrier family 16 member 2

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SNPs ..................  Single nucleotide polymorphisms
T2 .....................  Diiodothyronines
T3 .....................  3,3’,5-triiodo-L-thyronine
T4 .....................  L-thyroxine
TBI .....................  Traumatic brain injury
THs .....................  Thyroid hormones
TNFα ...................  Tumor necrosis factor α
TR .........................  Thyroid hormone receptor

Introduction

More than two decades ago, it was already postulated that glial cells may play a significant role in the link between the endocrine and nervous systems [1]. In those days, THs, glucocorticoids, gonadal steroids, and neurosteroids were known to affect myelinization by acting on oligodendroglia, modulate astrocyte morphology, differentiation, and gene expression, and activate micoglia. Recently, more and more information has been supplied on the beneficial effects of hormone on the brain function. Pathologically, reduced level of hormones in aged brain or cerebrospinal fluid are reported, for example, noradrenaline (NA) [2], insulin [3, 4], THs, growth hormone, estrogen, etc. Among them, insulin, NA and THs regulate metabolic plasticity of astrocytes in aged brain [5]. Therefore, increasing the hormone is one of the ways to improve the aged brain. For example, intranasal insulin administration is speculated as a promising treatment of AD [6, 7], age-related cognitive deficits [8], and traumatic brain injury (TBI) [9]. The mechanism may be due to that insulin reduces nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor α (TNFα) production, inducible NO synthase (iNOS) expression, while increases phagocytic activity in activated microgla [10].

Not only metabolism-related hormones, social behavior-related hormones also target glial cell. For example, oxytocin seems to target microgla, in addition to neurons, and reduces inflammation in activated microgla [11], and perinatal brain damage [12], or improves neuropsychiatric disorders [13]. Among wide variety of hormones related to brain function, THs are focused and recent advancement in glial research is described.

Thyroid hormones in the CNS

Among hormones, THs are critical for the regulation of development and differentiation of neurons and glial cells, and hence for development and function of the CNS. In developing CNS, T3 exerts numerous effects regulating astrocyte and oligodendrocyte differentiation [14-21] and myelination [22]. In addition, THs may control the ratio of oligodendrocytes to astrocytes in white matter [23]. TH is also an important promoter of microglial growth and morphological differentiation [24]. Any impairment of THs supply to the developing CNS causes severe and irreversible changes in the architecture and function of the brain, leading to various neurological dysfunctions as mentioned below. Though the importance of THs during developing brain is obvious, there are few reports on the role of THs in glial cells in adult brain. In the adult brain, THs pathologies, for example hypothyroidism and hyperthyroidism, can cause psychiatric abnormalities such as schizophrenia, bipolar disorder, anxiety and depression. While impact of hypothyroidism and hyperthyroidism on synaptic transmission and plasticity is getting obvious, their effects on glial cells and related cellular mechanisms remain enigmatic.

THs are transported into the brain, metabolized in astrocytes and affect various cell types in the CNS including astrocyte itself. THs have to cross multiple membranes in order to reach their receptors in the nuclei and mitochondria in addition to the ones in the cytoplasm. Especially, THs need to enter the brain through the blood brain barrier (BBB). Astrocytes, forming partly the BBB, are the main cell population incorporating circulating L-thyroxine (T4) through TH transporters. Circulating T4 is transported across the BBB via specific transporters, such as organic anion-transporting polypeptides (OATPs) containing OATP14/SLCO1C1 (OATP1c1) [25-27] and OATP1a2 [28-30], L-type amino acid transporters (LAT1 and LAT2) [31], and monocarboxylate transporters 8 (MCT8) (SLC16A2) (for both T3 and T4) [32] (for review, see [33]).

Recently, an important role of radial glia in controlling TH delivery and metabolism is also suggested [34]. Transported T4 into astrocytes is de-iodinated by type 2-deiodinase (D2) to produce T3 [35-37]. Subsequently T3 is released via LAT [38, 39], presumably LAT2, and taken up by other cells via distinct transporters (paracrine signaling). For example, adjacent neurons express MCT8. They also express TH receptors and type 3-deiodinase (D3) which inactivates T3. Since the neuronal paracrine pathway is regulated by hypoxia, ischemia, or inflammation, it is postulated that deiodinases could act as potential control points for the regulation of TH signaling in the brain during health and disease [40]. Since T3 is apparently released from astrocytes in the CNS, it is a typical example of glioendocrine system, a term originally proposed to generally describe interactions between endocrine system and glial cells (Figure 1).

The prevalence of thyroid disorders increases with age [41, 42]. Abnormal levels of THs often causes psychological and behavioral abnormality. Hypothyroidism is one of the most common causes of cognitive impairment [43-46], and can lead to psychiatric symptoms [47]. The complicated problem
Effects of THs on microglia

Microglia express TH transporters such as OATP4a1, LAT2 and MCT10 [58] and TH receptors such a TRα1 and TRβ1 in cultured rat microglia [24]. T3 is important for microglial development [24], and could directly or indirectly stimulate morphological maturation of amoeboid microglial cells and limit their degeneration [59].

In addition to their genomic effects during development, nongenomic signaling of THs through a plasma membrane-localized receptor has been described [60]. For example, in osteoblast cells, TH signaling is induced through plasma membrane-bound TH receptors and couples to increases in intracellular Ca²⁺ concentration, NO, and cyclic guanosine phosphate (cGMP), leading to activation of various kinases such as protein kinase G II, tyrosine kinase Src, extracellular signal-related kinase (ERK), and serine/threonine kinase Akt [61]. Similarly in primary cultured microglial cells, increased migration induced by T3 was observed within 15 min and seems to be due to distinct intracellular signaling pathways [62] (Figure 1). T3 stimulates microglial migration and phagocytosis in vitro and in vivo [62, 63] and induces their morphological changes in sex- and age-dependent manner [64], which are summarized in a review [65]. Microglial migration is mediated through T3 uptake by TH transporters and binding to the TRs. Then TH signaling in microglia involved several signaling pathways including G/β-protein, phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK)/ERK, as reported in ATP-induced microglial migration [66] or bradykinin [67] or galanin [68] with slight difference. T3-induced NO signaling [61] is also present in microglia [62]. In addition, Na⁺/K⁺-ATPase, reverse mode of Na⁺/Ca²⁺exchanger, activation of Ca²⁺-dependent K⁺ channel, and GABA receptors likely contribute to T3-induced microglial migration [62], although it is only speculated from pharmacological analyses and the precise mechanism is still unknown. Considering these information, microglial dysfunction in hypothyroidism or hyperthyroidism may be closely related to psychological or cognitive symptoms in elderly patients, which needs be investigated in the future.

Effects of THs on astrocytes

Effects of THs on astrocytes and regulation of gene expression by THs in cultured astrocytes have been reviewed [27, 69, 70]. However, non-genomic effects of THs in astrocytes still remain to be investigated. Since astrocytes metabolize T4 to active form (T3) [71], they play a central role in the endocrine control of neural environment [27]. Cultured astrocytes express relevant genes of T3 receptors, TH receptor α1 (Thrα1) and TH receptor β (TRβ), presumably both in the nucleus/mitochondria and in the cytoplasm, and nuclear coressper (Ncor1) and coactivator (Ncoa1), in addition to D2 and TH transporter (Mct8/Sic16a2) (autocrine signaling) [70]. During CNS development, T3 exerts various effects in astrocyte differentiation [17, 72], as well as neuronal maturation due to astrocytic production of extracellular matrix proteins and growth factors [71]. Mitochondrial metabolism in astrocytes plays a significant role in neuroprotection. Mitochondrial energy production is rapidly increased via a mitochondrial targeted TH receptors after treatment with T3 [73]. Therefore, targeting astrocyte metabolism to increase brain ATP levels could be an efficient strategy to enhance neuroprotection. Stimulating endogenous ATP release from astrocytes has also been reported to induce antidepressant-like effects in mouse models of depression [74]. Although most energy in the CNS is derived from glucose catabolism, significant energy can also be derived from fatty acid oxidation (FAO) which is stimulated by THs. It has been
shown that hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase alpha (HADHA), an essential component of the mitochondrial trifunctional protein complex in the FAO cycle, is critical for the FAO regulation by T3 [75]. Since 95% of HADHA co-localize with glial-fibrillary acidic protein (GFAP) in the brain, T3 is considered to upregulate HADHA and subsequent neuroprotective mitochondrial energy production via FAO in astrocytes.

Expression alterations of genes using hypothyroidism model rats show that immature astrocytes immunoreactivity for vimentin and GFAP are increased in the corpus callosum (Shiraki et al., 2014). Analyses of human brain gene expression databases indicate that the chromosome 12p12 locus, where many genomic markers are related to dementia risk, may regulate particular astrocyte-expressed genes induced by T3. Two single nucleotide polymorphisms (SNPs) on chromosome 12p12, rs704180 and rs73069071, were found as risk alleles for non-Alzheimer’s neurodegeneration [76, 77] and hippocampal sclerosis pathology [78]. The rs73069071 risk genotype is also associated with altered expression of a nearby astrocyte-expressed gene, SLCO1C1. SLCO1C1 protein transports TH into astrocytes from blood. Interestingly, total T3 levels in cerebrospinal fluid (CSF) are elevated in hippocampal sclerosis cases but not in Alzheimer’s disease cases, relative to controls [78]. This suggests that even normal level of T3 in the CSF, astrocyte-TH dysregulation in the brain due to genetic modification contributes to dementia in the elderly. Energy metabolism in hypothroid brain leads to disruption in astrocyte cytoskeleton as well as glutamatergic and cholinergic neurotransmission, Ca** equilibrium, redox balance, morphological and functional aspects in the cerebral cortex even in young rats from maternal hypothyroidism [79].

**Effects of THs on oligodendrocytes**

TH signaling in oligodendrocytes has been also reviewed [80], which suggest both non-genomic and genomic pathways. Requirments of THs in growth and development of oligodendrocyte both in vitro and in vivo are reported [81-83]. THs also regulate oligodendrocyte accumulation in developing rat brain white matter tracts [20] as well as neural stem cells and oligodendrocyte precursor cells (OPCs) in adult brain [84]. A direct effect of T3 on oligodendrocytes is reported as a stimulant of sulfolipid synthesis, cholesterogenesis and lipogenesis by oligodendrocytes in neurone-free culture system [85]. TH receptors and their isoforms are also reported in oligodendrocytes [86-89]. THs are required for different timing in oligodendrocyte differentiation and devlopment [90, 91], for example at the terminal differentiation [92, 93] or during early stage [94] of OPCs into myelinating oligodendrocytes, by regulating the probability of cell-cycle withdrawal [95] or depending on the expression of TRα1 [96]. There are bimodal effects of TRα1 on cerebellum oligodendrocyte differentiation; At the early postnatal stage, it promotes the secretion of several neurotrophic factors by acting in Purkinje neurons and astrocytes. At later stages, TRα1 acts in a cell-autonomous manner to ensure the complete arrest of OPC proliferation, explaining contradictory observations made on various models, T3 signaling for synchronizing postnatal neurodevelopment, and restraining OPC proliferation in adult brain [97]. TRβ seems to be also important; a β receptor selective thyromimetic can enhance oligodendrocyte differentiation in vitro and during developmental myelination in vivo, suggesting a usefulness as a therapeutic agent for demyelinating models [14].

Important components of TH-regulated timer are cycline-dependent kinase inhibitor (CKI), p27/Kip1 (p27) or p18/INK (p18) [98]. On the other hand, during TH-induced OPC differentiation, both p53 and p73, but not p63, are involved [99]. During oligodendrocyte differentiation and myelin regeneration, 4 transcription factors are regulated specifically by T3; They are Kruppel-like factor 9 (KLF9), basic helix-loop-helix family member e22 (BHLHe22), Hairless (Hr), and Albumin D box-binding protein (DBP) [100] which is also known as D site of albumin promoter (albumin D-box). Perinatal rodent OPCs cultured with TH under hypoxia become quiescent and acquire adult OPCs-like characteristics, though the mechanism is not clear yet. So far, it is known that the CDK inhibitor, p15/INK4b, plays crucial roles in the TH-dependent cell cycle deceleration in OPCs under hypoxia, while KLF9 is a direct target of TH-dependent signaling [101].

THs affect Schwann cell and oligodendrocyte gene expression [102] and distribution of oligodendrocyte/myelin markers during differentiation [103]. Though glutamine synthetase (GS) is an marker of astrocytes [104], GS as well as myelin/oligodendrocyte glycoprotein (MOG) are involved in maturation of oligodendrocytes [105]. While T3 does not affect on myelin basic protein (MBP) gene expression, T3 stimulates the expression and activity of GS in oligodendrocytes after a lag time through a posttranscriptional event [106]. Therefore THs independently regulate proliferation of OPCs and oligodendrocyte maturation [92, 105]. In addition, it is noteworthy that responsiveness of OPCs to THs is different in different brain area [107].

Using human cultured CD34+ stem cells, differentiation of stem cells into OPCs is stimulated by THs [108]. However, interferon-gamma (IFN-γ) produces a dose-dependent apoptotic response in OPCs [109] or abrogates TH-induced differentiation of OPCs into oligodendrocytes but not into astrocytes. Therefore, as a result, action of IFN-γ gives rise to astrocytes [110].
Therapeutic importance of THs and glial cells

As mentioned above, THs deficiency in developing brain results in low number of microglial cells [24], and immature differentiation of both astrocytes and oligodendrocytes, causing morphological changes in the brain. In hypothyroid model animal, anxiety-like behavior is reported in the male mice [111]. In this model, the spine density on basal dendrites in the CA1 of the hippocampus is not changed but T3-treated hypothyroid mice show lower spine density. This additional effect may be explained by the result of increased microglial phagocytosis [62], though the contribution to the therapeutic outcome is not known. As for the spine density, decrease in spine density by T3 in CA1 region was also reported in adult female rats [112]. Dysfunction of THs impairs myelination. Not only during development but also in the adult brain. For example, THs promote differentiation of oligodendrocyte progenitor cells and improve remyelination after injury [113].

Human mutations of the gene, solute carrier family 16 member 2 (SLC16A2), encoding MCT8, result in the X-linked inherited psychomotor retardation and hypomyelination disorder, Allan-Herndon-Dudley syndrome (AHDS). It is also reported that mutation of neuronal MCT8 and disrupted T3 uptake by neurons are responsible [114]. Likewise, pharmacological and genetic blockade of MCT8 induces significant oligodendrocyte apoptosis, impairing myelination as a result. Treatment with an MCT8-independent TH analog limits oligodendrocyte apoptosis mediated by SLC16A2 down-regulation, driving myelination. Therefore, MCT8-independent TH analog is implicated as a promising treatment for developmentally regulated myelination in AHDS [115]. It was also reported that THs alleviates demyelination induced by cuprizone through its role in remyelination [116]. On the contrary, lowering T3 signaling accelerates the reinnervation of the optic tectum following optic nerves crush in adult zebrafish [117]. Since TH is known as a promoter of differentiation of oligodendrocyte, TH is used to validate high-throughput drug screening assay to identify compounds that promote oligodendrocyte differentiation [118].

Conclusion

THs are important factors both functionally and morphologically for glial cells during development and in adulthood. Therefore, brain dysfunction due to abnormal level of THs could be treated, at least partially, by targeting glial cells.

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Conflicts of Interest Statement

The author declares that there is no competing interest.

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**Figures**

**Figure 1.** Glioendocrine system and functions of THs in the CNS. Circulating T4 is transported across the blood-brain barrier via specific transporters and enters into astrocytes, where it is type 2-deiodinase (D2) to produce T3. Subsequently T3 is released by transporters, and taken by other cells such as microglia, oligodendrocytes, and neurons via distinct transporters. T3 also affects astrocytes as autocrine signal.