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The role of Thyrotropin Releasing Hormone in aging and neurodegenerative diseases

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Abstract

Thyrotropin releasing hormone (TRH) is primarily known as the central regulator of the hypothalamic-pituitary-thyroid (HPT) axis. However, TRH also exerts a variety of central nervous system effects independent from its activity in the HPT axis. With advancing age, decreases in TRH synthesis, expression, and activity have been demonstrated. Associated with this emerging evidence suggests that TRH is implicated in neurodegenerative diseases of aging, including Alzheimer's disease and Parkinson's disease. TRH and its synthetic analogs have been recognized as trophic factors in neurons of the diencephalon and spinal cord, and as neuroprotectants against oxidative stress, glutamate toxicity, caspase-induced cell death, DNA fragmentation, and inflammation. In this review, we will provide an overview of some of the roles of TRH, outside of the HPT axis, associated with pathological aging and neurodegeneration and we shall discuss the potential of TRH and TRH analogs for the treatment of neurodegenerative diseases.

Keywords

Thyrotropin Releasing Hormone; Alzheimer's Disease; Parkinson's Disease; Neuroprotection; Aging

1. Introduction

The tripeptide thyrotropin releasing hormone (TRH; L-pyroglutamyl-L-histidyl-L-prolineamide (L-pGlu-L-His-L-ProNH₂), Fig. 1A) is primarily known for its role as the central regulator of the hypothalamic-pituitary-thyroid axis (HPT axis). The HPT axis plays a crucial role in regulating and maintaining somatic metabolism, thermogenesis, blood pressure, core body temperature, respiration rate, and food and water intake (Jackson 1982; Nillni, 2010). TRH is distributed throughout the brain and the periphery; reports describe the presence of TRH in the hypothalamus, pituitary, brainstem, cerebellum, cortex, thalamus, hippocampus, as well as the pancreas, gastrointestinal tract, and spinal cord (Nillni, 2010; Koch and Okon, 1979; Low et al., 1989; Winters et al., 1974; Kardon et al., 1977; Engler et al., 1981).

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Produced in the hypothalamus, TRH acts upon cognate G protein-coupled receptors (GPCRs) expressed in anterior pituitary thyrotroph cells to evoke the release of thyroid stimulating hormone (TSH) (Nillni, 1999). TSH then stimulates the release of thyroid hormones thyroxine (T_4) and its modified product triiodothyronine (T_3), which in turn act upon the thyroid and influence energy metabolism, endocrine hormonal signaling, and generic protein synthesis. In addition to the release of thyroid hormones, TRH also stimulates the release of prolactin and growth hormone, the latter of which is specifically affected by the presence of various pathophysiological conditions including acromegaly, renal failure, liver disease, cancer, diabetes mellitus, anorexia and bulimia nervosa, schizophrenia, and depression (Freeman et al., 2000; Harvey, 1990; Ohbu et al., 1995). Circadian rhythms play a large role in affecting thyroid function (Gan and Quinton, 2010), as rat studies have shown TRH release to be dependent upon the light-dark cycle and TSH release in humans show a peak response between the hours of 2 and 4 AM (Haus, 2007).

While the primary functions of TRH are classically associated with the HPT axis, TRH also exerts a number of central nervous system (CNS)-mediated actions that are not classically associated with HPT activity (Gary et al., 2003). For example, TRH is also known to play a role in regulating mood (Sun et al., 2010), arousal (Hara et al., 2009), cognition (Molchan et al., 1990), anxiety (Gutierrez-Mariscal et al., 2008), and motor coordination (Pitts et al., 1995; Kinoshita et al., 1998). Additionally, some of the peripheral effects of TRH and its analogs include the ability to increase insulin absorption in the pancreas (Koo et al., 2011), regulation of motility (Varanasi et al., 2002) and acid secretion (Tache et al., 1980) in the gastrointestinal tract, ionotropic support in the heart (Jin et al., 2004), and regulation of hair growth (Gaspar et al., 2010). TRH has also been demonstrated to exert trophic actions in lower motor neurons of the spinal cord (Van den Bergh et al., 1991), and pro-TRH gene expression has been shown to play a role in preventing neuronal apoptosis in the CNS. Furthermore, long-term stimulation of clonal human fibroblast cells (HEK293) cells with TRH can engender multiple antiapoptotic effects, such as a decrease in caspase 3 and increased expression of mitochondrial proteins thought to play a role in antiapoptotic activity (Drastichova et al., 2010). Many of the CNS effects of TRH are coordinated through the coherent modulation of neurotransmitters such as glutamate, dopamine, norepinephrine, serotonin, acetylcholine, and GABA (Malthe-Sorensen et al., 1978; Yarbrough, 1979; Deng et al., 2006; Jantas et al., 2009). As with most complex CNS signaling systems, it is evident that many of these same neurotransmitters (nor/epinephrine, dopamine, serotonin) also possess the ability to feedback and influence TRH release (Jackson, 1982; Wittman, 2008). In particular, the ability of dopamine to functionally regulate TRH activity represents an important mechanistic locus in Parkinson's Disease (PD).

The central effects of TRH have attracted considerable attention for their potential use as treatments of various neurological conditions, such as CNS trauma, epilepsy, depression, spinocerebellar degeneration, and Alzheimer's disease (AD) (Faden and Salzman, 1992; Horita, 1998; Vetulani and Nalepa, 2000; Kubek and Garg, 2002; Luo et al., 2002). We will focus specifically on the potential therapeutic value of TRH and TRH analogs in this regard to age-related neurodegenerative disorders. We summarize the most recent evidence concerning TRH synthesis, processing, and clearance and TRH receptor expression and signaling. We also will discuss the most recent literature focused upon age-associated changes in TRH functionality, and its mechanistic role in multiple neurodegenerative disorders. We conclude with a discussion of potential TRH analogs which could prove therapeutic for neurodegenerative disorders.

2. TRH synthesis, processing, and clearance

2.1 TRH synthesis and processing

TRH is primarily synthesized in the hypothalamus (Jackson, 1982). TRH is synthesized in the lateral hypothalamic regions of the hypothalamus, in particular the paraventricular nuclei and the anterior paraventricular nuclei (Jackson, 1982). In the medulla, nuclei in the raphe pallidus, raphe obscurus, and parapyramidal regions also contain TRH synthesizing neurons (Palkovits et al., 1986). Additionally, there is a possibility that a small portion of the TRH present in the hippocampus is produced locally (Low et al., 1989), as CA3 pyramidal cells have been shown to contain TRH pro-hormones immunoreactive to TRH, though the majority of TRH found in the hippocampus is produced extrinsically. Following TRH transcription, ribosomal translation of the mRNA results in pro-TRH (Monga et al., 2008). Mature TRH is derived from pro-TRH by post-translational modifications - specifically the cleavage of pairs of Lys-Arg residues - by the prohormone convertases PC1 (also known as PC3) and, to a lesser degree, by PC2 (Nillni et al., 1996). Additional amidization and cyclization results in the formation of the final active TRH peptide (Monga et al., 2008).

Regulation of TRH expression occurs via a negative-feedback mechanism occurring within the paraventricular nucleus (PVN) of the hypothalamus. Hence, levels of circulating thyroid hormone are inversely related to the level of pro-TRH mRNA present in the PVN (Sergerson et al., 1987; Chiamolera and Wondisford, 2009). Additional evidence suggests that it is T₃, and not T₄, that is responsible for exerting this effect (Maruta and Greer, 1988). Prohormone convertases are also capable of influencing TRH expression, as drug-induced hypothyroidism can result in increased levels of PC1/3 and PC2 expression and thus increased pro-TRH levels within the ventromedial nucleus and lateral hypothalamus (Espinosa et al., 2007). Pekary and colleagues have identified other modulators of TRH and TRH-like peptide release including: ghrelin (Pekary et al., 2012), prazosin (Sattin et al., 2011), corticosterone (Pekary et al., 2008), lipopolysaccharides (LPS) (Pekary et al., 2007), and leptin (Pekary et al., 2010). Additionally, corticotrophin releasing hormone (CRH) has demonstrated a capacity to decrease TRH levels in multiple regions of the brain (Tsigos and Chrousos, 2002).

2.2 TRH Clearance

TRH is rapidly metabolized with a half-life ($t_{1/2}$) ranging from 4 to 5 minutes in both rats and humans (Griffiths, 1976). At the cellular level, cytoplasmic TRH is inactivated by two enzymes: prolyl oligopeptidase (POP, prolyl endopeptidase (PEP)) and pyroglutamyl aminopeptidase I (PGP I (PAPI, PPI)) (Agirregoitia, et al., 2007). POP is responsible for the deamidation of TRH (cleavage of the Pro-NH₂ bond), while PGP I removes the N-terminal pyroglutamyl group (cleavage of the pGlu-His bond) (Agirregoitia et al., 2007). Both of these enzymes are distributed widely throughout the body, including the brain, spinal cord, liver, kidney, pancreas, adrenal glands, and blood (Griffiths et al., 1983). POP is present in high levels within the kidney, cortex, and liver, and to a moderate degree in the hypothalamus, adrenal, testis, and ovary (Fuse et al., 1990). High enzymatic activity levels of PGP I were reported in the kidney and liver, while moderate activity was reported in the hypothalamus, cortex, and spleen (Fuse et al., 1990). Conflicting evidence is reported in regard to peptidase expression in the pituitary gland. While some studies have found little to no peptidase activity in the pituitary, (Fuse et al., 1990), others report functional activity in the anterior pituitary (Griffiths et al., 1983). Another pyroglutamyl aminopeptidase, PGP II (thyroliberinase) is a membrane-bound enzyme that is mainly expressed in brain synaptosomes, and is found in highest concentrations in the cortex and hippocampus (Friedman and Wilk, 1986).

3. TRH receptor expression and signaling

3.1 TRHR expression

TRH exerts the majority of its effects through activation of two GPCR isoforms, the thyrotrophin releasing hormone receptor 1 (TRHR1) and TRHR2. Discovered and characterized in the early 1990s, both TRHRs are members of the rhodopsin/ α -adrenergic receptor-like family of GPCRs (Sun et al., 2003). In humans, the gene encoding TRH receptors has been assigned to chromosome 8 (Yamada et al., 1993). Morrison et al. (1994) later confirmed that the TRHR encoding gene is localized to region q23 on chromosome 8. TRH receptor expression is regulated by both TRH and T_3 , as both have been shown to be able to reduce the number of TRHRs in a mouse pituitary tumor cell line (Gershengorn, 1978). While both humans and rats express the TRHR1, to date TRHR2 expression has not been demonstrated in humans. It has, however, been shown to exist in rats, primarily in the CNS (Cao et al., 1998). Interestingly, a third TRH receptor subtype has been identified in *Xenopus laevis*, though a mammalian homologue has not been identified yet, and possible distinct functional roles of this third subtype have yet to be elucidated (Bidaud et al., 2002). In species possessing both TRHR1 and TRHR2, these two GPCRs show similarly high binding affinities to TRH. In rats the presence of TRHR2 in the brain is limited to select areas of the cortex, thalamus, hypothalamus, midbrain, hindbrain, cerebellum, amygdala and septal region (Sun et al., 2003). TRHR1 is found in all of these regions and in addition is also found in the hippocampus, pituitary, and alpha-motorneurons in the spinal cord. As expected however, the highest expression levels of TRHR1 are typically found in the pituitary. The notable absence of TRHR2 in the pituitary, combined with its presence in somatosensory and higher CNS activity regions in the brain, has led to speculation that TRHR2 is an important regulator of the non-endocrine, neuro-specific functions of TRH (Kaur et al., 2005). Peripherally, TRHR1 expression has been demonstrated in the heart, spleen, liver, lung, skeletal muscle, kidney, testes, stomach, small intestine, colon, adrenal medullas, and pancreas (Hokfelt et al., 1989; Mitsuma et al., 1995). In the periphery, TRHR2 has been found in the retina, testis, and the gastrointestinal tract (Mitsuma et al., 1999).

3.2 TRHR Signaling

In brief, activation of the TRH receptor (both TRHR1 and TRHR2) via TRH ligand binding leads to the activation of phospholipase C- (PLC-), which in turn hydrolyses phosphatidylinositol 4,5-P₂ (PIP₂) leading to the creation of 1,2-diacylglycerol (DAG) and inositol 1,4,5-triphosphate (InsP₃). These second messenger products can subsequently activate protein kinase C isoforms and mediate increases of intracellular calcium levels respectively (Gehret and Hinkle, 2010). As with many other rhodopsin-like GPCRs, the mitogen-activated protein kinase (MAPK) pathway has also been found to be a downstream effector of TRHR signaling (Ohmichi et al., 1994). Though both TRH receptors share a similar signaling pathway, Wang and Gershengorn have found striking differences in basal (ligand-independent) signaling activities (Wang and Gershengorn, 1999). Compared to TRHR1, TRHR2 demonstrates a higher basal signaling rate as measured by activation of pathways mediated by the transcription factors AP-1, Elk1, and CREB as demonstrated in the HEK293 cell line transfected with rat TRHR cDNA (Wang and Gershengorn, 1999). In addition to these factors, the regulator of G protein signaling 4 (RGS4) has also been shown to inhibit the basal activity rate of TRHR2 (Harder et al., 2001).

4. TRH and Aging

4.1 Age-related changes in TRH synthesis

It is generally agreed that major functional alterations in nearly every organ system result in diseases and other pathological conditions associated with the aging process (Maudsley et al., 2007; Cefalu, 2011; Maudsley et al., 2012). Not surprisingly, thyroid functioning and the HPT axis have been shown to undergo numerous changes with age (Stan and Morris, 2005). Thyroid function, in general, has often been studied in relation to cognition, and thereby cognitive disorders related to age. TSH levels are routinely used as a biomarker of cognitive decline in the elderly, and thyroid hormones influence cognitive development from the 10th week of gestation to adulthood, affecting such processes as maturation of neurons, mitochondrial enzyme activity, and expression of astrocyte structural proteins (Tan and Vasan, 2009). Indeed, thyroid hormones are necessary for proper brain development as demonstrated by the condition congenital hypothyroidism, in which the thyroid gland does not release sufficient thyroid hormone and mental deficiencies are then often observed (Morreale de Escobar et al., 2004).

At birth, CNS TRH levels are barely detectable; it is not until 2–3 weeks *post partum* that large increases in tissue TRH ligand binding (indicative of TRH receptor expression) and TRH mRNA levels are observed (Bayliss et al., 1994). These increases in TRH level off as rats approach adulthood, however with advancing age, TRH levels show a marked decrease in the hypothalamus and elsewhere in the brain (Cizza et al., 1992; Pekary et al., 1987). In addition to this, most animal studies also report a decrease in circulating T₄ levels with old age (Stan and Morris, 2005). Changes in TSH and T₃ with age however are less consistent and appear to be gender and strain specific. Greeley et al. (1982) found that increased age in female rats led to decreases in T₃ and T₄ while TSH remained unchanged (Greeley et al., 1982), however the same study found decreased T₄ and TSH mRNA in aged male rats, yet no change in serum T₃ levels. Similarly, enzymatic processing, receptor expression, and synthesis of TRH have also been demonstrated to change with age (Cizza et al., 1992; Stan and Morris, 1995).

In humans, lower levels of TSH have been found in the elderly, although no significant differences have been shown in TRH and free thyroxine serum levels between young, middle-aged, and elderly subjects (Mazzocchi et al., 2010). Decreased TSH responses to TRH stimulation have though been observed with advancing age in the human population (Monzani et al., 1996; Leitol et al., 2002), in addition to decreased secretion and degradation of T₄ (Fisher 1996); Hornick and Kowal, 1997) and decreased production of T₃ (Mariotti et al., 1995; Chiovato et al., 1997).

4.2 Age-related changes in TRHRs

In parallel to the age-related changes in TRH synthesis, expression of TRH receptors has been shown to decrease in rat cortex with age (Ogawa, 1985), coinciding with age-dependent decreases in TRH ligand immunoreactivity with age in rats (Shinoda et al., 1995). In the spinal cord, it has been shown that TRH decreases with age, though increases in preproTRH mRNA was found (Johnson et al., 1993). No study to date has examined changes in receptor expression in humans with age and thus further work is warranted in this regard.

4.3 Age-related changes in POP/PGP

Relatively little is known about the age-dependent expression of POP or PGP. POP activity has been found to be 2 to 5 times higher in newborn versus adult rat lung, heart, kidney and liver (Agirregoitia et al., 2003). The same generalization regarding the influence of PGP I on

development and maturation may also be made, although such conclusions appear highly dependent on the specific tissue examined, *i.e.* the trend for reduced activity with advancing age is clearly observed in the cortex but is less profound in the liver or heart. In contrast to these peripheral systems, POP gene expression has been shown to increase in the cortex and hypothalamus of mice (Jiang et al., 2001); furthermore, POP mRNA expression is also known to increase in the hippocampus with age and POP inhibitors have been shown to restore hippocampal levels of TRH in age accelerated mice (Rossner et al., 2005). In the periphery, POP is decreased with age though no significant changes were found in respect to the liver, kidney, and heart in rats (Agirregoitia et al., 2003). While some human clinical studies (Agirregoitia et al., 2003) have failed to find any significant changes associated with PGP I and aging, cerebrospinal fluid (CSF) levels of PGP I have been shown to decrease with advancing age (Prasad et al., 1987).

5. The potential role of TRH in neurodegenerative diseases

5.1 Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by gradual memory loss and dysfunction in at least one cognitive domain, ultimately leading to severe dementia and death (Maudsley and Mattson, 2006; Huang and Mucke, 2012). In 2012, 5.4 million Americans are reported to suffer from AD. This widespread prevalence places an enormous economic burden therefore in the health system, costing approximately \$200 billion dollars each year in health care fees (Alzheimer's Association, 2013). One of the primary risk factors for AD is advancing age and therefore with the progressive increase in lifespan in westernized societies, there is a likelihood of further increases in the AD numbers in the general population. In a small subset of AD cases, known as early-onset AD, age of onset is typically 40 to 50 years (Bertram et al., 2010), while 'classical' (late-onset) AD is typically more prevalent in the 60–80 year old population. It is believed that mutations of three key genes-amyloid precursor protein (APP), presenilin-1 (PS-1), and presenilin-2 (PS-2)- are responsible for the majority of early-onset AD cases (Bertram et al., 2010). In addition to these genomic loci for early-onset AD, the etiology of this disorder is also strongly influenced by a number of lifestyle and environmental factors such as cardiovascular health, exercise status and continued mental activity (Hebert et al., 2003). Classically, cognitive decline in late-onset AD has been attributed to two hallmark lesions within the brain – the neurofibrillary tangle (NFT), comprised of hyperphosphorylated tau, and the senile plaque, comprised chiefly of amyloid- (A β) protein aggregates (Hebert et al., 2003). There are however human cases (Giannakopoulos, 2003) and experimental animal studies (Chadwick et al., 2011) in which high amyloid plaque loads are associated with normal cognitive functioning. These findings have therefore lead to the development of alternative explanations of AD-related pathology, such as describing the pathology as a culmination of aberrant neural network activity, synaptic loss and dysfunction, and population-specific neurodegeneration caused by the alterations in the interactions of many elements and pathways (Huang and Mucke, 2012).

5.2. TRH and Alzheimer's Disease

One of the first elements thought to play a role in the etiology of AD was the neurotransmitter acetylcholine (ACh). The cognitive decline that accompanies the aging process temporally coincides with a loss of cholinergic neurons, thereby a cholinergic dysfunction within the CNS was associated with AD-like pathology (Bennett et al., 1997). Specifically, loss of ACh functioning has been associated with the memory loss seen in patients with AD (Bennett et al., 1997), and reinforcing this concept, pharmacotherapeutics capable of enhancing ACh function, *e.g.* cholinesterase inhibitors that preserve synaptic ACh, have been a common avenue for drug development. However, it is highly unlikely that

a process as complex as AD-related neurodegeneration is mediated by a single neurotransmitter dysfunction, therefore consideration must also be made to additional neuromodulatory factors that facilitate the proper functioning of neurotransmitters such as ACh. Therefore in addition to therapeutic regulation of ACh, a therapeutic approach that also includes potential neuromodulators, such as TRH, is likely to yield more efficacious therapeutic compounds (Bennett et al., 1997). Indicative of the potential utility of TRH-modulation in AD pharmacotherapeutic design, TRH administration can lead to ACh release in the cortex and the hippocampus (Giovannini et al., 1991) as well as increases of regional cerebral blood flow (attributed to changes in the cholinergic system) in experimental rats (Inanami et al., 1988). TRH and TRH analogs can also accelerate ACh turnover rate in the hippocampus (Kinoshita et al., 1996; Malthe-Sorensen et al., 1978), and TRH and its analogs have also been shown to increase long-term potentiation, the biochemical process thought to underpin the cognitive ability to acquire new memories (Ishihara et al., 1991; Tamaki and Kameyama, 1982; Yamamoto and Shimizu, 1988; Morimoto and Goddard, 1985). TRH can also demonstrate neuroprotective effects through an effective inhibition of GSK-3 β activity (Luo and Stopa, 2004). In addition, TRH gene depletion can enhance tau and GSK-3 β expression in cultured rat hippocampal neurons; while in contrast, TRH administration can effect a 75% decrease in GSK-3 β and a 90% decrease in tau phosphorylation (Luo and Stopa, 2004). TRH analog ligands can also exert protective effects against A β toxicity in neuronal cell culture (Faden et al, 2005), reduce inflammatory cytokines TNF- α and IL-6 and attenuate lipid peroxidation, all of which have been implicated in oxidative stress and the predisposition for AD (Rajput et al., 2011). The TRH analog, 3-methyl-histidine-TRH, has also been shown to functionally antagonize glutamate-mediated neurotoxicity in fetal neurons in a concentration-dependent manner (Veronesi et al., 2007). Administration of L-T₄ in mice injected intrahippocampally with aggregated A β was shown to prevent cognitive impairment and improve memory function (Fu et al., 2010). Further highlighting the potential neuroprotective role of TRH in the CNS, interactions have been reported between TRH and calpain, a calcium-sensitive protease that when over-activated has been linked to multiple degenerative conditions including AD (Vanderklish and Bahr, 2000). Eto et al. (1995) have shown that TRH is capable of inducing translocation of m-calpain from the cytosol to the cell membrane while also up-regulating the endogenous calpain protease inhibitor calpastatin in rat pituitary GH4C1 cells. A recent study has additionally shown that CNS-specific calpain-1/calpain-2 knockout mice show significant reductions in dendritic branching complexity and density, suggesting that calpain plays a crucial role in synaptic plasticity, thereby having obvious therapeutic implications for both aging and age-related disorders like AD (Amini et al., 2013).

TSH and T₃ have also been studied in relation to the activity of amyloid precursor protein (APP). TSH influences the expression, maturation, and secretion of APP in thyrocytes (Graebert et al., 1995) and T₃ has been shown to regulate APP gene splicing, in addition to processing and secretion of APP peptides (Latasa et al., 1998). Additionally, intracellular levels of both APP protein and mRNA in human neuroblastoma SH-SY5Y cells are decreased in response to T₃ dosing (Latasa et al., 1998) and in murine neuroblastoma cells T₃ treatment represses APP gene expression (Belandia et al., 1998). Further linking APP functionality to TRH activity, it has been demonstrated that in rat models of hypothyroidism, increases in the APP protein are observed in the cortex and hippocampus (Contreras-Jurado and Pascual, 2012). Luo et al. (2002) have shown that total TRH is decreased in the hippocampus of AD patients (Luo et al., 2002), while modest improvements in indices of cognitive function in patients with AD from high dose TRH hormone infusion have also been demonstrated (Mellow et al., 1989). Alterations in TSH have also been implicated as a risk factor for AD and dementia, though associations between both increased (Ganguli et al., 1996; Labudova et al., 1999) and decreased (Van Osch et al., 2004; Kalmijn et al., 2000; Annerbo et al., 2006) levels of TSH or TSH receptors and AD/dementia have been reported

by multiple groups. One study reported that women, but not men, with both lower or higher than normal thyrotropin levels were at an increased risk of developing AD (Tan et al., 2008). Furthermore, TSH levels and regional cerebral blood flow concentrations have been correlated in the right hemispheres of patients with AD (Kimura et al., 2011), while higher T₄ levels and T₃:T₄ ratio have also been shown to correlate with an increased risk for AD/dementia and a worsening of cognitive function in subsequent tests (Sampaolo et al., 2005; Steurenburg et al., 2006; de Jong et al., 2009). Lower T₃ levels have been observed in post-mortem AD patients, leading to speculation that perhaps conversion from T₄ to T₃ is affected in AD (Davis et al., 2008). As with many studies involving the complex interplay between hormonal axes, often contradictory evidence is also found for the involvement of a specific hormone in pathophysiological processes. For example, in individuals already diagnosed with a thyroid disorder, administration of thyroid-treating medication can actually lead to a faster progression of a diagnosis of Dementia of the Alzheimer type (DAT) (Harper and Roe, 2010). However, it is also the case that studies have tried to corroborate the connection between thyroid dysfunction and cognitive functioning and instead found no strong association between thyroid dysfunction and increased risk for AD or poorer performance in cognitive functioning tests (Amaducci et al., 1986; Lawlor et al., 1988; Small et al., 1985; Franceschi et al., 1988). Despite these divergent reports, there is ample evidence to suggest a mechanistic relationship between thyroid functioning and AD and other types of dementia, even if the mechanism underlying this relationship is not completely understood.

With respect to the processing of TRH in a neurodegenerative setting, POP activity has been shown to be significantly upregulated in the hippocampus and hypothalamus of murine AD models (Rossner et al., 2005). The potential actions of POP in AD may not though be solely limited to modifying TRH processing as POP also plays a role in hydrolyzing several other peptides and hormones, many of which are affected in AD and neuroinflammatory conditions (Penttinen et al., 2011). For example, alterations consistent with inflammation have been observed in microglia and astrocytes surrounding senile plaques, in addition to the presence of proinflammatory markers and elevated chemokines and cytokines surrounding these plaques (Glass et al. 2010).

Though the relationship between TRH and AD is far from completely understood, initial clinical findings show promise. The effects of TRH upon ACh release/turnover and the thyroid hormone effects on APP expression/processing are also encouraging. Taken together, varied lines of evidence suggest an interaction between TRH and AD, though future studies are needed to more comprehensively understand this interaction.

5.3 Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disease characterized by the presentation of dysregulated motor functions, including bradykinesia, tremors, and muscle stiffness. A number of non-motor symptoms can also characterize PD including memory loss, changes in mood and cognition, changes in sensory perception, sleep patterns, and a loss of smell (Fritsch et al., 2012). According to the National Parkinson Foundation, 50,000–60,000 new cases of PD are diagnosed each year, in addition to the approximately one million patients currently suffering from PD. PD is typically caused by a degeneration of dopamine-producing cells in the striatum, but the initial cause of this degeneration is still not completely understood (Heisters, 2011). Similar to the amyloid and tau protein aggregates in AD, PD patients also demonstrate pathological protein inclusions of the synaptic protein α -synuclein. These α -synuclein-rich protein inclusions are also known as Lewy bodies and accumulate in dopaminergic neurons, especially those present in the substantia nigra (Crosiers et al., 2011). In addition to aging and gender (Hindle, 2010), environmental (Elbaz and Moisan, 2008) and genetic (Crosiers et al., 2011) factors are thought to play a role in the

initiation and etiology of PD. Similar to AD, PD exists in two temporally-distinct forms: early and late onset PD. Early-onset PD is primarily attributed to mutations in the α -synuclein gene (Singleton et al., 2003), which is thought to play a role in synaptic transmission, axonal transport, and regulation of dopamine release (Myohanen et al., 2012). Early-onset PD is also linked to the presence of mutations in leucine-rich repeat kinase-2 and dysregulation of neuronal manganese homeostasis (Covy and Giasson, 2009).

5.4 TRH and Parkinson's Disease

TRH is known to activate presynaptic dopaminergic neurons in the striatum, causing the release of dopamine from nerve terminals (Crespi et al., 1986). Other studies have demonstrated that intrastriatal injection of TRH can effectively increase synaptic dopamine release (Cantuti-Castelvetri et al., 2010). From a functional therapeutic standpoint, sustained release of TRH has been shown to ameliorate PD-related symptomology in experimental rat PD models (Ogata et al., 1998). In addition to improvements in motor function, sustained release of TRH also resulted in increased striatal levels of dopamine. Additional studies have examined the effects of the TRH analogs montirelin (CG-3703), RGH-2202, and Z-TRH (N-(carbobenzyloxy)-p-Glutamyl-Histidyl-Proline) on human neuroblastoma SH-SY-5Y cells, which can demonstrate a strong dopaminergic phenotype. Treatment of the SH-SY5Y cells with any of these three analogs was able to attenuate cell damage experimentally induced by excitotoxicity and apoptotic agents (Jaworska-Feil et al., 2010).

While some of the first studies conducted in PD patients found no direct evidence of alterations in TRH or thyroid hormone levels (Javoy-Agid et al., 1983; Berger and Kelley, 1981), more recent studies however have since demonstrated elevated TSH levels in PD patients in response to a TRH response test (Otake et al., 1994; Lestingi et al., 1992). Similarly, Kihara et al. (1993) concluded that TRH-induced functioning of the sympathetic nervous system must be impaired in PD patients, as patients given TRH failed to respond normally when compared to controls in a 'sweat test' (Kihara et al., 1993). Overall thyroid function has also been measured patients with PD, though the results do not reveal a conclusive answer in regard to what role, if any, thyroid function plays in the presentation of PD. Some groups have found no significant relationship between thyroid functioning and PD (Schaefer et al., 2008; Vogel and Ketsche, 1986; Novakova et al., 2011), while others have found associations between thyroid functioning and PD. For example, slight increases in free T₄ were found in early-stage PD (Aziz et al., 2011) and both hyperthyroidism and hypothyroidism are reportedly more common in PD patients than in the general population as a whole (Tandeter et al., 2001; Munhoz et al., 2004; Berger and Kelley., 1981; Verges et al., 1988; Lavy et al., 1974). In one case report, Parkinsonian tremors reportedly showed improvement as a man presenting with hyperthyroidism was treated for his thyroid condition (Kim et al., 2005). While a considerable degree of further investigation is warranted on this specific neurodegenerative connection to TRH, there is clearly some emerging evidence to suggest a potentially therapeutically important link between TRH, or thyroid function more generally, and PD exists.

Perhaps more promising is the connection between POP inhibitors and the treatment of PD. POP has been shown to accelerate the aggregation of wild-type α -synuclein, while POP inhibitors have been shown to decrease the number of cells with α -synuclein inclusions (Lambeir 2011). In transgenic mice, a 5-day treatment with the POP inhibitor KYP-2047 reduced the amount of α -synuclein immunoreactivity and soluble α -synuclein protein present in the brain (Myohanen et al., 2012). Similarly, S 17092, another POP inhibitor, was effective in improving cognitive functioning in a primate model of early-onset Parkinsonism (Schneider et al., 2002). Reinforcing the role of POP in neurodegenerative conditions, lower POP activity rates have been found in multiple neurodegenerative disorders, including both PD and as well as Huntington's disease (Mantle et al., 1996).

6. TRH analogs as potential treatments for neurodegenerative disorders

While administration of TRH to patients with AD has produced moderately beneficial effects (Mellow et al., 1989), the benefits are only observed when high levels of hormone are infused. Indeed, given that TRH requires a considerable amount of time to cross the blood brain barrier (BBB), yet is rapidly inactivated (Jackson, 1982), it is perhaps more viable to consider analogs of TRH as possible therapeutics, as they are longer lasting and more able to cross the BBB (Prokai-Tatrai & Prokai, 2009). As TRH is a tripeptide, modification of either the pGlu, His, or proNH₂ residues, or any combination of these residues, will result in an analog of the compound. All of these theoretical synthetic modifications have been created, though analogs with a modified proNH₂ residue have not yielded particularly effective compounds (Monga et al., 2008) and thus will not be discussed here.

6.1 pGlu modified analogs of TRH

TRH analogs have been classically used for the treatment of diseases of cerebellar ataxia, such as spinal muscular atrophy (Kato et al., 2009). Synthesized by replacing the c-terminal pyroglutamyl residue of TRH with (S)-4,5, dihydroorotic acid (Suzuki et al., 1990), Taltirelin (TA-0910, (-)-N-[(S)-hexahydro-methyl-2,6-dioxo-4-pyrimidinyl carbonyl]-histidyl-prolinamide tetrahydrate (Ceredist) (Fig. 1B), an orally administered synthetic TRH analog, was launched in 2000 in Japan for the treatment of neurodegenerative diseases. Taltirelin demonstrates CNS activity 10 to 100 times stronger and is 8 times longer-lasting than TRH, with the added benefit of reduced endocrine side-effects. The compound has a $t_{1/2}$ of approximately 2.19 hours, and its metabolite has a $t_{1/2}$ of approximately 6.36 hours (Morikawa et al., 1998). *In vivo*, Taltirelin has been shown to potentiate ACh-induced neuronal excitation in the rat cerebral cortex and inhibit high concentration ACh-mediated desensitization of neuronal excitation (Brown, 1999). Taltirelin has also been shown to enhance the release of dopamine and to accelerate dopamine release and synthesis at cholinergic neuronal terminals in the hippocampus of normal rats (Fukuchi et al., 1998). In parallel to its effects on ACh release and synthesis, Taltirelin has demonstrated an ability to improve memory function in mice pre-treated with the anticholinergic drug scopolamine (Yamamura et al., 1991). Furthermore, Taltirelin has been shown to generate neurotrophin-like activity in the rat embryo spinal cord *in vitro*, and Taltirelin-treated ventral spinal cord cultures demonstrate significantly increased neurite outgrowth (Iwasaki et al., 1992). Taltirelin has also been shown to prevent the death of motor neurons and preserved motor neuron diameter on lesioned sciatic nerve *in vivo* experiments (Iwasaki et al., 1997).

Other analogs that are created by modifying the pGlu residue include: CG-3703 (Montirelin, currently administered for recovery from head trauma, Fig. 1C), DN-1417 (Fig. 1D), and JTP-2942 (Fig. 1E) (Monga et al., 2008). DN-1417 has also been evaluated as a therapeutic for head trauma and has been shown to ameliorate memory impairment in animals (Miyamoto et al., 1981). Compared to TRH, JTP-2942 effects a 300% increase in ACh release in rat prefrontal cortex and hippocampus (Toide et al., 1993). Despite their ability to increase release of neurotransmitters known to be functionally impaired in neurodegenerative conditions, or the fact that some of these compounds are currently approved to treat other disorders, these compounds have yet to be clinically tested in individuals with AD or PD, or in experimental animal models of these disorders.

6.2 His-modified analogs of TRH

NP-647 (L-pGlu-(2-propyl)-L-His-L-ProNH₂, Fig. 1F), is synthesized by substituting the C-2 position of the imidazole ring of the histidine amino acid of TRH with a propyl group (Khomane et al., 2011). NP-647 and other TRH analogs in which the central histidine

residue is substituted at the C-2 position of the imidazole ring with alkyl groups of varying size have been found to exhibit significant selectivity toward TRHR2, as compared with TRHR1, suggesting that NP-647 may exert more CNS rather than peripherally-targeted activity (Kaur et al., 2005). Indeed, in preclinical studies, plasma TSH levels and mean arterial blood pressure were not affected following NP-647 administration (Rajput et al., 2009). Similarly to Taltirelin, NP-647 is also available for oral and parenteral delivery, but its therapeutic effects in humans have yet to be evaluated (Khomane et al., 2011). In experimental murine models NP-647 has been shown to reduce inflammation in stroke models via the actions of the cytokines TNF- α and IL-6, as well as having the ability to reduce lipid peroxidation and experimentally-induced caspase 3 activation (Rajput et al., 2011).

6.3 TRH analogs with modified pGlu and His residues

Posatirelin (RGH-2202, L-6-keto-piperidine-2-carbonyl-L-leucyl-L-prolinamide, Fig. 1G) is created by substituting both the pGlu and His residues. Posatirelin is approximately 5 times more potent in regard to its CNS effects than TRH, however its effects on TSH release are diminished 30-fold compared to native TRH (Szirtes et al., 1986; Oka et al., 1989; Culum and Forbes, 2008). Posatirelin has been shown to enhance norepinephrine and dopamine turnover in the cerebral cortex, nucleus accumbens, and striatum, and increase cyclic GMP levels in the cerebellum of rats (Oka et al., 1989). In motor neurons of the ventral spinal cord, Posatirelin can also exert trophic effects similar to TRH (Takeuchi et al., 1994) and is capable of stimulating functional neurite growth (Askanas et al., 1989). Posatirelin has been administered to AD and vascular dementia patients, resulting in improvements in cognitive function (Parnetti et al., 1995; Parnetti et al., 1996; Gasbarrini et al., 1998). 2-ARA-53a (Fig. 1H), another analog created by modifying both pGlu and His residues, has been shown to improve motor and cognitive functioning in rats (Faden et al., 1999). The effects of other pGlu and His residue modified TRH analogs have not been fully evaluated in humans.

6.4 TRH-like agonist compounds

Synthetic peptides that mimic and enhance the CNS-mediated actions of TRH, and block the degradative actions of prohormone convertases have also been developed. In contrast to POP, PGP I displays a high selectivity for TRH, therefore, PGP I inhibitors have the ability to more selectively enhance the biological actions of TRH (Scalabrino et al., 2007). Inhibitors of POP, on the other hand, exhibit widespread effects which prevent the degradation of a wide range of peptides cleaved by POP (Garcia-Horsman et al., 2007), however some of these compounds can still delay neuronal death (Shishido et al., 1999). Despite this potential mechanistic flaw, several selective POP inhibitors have been developed and are discussed here.

The development of enzyme-specific inhibitors and the production of degradation-stabilized mimetic analogs are sometimes combined in a single compound, as in pGlu-Asn-Pro-D-Tyr-D-TrpNH₂ (Scalabrino et al., 2007). This compound acts as a potent competitive PGP I inhibitor and also as a central, but not peripheral, TRH receptor ligand. It also mimics, as well as potentiates the central actions of TRH, without evoking TSH release (Scalabrino et al., 2007). The addition of D-amino acids is a common method used to confer stability to proteolysis, while stabilizing peptide conformations (Hruby, 2002). The effects however of pGlu-Asn-Pro-D-Tyr-D-TrpNH₂ have yet to be evaluated in either mouse models or clinical cases of neurodegenerative disorders.

In rats, the POP inhibitor, JTP-4819, has been shown to effect increases in ACh release in the frontal cortex and the hippocampus, as well as improving ChAT activity and enhancing choline uptake (Toide et al., 1996). Not surprisingly, improvements in learning and memory

tasks were also observed with JTP-4819 administration. JTP-4819 was also shown to inhibit pro-neurodegenerative A β production in murine neuroblastoma NG108-15 cells (Shinoda et al., 1997). Y-29794, another selective POP inhibitor, has also been shown to prevent the development of A β deposits in the hippocampus of a senescence-accelerated mouse model of natural aging (Kato et al., 1997). It is clear from these data that such hybrid compounds may be of great use for the treatment of age-related neurodegenerative disorders and further testing represents an important goal.

7. Conclusions

It has been shown that age-related changes in TRH, and the HPT axis in general, occur and that these changes are also manifested in age-related disorders including neurodegenerative diseases. Given that multiple effects have been observed through administration of TRH, TRH analogs, and TRH-like compounds, the benefits of TRH as a therapeutic strategy for AD and related neurodegenerative disorders is clear, yet there are currently no ongoing clinical trials of these compounds for the treatment of cognitive and neurodegenerative diseases. More research is needed to understand how the structure-activity relationships of the various synthetics correlate to their beneficial effects in animal disease models as well as humans with neurodegenerative disorders such as AD. In particular, it is imperative that the receptor-based mechanisms of TRH activity in the CNS of humans are better understood. It is possible that in a similar manner to other receptor systems, *e.g.* the gonadotrophin-releasing hormone (GnRH) receptor system, the TRHR1 in humans, can be expressed in multiple tissue regions in a *de facto* distinct pharmacological state that is mediated by receptor interactions with tissue-specific GPCR accessory proteins (Maudsley et al., 2004; Maudsley et al., 2005). Therefore unlike rodent species the specific CNS effects of TRH in humans could be mediated via a differentially coupled and stabilized isoform of the TRHR1, rather than having the need for an extra GPCR gene. Clearly this interesting hypothesis requires more testing but such a concept may assist in the future understanding of this important receptor system. Given the increasing prevalence of AD and related neurodegenerative disorders, developing a broad variety of effective therapeutics is of critical importance and thus greater interest in the TRH-degenerative axis is likely to yield future therapeutic benefits.

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Abbreviations

A	Amyloid
ACh	Acetylcholine
AD	Alzheimer's disease
APP	Amyloid precursor protein
ChAT	Choline acetyltransferase
CNS	Central nervous system
CRH	Corticotrophin releasing hormone
DAG	1,2 diacylglycerol
DAT	Dementia of the Alzheimer type

GABA	-aminobutyric acid
GPCR	G protein-coupled receptor
HPT	Hypothalamic-pituitary-thyroid axis
InsP3	Inositol 1,4,5-triphosphate
MAPK	Mitogen-activated protein kinase
NFT	Neurofibrillary tangle
LPS	Lipopolysaccharides
PC	Prohormone convertases
PD	Parkinson's disease
PGP I/II	Pyroglutamyl aminopeptidase I and II
PLC-	Phospholipase C-
PIP2	Phosphatidylinositol 4,5-P2
POP	Prolyl oligopeptidase (prolyl endopeptidase, PEP)
PS-1	Presenilin-1
PS-2	Presenilin-2
PVN	Paraventricular nucleus
T₃	Triiodothyronine
T₄	Thyroxine
TRH	Thyrotropin releasing hormone
TRHR	Thyrotropin releasing hormone receptor
TSH	Thyroid stimulating hormone

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Figure 1. Chemical structures of TRH and TRH analogs

(A) The chemical structure of the tripeptide thyrotropin-releasing hormone (TRH) (L-pyroglutamyl-L-histidyl-L-prolineamide (L-pGlu-L-His-L-ProNH₂). TRH analogs with a modified pGlu terminal: (B) Taltirelin (*N*-[[(4*S*)-1-methyl-2,6-dioxohexahydropyrimidin-4-yl]carbonyl]-L-histidyl-L-prolinamide); (C) Montirelin ((6*R*)-*N*-[(2*S*)-1-[(2*S*)-2-carbamoylpyrrolidin-1-yl]-3-(1*H*-imidazol-5-yl)-1-oxopropan-2-yl]-6-methyl-5-oxothiomorpholine-3-carboxamide); (D) DN-1417 (2-hydroxypropane-1,2,3-tricarboxylic acid; (2*S*)-1-[(2*S*)-3-(1*H*-imidazol-5-yl)-2-[(5-oxoxolane-2-carbonyl)amino]propanoyl]pyrrolidine-2-carboxamide); (E) JTP-2942 (2*S*)-1-[(2*S*)-3-(1*H*-imidazol-5-yl)-2-[(1*S*, 2*R*)-2-methyl-4-oxocyclopentanecarbonyl]amino]propanoyl]pyrrolidine-2-carboxamide. (F) NP-647 (L-pGlu-(2-propyl)-L-his-L-ProNH₂), a TRH analog with a modified His residue. TRH analogs with modified pGlu and His residues include (G) RGH-2202 (2*S*)-*N*-[(2*S*)-1-[(2*S*)-2-carbamoylpyrrolidin-1-yl]-4-methyl-1-oxopentane-2-yl]-6-oxopiperidine-2-carboxamide and (H) the diiodinated 2-ARA-53a.