TYREOLIBERIN (TRH) – THE REGULATORY NEUROPEPTIDE OF CNS HOMEOSTASIS

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DOI: 10.2478/v10052-010-0008-4

Summary: The physiological role of thyreoliberin (TRH) is the preservation of homeostasis within four systems (i) the hypothalamic-hypophysiotropic neuroendocrine system, (ii) the brain stem/midbrain/spinal cord system, (iii) the limbic/cortical system, and (iv) the chronobiological system. Thus TRH, via various cellular mechanisms, regulates a wide range of biological processes (arousal, sleep, learning, locomotive activity, mood) and possesses the potential for unique and widespread applications for treatment of human illnesses. Since the therapeutic potential of TRH is limited by its pharmacological profile (enzymatic instability, short half-life, undesirable effects), several synthetic analogues of TRH were constructed and studied in mono- or adjunct therapy of central nervous system (CNS) disturbances. The present article summarizes the current state of understanding of the physiological role of TRH and describes its putative role in clinical indications in CNS maladies with a focus on the action of TRH analogues.

Key words: thyreoliberin, metabolism, neuromodulator, nootropic factor, analepsy, antidepressant, neuroprotection

INTRODUCTION

TRH (thyreoliberin, thyrotropin releasing hormone) was one of the first described factors released from the hypothalamus which acts as a neurohormone [4, 7]. It is a tripeptide with a molecular weight of 359.5 Da, which is known mainly for its physiological role as a regulator of the hypothalamus-pituitary-thyroid (HPT) axis. In addition to its stimulatory action at the level of the pituitary, promoting the release of thyreotropin (TSH, thyroid stimulating hormone) and prolactin, TRH also has a profound action on the central and peripheral nervous systems. Wide distribution of TRH and its receptors in the central nervous system

(CNS) has provided the basis for investigating its role in the physiology and pathology of the CNS, which has lead to the description of its potential clinical applications (Table 1). Since TRH as a drug has many limitations, e.g. short half-life, low bioavailability, and peripheral side effects, a number of its synthetic analogues were constructed and investigated as potential drugs in the treatment of CNS maladies.

This review article summarizes the current state of knowledge on the role of TRH in the regulation of several processes in the CNS, with an emphasis on its homeostatic properties. It aims to describe the potential clinical value of synthetic analogues of TRH in treatment of CNS disorders.

TABLE 1. Potential clinical implications for TRH and its analogues.

POTENTIAL CLINICAL IMPLICATIONS FOR TRH AND ITS ANALOGUES
Depression
Chronic fatigue syndromes
Narcolepsy, neurasthenia, lethargy
Sedation secondary to drugs, chemo- or radiation therapy
Sedative intoxication/Respiratory distress
Recovery from general anesthesia
Attention deficit/hyperactive disorder (ADHD)
Disturbances of circadian rhythm (e.g. jet lag)
Bipolar affective disorder*
Anxiety disorders *
Alzheimer's disease and other dementias with cognition deficits *
Seizure disorders *
Motor neuron disorders *
<i>* may be particularly effective as adjunctive therapy</i>

TRH – BIOSYNTHESIS, METABOLISM, DISTRIBUTION AND INTRACELLULAR MECHANISMS OF ACTION

TRH (L-pyroglutamyl-L-histidyl-prolineamide; pGlu-His-ProNH₂) is synthesized mainly in the paraventricular nuclei of the hypothalamus (PVN) and secreted into hypothalamo-hypophyseal portal vessels. It functions in the anterior pituitary by stimulating secretory cells (thyrotropes – TSH releasing cells, mammatropes – prolactin releasing cells) to produce thyreotropin and prolactin [11, 23]. TRH can be synthesized locally in some regions of the CNS (cerebral

cortex, hippocampus, spinal cord), as well as in the periphery (pancreatic beta cells, testes) where it is involved in the local regulation of several cellular processes [11, 23]. The gene encoding TRH contains three exons separated by two non-coding introns. The biosynthesis of TRH is a five-step process, beginning in the nucleus with the transcription of DNA from the TRH gene to the TRH mRNA, and the production of the prepro-TRH mRNA form, which encodes for five or six mature TRHs in the murine and human mRNA, respectively. Transcription is followed by translation to the pro-TRH peptide (Lys-Arg-Gln-His-Pro-Gly-Lys-Arg) on the ribosome [11, 23]. The next steps are the post-translational processing of pro-TRH, beginning with the cleavage of pairs of Lys-Arg residues by the enzymatic action of carboxypeptidase E to generate the intermediate Gln-His-Pro-Gly product. This peptide is subsequently amidated at the proline residue by a peptidyl-glycine α -amidating monooxygenase. The final step of TRH biosynthesis is the Gln cyclization to the pGln form by glutaminyl cyclase and the generation of active tripeptide pGlu-His-ProNH₂. Interestingly, the cleavage of pro-TRH peptide leads not only to production of TRH but also to the generation of other bioactive peptides (TRH-like peptides), although their biological role has not yet been fully identified [11]. It is hypothesized that the post-translational modifications of pro-TRH occurs mainly in neuronal cell bodies because to date, the presence of pro-TRH in neuronal processing (dendrites and axons) has not yet been shown [11]. The biosynthesis of TRH in PVN is strictly regulated by hormones secreted by the pituitary (TSH) and thyroids (triiodothyroine and thyroxine) via a system of negative feedback loops [11]. Moreover, the function of TRH-ergic neurons of PVN can be regulated by other neuroendocrine substances (e.g. vasopressin, oxytocin, glucocorticoids, leptin, galanin, somatostatin, neurotensin), and several neurotransmitters and neuromodulators (e.g. norepinephrine, adrenaline, dopamine, neuropeptide Y, opioids, glutamate, GABA) [9-11, 53]. The TRH half-life in plasma is rather short and ranges from 2 to 6 min in both animals and humans [34]. The rapid degradation of TRH after release from cells is the main factor limiting its potential use as a therapeutic agent. Specific proteolytic enzymes which act on TRH can be found in many tissues, including brain, spinal cord, pituitary, liver, kidney, pancreas, adrenal glands and blood [11, 34]. Tyreoliberinases (histidyl-proline imidopeptidases) are mainly responsible for TRH degradation in blood, while pyroglutamyl endopeptidases (PPI and PPII) and propyl endopeptidase act mainly in the CNS. A result of the action of TRH metabolizing enzymes is the generation of physiologically active substances like stable cyclized metabolite CHP (histidyl-proline-diketopiperazine) and deamidated free acid, TRH-OH [11, 34].

FIGURE 1. Intracellular mechanisms of TRH action

TRH appears to initiate its biological activity by binding with high affinity to the cell membrane of thyrotropin releasing hormone receptors (TRH-R) (Fig. 1). TRH-R belongs to the family of metabotropic receptors, which have 7 transmembrane domains, and is coupled to the G_{q11} protein. Activation of this protein leads to the stimulation of an intracellular secondary transducer system connected with the phospholipase C (PLC) pathway [13, 46]. PLC hydrolyzes the phosphoinositols of the cell membrane (phosphatidylinositol - PI, phosphatidylinositol-3-phosphate - PIP, phosphatidylinositol-4,5-diphosphate - PIP_2) and generates secondary messengers such as diacylglycerol (DAG) and inositol-(1,4,5)-triphosphate (IP_3). Subsequently, DAG can stimulate protein kinase C activity (PKC) which in turn, can activate some transcription factors (e.g. AP-1), or modulate the action of other intracellular proteins via phosphorylation. IP_3 binds to its receptor localized on the endoplasmic reticulum (ER), leads to calcium outflow and an increase in the cytoplasmic Ca^{2+} level. Released Ca^{2+} binds to calmodulin and these complexes activate Ca^{2+} /calmodulin-dependent protein kinases (CaMK) which can influence the activity of transcription factors (e.g. CREB - cAMP-response binding protein). It was shown that TRH can also act via its receptors and stimulate the intracellular MAPK (mitogen-activated protein

kinases) pathway, which activates other transcription factors such as Elk-1. After ligand binding, TRH-R like other metabotropic receptors, are quickly desensitized and internalized [46]. There is widespread distribution of TRH receptors in the brain with the highest occurrence in the limbic regions (hypothalamus, amygdala) and the lowest in the brain stem and cerebellum [11, 34].

The first cloned TRH receptor was TRH-R1, which was discovered in rodents and later in humans [11, 34]. There is relatively high DNA (90%) and amino acid (95%) homology in the TRH-R1 gene and protein among different animal species. The second described receptor for thyreoliberin was TRH-R2, which was first discovered in rats and later in other animals, but to date its existence in humans has not been confirmed [34, 46]. There is approximately 50% homology between TRH-R1 and TRH-R2 receptors at the amino acid level within an animal species. The two types of TRH-R differ in their localization within the brain, with concentrated expression of TRH-R1 in neuroendocrine regions and autonomic nervous system and TRH-R2 dominance in cerebral cortex, midbrain, thalamus and subthalamus [34]. There are also regions in the brain, such as the brain stem, where both types of TRH receptors colocalize. Recently, a third type of TRH-R was described (TRH-R3) in *Xenopus laevis* [3], but its existence in other animal species has not yet been reported. Thyreoliberin possesses similar affinity to TRH-R1 and TRH-R2 and after binding to the receptor, activates the intracellular signaling pathway, connected with the G_{q11} protein, to induce a similar maximal signaling level [34]. The only difference between the two types of TRH receptors is the level of basal signaling activity, with TRH-R2 being higher than TRH-R1. This could influence the rate of receptor desensitization and internalization and subsequently, could have an impact on downstream secondary intracellular signaling. TRH evokes its biological effect not only via secondary messenger systems, but TRH receptor activated G proteins can also directly inhibit potassium (K^+) or sodium (Na^+) channels. The above mechanism could explain some central effects of TRH, such as nootropic, and anti-epileptic activity [55]. Finally, it was shown that in addition to the specific action of TRH on its own receptors (TRH-R), it is also able to bind to others, such as the melanocortin MC_1 receptor, which is a promising target for the development of anti-inflammatory and immuno-modulatory drugs [45, 52].

STIMULATORY EFFECTS OF TRH IN THE CNS AND ITS POTENTIAL CLINICAL IMPLICATIONS

TRH plays a key role in the HPT axis in regulating the function of peripheral endocrine organs, mainly the thyroid. Its endocrine action is profoundly connected with regulation of metabolism at the whole body level as well as single cells [23]. Approximately 2/3 of the body's TRH content is localized away from

the HPT axis, and is concomitant with the widespread distribution of TRH receptors throughout the brain, thus potentially resulting in a wide spectrum of central stimulatory effects [23, 34]. TRH is recognized as a neurotransmitter, which, considering its specific receptors in the CNS could evoke different effects within the brain. It can also act as a neuromodulator, which regulates the action of several neuronal pathways like the dopaminergic, serotonergic, acetylcholinergic and opioid systems.

TRH invokes an ergotropic action in the CNS (mobilizing organisms to work as a source of energy) and influences body arousal, sleep, cognition, locomotion and mood [31]. Recently, the role of TRH as the CNS homeostatic regulator has been described [21]. The preservation of homeostasis in the brain is a result of the action of TRH on four systems: the hypothalamic-hypophysisotropic neuroendocrine system, the brain stem/midbrain/spinal cord system, the limbic/cortical system and the chronobiological system.

A very important role of TRH at the level of midbrain and brain stem is in the regulation of water and food intake, as well as an involvement in thermoregulation [23]. As TRH inhibits food and water intake, it was considered for potential use in the treatment of obesity. The anorexiogenic mechanisms of action of TRH are complex and the TRH expression is stimulated in part by other anorexiogenic peripheral (leptin) and central (proopiomelanocortin – POMC; CART - cocaine and amphetamine regulated transcripts; α -melanocortin - α -MSH) peptides, but is also inhibited by the orexigenic peptide, neuropeptide Y [23, 48]. Another biological role of TRH is in maintaining homeostasis in thermoregulation centers, which are susceptible to cold and the induction of hyperthermia. The thermoregulatory feature of TRH is important not only from a biological point of view (the role TRH in hibernation), but could also be used in a clinical setting for the restoration of body temperature after treatment with certain drugs which can cause hypothermia (e.g. barbiturates, chlorpromazine, alcohol, morphine, neurotensin) [34].

TRH peptide and its receptors are expressed in the SCN (hypothalamic suprachiasmatic nuclei) - a main region of chronobiological system [21, 34], and are involved in modulation of circadian rhythms. TRH has been clinically tested in treatment of some dysfunction of circadian rhythms, such as narcolepsy, jet lag or depression [34].

There is strong evidence concerning the antidepressant effects of TRH, which were intensively investigated late last century [1, 20, 21, 50]. The initial clues that lead to studying TRH as a putative antidepressant were observations of common clinical manifestations of patients with depression and hypothyroidism. The first clinical trials with TRH showed promise, as the antidepressive effects were achieved in relatively short time (1 day), as compared to the time required for the clinical action of classical antidepressants (3-4 weeks) [21]. The beneficial effect of TRH was also shown in treatment of bipolar disorder. While the first clinical trials with TRH were promising, further studies gave inconsistent results, which could have been influenced by the biological instability of TRH or side

effects evoked by this peptide. Interestingly, recently published data point to the involvement of TRH in the therapeutic action of some drugs used in treatment of affective disorders. It was shown that TRH and TRH-R expression could be regulated by some antidepressants (escitalopram) and mood stabilizers (valproate, lithium salts) [38, 42, 43].

Other strong evidence for the connection between TRH and mood regulation has been found in TRH-R knock-out animals. TRH-R1 knock-out mice showed central dysfunction of HPT axis, mild hyperglycemia and only slight changes in growth, body weight and food intake. In these animals, an increased level of depressive and anxiogenic behavior was observed [56]. In contrast, in TRH-R2 knock-outs, neither the function of the HPT axis, metabolism of glucose, development nor growth were disturbed when compared to wild type mice. Interestingly, in female but not male TRH-R2 knock-out mice, the elevated depressive and attenuated anxiogenic behaviors were seen [47]. The above mentioned studies could provide a rationale for the potential use of TRH-R knock-outs as an animal model for identifying potential drugs with antidepressive and/or anxiolytic action. As shown recently, the anxiolytic effects of TRH are mainly connected with action of this peptide on neurons located in amygdala [23].

Another interesting action of TRH is in the modulation of seizures. It has been shown that expression of TRH and its receptors is increased in the brain regions which were activated during seizure episode. On the other hand, exogenously administrated TRH was protective in limbic regions which were affected by drug-induced seizures in experimental animals [24-26, 30]. These data point to the potential for the use of TRH as a sole or adjuvant anticonvulsant drug [21].

Among the central effects of TRH, is its analeptic action. Peripheral administration of high doses of TRH, or lower doses injected directly into the brain evokes a 50% reduction in pentobarbital-induced sleeping time in different animal species [34].

The analeptic properties of TRH are mainly due to its influence on the cholinergic system. This could potentially be used clinically to aid recovery after anesthesia, in consciousness disturbances after brain and spinal cord trauma, to antagonize sedation evoked by other factors (e.g. chemotherapy, radiotherapy, intoxication) [21]. The second action of TRH connected with stimulation of the cholinergic system is its beneficial influence on learning and memory processes. This is supported by observations made *post mortem* in Alzheimer's disease (AD) patients, where a decrease in TRH expression was found when compared to age-matched healthy subjects [32]. On the other hand, the positive reinforcement of learning and memory processes after TRH administration in AD patients [33], has provided the rationale for testing TRH as a treatment of various type of dementias. However in humans, only slight improvements in cognition and memory were noticed in AD and alcohol-induced dementia [34].

As TRH is stimulatory for dopaminergic neurons and possesses some neuroprotective features, it was investigated as a treatment for Parkinson's disease [34]. The dopaminemimetic action of TRH is also associated with its influence on locomotor activity. Intracerebral and peripheral administration of TRH, has a similar effect as that of cocaine, increasing dopamine and serotonin release in rat nucleus accumbens and striatum, which is connected with the animal's elevated locomotor activity. Interestingly, the administration of TRH before cocaine, blocks the locomotor activity induced by the latter drug. Similar observations were made for morphine-induced place preference, where TRH was able to block the effect of morphine in this test, however was inactive when administrated alone [34].

All the above mentioned observations in this section describing the central effects of TRH, support the role of TRH as a CNS homeostatic regulator. Its action could be further characterized by two features of TRH, its analeptic and anti-epileptic action. TRH is analeptic only when the subject is under sedation (for example after anesthetic drugs) and shows an anti-epileptic action only when the subject is threatened by seizures [34].

Apart from in the CNS, TRH also displays a significant physiological role in the peripheral nervous system. It stimulates motor neurons, and thus could be important in the treatment of motor neuron diseases. Some improvements, after treatment with TRH, were seen in patients with ALS (amyotrophic lateral sclerosis) and spinocerebellar degeneration [6, 21, 34]. TRH could elevate the activity of the sympathetic and parasympathetic nervous system, but these effects are dose-dependent. This action is manifested by an increase in gastric acid secretions, elevated blood pressure and heart rate, and a (dose related) increase in the respiratory rate [34]. An interesting role of TRH, which has been extensively studied recently, is its influence on proper development and function of the pancreas, which in turn, is connected with regulation of glucose metabolism [54]. On one hand, the peripheral action of TRH could provide the rationale for use of this peptide in the treatment some peripheral disorders (e.g. cardiovascular diseases, diabetes). On the other hand, all above mentioned peripheral actions of TRH are undesired when considering TRH as a drug for treatment of CNS maladies.

There is an interesting group of endogenous peptides with a chemical structure similar to TRH, called TRH-like peptides, which are built according the scheme pGlu-X-ProNH₂, where X can be any amino acid residue [34]. High concentrations of these peptides were found in the limbic regions of the brain, which could be connected with their influence on mood regulation. Substances from this family showed neuroprotective, antidepressant, euphoric and analeptic activities. Their biological action is not connected with TRH receptors (TRH-R1 and TRH-R2), but they can regulate several neuronal pathways in order to maintain body homeostasis, and appear to be a good target for the development new CNS active drugs [34].

SYNTETHIC ANALOGUES OF TRH

Enzymatic instability, low bioavailability after peripheral administration, and undesirable side-effects (hormonal and peripheral) of the naturally occurring form of TRH, were grounds for the development several synthetic analogues of TRH [34].

The first generation of TRH analogues was a result of specific single or dual substitution of particular amino acid residues in the TRH structure. These modifications gave substances which were resistant to degradation by TRH metabolizing enzymes, and possessed higher CNS activity, while having a lower influence on hormonal function.

Several promising analogues were created by the replacement of a N-terminal pGlu residue. An example of this substitution is an orally active peptide, TA-0910 (taltirelin, Ceredist), which was patented by Mitsubishi Tanabe Pharma Corp as a neuroprotective drug, and since 2000, has been used in Japan to treat spinocerebellar degeneration. Taltirelin is active at concentrations of 100 times less, and for 8 times longer than the parent TRH peptide. Another interesting analogue from group of N-terminal pGlu residue substitutions is montirelin (CG3703, NS3). This can act on TRH receptors and increase acetylcholine release. This analogue was patented by Grunenthal (Germany) as a potential drug for treatment of AD, hypertension, for recovery from anesthesia and coma. A wide range of experimental studies performed in late last century, showed beneficial effects of montirelin on the inhibition of seizures, in recovery from anesthesia, and antagonizing the loss of consciousness after head trauma. Montirelin is effective in doses 10 times lower than TRH and is active for longer time. Additionally antidepressive and nootropic features of montirelin were showed in several animal studies.

Another synthetic peptide created by modification of pGlu residue was azetirelin (YM-14673), which was 10-100 times more potent than TRH in mice, and produced 8-36 times longer lasting analeptic activity and reversal of reserpine induced hypothermia. It was documented in the third phase of clinical trials that azetirelin could act as an anticonvulsant and cognition enhancer. Additionally, in animal models of ischemia its neuroprotective features were also demonstrated. However, clinical use was stopped due to its low bioavailability after oral administration and lack of lipophilicity.

There is also another group of analogues, which consist of peptides in which a middle peptide residue (L-His) is modified. By specific substitution of this residue, it was possible to create analogues with higher or lower hormonal and peripheral activity. Thus, these peptides could be beneficial for the treatment of HPT axis dysfunctions or in treatment of cardiovascular disorders. By replacement of L-His residue with pyridinium moieties, it was possible to obtain peptides with higher CNS activities, which were then tested as potential nootropic and anti-

epileptic drugs. Specific modification of the L-His residue allowed the development of agents which are more selective to TRH-R2 than TRH-R1 and as a result they were devoid of hormonal activity.

TRH analogues developed as potential CNS drugs by dual substitutions in pGlu and L-His residues have shown great promise. In this way, the analogue RGH-2202 (posatirelin) was created, which was patented by Gedeon Richter (Hungary) as a putative neuroprotective drug. It showed nootropic and anti-epileptic action, and improved learning and memory in experimental and clinical studies. Additionally, it has been shown to be 5 times more centrally active, and has only a slight influence on hormonal activity as compared to TRH. Its clinical development was stopped however due to its strong anorexiogenic and hypothermic action. Moreover, inconsistent data from clinical studies also added to its failure as a potential drug. However, new analogues with dual modification in the pGlu and L-His residues are still under development and are being tested as putative CNS active drugs [27].

The other group of TRH analogues was obtained by dual substitution of pGlu and L-ProNH₂ residues. These analogues are also characterized by their increased proteolytic resistance and increased central activity, but unfortunately are not devoid of hormonal activity [34].

Currently the new generation of TRH analogues is under development (second generation). These agents have been created with lower affinity and higher effectiveness with regard to the stimulation of TRH receptors, especially TRH-R2 [14]. At the same time there have been attempts to develop TRH mimetics, which will possess two features: high affinity to centrally located TRH receptors, and an ability to act as an inhibitor of pyroglutamyl endopeptidase II (PPII) [44]. However, these agents are still in their early stages of development as CNS active substances, and further studies will show their effectiveness as putative drugs.

Apart from TRH analogues, synthesized derivatives of a TRH metabolite, dipeptide CHP, have also been developed. It has been shown that cyclic derivatives of CHP are neuroprotective in both acute and slowly progressing models of neuronal cell injury, while being devoid of hormonal and analeptic activity [17, 18].

Apart from chemical modifications of the TRH structure, efforts have been made to search natural substances in plants or sea invertebrates, which show affinity to TRH receptors, especially TRH-R2. As a result of large screening studies, it was found that two active substances from the plant *Corymbia peltata* (corymbone A i corymbone B) possess strong affinity to the TRH-R2 receptor [8]. These will undoubtedly be investigated in the near future for their potential use in the treatment of some CNS disorders.

TRH ANALOGUES AND NEUROPROTECTION

The first observations that pointed to the neuroprotective capacity of TRH, were made in an animal model of spinal cord injury. After intravenous TRH administration lower neurological deficits were seen as compared to an animal that received only buffered saline after neuronal injury [15]. Further studies using animal models of seizures demonstrated increased expression of TRH and its receptors in the regions of injury. This suggested an adaptive endogenous response of the central nervous system for pathologically elevated neuronal activity. Exogenously administrated TRH diminished the level of neuronal cell loss which was induced by convulsion episodes in genetic and chemical animal models of seizures [25, 26, 28, 29, 41]. However, due to TRH enzymatic instability a high dose was necessary to achieve a biological effect, and this lead to strong, undesirable side effects (hormonal and peripheral). During the years of development of the various kinds of TRH analogues, it was found that in order to maintain the neuroprotective effects of TRH, it is crucial to conserve the L-ProNH₂ residue [17, 19]. The neuroprotective effects of TRH and its analogues (tartelin, montirelin, RGH-2202), were demonstrated in animals models of traumatic brain and spinal cord injury, as well in ischemia [2, 5, 16, 36, 39, 40, 51]. Studies with cyclic derivates of the TRH metabolite CHP, showed their efficiency as an anti-excitotoxic, anti-necrotic and anti-apoptotic agent in neuronal cells [16-18, 49]. This group of agents deserves special attention, as these peptides do not evoke the classic undesirable effects characteristic of TRH and its first generation analogues (hormonal, peripheral, analeptic, hyperthermic).

The mechanisms of the neuroprotective action of TRH are only partially understood. During acute injury of neuronal tissue, TRH could influence on release of glutamate, GABA, acetylcholine, endogenous opioids or leukotriens and restore an energetic status of cells which was affected during injury [12, 17, 35, 37]. Recently there has been very interesting data released, that points to receptor independent, intracellular mechanisms of the TRH neuroprotective action. It was reported that the protective action of some derivates of the TRH metabolite, CHP could be connected with their ability to down-regulate the expression of genes which are induced during neuronal injury (e.g. calpains, cathepsins, aquaporins). CHP can also be associated with the up-regulation of endogenously protective genes like BDNF – brain derived neurotrophic factor, heat shock proteins - Hsp70 and HIF-1 – hypoxia induced factor 1 [18]. The widespread action of derivates of the TRH metabolite, CHP, provides the rationale for further studies of these compounds in relation to their potential use as neuroprotective drugs.

SUMMARY

Potential clinical applications of TRH, which have attracted special attention, have arisen from its nonhormonal action via stimulatory (nootropic) effects in the CNS. However, the mechanism of this phenomenon is still not fully understood, as there has been a lack of evidence of specific antagonists of the TRH receptor, which have limited the mechanistic studies. Recently, new agents with antagonistic action on TRH-R have been created, but they are still in the early stages of development [34]. The detailed explanation of the mechanisms of central effects of TRH is complicated, as there are several targets regulated by this endogenous peptide. Nevertheless, experimental studies have shown the clinical benefit of some of the TRH analogues. Examples of these include Taltirelin, which is used in Japan in treatment of spinocerebellar degeneration, Montirelin, which is studied as putative analeptic drug after brain injuries, and RGH-2202, which is in the second phase of a clinical trial as a memory enhancer. The role of TRH as a homeostatic regulator has been recently outlined [21], providing a rationale for the further development of new synthetic analogues, which will be investigated as potential drugs for treatment of CNS disorders. A wide range of such analogues continue to be constructed and studied in various experimental designs.

ACKNOWLEDGMENTS

This work was supported by grant KBN no. 2PO5A15530

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