ABSTRACT

The functions of thyrotropin-releasing hormone (TRH) in the central nervous system (CNS) can be conceptualized as performed by four anatomically distinct components that together comprise a general TRH homeostatic system. These components are 1) the hypothalamic-hypophysiotropic neuroendocrine system, 2) the brainstem/midbrain/spinal cord system, 3) the limbic/cortical system, and 4) the chronobiological system. We propose that the main neurobiological function of TRH is to promote homeostasis, accomplished through neuronal mechanisms resident in these four integrated systems. This hypothesis offers a unifying basis for understanding the myriad actions of TRH and TRH-related drugs already demonstrated in animals and humans. It is consistent with the traditional role of TRH as a regulator of metabolic homeostasis. An appreciation of the global function of TRH to modulate and normalize CNS activity, along with an appreciation of the inherent limitations of TRH itself as a therapeutic agent, leads to rational expectations of therapeutic benefit from metabolically stable TRH-mimetic drugs in a remarkably broad spectrum of clinical situations, both as monotherapy and as an adjunct to other therapeutic agents. The actions of TRH are numerous and varied. This has been viewed in the past as a conceptual and practical impediment to the development of TRH analogs. Herein, we alternatively propose that these manifold actions should be considered as a rational and positive impetus to the development of TRH-based drugs with the potential for unique and widespread applicability in human illness.

Thyrotropin-releasing hormone (pGlu-His-Pro-NH₂) was the first hypothalamic releasing factor to be identified. Soon after this seminal event, however, it was clear that the biological functions of TRH extend far beyond regulation of the thyroid axis. Greater than two-thirds of immunoreactive TRH in the CNS is detected outside the thyrotropic zone of the hypothalamus (Winokur and Utiger, 1974). Consistent with this widespread distribution, TRH has been implicated in the regulation of arousal, autonomic function, control of circadian rhythmicity, endotoxic and hemorrhagic shock, mood, pain perception, seizure activity, and spinal motor function (Nillni and Sevarino, 1999). As this new information emerged, clinical trials have proceeded to test TRH as a treatment for various disorders including depression, schizophrenia, amyotrophic lateral sclerosis (ALS), and spinocerebellar degeneration (SCD; Griffiths, 1986). Possibly reflecting the consistent use of a metabolically stable TRH analog, trials in SCD have been generally positive. In other conditions, generally employing TRH, early trials showed promise although later trials produced inconsistent results. This variability may reflect the fact that native TRH is poorly suited as a therapeutic agent. It has low bioavailability, and its half-life in plasma is about 5 min.

Herein, we first review data concerning the neurobiological mechanisms of TRH systems, and we suggest a new anatomical and functional framework in which to conceptualize these systems. Next, we describe findings related to physiological and behavioral effects of TRH that collectively support...
a new perspective on TRH as a CNS homeostatic modulator. After a brief discussion of clinical trials of TRH and the development of various TRH analogs, we propose that this new understanding of the physiological role of TRH systems provides a rationale for new therapeutic applications for TRH-based drugs.

Like many other neuroactive peptides, TRH is thought to subserve neurotransmitter or neuromodulatory functions that affect neuronal excitability (Dettmar and Metcalf, 1981). Consistent with this notion are data documenting that:

- TRH is enzymatically processed from a larger precursor, prepro-TRH, which contains multiple copies of the TRH progenitor sequence as well as several distinct non-TRH products.
- TRH is widely distributed in anatomically distinct pathways throughout the neuroaxis.
- TRH is stored as a regulated releasable pool in secretory granules in synaptic terminals and is selectively degraded by specific enzymes.
- TRH interacts with at least two known G-protein coupled receptors, TRH-R1 and TRH-R2.

Signaling occurs mainly through the phosphoinositide-specific phospholipase C pathway, with subsequent elevations in intracellular calcium, modulation of K⁺-channel conductances, etc. Greater diversity in TRH signaling may occur via a putative third TRH receptor subtype recently described in Xenopus, although affinity data cast doubt as to whether the endogenous ligand(s) for this receptor is TRH (Bidaud et al., 2002). A more precise and conventional understanding of the CNS functions of TRH is impeded by the lack of known selective and potent isosteric TRH receptor antagonists. Much of the above information has been reviewed (Nillni and Sevarino, 1999; Gershengorn and Osman, 2001). In the following paragraphs, we provide a new synthesis of this and other information that supports novel therapeutic possibilities for TRH analogs.

**Neurobiology of TRH-Mediated Homeostasis**

In this section, data about the regional anatomical distribution of TRH systems and the diverse physiological and behavioral effects produced by TRH are reviewed. Figure 1 presents a schematic depiction of the proposed TRH homeostatic system. Four distinct yet functionally integrated components of this system are conceptualized: the hypothalamic-hypophysiotropic neuroendocrine system, the brainstem/midbrain/spinal cord system, the limbic/cortical system, and the chronobiological system. We hypothesize that these components of the TRH homeostatic system function in a coordinated fashion to normalize the intensity and quality of CNS activity.

**The TRH Hypothalamic-Hypophysiotropic Neuroendocrine System.** The hypothalamic-hypophysiotropic neuroendocrine axis serves as a key regulator of metabolism. As part of this function, hypothalamic TRH is the key positive regulator of thyrotropin (thyroid-stimulating hormone; TSH) release from the pituitary gland. Thyroid hormones, in turn, negatively regulate TRH release and hypothalamic prepro-TRH mRNA content (Scanlon and Toft, 2000). The thyroid axis governs slowly developing, but long-lasting, increases in metabolic activity; it appears that TRH has evolved as its CNS activator.

The TRH stimulation test is a diagnostic tool that measures thyrotropin secretory responsiveness. Since 1972, numerous reports have characterized the TSH response to TRH administration in depressed patients (Loosen and Prange, 1982). In virtually all reported studies, a subset of depressed patients demonstrated a diminished TSH response to TRH stimulation. The pathophysiological mechanisms that account for the blunted TSH response have not been elucidated, although down-regulation of TRH pituitary receptors has been suggested. The TRH response also is blunted in patients with other psychiatric conditions, including schizophrenia, bipolar disorder, and alcoholism (Winokur, 1991). Although
the majority of studies applying the TRH stimulation test in depressed patients have employed a morning TRH infusion paradigm (typically at 8:00 AM), Duval et al. (1990) employed TRH stimulation tests both in the morning and evening (8:00 AM and 11:00 PM). They subtracted the morning response from the evening response, a technique that magnifies the response deficit shown by patients as compared with controls. This finding suggests that thyroid axis abnormalities in depression may demonstrate a circadian component.

The TRH Brainstem/Midbrain/Spinal Cord System. Spinal tissue from several species, including humans, contains substantial concentrations of TRH and TRH receptors (Winokur et al., 1989). Cell bodies containing TRH within the raphe nuclei project through the spinal cord central canal region and terminate in lamina II and lamina IX. The raphe neurons containing TRH also contain serotonin and, in some cases, substance P, suggesting physiologically significant interactions between TRH and these colocalyzed neuroactive substances. In both rat and human spinal cord, substantial concentrations of TRH receptors (consistent with the TRH-R2 receptor subtype) have been identified in lamina II, which contains the substantia gelatinosa, and in lamina IX (predominant receptor subtype TRH-R1), in proximity to anterior horn α-motoneurons (Heuer et al., 2000). The localization pattern for TRH projections in spinal cord suggests likely involvement in motor function and modulation of pain transmission. Electrophysiological studies on spinal cord preparations have reported excitatory effects of TRH on motoneuron activity and spinal reflexes, with some data suggesting synergistic effects associated with the coadministration of TRH and serotonin. In several animal models of spinal cord injury, TRH administration was associated with improved motor function (Faden et al., 1989). Additionally, administration of TRH in the Rolling mouse Nagoya model of hereditary ataxia resulted in improved motor function and decreased ataxic symptoms (Sobue et al., 1983). As discussed below, these results led to clinical trials of TRH and a TRH analog in human SCD.

The proposal that midbrain/brainstem TRH systems modulate a variety of vegetative functions is supported by numerous studies in which peripheral, intracisternal, or in situ administration of TRH or TRH analogs has been reported to produce effects such as stimulation of gastric acid secretion, cytoprotective effects minimizing gastric ulceration induced by ethanol, increases in heart rate and blood pressure, secretion of catecholamines from the adrenal medulla, and increases in respiratory effort (Horita et al., 1986). Thus, in conjunction with numerous behavioral effects, a coordinated pattern of autonomic modulation suggests a role for TRH in the adaptive responses to stress.

The TRH Limbic/Cortical System. Many effects of TRH appear linked to TRH systems localized in limbic and cortical areas. These effects often involve interactions with other neurotransmitters. The first report involved the dihydroxyphenylalanine potentiation test (Plotnikoff et al., 1972), in which antidepressant-like effects were noted. Notably, hypophysectomized and/or thyroidectomized animals demonstrated full behavioral responses. These findings coincided with clinical studies of TRH efficacy in the treatment of depression as discussed below. TRH has also been found active in a conflict test involving punished responding (Vogel et al., 1980), a paradigm used to screen compounds for likely efficacy in clinical anxiety.

Another prominent behavioral response to TRH administration involves reversal of sedation (Horita, 1998). Initially described on the basis of TRH's potency to shorten sleep induced by ethanol or barbiturates, this striking analeptic effect also has been described following administration of other CNS depressant compounds, including opiates, phe-nothiazines, and benzodiazepines. Neuroanatomical substrates of this analeptic effect were mapped by microinjection studies, with the medial septal area demonstrating the greatest degree of sensitivity. The circuitry of this behavioral response to TRH appears to involve the classical cholinergic septohippocampal projection pathways. Moreover, it is thought that many other effects of TRH are also mediated by cholinergic mechanisms (Yarbrough, 1983).

TRH reversal of drug-induced sedation has been extended to reversal of natural states of sedation in the hibernating ground squirrel (Winokur, 1991). When microinjected into the dorsal hippocampus, TRH produced physiological and behavioral arousal from hibernation. Furthermore, TRH similarly administered in the euthermic ground squirrel studied during slow wave sleep produced physiological and behavioral activating effects. In contrast, TRH injections in conscious euthermic ground squirrels produced inhibitory effects. These inhibitory effects were directly proportional to the extent of behavioral activation at the time of TRH administration. These findings, taken together, were the first to suggest that TRH can act as a state-dependent modulator of CNS activity.

Consistent with its cholinergic link in analepsis, TRH along with many of its analogs enhances performance on several parameters of learning and memory (Horita, 1998). Thus, TRH or TRH analogs improve maze test performance in medial septum-lesioned animals and also reverse memory deficits produced by scopolamine, CO₂ exposure, or lesions of the nucleus basalis of Meynert in some, although not all, published studies.

Extensive experimental evidence links seizure induction to TRH neuronal systems (Kubek and Garg, 2002). Induction of generalized seizures through a variety of experimental procedures, including administration of pentylenetetrazol, kainic acid, tetanus toxin, amygdala kindling, and electroconvulsive shock elevate levels of TRH mRNA and reduce TRH receptor concentrations in limbic regions such as amygdala and hippocampus. The increases in limbic region TRH following several alternate day electroconvulsive shock administrations suggests that activation of TRH neuronal systems underlies the antidepressant effect of clinical electroconvulsive therapy (Sattin, 1999). Studies of TRH or TRH analogs in animal seizure models have reported inhibition of seizure activity in amygdala-kindled seizures, tonic, and absence-like seizures. Studying the effects of amygdala-kindled seizures, Post and Weiss (1996) reported activation of hippocampal TRH systems. They speculated that the activation of TRH neuronal systems by seizures represents a compensatory mechanism to terminate excessive neuronal activity (Post and Weiss, 1996), a homeostatic function.

Unpublished studies (K.A.S.) in the field of addictions also illustrate homeostatic modulation by TRH. TRH is a locomotor activator when injected into the nucleus accumbens, a key brain reward region mediating effects of drugs of abuse (Ka-
livas et al., 1987). Nevertheless, accumbens injections of TRH block the development of locomotor sensitization to the psychostimulant cocaine. In this phenomenon, repeated exposure to cocaine causes progressively greater locomotor responses. Similarly, systemic TRH blocks development of conditioned place aversion to opiate withdrawal in rats, whereas TRH by itself does not produce conditioned place preference.

The TRH Chronobiological System. We propose that a TRH chronobiological system represents a fourth functionally integrated component of the TRH homeostatic system. Numerous findings support interrelationships between TRH and biological systems that exhibit rhythmic activity. TRH and TRH receptors are localized in the hypothalamic suprachiasmatic nuclei (SCN; Manaker et al., 1985), the primary circadian pacemaker. Although the source of TRH in the SCN remains unknown, TRH has been localized in two of the three chiasmatic nuclei (SCN; Manaker et al., 1985), the primary circadian pacemaker. Although the source of TRH in the SCN remains unknown, TRH has been localized in two of the three primary afferent projections to the SCN, the dorsal raphe nuclei (Merchenthaler et al., 1988) and the ganglion cells of the retina (Lexow, 1996).

The most direct evidence in support of an effect of TRH on chronobiological function was provided in a study involving microinjection of TRH into the SCN of hamsters housed in constant low-level illumination (Gary et al., 1996). A phase response curve was established by injecting TRH into the SCN at various time points across the circadian period. Microinjection of TRH during the animals’ subjective day resulted in a pronounced phase advance in the circadian pattern of wheel running activity.

In this section, we have reviewed both old and new data concerning four TRH neuronal systems and the physiological and behavioral effects produced by administration of TRH or TRH analogs. These findings support our proposal that TRH neuronal systems subserve a broad role as a CNS homeostatic modulator, a concept depicted in Fig. 2. This figure implies that TRH effects are dependent on the state of the organism at the time TRH is activated or administered. This schema provides a way to reconcile much of the variability in the results reported after TRH administration. Appreciation of this role provides a rationale for the therapeutic application of TRH analogs, as described below.

Therapeutic Implications of TRH-Mediated Homeostasis

Clinical Effects of TRH. A limited number of clinical studies have extended preclinical findings to examine the possible therapeutic value of TRH. Initial reports of a rapid onset of antidepressant effects following TRH administration to depressed patients were followed by other studies examining the efficacy of TRH in the treatment of depression (Winokur, 1991). Inconsistent positive and negative findings were reported following i.v., oral, and intrathecal administration of the peptide (Mason et al., 1995). In considering these results, it is important to recall that the short half-life of TRH in plasma and the uncertain ability of the peptide to gain access to the CNS after peripheral administration limit the interpretation of all clinical findings with native TRH. Despite these limitations, however, some additional findings from studies of TRH administration to depressed patients are noteworthy. First, Itil et al. (1975) reported not only rapid improvement in symptoms following a single i.v. dose of TRH but also activation of EEG patterns in a manner that simulated the effects produced by stimulants and by antidepressant drugs with activating properties (Itil et al., 1975). Second, Marangell et al. (1997) administered TRH (500 μg) by intrathecal injection to eight patients with refractory depression and noted significant reduction of depression in five, with responses being observed on the day of TRH administration or a day later (Marangell et al., 1997). Finally, Szuba et al. (1996) administered TRH (500 μg, i.v.) or placebo to 20 bipolar patients in a depressive episode, with administration occurring at midnight. Rapid improvement in depressive symptoms was observed in 60% of patients receiving TRH and 10% of patients receiving placebo. These data support the possibility that circadian factors influence the response to TRH, findings that complicate the interpretation of clinical trials but support a chronobiological influence of the peptide.

Mellow and coworkers (1989) noted reports of improvement in cognitive function in various animal paradigms after TRH administration and also recognized the limited CNS penetration of the peptide. Accordingly, they used high doses of i.v. TRH (0.5 mg/kg) in their studies of normal volunteers, with transient cognitive impairment produced by administration of anticholinergic agents and of patients with Alzheimer’s disease (Mellow et al., 1989; Molchan et al., 1990). Modest improvements in some indices of cognitive function were observed in both groups.

Studies of the therapeutic effects of TRH in ALS were undertaken based on the demonstration that TRH systems are located in pertinent regions of spinal cord, on evidence of physiological enhancement of motoneuron activity following administration of TRH, and on reports of trophic effects of TRH on spinal cord explants (Engel, 1989). Initial positive studies indicating that TRH produced acute enhancement of motor strength and coordination were followed by long-term studies in which only minimal evidence of therapeutic benefit was observed. A subsequent study showed that TRH receptor concentrations in postmortem spinal cord samples from ALS patients are reduced from 60 to 90% in the lamina IX region (Winokur et al., 1988), however. Thus, the paucity of positive TRH effects in patients with ALS may be explained by loss of receptor targets as well as by the limited access of TRH to the CNS.

As noted above, TRH has been studied in several preclinical seizure models; other studies have tested the use of TRH in the treatment of seizure disorders in humans. As reviewed by Kubek, limitations of the clinical studies stem from the facts that TRH was always studied as “add-on” therapy and that none of the trials were placebo-controlled (Kubek and

**Fig. 2.** Conceptualization of the homeostatic modulatory role of TRH-based drugs. Significant alterations in CNS neuronal activity, resulting from either hyper- or hypofunction, can clinically manifest as anxiety and seizures or depression and fatigue, respectively. TRH neuronal systems are activated by the perturbed CNS function and respond by returning the system back to homeostasis.
Garg, 2002). Additionally, studies have tended to involve small numbers of subjects. These limitations notwithstanding, some evidence exists for beneficial effects of TRH in the management of infantile spasms, Lennox-Gastaut syndrome in children, partial seizures, and myoclonic seizures.

**TRH Analogs.** Delineation of the pharmacophoric domains of TRH led to the development and clinical assessment of several metabolically stable analogs of TRH. These compounds can be classified as follows:

1. Modifications of the native C-terminal pyroglutamyl residue of TRH:
   - TA-0910 (Ceredist) (Tanabe Seiyaku Co., Ltd, Osaka, Japan);
   - CG-3703 (montirelin) (Grüenthal GmbH, Aachen, Germany);
   - JTP-2942 [Na-((1S,2R)-2-methyl-4-oxocyclopentyl-carbonyl)-l-histidyl-l-prolin amide monohydrate] (Japan Tobacco, Inc., Tokyo, Japan);
   - YM-14637 (azetrelin) (Yamanouchi Pharmaceutical Co., Ltd, Tokyo, Japan).

2. Modifications of N-terminal prolineamide residue of TRH:
   - RX-77368 (pyroglutamyl-2-histidyl-3′,3′-dimethyl-prolineamide) (Ferring Pharmaceuticals, Inc., Copenhagen, Denmark).

3. Modifications of the C-terminal pyroglutamyl and N-terminal prolineamide TRH residues:

4. Modifications of the C-terminal pyroglutamyl and histidyl residues of TRH:
   - RGH 2202 (posatirelin) (Gedeon Richter Pharmaceuticals, Budapest, Hungary).

5. Substitution of a cyclohexane backbone to replace the peptide linkages in native TRH:
   - Ro 24-9975 [1S,3′R,5′(2′S),5S]-5-{[5-oxo-1-phenylmethyl]-2-pyrrolidinyl]-methyl]-5-[(1′F-imidazol-5-yl)methyl]-cyclohexanecetamide] (Hoffman-La Roche, Basel, Switzerland).

To varying degrees, all these compounds have been evaluated and shown to be TRH mimetics in preclinical experimental paradigms. Compared with TRH, each compound exhibits the following properties: reduced affinity for TRH receptors (thus reducing TSH release), resistance to metabolic degradation, and augmented CNS penetration. Thus, each analog represents a candidate for therapeutic intervention where TRH agonism might be useful, and indeed, some have been the subject of clinical trials. The net result to date is that one compound, TA-0910, is now marketed in Japan under the trade name Ceredist for the treatment of SCD. We think that several if not all these TRH analogs merit renewed clinical attention in light of our suggested perspective on TRH as a homeostatic agent.

**Experience with Selected TRH Analogs: TA-0910.** Although TA-0910 clearly mimics the biological actions of TRH, it has reduced affinity for brain and pituitary TRH receptors, especially the latter, compared with TRH. The plasma half-life and bioavailability of TA-0910 are substantially enhanced in all species examined, including humans. This enhanced metabolic stability provides greater and longer lasting access to its CNS site(s) of action.

Knowledge of the brainstem TRH system, as noted above, provided a basis for clinical studies of TRH in SCD (Sobue et al., 1986), which yielded positive results. Moreover, a hereditary animal model reflecting the pathophysiology of human SCD has been developed (Nishimura, 1975), and both TRH and TA-0910 were found to be active in this model as well as in other animal models of motor dysfunction (Kinoshi et al., 1998). The positive results with TRH and TA-0910 in early clinical trials and animal models provided an impetus for detailed testing in human SCD (Kinoshi et al., 1998). Improvements were noted in gait, speech, and coordination in both phase II and phase III trials. The drug appeared to slow disease progression in large phase III studies (n = 400). These findings are consistent with reports of trophic effects of both TRH and TA-0910 in neurons in the spinal cord and may indicate therapeutic benefits beyond symptomatic relief.

TA-0910 is the first TRH analog approved for marketing by a major regulatory agency. It was launched in Japan in 2001 for the treatment of patients with spinocerebellar degenerative diseases, with reported sales of about $70,000,000 in its second year (Tanabe, 2002).

**CG-3703.** Grüenthal patented CG-3703 in 1984 for the treatment of ALS. More potent and longer acting than TRH, CG-3703 produced beneficial effects in animal models of concussion-induced unconsciousness, cerebral ischemia, memory disruption, spontaneous convulsions in rats, narcolepsy, and spinal trauma (Grüenthal, 1997). Given its efficacy in these models, the potential indications were broadened to include seizures, nerve trauma, cognitive dysfunction, and sleep apnea.

Grüenthal’s licensee, Nippon Shinyaku Company (Kyoto, Japan), conducted clinical trials of montirelin in patients exhibiting “disturbances of consciousness”. Phase I evaluation (n = 34) demonstrated safety, tolerability, and a favorable side effect profile. An initial dose-finding phase II study (n = 60) was followed by a placebo-controlled, double-blind, safety and efficacy trial in 292 patients. In both studies, 0.5 mg of montirelin administered over 14 days improved ratings of global clinical state in 73% of patients. Phase III studies examining the efficacy of montirelin in a similar patient population (n = 240) demonstrated similar positive results (reviewed in Grüenthal, 1997). These findings notwithstanding, it is our understanding that the development of this compound has been suspended.

**Future Therapeutic Applications of TRH Analogs**

We have presented new perspectives on the organization and functions of TRH and have proposed that an array of anatomical, physiological, and behavioral data support a role for TRH as a CNS homeostatic modulator. The astonishing array of actions of TRH—proven in animals and at least suggested in humans—requires a novel conceptualization. This need can be illustrated by holding in juxtaposition only one circumstance and mimic it in another. Thus, TRH is a normalizer, a homeostatic agent. Many systems contribute to the defense of the internal milieu. Through activation of one
or several of its four subsystems, TRH contributes to this defense and appears to coordinate the overall effort toward homeostasis. It may be useful to state our position as a hypothesis, the TRH hypothesis of homeostatic regulation. Thus, thyrotropin-releasing hormone is a homeostatic agent that opposes many, if not all, perturbations in the central nervous system and in its autonomic outflow, tending to restore its function to normal limits.

To be clinically useful, a TRH analog should exert weak TSH-releasing effects. As noted, most TRH analogs demonstrate this property while at the same time producing enhanced “nonendocrine” CNS effects. If analogs were developed with selective affinity for TRH-R1 and TRH-R2, they would probably demonstrate more specific profiles of CNS effects. Moreover, additional TRH receptor subtypes may yet be discovered, as suggested by the report of Bidaud et al. (2002).

The range of physiological and behavioral effects produced by TRH provides a basis for considering a variety of therapeutic indications for TRH analogs, as indicated in Table 1. A parsimonious and heuristic unifying concept for these diverse indications relates to the homeostatic modulatory role subserved by endogenous TRH systems. Although such a broad range of therapeutic indications might be seen as a liability, we propose that the putative ability of TRH analogs to exert homeostatic effects represents a rational, novel, and uniquely promising profile. In some instances a TRH analog by itself may represent a sufficient therapeutic intervention to normalize a dysregulated physiologic system. For example, one might consider what is commonly called jet lag while contemplating the putative chronobiological properties of TRH. The ability of a TRH analog to both phase shift circadian rhythms and enhance alertness and cognitive function may endow it with unique therapeutic value. In other circumstances, a TRH analog might serve as an ancillary agent to a primary standard treatment (e.g., a selective serotonin reuptake inhibitor in the treatment of depression) and provide a needed permissive or synergistic effect (e.g., in a patient with treatment refractory depression). While such speculation requires empirical validation, we think that the promise of TRH analogs for therapeutic application in a variety of disorders represents an area of striking opportunity that has hitherto gone largely unrealized.

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